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Hemodialysis

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HEMODIALYSIS

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Contributors

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Meet the editor

Dr. Suzuki graduated from Hokkaido University School of Medicine in 1975 and received the residency program of internal medicine in Keio University Hospital. He spent four years as clinical fellow in Nephrology and Endocrinology, Keio University Hospital from 1977 to 1982. After that, Dr. Suzuki studied as a Research Fellow of Basic Nephrology and Hypertension in Cleveland Clinic Foundation, Ohio, USA. from 1982 to 1984. Coming back to Japan, he became an Assistant & Associate Professor, Department of Internal Medicine, Keio University, School of Medicine and carried out these Professor ship until 1995. Dr. Suzuki became a Professor, Department of Nephrology, Saitama Medical School and continued this job until the present time. He is involved in clinical nephrology including dialysis and hypertension.

Contents

Preface

Populations on dialysis are showing a rapid worldwide increase. In developed countries, remarkable increases in elderly patients and those with diabetes have been noted. In developing countries, changes in life style and economic development have made hemodialysis (HD) therapy available to many more patients. In this special issue, reviews of various aspects of HD therapy were submitted from both groups. In particular, various methods for vascular access were discussed by many contributors. From these reviews, the reader will gain precious hints and suggestions in every day practice. I appreciate tremendous efforts of the authors to complete this special issue.

Lastly I thank Ms Iva Simcic, who carried out an exceptional secretarial task of collecting and editing the manuscripts.

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Section 1

Complications in Dialysis Therapy

Chapter 1

Cardiovascular Disease in Hemodialysis Patients

Han Li and Shixiang Wang

Additional information is available at the end of the chapter

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1. Introduction

Cardiovascular disease (CVD) is a most common complication and a chief cause of death in patients with end stage renal disease (ESRD) accounting for 45% to 50% of causes of death in ESRD patients. In ESRD patients, mortality due to CVD is 10~30 times higher than in the general population. 80% patients on maintenance homodialysis (MHD) had cardiovascular complication. In Chinese patients, the prevalence of CVD in young MHD patients was as high as 63.8%, and its characteristics were similar to middle- and old-aged MHD patients. This is likely due to ventricular hypertrophy as well as nontraditional risk factors, such as chronic volume overload, anemia, inflammation, oxidant stress, homocysteine and other aspects of the uremic milieu. China collaborative study on dialysis: a multi-centers cohort study on cardiovascular diseases in patients on maintenance dialysis showed that cardiovascular morbidity during chronic dialysis was more prevalent in peritoneal dialysis (PD) than HD patients among those with old age and long-term dialysis. Metabolic disturbance-related risk factors were independently associated with CVD only in PD patients. Better understanding the impact of dialysis modality on CVD would be an important step for prevention and treatment [1]. In this chapter we focus on epidemiology and management of traditional and nontraditional CVD risk fators and on ischemic heart disease, heart failure and arrhythmia.

2. Traditional risk factors

2.1. Hypertension

2.1.1. Epidemiology and pathophysiology

Hypertension is a common complication in patients with chronic kidney disease. The incidence of hypertension grows along with the decrease in glomerular filtration rate (GFR). It

was reported that the incidence of hypertension in patients with GFR less than 60 ml/min was 50%-75%. However, the incidence of hypertension was extraordinarily higher in MHD patients. In 69 dialysis units in the United States, almost 86% of MHD patients were suffering from hypertension, and the control rate for their BP was merely 30%[2]. Hypertension is a significant risk factor for cardiovascular disease in MHD patients. Foley et al [3] found that with each 10 mm Hg increase of BP in MHD patients, the risk of LVH increased by 48%, ischemic heart disease increased by 39% and congestive cardiac failure increased by 44%.

The causes of hypertension in MHD patients are miscellaneous, including volume overload [4], activation of the RAS [5], sympathetic hyperactivity [6] and increases in inhibitors of nitric oxide (NO) in the blood circulation, such as ADMA [7]- which result in a high incidence of hypertension and difficulties in BP control. MHD patients always need to be treated with combinations of 3 or more categories of antihypertensive drugs.

2.1.2. Definition and drug therapy

a. Definition: Predialysis systolic pressure >140mmHg and/or diastolic pressure >90mmHg when the patient is believed to be at so-called "dry weight".

b. Drug Therapy goal: Arterial pressure goals should be established individually, taking into account age, comorbid conditions, cardiac function, and neurologic status. In patients with raised systolic and diastolic pressure and few background cardiovascular complications, a reasonable predialysis BP goal is <130/80mmHg, that targeted by JNC7 for patients with chronic renal disease. In patients with isolated systolic hypertension and wide pulse pressure (usually elderly patients with atherosclerotic complications), excessive lowering of BP may be hazardous. For them a target predialysis systolic pressure of about 140-150mmHg is prudent.

2.1.3. Treatment

a. Sodium and fluid restricton. Most fluid ingestion is driven by salt ingeston. Sodium restriction of 2g per day(87mmol) should not be onerous, and of the patient is open to a more stringent sodium restriction and caloric and protein intake seem adequate, then this should be encouraged.

b. Longer and/or more frequent/longer dialysis sessions. In some ESRD patients, a regular dialysis schedule, three times per week using 4-hour session lengths will be insufficient to maintain euvolemia. In such patients, the choics are to increase the dialysis session length, or to switch to a four times per week, or even daily dialysis[8].

c. Antihypertensive drug use

The regular antihypertensive drugs in MHD patients include angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), calcium channel blocker (CCB) and β-receptor blocker or α-receptor blocker. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality.

The ACCOMPLISH trial [9] was a 3-year multicenter, event-driven trial involving patients with high cardiovascular risk who were randomized in a double-blinded manner to benazepril plus either hydrochlorothiazide or amlodipine and titrated in parallel to reach recommended blood pressure goals. Of the 8125 participants in the United States, 1414 were of self-described Black ethnicity. The composite kidney disease end point, defined as a doubling in serum creatinine, end-stage renal disease, or death was not different between Black and non-Black patients, although the Blacks were significantly more likely to develop a greater than 50% increase in serum creatinine to a level above 2.6 mg/dl. They found important early differences in the estimated glomerular filtration rate (eGFR) due to acute hemodynamic effects, indicating that benazepril plus amlodipine was more effective in stabilizing eGFR compared to benazepril plus hydrochlorothiazide in non-Blacks. There was no difference in the mean eGFR loss in Blacks between therapies. Thus, benazepril coupled to amlodipine was a more effective antihypertensive treatment than when coupled to hydrochlorothiazide in non-Black patients to reduced kidney disease progression. Blacks have a modestly higher increased risk for more advanced increases in serum creatinine than non-Blacks.

A recent research in China showed that the nitrate can decrease BP, reduce the total categories and quantities of other antihypertensive drugs needed, reverse LVH modeling and reduce the rate of acute heart failure in MHD patients, with good tolerance and safety, by the release of NO which is probably antagonized by ADMA in ESRD subjects. It is, therefore, appropriate to consider sustained-release nitrates as the sixth category of antihypertensive drugs for MHD patients, in addition to ACEIs and ARBs, CCBs, β-receptor blockers and α-receptor blockers [10].

2.2. Smoking

Smoking is associated with progression early-stage CKD patients, and may well adversely impact residual renal function in dialysis patients [11]. Smoking strongly associates with incident heart failure, incident peripheral vascular disease, and all-cause mortality in the U.S. Renal Data System (USRDS). Post hoc analysis of the HEMO Study in patients with available comorbidity, clinical, and nutritional data. The results showed that 17% were current smokers and 32% were former smokers at baseline. After case-mix adjustment, compared with never smoking, current smoking was associated with greater infection-related mortality (hazard ratio [HR], 2.04; 95% confidence interval [CI], 1.32-3.10) and all-cause mortality (HR, 1.44; 95% CI, 1.16-1.79) and greater cardiovascular (incidence rate ratio [IRR], 1.49; 95% CI, 1.22-1.82) and all-cause (IRR, 1.43; 95% CI, 1.24-1.65) hospitalization rates. The population attributable fraction (i.e., fraction of observed deaths that may have been avoided) was 5.3% for current smokers versus never-smokers and 2.1% for current versus former smokers [12].

2.3. Diabetes

Diabetics are at higher risk for acute coronary syndromes. Additionally, there is increased prevalence of heart failure. Poor blood glucose control is associated with increased mortality in dialysis patients [13]. NKF-K/DOQI guidelines recommend a target HbA1c of <7% for patients with DM and CKD[14]. A prospective interventional study in patients with DM but

without renal failure showed an increase in all-cause mortality in patients with HbA1c <6% attained by intensive therapy compared to the standard therapy group[15]. Nonetheless some small observational studies mostly performed in Asian populations indicate the importance of good glycemic control for survival in dialysis patients with DM [16,17,18]. One observational study from Germany found higher HbA1c values to be a risk factor for all-cause mortality and cardiovascular disease[19]. However, in several studies no association between HbA1c and neither patient survival[20,21,22] nor cardiovascular disease [23] could be shown in dialysis patients with DM. Most of these studies were based on a single measurement of HbA1c values. Only two studies considered time-dependent analyses using all available measurements of HbA1c during the whole observation period instead of using only a baseline measurement [24]. Insulin resistance (IR) is highly prevalent in MHD patients and is associated with poor cardiovascular outcomes. Hyperinsulinemic euglycemic glucose clamp (HEGC) is the gold standard for measuring IR. An observational study in USA found that eighty-three percent of the subjects displayed either glucose intolerance or overt insulin resistance by HEGC (GDR median, 5.71; interquartile range [IQR], 4.16, 6.81). LAR and HOMA-AD were the best correlates of IR measured by HEGC (r=-0.72, P<0.001, and -0.67, P<0.001), respectively. Fat percentage, interleukin-6, and adipokines (leptin, adiponectin, and resistin) were strongly associated with GDR. HEGC, LAR, and HOMA-AD had the best intraclass correlation coefficients [25].

2.4. Dyslipidemia.

Dyslipidemia is a well-established metabolic disorder in dialysis patients. A recent study [26] found that a significant increase of serum triglycerides (p= 0.002), lipoprotein (a) (p = 0.001) and C Reactive Protein (p = 0.008) was observed in patients when compared with healthy controls. A significant decrease of serum total cholesterol (p=0.01), HDLcholesterol (p<0.001), LDL-cholesterol (p=0.005) and apolipoprotein AI (p<0.001) was also observed in patients. A study of cholesterol metabolism in patients with hemodialysis in the presence or absence of coronary artery disease showed that HD patients showed lower cholesterol concentrations than non-HD patients, and, as compensation, their cholesterol absorption might be accelerated. However, higher cholesterol synthesis, which was correlated with higher BMI, might be an independent predictor for the presence of coronary artery disease in HD patients [27].

2.4.1. Cholesterol

In dialysis, the relationship of total or low-density lipoprotein (LDL) cholesterol to mootality is U-shaped; patients with LDL cholesterol levels above 100 mg/dL (2.6 mmol/L) are most likely at increased risk for adverse cardiovascular outcomes, but low levels, probably indicating malnutrition, also are associated with higher mortality rates. Despite frequently reduced levels total and LDL cholesterol, atherogenic lipoprotein remnants and lipoprotein (a) are generally increased and high-density lipoprotein (HDL) cholesterol levels are generally reduced, likely contributing to CVD risk. On the other hand, Dialysis per se have neutral effects on serum lipid profile, however, certain dialysis-related parameters may have signifi-

cant affect on lipoprotein metabolism and modify the feature of dyslipidemia in hemodialysis (HD) patients. These parameters include; membrane used in dialyzer (high flux vs. low flux), type of dialyzate (bicarbonate *vs.* acetate), anticoagulant (heparin) and the phosphate-binder (sevelamer hydrochloride). The use of high-flux polysulfone or cellulose triacetate membranous instead of low-flux membrane is associated with a significant reduction in triglyceride levels and an increase in apolipoprotein Al and HDL-cholesterol levels[28].The use of bicarbonate dialyzate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate[29]. Chronic use of heparin as an anticoagulant releases lipoprotein lipase from the endothelial surface which may result in lipoprotein lipase depletion and defective catabolism of triglyceride rich-lipoprotein. Finally sevelamer hydrochloride significantly reduces the concentration of total cholesterol and apolipoprotein-b in HD patients[30].

2.4.2. Hypertriglyceridemia

Nearly one third of dialysis patients have hypertriglyceridemia, defined by levels above 200 mg/dL (2.26 mmollL), with levels occasionally up to 600 mg/dL (6.8 mmol/L). The predominant underling cause is a deficiency of lipoprotein lipase, resulting in reduced lipolysis of triglyceride (TG)-rich very low-density lipoproteins (VLDLs) and yielding high quantities of atherogenic remnant lipoproteins. Enrichment of LDL particles with triglycerides also suggests partial deficiency of hepatic lipase.

2.4.3. Measurement

If possible, dialysis patients should be evaluated with a fasting (although perhaps recommended we know not practical) serum lipid panel that includes total and HDL cholesterol as well as triglycerides.

a. LDL cholesterol. LDL cholesterol is commonly computed by subtracting the serum triglyceride level divided either by 5 (when TGs are measured in mg/dL) or by 2.19 (when TGs are measured in mmol/L) as well as the HDL cholesterol level from the total cholesterol.

b. Atherogenic, remnant lipoproteins and non-HDL cholesterol. In persons without elevated triglyceride levels (TG<200 mg/dL or 2.26 mmol/L), levels of atherogenic remnant lipoproteins correlate well with the calculated LDL cholesterol. When 200 <TG <500 mg/dL (2.26 <TG <5.64 mmol/L), levels of atherogenic remnant lipoproteins correlate well with VLDL levels.

2.4.4. Treatment

a. Target lipid levels. Because dialysis patients the highest risk group for CVD events, current KDOQI guidelines recommend that dyslipidemia shouldbe more aggressively treated than in the general population, with an LDL cholesterol target level below 100 mg/dL (2.6 mmol/L). Even lower LDL targets (70 mg/dL or 1.8 mmol/L) have been advocated in diabetic patients during the earlier stages of CKD based on extrapolation

from resuIts in nonuremic individuals. However, there is no direct trial evidence to support these lower LDL targets in diabetic patients with any srage of CKD. Treatment of very high TG levels (>500 mg/dl or 5.7 mmol/L) is recommended to protect against TG pancreatitis.

b. Drug (statins) therapy. Statins (HMG-CoA Reductase inhibitor) are the most commonly prescribed agents for the treatment of hypercholesterolemia. Statins primarily inhibit hepatic cholesterol biosynthesis through inhibition of HMG-CoA reductase. The net effect of statins administrations are reduction in serum total cholesterol and LDL-cholesterol, modest reduction in serum TG and modest elevation in serum HDL. Statins have multiple pleiotropic effects beside their significant cholesterol lowering effect. They include; reduction of proteinuria in human[31], anti-inflammatory effect and reduction of fibrosis of tubular cells. Treatment with HMG-CoA reductase inhibitors is associated with the attenuation of progression of atherosclerosis and reduction in cardiovascular and cerebrovascular events. The beneficial effects of statins are observed at the endothelial level, displayed by atherosclerotic plaque stabilization and in some case plaque regression[32]. The potential adverse effects associated with statin therapy are important to consider in the management of dyslipidemia in patients with ESRD. An recent study of Heart and Renal Protection showed that reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease [33].

3. Nontraditional risk factors

3.1. Chronic volume overload

Volume overload is a common manifestation in MHD patients [34]. Volume overload can increase returned blood volume, cardiac afterload, LVDd/LVEDV, and left ventricle wall pressure [35,36]. In early stage, the cardiac changes of adaptive ventricular chamber enlargement and myocardial hypertrophy induced by volume overload maybe reversible. Removal and control of excess fluid with dialysis is considered critical for protection against cardiovascular sequelae. A recent Chinese study found that antihypertensive agents including beta-blockers may influence hemodynamics, which may limit fluid removal during hemodialysis [37].

3.2. Anemia

Anemia is predictive of morbidity and mortality from cardiovascular causes in patients with CKD or on dialysis [38]. It leads to reduced oxygen delivery to tissues, causing organ dysfunction. It also causes hemodynamic adaptations including a high cardiac output state to maintain adequate tissue oxygenation leading to left ventricular dilatation and hypertrophy [39]. However, at the present time, correction of anemia to hemoglobin levels above 13 g/dL (130 g/L) has not been associated with a cardiovascular or survival benefit. Maintenance of hemoglobin levels above 11 g/dL (110 g/L) is currently recommended and may prevent further progression of LVH. Guidelines for the management of anemia and iron

deficiency in chronic hemodialysis (HD) patients have been developed to standardize therapy and improve clinical outcome. But a recent Dutch study found that compliance with anemia targets in stable HD patients was poor and showed a wide variation between treatment facilities [40].

3.3. Inflammation

The role of chronic inflammation as a putative cause of high mortality in ESRD has attracted considerable interest during the last decade. It has been hypothesized that in addition to its direct pro-atherogenic effects, chronic inflammation may serve as a catalyst and in the toxic uremic milieu may modulate the effects of concurrent vascular and nutritional risk factors [41]. ESRD has become a prototype for chronic inflammation. There is consistent evidence that CRP and pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α are risk factors for atherosclerotic complications and predict death and adverse cardiovascular outcomes in these patients [42,43,44,45]. Schwarz et al. [46] have shown that coronary atherosclerotic plaques in ESRD patients are characterized by increased medial thickness, infiltration by and activation of macrophages and marked calcification. Available evidence suggests that heavily calcified and inflamed plaques contribute to excessive cardiovascular risk in ESRD patients [47]. Levels of CRP increase as the renal function deteriorates and are particularly high in patients with ESRD. As many as one third to one half of patients with ESRD have CRP levels in the very high-risk category, and CRP continues to be an excellent predictor of adverse outcome in this population [48]. Parekh et al. [49] prospectively studied a cohort of more than 1,000 ESRD patients followed for a median of 2.5 years and reported that the highest tertile of CRP was associated with a two-fold increased adjusted risk of sudden cardiac death compared to patients in the lowest tertile.

3.4. Oxidant stress

Numerous factors in the dialysis patient increase o xidative stress (OxStress). These include inflammation (as marked by elevated C-reactive protein), malnutrition (by reducing antioxidant defenses), uremic toxins, and, potentially, the dialysis procedure itself. Many protective mechanisms are impaired, including reduced plasma protein-associated free thiols such as glutathione. This may magnify the impact of OxStress in the dialysis population. OxStress is recognized as a critical factor in the development of atherosclerotic cardiovascular disease (ACVD) [50,51]. According to the oxidation hypothesis of atherosclerosis, low-density lipoprotein (LDL) in its native state is not atherogenic [52,53]. LDL must undergo oxidative modification before it can contribute to the initiation and progression of atherosclerosis. Data from animal models of atherosclerosis, both diet-induced and genetically altered models, have demonstrated the presence of oxidized LDL (oxLDL) in plasma as well as in atherosclerotic lesions. Presence of oxLDL, autoantibodies against malondialdehyde-modified LDL, and of LDL-IgG immune complexes has also been reported in human plasma and human atherosclerotic lesions [54,55]. The pathways involved in the formation of these oxidative markers and the relationship between these markers and disease progression remain to

be elucidated. Advanced oxidation protein products (AOPP) accumulation is a marker of oxidative stress. A recent study in China [56] found that accumulation of AOPP was more significant in HD compared to CAPD patients. The level of AOPP was independently associated with ischaemic heart disease only in HD patients.

3.5. Hyperhomocysteinemia

3.5.1. Epidemiology

Hyperhomocysteinemia is much more common in dialysis patients than in the general population. Homocysteine is typically measured in the plasma and normal levels range between 5 and 12 mcmol/L. In the general population, hyperhomocysteinemia is an independent risk factor for adverse CVD outcomes and is commonly associated with deficiencies in folate and vitamins B_6 and B_{12}. B-vitamin and folate supplementation effectively reduce homocysteine levels in the general population and recent extensive folate supplementation in foods has lowered the overall prevalence of hyperhomocysteinemia in the nondialysis population. Homocysteine levels increase dramatically as kidney function declines, with as many as 80% of dialysis patients classified as having hyperhomocysteinemia. In dialysis patients, some but not all studies suggest that hyperhomocysteinemia is independently associated with CVD mortality. Nutritional status confounds these analyses, since better nourished patients tend to have higher homocysteine levels. The relationship between homocysteine levels and cardiovascular disease was described initially by observational studies, which may overestimate the effect of this relationship. Two meta-analyses of epidemiologic studies [57,58] suggested that reduced homocysteine levels could lower the risk of coronary heart disease, stroke, and cardiovascular disease. However, Bazzano et al [59] concluded that folic acid therapy did not significantly contribute to cardiovascular disease, stroke, or myocardial infarction.

3.5.2. Treatment

Folic acid supplementation may play an important role in carcinogenesis, because when it is administered to individuals with established cancers, it potentially promotes tumor growth [60,61]. It has also been reported that the introduction of folic acid may increase the risk of colorectal cancer [62]. According to our review, folic acid therapy resulted in an 8% increase in the risk of cancer, although this difference was not statistically significant. The reason for this increase in carcinogenesis can be explained by the fact that folic acid supplementation may affect endothelial function and support cell growth through mechanisms independent of homocysteine [63]. Importantly, folic acid and B vitamins are water-soluble and excreted by the kidney; therefore, therapy toxicity may be of great concern in patients with impaired renal function. In patients with end-stage renal failure who have hyperhomocysteinemia wherein homocysteine levels must be reduced, alternative, non-vitamin therapies are important. For example, enhancing urinary excretion can help to avoid a decrease in glomerular filtration rate and an increase in major cardiovascular events [64].

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4. Ischemic heart disease

4.1. Epidemiology

Acute myocardial infarction(AMI) is common in the ESRD population. Outcomes for patients with AMI are poor, with 50% 1-year mortality. Both atherosclerosis and atheriosclerosis and arteriosclerosis contribute to pathogenesis; arteriosclerosis may cause LVH with increased myocardial oxygen demand and altered coronary perfusion with subsequent subendocardial ischemia.

4.2. Diagnosis

Routine screening is not currently recommended. There are no preoperative screening guidelines specific to dialysis patients, and it is reasonable to use general population guidelines, recognizing that the extent of comorbid conditions prevalent in the dialysis population is Iikely to place them into the highest cardiovascular risk group. Because many dialysis patients are unable to achieve adequate exercise levels for valid stress tests, pharmacologic stress test should be used in this population. Furthermore, because of the high incidence of baseline electrocardiogram abnormalities, either nuclear or echocardiographic imaging should be utilized in stress testing.

4.3. Prevention

Aspirin, beta-blockers, ACE inhibitors, and nitrate preparations are all appropriate for primary therapy of AMI and are likely appropriate for secondary prevention, although data on aspirin for secondary prevention of coronary artery disease remain inadequate to date. Observational studies suggest that medical therapies including aspirin, beta- blockers, and ACE inhibitors may be underutilized in dialysis patients. Using the ESRD database and the Cooperative Cardiovascular Project (CCP) database, Berger AK, et al [65]found that ESRD patients are far less likely than non-ESRD patients to be treated with aspirin, beta-blockers, and ACE inhibitors during an admission for AMI. The lower rates of usage for these medications, particularly aspirin, may contribute to the increased 30-day mortality.

4.4. Treatment

4.4.1. Management of angina pectoris

The pharmacologic approach to angina in dialysis patients is similar to that in the general population. The progressive introduction of sublingual nitrates, oral long-acting nitrates, beta-blockers, and calcium channel blockers is appropriate. The usual dosages of sublingual and oral nitrates can be given to dialysis patients.

4.4.2. Angina during the hemodialysis session

For patients whose angina manifests primarily during hemodialysis session, a number of therapeutic options available. Nasal oxygen should be given routinely. If the anginal episode is associated with hypotension, then initial treatment should include raising the blood pressure by elevating the feet and by cautiously administering saline. Sublingual nitroglycerin can be given as soon as the pressure has increased to a clinically acceptable value. Consideration should be given to reducing the blood flow rate and stopping ultrafiltration until the anginal episode subsides. Predialysis administration of 2% nitroglycerin ointment may be of benefit when applied 1 hour prior to a hemodialysis session, assuming that the blood pressure will tolerate this intervention.

5. Heart failure

Heart failure is the commonest manifestation of cardiac dysfunction in patients on maintenance dialysis. According to the cross-sectional survey by Harnett and coworkers, which included both hemodialysis and peritoneal dialysis patients, nearly one-third of the patients developed heart failure on initiation of dialysis, of which 56% had further recurrences [66]. Even among patients with no heart failure at baseline, around 25% of patients developed heart failure at a rate of 7% per year. In addition, the presence of heart failure was associated with a worse prognosis in that median survival was 36 months for patients with heart failure at baseline compared to 62 months for patients without heart failure. They also found that increasing age, diabetes mellitus and ischemic heart disease were associated with heart failure at initiation of dialysis, while ischemic heart disease, anemia, hypoalbuminemia and systolic dysfunction were important predictors of heart failure recurrence [67]. The presence of ischemic heart disease is associated with greater left atrial diameter, greater left ventricular end-systolic diameter, lower fractional shortening and, thus, more systolic dysfunction [68].In the Canadian Prospective Cohort Study, which included 433 incident dialysis patients, 74% had left ventricular hypertrophy at baseline, 30% had left ventricular hypertrophy with dilatation, and 15% had systolic dysfunction [69], indicating that much of the cardiac hypertrophy and dysfunction was already established by the time patients started their dialysis therapy. This may also explain why dialysis patients are prone to develop heart failure.

6. Arrhythmia

Paroxysmal atrial fibrillation attack is one of most common tachyarrhythmia in MHD patients. Paroxysmal atrial fibrillation attack not only can affect the dialysis to proceed smoothly, but also it can increase the death risk in MHD patients. In the Dialysis Outcomes and Practice Patterns Study [70], which analyzed 37,765 participants in 12 countries in the Dialysis Outcomes and Practice Patterns Study to explore the association of the following

practices with sudden death (due to cardiac arrhythmia, cardiac arrest, and/or hyperkalemia): treatment time [TT] <210 minutes, Kt/V <1.2, ultrafiltration volume >5.7% of postdialysis weight, low dialysate potassium [K(D) <3 mEq/L]), and prescription of Q wave/T wave interval-prolonging drugs,indicating that identified modifiable dialysis practices associated with higher risk of sudden death, including short TT, large ultrafiltration volume, and low K(D). Because K(D) <3 mEq/L is common and easy to change, K(D) tailoring may prevent some sudden deaths. Individualized interventions may effectively reduce paroxysmal atrial fibrillation attack during dialysis in MHD patients. The general individualized intervention in MHD patients are, (1) individualized dialysis programmes, such as increasing the dialysis or hemodialysisfiltrition frequency or be changed to daily dialysis for atrial fibrillation with frequent seizure. Regular monitoring of serum potassium levels before and post dialysis, adjusting dialysate concentration of potassium ions in a timely manner, using different prescription of individualized dialysate for hemodialysis treatment. (2)Behavioral interventions, such as improving their way of life to develop good habits and patterns of dialysis. (3) Closely monitoring the patients' vital signs during hemodialysis, such as heart rate, blood pressure and pulse rate. (4) Controlling interdialytic weight gain (IDWG), strict volume policy including salt restriction and adequate ultrafiltration is fundamental to reach normovolemia/normotension together with regression of left atrial hypertrophy in patients on hemodialysis. In HD patients, IDWG is significantly associated with left atrial volume/diameter. Together with better volume control, left atrium volume must be decreased. Most importantly, they should focus on salt restriction not water restriction. (5) Psychological intervention to reduce sympathetic excitement to induce atrial fibrillation.

7. Conclusion

A high prevalence of cardiovascular disease is observed in ESRD patients receiving dialysis therapy. This usually constitutes a combination of vascular and myocardial disease related to both traditional and nontraditional risk factors. Most of these cardiovascular complications are already established and advanced by the time patients are started on dialysis treatment, thus indicating the need for earlier and more active screening for cardiovascular disease even before patients progress to end-stage kidney disease. More attention should be focused on improving cardiovascular outcomes in ESRD patients receiving maintenance dialysis therapy.

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Chapter 2

Medical Nutrition Therapy for Hemodialysis Patients

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Additional information is available at the end of the chapter

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1. Introduction

Nutrition in hemodialysis is very important in decreasing complications and improving quality life of patients. Nutrition program on patients with chronic renal failure on dialysis plays an important role in the process of treatment.

The purposes of medical nutrition therapy in dialysis patients are to promote the nutrition to correct patients' appetite, to correct systemic complications composed by the loss of nephrons in progress, to reduce of protein catabolism to the lowest level, to relieve or prevent the cardiovascular, cerebrovascular, peripheral vascular diseases formation, to prevent increasing fluid and electrolyte disorders, to reduce uremic symptoms such as itching, nausea, vomiting, loss of appetite and to ensure optimum nutrition. In addition, medical nutrition helps to avoid high-potassium and sodium from the diet, to prevent pulmonary edema, hypertension and heart failure, to prevent renal osteodystrophy keeping the consumption of calcium and phosphorus under control, to prevent protein energy malnutrition with saving patients' food consumption and detecting nutritional status with methods such anthropometric measurements, laboratory findings, subjective global assessment (SGA) (Cianciaruso 1995, Kopple 2004, Mahan 2012). Negative changes (hyperkalemia, hiperfosfotemi, peripheral and pulmonary edema) in fluid-electrolyte balance occur in patients who do not comply to the diet.

In this chapter, assessment of nutritional status in hemodialysis patients and preparation of individual dietary training programs for patients will be discussed.

2. Assesment of the nutritional status

Regular assessment of nutritional status in hemodialysis patients is important and early detection of malnutrition can be helpful in improving this condition (Fouque 2003).

The results of studies indicate that hemodialysis patients are at risk of malnutrition. The evaluation methods used in the nutritional status showed that 18-75% prevalence of malnutrition in hemodialysis patients, malnutrition could cause a worse outcome and subsequent mortality(Dwyer 2005). Chazot's study was assessed the nutritional status of twenty hemodialysis patients receiving hemodialysis treatment more than 20 years and was showed that hemodialysis treatment caused to malnutrition the long period of time(Chazot 2001).

Malnutrition occurs depending on several factors in hemodialysis patients. Especially, there is reduction of protein-energy intake because of inappropriate dietary restrictions, anorexia, and taste alterations, promoting malnutrition in most patients entering dialysis (Lavılle 2000). Studies illustrate that there are two types of malnutrition in dialysis patients: The first type is specified by uraemic syndrome and reduction in serum albumin levels due to decreasing energy and protein intake. It should be provided improvement with adequate energy and protein intake. The second type is associated with inflammation and atherosclerosis, high cardiovascular mortalite(MIA Syndrome). Prominent features of this type, proinflammatory cytokines, increased oxidative stress, increased protein catabolism, increased resting energy expenditure, hypoalbuminemia (Stenvınkel 2000, Baltzan 1998). İn addition, malnutrition due to poor nutrition, chronic volume overload congestive heart failure and systemic hypertension, uraemic bone disease and extraskeletal metastatic calcification due to hyperphosfotemia development are other adverse conditions encountered as a result of the diet incompatibility.

In general, there are catabolic and inflammatory situation in patients with end-stage. Patients receiving dialysis treatment are seen in tissue loss in the course of time. At the start of dialysis treatment, having a high level adipocyte tissue can be advantageous for individuals. Dialysis patients who have excess body fat mass are being protected against this situation because of more energy storage. Recent data shows that patients who are overweight or obese had higher rates of survival than normal or in hemodialysis patients. Low serum albumin level (hypoalbuminemia) revealed that the obese are less in HD patients. Reduction in mortality in overweight patients was reported as well as indicators of nutritional status of overweight HD patients was significantly higher than underweight HD patients and to be shorter than the duration of hospital stay. (Glanton 2003, Guida 2004, Kalantar-Zadeh 2005)

Different methods are used in the evaluation of nutritional status in hemodialysis patients. Biochemical, anthropometric measurements, nitrogen and energy balance techniques, record of food intake, subjective global assessment, bioimpedance analysis (BIA), Dual-Energy X-ray Absorptiometry (DEXA), creatinine kinetics, neutron activation analysis and nuclear magnetic resonance spectrometry and serum markers: albumin, pre-albumin, insulin-like growth factor-1 (IGF-1) and transferrin; main proteins of the acute phase (C-reactive protein (CRP), serum amyloid A), secondary proteins of the acute phase (fibrinogen, ferritin, complement), cytokines (interleukin-6 (IL-6), tumour necrosis factor) are used to assess the nutritional status of patients with chronic renal failure (Basile 2003).

Some studies (Beddhu 2002, Panichi 2006) describe hypoalbuminemia in HD patients as a strong indicator for mortality and morbidity. As a result of malnutrition, albumin synthesis

decreases and develops hypoalbuminemia. In fact, the serum albumin level is a powerful way directly correlated with dietary protein, but recent literature emphasizes that the effect of serum albumin concentration on the inflammatory response. Albumin is a negative acute phase protein, except nutritional status, and its synthesis is supressed during inflammation. For this reason, there are limitations in the use of serum albumin level in order to assess the nutritional status of patients due to be affected by malnutrition and inflammatory reactions (Santos 2003). Indeed, because of longer half life, it cannot be a sensitive indicator for nutritional therapy. In studies, significant negative correlation was found between prealbumin and CRP (Kaysen 1995, Owen 1998, Sathishbabu 2012). Prealbumin is a negative marker of inflammation level that correlates positively and significantly with other nutritional markers in ESRD patients on hemodialysis (Sathishbabu 2012). Because of the shorter half life of prealbumin, many authors consider prealbumin to be a better marker of nutrition than serum albumin (Mittman 2001, Kalantar-Zadeh 2003). That is considered one of the indicators of uremic malnutrition less than 29mg/dl of serum prealbumin levels in patients on dialysis, serial measurements are recommended in the evaluation of nutritional status (Pupim 2004). Serum creatinine concentration (less than 10 mg/dl) should be evaluated for PEM and skeletal muscle wasting, because it indicates reduced dietary protein intake and skeletal muscle mass(Janardhan 2011).

Subjective Global Assessment (SGA) is often preferred by experts to assess the nutritional status in chronic dialysis patients as relatively quick, easy, and cheaper than other methods (Mutsert 2009). İt is important that SGA was proposed by the National Kidney Foundation (NKF) Kidney Disease/Dialysis Outcomes and Quality Initiative (K/DOQI) for nutritional assessment in the adult dialysis patients(K/DOQI 2000).

Subjective Global Assessment (SGA) reveals that there are seven components to assess nutritional status; two components related to physical examination (indicator of fat and muscle loss and nutritional status-associated with changes in fluid balance) and five components of medical history (weight change, diet, gastrointestinal symptoms, functional capacity, disease and nutrition relationship needs) (Steiber 2004). While SGA scoring points are given in each section of 1-7 and are categorized as 1-2 points (bad), 3-5 points (moderate), 6-7 points (normal). If it is received from this SGA most 6 or 7 points refers mild malnutrition. Most of 3, 4 or 5 points show moderate malnutrition. Most of the findings of sections 1 or 2 points received are recognized as marked malnutrition and severe malnutrition (Janardhan 2011). European Best Practice Guidelines (EBPG) on diagnosis and monitoring of malnutrition proposed that the SGA can be used to determine malnutrition in hemodialysis patients (Fouque 2007).

Nutritional history and dietary record provide information about nutrition of patients and determine for malnutrition development at risk whether or not. Because of record of food intake is taken long-term, bored patients may cause to give false information. Therefore, record of food intake 3-day to get more accurate for patients (Kalantar-Zadeh 2003).

3. Energy

Enough energy should be taken for the effective use of dietary protein and the protection of the nutrients stores of body. Energy metabolism is impaired and is composed of negative energy balance because of disrupted cellular energy metabolism in hemodialysis patients (Mak 2011). Therefore, to consume enough energy identified by the daily energy requirements of ESRD patients provides a positive nitrogen balance and preventing tissue destruction and protein catabolism.

The anorexia nervosa was often encountered in patients in the next few months from the start of dialysis therapy. This is because, even though dramatic changes in their lives, psychological conditions, can not be adapted to a new and restricted diet. It has been reported if protein and energy intake are not increased in these patients, lost energy is stored with muscle mass of patients, and the amount of body fat is decreased (Fouque 2003). The studies have suggested that the dietary energy failure is more on dialysis treatment days than non dialysis treatment days (Burrowes 2003, Rao 2000). In a prospective multicenter clinical trial that included 1901 participants of the Hemodialysis Study, dietary energy intake was 1.02 kcal/kg/day less on dialysis treatment days than on nondialysis treatment days. (Burrowes 2003, Stark 2011).

Some studies indicated that energy intake was low in hemodialysis patients. Poor appetite and hypermetabolism fairly reduce food intake in hemodialysis patients (O'Keefe 2002, Nakao 2003, Morais 2005, İkizler 2002, Pumpkin 2002). When the recommended energy requirements compared with consumed amounts, it is concluded that energy intake is inadequate in 90% of patients (Rocco 2002)

When energy intake of hemodialysis patients was 32-38 kcal/kg/day, have not been reported any increasing or decreasing in nitrogen balance and anthropometric parameters, and developing a negative or a positive energy balance. (Kopple 2004).

Studies demonstrated that low-energy and with low protein diet cause weight loss and malnutrition in patients. For these reasons, sedentary, non-obese dialysis patients's requirements of energy coming from all sources should be determined, according to NKF-DOQI, ESPEN and EDTNA-ERCA 2002; respectively, 35 cal/kg/day (under the age of 60), 30-35 cal/kg/day(over the age of 60); 35 cal/kg/day and 30-35 cal/kg (ideal body weight)/day. (Kopple 2001, Kopple 2004, Cano 2006, Fouque 2003). In some studies, it was shown that hemodialysis patients should receive daily energy as 30-40 kcal/kg (Kalantar-Zadeh 2003, Stenvinkel 2000).

4. Protein

Protein requirement increases due to the dialysate losses and catabolism in hemodialysis patients. In research, it is emphasized that the inadequate protein intake increases mortality (Ohkawa 2004).

Raj et al's study showed that hemodialysis increases both protein synthesis and degradation. The net effect of hemodialysis is loss of nitrogen in skeletal muscle. Protein synthesis and degradation increases by 50-100% of normal values. Hemodialysis causes to increase in catabolic indicators such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). This increasing in the production of cytokines causes in protein degradation. Reasons for increased protein requirement; amino acid losses into the dialysate, increased protein catabolism, metabolic and hormonal changes(Raj 2007).

There are 0.2-0.3 g/kg or 6-8 g/day of protein, amino acids (aa) and peptide losses with the dialysis fluid during hemodialysis. Protein catabolism increases with these losses due to metabolic disorders. The lost in amino acids needs to be replaced to avoid negative nitrogen balance. According to "National Kidney Foundation Dialysis Outcome Quality Initative (NKF-DOQI)" and studies by other investigators to compensate for residual renal losses, dietary protein should be adjusted at least 1.2 g/kg/day in hemodialysis patients as indicated (Kopple 2001, Mahan 2012, Kalantar-Zadeh 2003, Locatelli 2005).

According to ESPEN, adjusted diet protein should be consumed as 1.1-1.2 g / kg / day and should be high in the biological value (of animal origin) of 50 % protein in hemodialysis patients (Mehrotra 2001, Karalis 2002, Cano 2006). Furthermore, the amount of protein of the patient's diet is determined by considering the state of hydration adjusted body weight, glomerular filtration rate and with the course of illness (Nissenson 2008). To determine the adequacy of protein intake in dialysis patients, a good evaluation parameter is BUN value under 120 mg. When 1.2 g / kg / day protein intake, it was indicated protein catabolic rate is associated with low morbidity, provided adequate control of blood urea concentration, improved the nutritional parameters (anthropometric measurements) and biochemical findings (blood albumin, total protein, blood, blood cholesterol, etc.), provided a positive nitrogen balance in dialysis patients (Bergstrom 1993, Amanda 2010).

However, it is required that adequate caloric intake prevent the use of protein as an energy source with gluconeogenessis. Otherwise, a positive nitrogen balance can not be provided in spite of high protein intake. When patients were given a low protein diet, should be followed adequate energy intakes and adequate phosphorus intakes of patients to ensure optimal nutrition, and to prevent malnutrition (Locatelli 2005, Gribotto 2012).

Metabolic acidosis in hemodialysis patients increases protein catabolism, the branched-chain amino acid degradation and muscle glutamine release. Amino acids and glutamine metabolism allow the formation of ammonium and bicarbonate excretion. Changes at branched-chain amino acids levels of muscle and plasma occur in hemodialysis patients. As a result of hemodialysis treatment, plasma valine, muscle valine, plasma leucine are low, muscle leucine, plasma isoleucine, muscle isoleucine are normally observed (Cano, Fouque 2006). Branched-chain amino acids play a regulatory role against chronic acidosis. After acidosis subside is given a support and enriched with branched-chain amino acids and valine during hemodialysis, branched-chain amino acids level of plasma and intracellular are enhanced. (Raj 2000).

Branched-chain amino acids improve appetite in hemodialysis patients. 6.6-15.7 g daily intake of essential amino acids in hemodialysis patients corrected the their nutritional parameters. In patients who underwent 12 g oral branched-chain amino acid a day showed improvement in protein and energy purchases in one month, in the anthropometric measurements six months later. Consantrations of albumin increased 3:31 g / dL to 3.93 g / dL. (Cano, Fouque 2006) According to Raj, although amino acid repletion increased in muscle protein synthesis, no decrease in muscle protein breakdown during HD treatment was observed (Raj 2007)

There is a dynamic effect of animal protein (such as egg, dairy etc.) on renal function in short-term clinical trials. But long-term effects on the normal kidney functions are still unknown. There are mechanisms shown to reveal the different effects of animal and vegetable proteins on renal function including differences in hormones, protein metabolism and interaction with micronutrients. Healthy individuals with normal renal function, long-term consumed high-protein diet (whether of animal protein or vegetable protein) may cause kidney damage and accelerate chronic renal failure. However, long term studies are necessary to determine the different effect of the consumption of animal or vegetable protein diet on renal functions (Bernstein 2007).

5. Carbohydrate

Carbohydrate intake requires enough energy and to maintain reserve protein that can be used for the synthesis protein of tissue.

When dialysis fluid not containing glucose is used for 4 hours, 28 g glucose is lost in hemodialysis. However, when 11 mmol / L glucose was added to the dialysis fluid, the patient gained approximately 23 g of glucose. When glucose is removed by dialysis in the extracellular fluid, loss of the glucose is completed with absorbed carbohydrates, destruction of liver glycogen, and glyconeogenesis in order to avoid symptomatic hypoglycemia. Then, increased protein breakdown and urea synthesis begin. Glucose-free dialysis is reduced pyruvate. Pyruvate does not change with glucose dialysis. Glyconeogenesis may be stimulated with glucose-free dialysis. However, there are negative effects of glucose intake such as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity etc(Lindholm 1998).

Deterioration of glucose metabolism and insulin resistance develops in chronic renal failure. This situation results in rising levels of glucose and urea when coupled with increased hepatic gluconeogenesis. Insulin metabolism in uremia shows severe abnormalities. Basal insulin secretion is reduced and receives limited response to glucose infusion (Kopple 2004).

In one study, it was observed occurrence of the insulin resistance impaired, muscle glucose uptake and nonoxidative glucose metabolism, in the presence of chronic uremia, but recovered after dialysis (Foss 1996).

Uric acid is generated during fructose metabolism. Serum uric acid levels have been found to correlate with fructose intake. High serum uric acid was associated with hypertension, in-

flammation, chronic kidney disease and the intake of fructose and added sugars (Feig 2008, Brymora 2012). But fruits containing fructose have some beneficial substances such as antioxidants. Therefore, it is possible that fructose intake from natural fruits with regular diet. (Jalal 2010, Brymora 2012).

Carbohydrate from the diet should be higher to provide enough energy, to protect the backup protein to be used for tissue protein synthesis, to cover the energy deficit. It should provided 60-65% of daily energy from carbohydrates (Kopple 2004). Most patients have difficulty in meeting energy needs with low protein diets. For this reason, the energy gap can be covered by glucose polymers (starch), sugar, simple sugars, pure carbohydrate sources. Patients with diabetes should avoid concentrated sweets (Mahan 2012).

6. Lipids

Recent evidence suggests that protein calorie malnutrition often begins incipiently when the glomerular filtration rate (GFR) is about 28 to 35 mL/min/1.73 m2 or even higher (Kopple 1994) and continues to fall gradually as the GFR decreases below these values (Laville 2000). Reduced quantity of GFH causes a significant increase in plasma lipid levels(Liu 2004). Especially, hyperlipidemia consists when creatinine clearance is below 50 ml/min in patients. In Rutkowski's study, accumulation of triglycerides-rich lipoproteins was associated with increased lipogenetik gene expression of enzymes and the high quantity triglycerides production by renal deficiency (Rutkowski 2003, Liu 2004).

Usually, there are hypertriglyceridemia and hyperlipidemia in hemodialysis patients. Low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) are high concentration, high density lipoprotein (HDL) cholesterol concentration is low. The main reason of hypertriglyceridemia is the lack of removal of triglycerides from the circulation (Kwan 2007, Lacquaniti 2010). In these patients, it has been reported decreased lipoprotein lipase, hepatic lipase enzyme activity.

Generally it is known to decrease in carnitine storages in hemodialysis patients with malnutrition. In addition, carnitine leaves from the extracellular fluid during dialysis therapy and this situation causes a sudden drop in serum level of carnitine. Carnitine deficiency is caused by deterioration of long-chain fatty acid oxidation and thus deficiency of energy(Matera 2003, Flanagan 2010). İt was determined to put on 750 mg/day carnitine supplementation in diet of hemodialysis patients, reduced the level of plasma TG and LDL cholesterol and increased HDL cholesterol levels(Naini 2012).

Hyperlipidemia develops in a large part of dialysis patients, the amount of fat in the diet should not be higher. Saturated fat content of the diet should be reduced and unsaturated fat content should be increased (Vaziri 2006).

Hyperlipidemia progresses in the majority of patients with CKD; therefore, content of fat in the diet should not be high. Total energy from fat should not exceed 25% to 30. İt should be reduced saturated fat content of the diet and increased unsaturated fat content.

It is recommended reducing saturated fat intake (total energy <7%) and cholesterol intake (<200 mg / day). Total fat content of the diet should be between 25-35% of energy and monounsaturated fatty acids 15-20% of total energy, polyunsaturated fatty acids 10% of total energy of the diet (Nissesson 2008). Recommended foods for patients with a high biological value such as meat, eggs contain high cholesterol. Therefore assessment of serum cholesterol levels should be specific for each patient. If patients have hypertriglyceridemia and high cholesterol, regulation dietary fat content, weight control, increased physical activity, reducing the use of hypertonic solution, restriction of simple sugars of dietary intake are recommended.

Signs and symptoms of deficiency of essential fatty acids such as dry and itchy skin, hair loss, abnormal prostaglandin synthesis are observed in dialysis patients. EPA and DHA which replace arachidonic acid in cell membrane and prevents the formation of pro-inflammatory compounds are part of linolenic acid in fish oil (n-3 fatty acids). According to FDA, intake of n-3 fatty acid with food supplements should not exceed 3 g / day (Vergili-Nelsen JM 2003).

The studies were reported that omega-3 food supplementation reduced levels of triglyceride (Bouzidi 2010, Skulas-Ray 2008), LDL cholesterol and CRP (Saifullah 2007), as well as Omega-6 / omega-3 polyunsaturated fatty acids ratio was important for inflammation and mortality rate in hemodialysis patients(Noori 2011, Daud 2012).

7. Water and electrolytes

The fluid adjustment should be made according to edema and dehydration in the patient. In hemodialysis patients, if conditions such as swelling of the eyes, hands or feet, fluid weight gain, shortness of breath, increased blood pressure or tachycardia are observed, fluid consumption should be restricted (Hegel 1992, Saran 2003). Hemodialysis patients should reduce fluid intake and should limit food consumption such as tea, coffee, soda, water, fruit juices, ice cream, sherbet, gelatin, soups and heavy sauces.

Dietitians, especially renal dietitians, are most often cited as the trusted source on providing information on fluid management and delivering dietary advice (Smith 2010).Research about fluid balance dietician indicates that it is important to teach patients how to deal with thirst without drinking liquids. Proposals such as sucking on ice chips, cold sliced fruit, or sour candies and using artificial saliva are recommended (Mahan 2012).

Controlling sodium and fluid intake are important components of the HD diet. Extracellular volume expansion is the main pathophysiologic determinant of hypertension in HD patients. Water and sodium intake in hemodialysis patients are adjusted according to the amount of urine, fluid balance and blood pressure. With hemodialysis, potassium restriction is often necessary, but the measure of restriction depends on residual renal function (Stark 2011).

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Body weight gain during hemodialysis is recommended and should not exceed 1.5-2 kg. A recommended daily amount of fluid of hemodialysis patients should be 500ml + the urinary output in a day or around 1000-1500 ml. Sodium restriction should be based on the amount of urine. A mild salt restriction as 3-4 g / day is sufficient in oliguric patients that have an amount of urine totaling more than 1 liter per day. Anuric hemodialysis patients may consume up to 1 liter of liquid 1-1.5-2 g / daily of salt. If hypertension or heart failure is present, salt and water restriction should be more monitored more delicately. Excess salt intake causes an increase for the feeling of thirst and liquid intake (Fouque 2003, Lindley 2009).

To reduce sodium intake in hemodialysis patients, olives, pickles, cured meats, garlic sauce, soy sauce, canned foods, sausages, processed meats, ham, chips, pretzels and instant soups should be removed from the diet. Different spices, such as vinegar and lemon, can be used for consumption of unsalted foods or as a salt substitute.

Potassium levels are affected by hemodialysis therapy with the degree of residual renal function and net tissue breakdown (e.g. due to infections) and acid-base status. In HD patients, serum potassium concentrations may change to net intestinal potassium absorption or excretion. An example of this change or excretion is diarrhea. Serum potassium is impressed by dietary potassium intake. It is thought this relationship is stronger when the potassium intake is very low or very high in diets of HD patients (Kaveh 2001, Noori 2010).

Potassium restriction is often required because hemodialysis patients are usually anuric. Anuric HD patients are recommended to restrict their potassium intake to 1600-2000mg daily. Hypokalemia may occur with symptoms such as severe vomiting, diarrhea, diuretic use, due to the reduction of potassium. In this case, the potassium content of the diet should be increased (Fouquo 2003).

When blood potassium levels in dialysis patients are high, treatment of the patient's diet should be reviewed as a priority. The food consumption should be limited to reduce the intake of potassium levels, such as milk, meat products, fruits, legumes, cereals, dried fruits and vegetables,etc.

8. Vitamin and minerals

Some studies demonstrate vitamin and mineral supplements for the long-term hemodialysis patients. Hemodialysis patients are potentially at risk of deficiency and excess of trace elements (Inamoto 2003). Given that essential trace elements play key roles in multiple biological systems, including immunological defense against oxidation and infection. It has been hypothesized that the increased morbidity and mortality seen in hemodialysis patients may in part be due to the imbalance of trace elements that has not yet been recognized (D'Haese 1996, Coombes 2012).

In HD patients, there are many problems associated with the lack of food intake. Poor nutrition, restriction of foods that are rich in water-soluble vitamins, foods that are rich in potassium, metabolic disorders caused by uremia, infection and diseases such as gastrointestinal

diseases or complications associated with reduced intake of foods are some of the possible scenarios. The lack of foods containing vitamins leads to vitamin and deficiencies that could cause of further possible complications in dialysis patients. (Mahan 2012).

In dialysis patients, B6, folic acid and vitamin C deficiencies have been observed (Coveney 2011). Vitamin B6 deficiencies, especially as it plays in amino acid utilization and lipid metabolism and maintains a critical role as a coenzyme, are very important to monitor closely. Deficiencies in either folic acid, vitamin B6 or vitamin B12 can greatly affect to capacity of the others to function properly (Wierzbicki 2007). This bond requires all to work in synchrony for optimum performance of the metabolic pathway. İf Vitamin B6 and folic acid supplements are not used in dialysis treatment, pyridoxine and folic acid may often reduce red cells and plasma (Steiber 2011). In dialysis patients, an additional intake of vitamin B6 reduces plasma cholesterol and triglyceride levels and additional intake of folic acid can reduce the high levels of homocysteine, which has been determined to be a risk factor for cardiovascular disease (Dumm 2003). Vitamin B6 and folic acid intake in HD patients are higher than normal healthy subjects, and respectively, the recommended intake varied between 1 mg and 10mg per day in most studies (Steiber 2011).

In addition, the loss of vitamin C has been observed in HD patients. Increasing vitamin C in the diet to a recommended amount of 100-200 mg/daily was at once the standard suggestion of mending this problem. However, the intake of higher doses of ascorbic acid was found to possibly lead to the accumulation of oxalate, which is the metabolite of vitamin C. With oxalate accumulation, formation of calcium oxalate stones in the kidneys, the accumulation of calcium oxalate in internal organs and blood vessels, hypercalcemia and hiperoxalemia are all symptoms (Moyad 2009). Recently, the daily requirement of vitamin C in patients undergoing hemodialysis is suggested at 60-90 mg/daily (Kopple 2004). In addition, ascorbic acid supplementations, are composed of iron overload. In uremic patients, it is recommended to prevent resistance to erythropoietin. Vitamin C supplementation increased intestinal iron absorption in these patients, which may reduce the incidences of iron deficiency anemia (Handelman 2011).

Thiamine sources are whole grain and enriched bread and cereals, peas, beans, nuts, brown rice, and meats. It is absent in rice and some cereal products. Thiamine nutritional value is lost with cooking, polishing and purifying. Thiamine is not stored in the body and is excreted in the urine, because of a water-soluble vitamins (Steiber 2011). The addition of thiamin is controversial among some experts. However, 30 mg thiamine has been shown to support the improving of the activity of translocases red blood cells. Thiamine requirements should be 1.5 mg / daily, when dialysis patients have operations, infections have a high risk of developing, convulsions of the neurological symptoms can occur and large quantities of glucose adds to the diet(Fattal-Valevski 2011, Fouque 2003).

25 (OH) D3 levels of dialysis patients are known to be lower than the normal population. Treating vitamin D deficiencies shows the important contributions and progressions towards enhancing the quality of life with dialysis patients (Cheng 2007). The studies showed 25(OH)D3 levels significantly lower than 15 ng / mL (37 nmol / L) in patients. The lowest value of vitamin D is accompanied by high levels of secondary hyperparathyroidism (Gha-

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zali 1999). There are several reasons for this a) The patient should have a specific catered diet, but this diet may incude the reduction of the intake of vitamin D foods (milk, fish, cream, butter, etc.). b) The endogenous synthesis of vitamin D3 decreases in individuals over 60 years, due to increased melanin and reduced contact with sunlight in the skin (Godar 2012, Holick 1987). c) Urinary path 25 (OH) D3 and vitamin D binding protein loss is high (Saha 1994). d) The decrease of glomerular filtration rate (GFR)(Kawashima 1995, Thadhani 2012).

Hemodialysis treatment does not provide a change for vitamin A levels. B-carotene, ubiquinol, and laykopen levels were lower in patients that didn't have renal failure. The intake of dietary vitamin A should not exceed the RDA in HD patients of 800-1000 mg/ day(Koople 2004).

İncreased oxidative stress and cardiovascular risks are associated with hemodialysis patients. The antioxidant properties of vitamin E may be useful in preventing or reducing these risks. HD patients are recommended 400 IU/Daily intake of vitamin E (Galli 2004, Mann 2004, Kopple 2004).

Protein and phosphorus restriction, loss of appetite, and vitamin D deficiencies increase the need of calcium in HD patients. Support of calcium and control of serum phosphorus levels, by using calcium-containing phosphate-binding agents, are balanced simultaneously (Miller 2010). Calcium acetate or calcium carbonate are effective with reducing concentration of serum phosphorus, simultaneously, correcting hypocalcemia and negative calcium balance (Isakova 2009, Miller 2010). However, the use of vitamin D and calcium in hemodialysis patients concluded the risk for severe hypercalcemia and renal osteodystrophy (Tilman 2009). Increasing calcium during treatment should be done carefully. As a result, to ensure the positive balance of calcium levels in dialysis patients, 1000-1500 mg of calcium should be taken daily.

Lack of phosphorus excretion in the human body can be closely related to the glomerular filtration rate. Even if a single nephron loses its function, it may result in the accumulation of phosphorus in the plasma while showing an inability to the discharging of phosphorus (Kopple 2004). When GFR decreased 120 mL / min to 25 mL / min, the accumulation of phosphorus was observed very clearly in the plasma. In hemodialysis patients, the level of serum phosphorus 2.5-4.5 mg / dL, and patients who have a glomerular filtration rate (GFR) between 25 mL/min/1.73 m2 and 70 mL/min/1.73 m2, 8 mg/kg/d to 10 mg/kg/d of phosphorus may be given with the 0.55 g/kg/d to 0.60 g/kg/d of protein. High biological value protein sources including essential amino acids are rich foods from phosphorus, therefore there are difficulties on the limitation of phosphorus. For this reason, the absorption of phosphorus is prevented with the phosphorus binding agents from the outside. Egg white is a rich source of high biological value protein have one of the lowest phosphorus-protein ratios and is also deprived from cholesterol; therefore, it is a particularly healthy food source of protein for patients on dialysis (Noori 2010). Whole eggs instead of egg whites, whole bread instead of white bread, dried beans instead of peas and preferably fish (cod, tuna) that have a low phosphorus / protein ratio, should be consumed to reduce dietary phosphorus intakes in dialysis patients (Cupisti 2003). The active form of vitamin D is added in the treatment, this is an important step in the control of serum parathyroid hormone activity (Steiber 20109).

About 80% absorption of dietary phosphorus from the gastrointestinal tract requires the use of phosphorus-binding agents (Locatelli 2002, Guarneri 2003, Noori 2010, Noori 2010). Niacin working with a different mechanism than phosphate binders, is helpful to lower phosphate levels while causing a decrease transport of phosphate without interfering with the sodium-phosphate pump in the GI lumen (Mahan 2012, Cheng 2006).

Patients with kidney disease are more difficult to assess whether there is sufficient amount of trace elements in the body. Iron (Fe), calcium and zinc deficiencies are demonstrated in dialysis patients. Frequently anemia is shown in dialysis patients due to an iron deficiency (Tarng 1999, Vinay 2009). Because the amount of iron absorbed in the intestine is decreased, severe blood loss can be a symptom. In addition, the formation of erythropoietin decreases due to bone marrow suppression by urea (Mahan 2012). Adding iron is recommended after assessing the patient's serum ferritin and iron levels (Rambod 2008). Intravenous iron therapy can be applied to patients for the treatment of anemia. With this treatment, hemoglobin was shown to be removable at 5-7 g / dL to 10 g / dL. Due to the fact that erythropoietin therapy increases usage of iron, it is recommended for patients to take iron supplementation.

Uremic symptoms, such as anorexia, impaired taste sensation, reduced oxidative stress improved immune function and sexual dysfunction are associated with Zn deficiency in HD patients. CRP is a sensitive marker of inflammatory activity; an association between decreased plasma Zn concentrations with higher CRP levels in hemodialysis patients has been noted (Guo 2010). Concentrations of serum Zn may affected from medications used by hemodialysis patients such as calcium carbonate, calcitriol (Dashti-Khavidaki 2010), aluminum phosphate-binders. For these reasons, Zn, Fe, magnesium (Mg) are needed, respectively, 15 mg / day, 10-18 mg / day, 200-300 mg / daily in dialysis patients (Fouque 2003). In addition, good sources of zinc are meat, poultry, nuts, and lentils and fortified breakfast cereals (Rucker 2010).

Mild selenium deficiency also appears to increase susceptibility to oxidant stress (Klotz 2003, Rayman 2002), which may be especially relevant to HD patients in whom oxidative stress is markedly increased (Stenvinkel 2003) and may contribute to accelerated atherosclerosis. Selenium deficiency may contribute to the risk of infection (Field 2002) and perhaps to uremic cardiomyopathy, thus contributing to the increased risk of CVD in the HD population. The selenium content of grains and seeds is variable, and depends on the selenium content of the soil and the form in which selenium is present (Rucker 2010). Selenium is also present in some meats, seafood, and nuts (particularly brazil nuts); levels in these foods may again be influenced by ambient soil levels (Rayman 2000). Some studies demonstrated oxidative stress and atherosclerosis is associated with selenium deficiency, because of its link to infection and uremic cardiomyopathy. Selenium deficiency increases risk of cardiovascular disease in HD patients(Fujishima 2011).

Recommended dietary nutrient intake for hemodialysis patients are shown below in Table 1 (Nissesson 2008, Rucker 2010, Fouque 2007).

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Macronutrients and Fiber	
Dietary protein intake (DPI)	• 1.2 g/kg/d for clinically stable patients (at least 50% should be of high biological value)
Daily energy intake (DEI)	• 35 kcal/kg/d if <60 years • 30–35 kcal/kg/d if 60 years or older
Total fat	25–35% of total energy intake
Saturated fat	<7% of total energy intake
Polyunsaturated fatty acids	Up to 10% of total calories
Monounsaturated fatty acids	Up to 20% of total calories
Carbohydrate	Rest of calories (complex carbohydrates preferred)
Total fiber	"/>20–25 g/d
Minerals and Water (Range of Intake)	
Sodium	750–2000 mg/d
Potassium	2000-2750 mg/d
Phosphorus	800-1000 mg/d
Calcium	<1000 mg/d
Magnesium	200–300 mg/d
Iron	10-18 mg/d
Zinc	15 mg/d
Selenyum	55 µq/d
Water	Usually 750–1500 mL/d
Vitamins (Including Dietary Supplements)	
Vitamin B1 (thiamin)	1.1–1.2 mg/d
Vitamin B2 (riboflavin)	1.1–1.3 mg/d
Pantothenic acid	5 mg/d
Biotin	30 µg/d
Niacin	14–16 mg/d
Vitamin B6 (pyridoxine)	10 mg/d
Vitamin B12	2.4 µg/d
Vitamin C	75–90 mg/d
Folic Acid	1–5 mg/d
Vitamin A	800-1000 µg/d
Vitamin D	1000-1500 IU
Vitamin E	400–800 IU

Table 1. Recommended Dietary Nutrient Intake for Hemodialysis Patients

9. Conclusion

To evaluate the amount of food intake and food preference, the patient's diet history should be taken. The patient's age, gender, social environment, economic, psychological, and educational status and history of the disease should be considered due to nutrition effect. Also, including weekends, during the 3-7 days whole foods is recorded by the patient along with the amount. Daily intake of calories and nutrients of the patients are calculated with information from those records. In addition, laboratory values and SGA as a scoring tool are very important for preparing a appropriate diet for HD patients.

The hemodialysis therapy should be dealt with by a multidisciplinary team, as recommended for other high risk populations (Morais 2005). A part of medical nutrition therapy is to provide nutrition education and periodic counseling by dietitians. For effective intervention, dietitians should present a guide for educating HD patients about individual nutritional needs. This guide should provide information about food sources, nutrients and usage exchange food lists. Adapting to patients requirements of intakes should be based on their laboratory values. Patients may be predisposed to receiving lower than recommended amounts of energy and macro-nutrients to the diet and patients who received information or counseling about their diet must be followed up closely by renal dietitians (Mahan 2012).

If a patient has diabetes, the control of blood sugar is required with a specialized diet therapy. Due to high serum glucose levels, osmolality increases, water and potassium are pulled out of cells. There are the relationship between glycemic control and survival of hemodialysis patients (Mahan 2012). Poor glycemic control causes to macrovascular complications and generation of advanced glycation end products (AGEs)(Ricks 2012). The diet for diabetes management can be modified for a patient on dialysis.

Recently, dialysis treatment is increasing in elderly patients with end-stage renal disease (ESRD) (Tamura 2009). Elderly hemodialysis patients have some diseases such as ischemic heart disease, diabetes mellitus, infectious diseases, bone fracture, cerebrovascular disease in common with ESRD. Specific prescriptions should prepare for elderly dialysis patients such as longer treatment time, nutritional support, and a personalized treatment schedule(Burns 2003). In addition, tube feeding and parenteral interventions may reinforce protein and energy intake among patients with malnutrition and anorexia.

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Chapter 3

Rare Inherited Diseases Among Hemodialysis Patients

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Additional information is available at the end of the chapter

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1. Introduction

Several diseases can be observed in patients submitted to hemodialysis treatment. Besides all variants of renal failure, hypertension and diabetes are the most common disorders that can be observed among these patients.

On the other hand, diagnosis of rare inherited diseases is more difficult and often done too late, because knowledge about them is limited, included among medical staff. It is estimated that 6-8% of the population in general will lead to some kind of rare disease and about 80% of that have a genetic background.

Although this is an extensive theme, the goal of this chapter is describe briefly two group of rare inherited conditions observed in patients submitted to hemodialysis: (1) tubular and (2) glomerular diseases. The major clinical features, genetic and molecular aspects and the management of the patient will be presented in the next pages.

2. Tubular diseases

2.1. Polycystic Kidney Diseases (PKD)

Up to 10-15% of the patients in hemodialysis can present cystic kidneys and different diseases with several phenotypes should be considerate in these situations. The autosomal dominant (ADPKD) and recessive (ARPKD) polycystic kidney diseases are the most important examples of these clinical conditions.

Approximately 50% of patients with ADPKD progress to End Stage Renal Disease (ESRD). In most cases, regular clinical monitoring is essential and the adoption of a method of renal replacement therapy (RRT - hemodialysis, peritoneal dialysis or transplantation) becomes indispensable in the treatment.

Reference	Year	Etnicity	% ADPKD
Iglesias *et al.*	1983	Euro-descendant	2.75
Gabow	1993	Euro-descendant	8-10
Sesso *et al.*	1994	Euro-descendant	3
Higashira *et al.*	1998	Asian	2.5
Glassberg *et al.*	1998	Caucasian	10
Hwang *et al.*	2000	Asian	3.2
Nunes *et al.*	2008	Euro-descendant	7.5
Harris < Torres	2009	Euro-descendant	4.4

Table 1. Percentage of ADPKD among hemodialysis patients.

Although an apparent 100% penetrance, is considered to ADPKD heterogeneous genetic viewpoint, caused by mutations in one of two genes known to be associated with the disease: PKD1 (polycystic kidney disease 1), located in chromosome 16p13.3 and PKD2 (polycystic kidney disease 2), mapped on 4q21. Most cases (80-85%) results from mutations in PKD1, causing ADPKD type 1 ADPKD1. In the remaining patients (15-20%) mutations are identified in PKD2 and give rise to ADPKD type 2 ADPKD2.

The PKD1 gene encompasses 46 exons distributed over a genomic segment of about 52kb to produce a 14.2 kb mRNA and associated with an open reading frame of approximately 12.9 kb. The PKD1 gene encoding polycystin-1 (PC1), an integral membrane glycoprotein of 4303 amino acids. The PC1 has a large extracellular amino-terminal portion with approximately 3000 amino acids, 11 transmembrane domains and a short intracellular carboxy-terminal portion. The extracellular portion has a complex combination of fields, apparently involved in protein-protein and protein-carbohydrate bindings. This group comprises many domains types, like 16 copies of a repeat of 80 amino acids to similar regions of immunoglobulin domains PKD, a signal sequence segments of the leucine-rich repeats, a domain WSC, lectin-binding domains of type-C and LDL-A plus a field REJ (receptor for egg jelly) domain and a GPS domain.

PKD2 gene, in turn, expresses a 5.4 kb mRNA which encodes a polypeptide of 968 amino acids, polycustin-2 (PC2). The PC2 has six transmembrane domains and the two tails, amino and carboxy terminals, are intracytoplasmic.

Furthermore, PC2 shows homology with the last six transmembrane domains of PC1. Together, the polycystins form a subfamily to the part TRP channels (transient receptor poten-

tial). The PC2 works also as a channel of non-selective cation permeable to Ca^{++}, whose activity is regulated by PC1. Note also the presence of a field EF hand in the carboxy-terminus of PC2, involved in binding to Ca^{++}.

Of clinical point of view, although both forms are similar in their phenotypes, the greater severity ADPKD1 shows that ADPKD2, and the median age at diagnosis and progression to ESRD are lower. In addition, the patient is more likely to ADPKD1 hypertension, hematuria and urinary tract infections. The early development of a greater number of cysts in patients with ADPKD1 explain the fact seems to be virtually thus more serious than ADPKD2, since there seems no difference between these two forms on the rate of formation and/or cystic expansion. In terms of phenotype, ADPKD presents a great variability between different families and between members of one family. Cases of infants born to families living with ADPKD, with signs of established disease are good examples of this variability.

Several studies agree that this model of two events, also known as 'second hit', might explain the heterogeneous and focal mechanism of cyst formation of ADPKD kidney and liver. This process, which can be applied to both forms of genetic disease (ADPKD1 and ADPKD2) has the first blow the germline mutation inherited from one parent and all present in the patient's renal tubular cells, while the second event is represented by a somatic mutation in allele previously normal gene.

In addition to the genetic *locus* involved in the disease, the position of intragenic germline mutation and the nature of some mutations may account for the variation clinical interfamily, but cannot explain how a germline mutation subjects with common phenotype can significantly different. The specific type of this mutation does not appear to correlate with the phenotype of a decisive manner, but mutations located at the 5′ portion of the PKD1 gene have been associated with progression to ESRD earlier than other positioned at the 3′ portion of the same gene. Furthermore, the presence aneurysm also was more prevalent in patients with mutations in the 5′ PKD1.

Recently, some studies in animal models are supporting the hypothesis that there is still a 'third hit' involved in the evolution of ADPKD. According to this hypothesis, the genetic basis associated events to accelerate cystogenesis in adult kidney may contribute to the clinical variability of ADPKD and its prognosis. Experiments carried out in animal models of ischemia/reperfusion demonstrated that the ischemic insult can be considered as additional blow to the formation of kidney cysts.

In fact, comparative observations between identical twins and siblings show that the regular course of renal disease is heterogeneous even among individuals with similar genetic heritage. Another important aspect is the fact that mechanisms of different nature, can influence the rate of somatic mutations on renal tubular epithelial cells, can potentially interfere with the severity of renal phenotype, also contributing to the observed variability in ADPKD.

Family history is essential for the diagnosis of ADPKD. For preparation of the interview should be alert to family history of cystic disease, with or without renal impairment. By presenting a pattern of dominant inheritance, are expected to be found members of ADPKD patients in all generations. However, the occurrence of new cases should be con-

sidered in those genealogies where prior registration is not found in polycystic kidney disease or kidney disease.

In the absence of a family history, which occur about 10% of all cases, the presumptive diagnosis may be done with evidence of bilateral renal cysts, according to criteria recently standardized by Pei *et al.* (2009). The adoption of more specific criteria relating to age of the patient increased the predictive value of diagnostic imaging. Furthermore, the inclusion of genetic tests, such as genetic linkage studies or direct DNA sequencing also allowed the identification of new cases with more accuracy and robustness. Besides that, the existence of one or more of the following criteria should also be considered: bilateral enlargement of the kidneys, hepatic, pancreatic or spleen cysts, brain aneurysm, cyst arachnoid alone in the pineal gland and diverticulitis.

The imaging examination is also essential for the diagnosis. In this sense, ultrasonography (US) is very useful in the diagnosis and can detect cysts from 1.0 to 1.5 cm. The presence of liver or pancreatic cysts helps confirm the diagnosis. The US diagnostic criteria include the number of cysts for each kidney and age of patients, as described in Table 2. In terms of sensitivity, computed tomography (CT) is the imaging test that can detect cysts from 0.5 cm. However, this test is not as the first choice is to use radiation or by having a higher cost. Finally, magnetic resonance imaging (MRI) is considered a more accurate tool than the US and must be requested in cases in which the distinction between carcinoma and renal cysts becomes necessary. The MRI examination allows detection of cysts from 0.3 cm in diameter and is able to assess more accurately the size of the kidneys.

Age	Diagnostic criteria for Inclusion
15-39 years	3 or more cysts unilaterally or bilaterally
40-59 years	2 or more cysts in each kidney
≥ 60 years	4 or more cysts in each kidney
	Diagnostic Criteria for Exclusion
≥ 40 years	Less than 2 cysts

Table 2. Diagnostic criteria for ADPKD.

The goal of treatment for patients with ADPKD is to preserve renal function and blood pressure control. In this context it is important to reduce progression to chronic kidney disease and monitor the risk of rupture of intracranial aneurysms and subarachnoid hemorrhage. Another important practice is to guide the patient to avoid sporting activities in which there is possibility of trauma in the lower back or abdominal in felt to minimize the risk of rupture of the cysts.

In normotensive patients with normal renal function annual US tests and renal function must be regular, keeping intervals not exceeding 12 months between assessments. For the control of blood pressure, angiotensin I to angiotensin converting (ACE), or receptor An-

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tagonists of angiotensin II (ATII) are the drugs of choice, as the system renin-angiotensin system plays a central role in the pathophysiology of hypertension in this clinical situation.

Inhibition of vasopressin receptor also occupies a significant challenge as a therapeutic agent for ADPKD, since the increase of these receptors may directly contribute to increase the concentration of cAMP and interact with many other proteins associated with cyst formation. Studies with drugs specific to this scenario are underway and their results may help in clinical management soon.

Abdominal pain is managed with analgesics and rest. Avoid nonsteroidal anti-inflammatory effect due to the nephrotoxic potential of these drugs. When the cysts become infected patients should be hospitalized and monitored. It is recommended in this situation, administer antibiotics able to penetrate the cyst, such as ciprofloxacin, clindamycin, chloramphenicol and trimethoprim-sulfamethoxazole.

Surgical intervention may be needed in the following cases: *(1)* Pain: Acute pain can be caused by intracystic hemorrhage or renal obstruction, either by clot or lithiasis. Decompression of cyst is effective in relieving pain in approximately 60-80% of cases. One option is the percutaneous drainage followed by instillation of sclerosing substance. Another possibility is the decortication of cysts by laparotomy. *(2)* Cysts infected: non-responsive to conventional antibiotic therapy. *(3)* Nephrectomy: cysts suitable for high volume (> 35cm), recurrent infections, uncontrolled hypertension and possibility of malignancy. *(4)* Massive polycystic liver disease: when liver cysts, due to the large volume, preclude the patient adequate nutrition or cause severe abdominal discomfort.

2.2. Bartter's Syndrome (BS)

Bartter syndrome (BS) was so named after Dr. Frederic Bartter, in collaboration with Dr. Pacita Pronove, describes the first case in 1960. BS is a rare inherited defect in the thick ascending limb of the loop of Henle. Hypokalemia (low potassium levels), alkalosis (increased of blood pH) and normal to low blood pressure and elevated plasma renin and aldosterone are the major features of this disorder. There are two types of BS: neonatal (NBS) and classic (CBS). A closely associated disorder, Gitelman's syndrome (described below) is milder than both subtypes of Bartter's syndrome.

NBS are observed between 24 and 30 weeks of gestation with polyhydramnios (excess amniotic fluid) in 90% of cases. In first time after birth, the newborn presents polyuria (excess of urine production) and polydipsia (excessive thirst). Life-threatening dehydration may result if the infant does not receive adequate fluids. About 85% of infants dispose of hypercalciuria (excess of calcium in the urine) and nephrocalcinosis (excess of calcium in the kidneys), which may lead to kidney stones. In rare occasions, the infant may progress to renal failure.

Patients with CBS may have symptoms in the first two years of life, but they are usually diagnosed at school age or later. Like infants with the neonatal subtype, patients with CBS also have polyuria, polydipsia, and a tendency to dehydration, but normal or just slightly increased urinary calcium excretion without the tendency to develop kidney stones. These

patients also have vomiting and growth retardation. Kidney function is also normal if the disease is treated, but occasionally patients proceed to ESRD.

Numerous causes of this syndrome probably exist. Diagnostic pointers include high urinary potassium and chloride despite low serum values, increased plasma renin, hyperplasia of the juxtaglomerular apparatus on renal biopsy, and careful exclusion of diuretic abuse. Excess production of renal prostaglandins is often found. Magnesium wasting may also occur.

The differential diagnosis should be made to avoid mistake with other identical symptoms like those observed in patients that use furosemide, for example. Although the major clinical findings characteristic of BS are hypokalemia, metabolic alkalosis, and normal to low blood pressure, these findings may also be caused by chronic vomiting, abuse of diuretic medications and magnesium and calcium deficiencies. These conditions should be available in all BS suspects.

Different mutations are associated to BS pathophysiology. These mutations are related to genes that encoding proteins with ions transporter role across renal cells in nephron, mainly in thick ascending limb.

BS type	Common name	Mutated gene	Deficiency
1	Neonatal Batter's Syndrome	SLC12A2 (NKCC2)	Na-K-2Cl symporter
2	Neonatal Batter's Syndrome	ROMK/KCNJ1	Thick ascending limb K^+ channel
3	Classic Batter's Syndrome	CLCNKB	Cl^- channel
4	BS with sensorineural deafness	BSND	Cl^- channel accessory subunit
5	BS associated with autosomal dominant hypocalcemia	CASR	Calcium-sensing receptor (activating mutation)

Table 3. Major characteristics of different types of BS.

In addition to hemodialysis the BS patient can received specific treatment to avoid the potassium loss. Spironolactone and potassium supplements can be required. Besides that, an increased sodium diet also can be associated. In specific cases, angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs can also be used, mainly in NBS patients.

In terms of prognostic, the limitation of knowledge about BS hampers any extrapolation on this field. In any case, early diagnosis remains the best predictor of successful treatment. For example, in CBS patients, the early treatment of electrolyte imbalances promotes good responses and patients tend to have few developmental failures.

2.3. Gitelman's Syndrome (GS)

Gitelman's syndrome (GS) was discovered in 1966 by Dr. Hillel Gitelman. It was discovered that some patients with BS showed a different myriad of symptoms. GS is also a renal salt

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wasting disorder but the defective tubule is in the thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule (DCT). Both disorders are associated with hypokalemia, renal potassium wasting, activation of the renin-angiotensin-aldosterone axis, and normal blood pressure. Unlike patients with Bartter's, patients with Gitelman's syndrome have hypomagnesemia, increased urinary magnesium and decreased calcium excretion.

GS is characterized by a milder and later clinical presentation. Often, this disorder is diagnosed in asymptomatic adults who present with unexplained hypokalemia. Pediatric cases typically present in the school age period with fatigue, muscle weakness, and symptoms of neuromuscular irritability. Growth retardation and polyuria-polydipsia are not prominant features of GS. Joint pain secondary to chondrocalcinosis has been described in this subset of patients and attributed to the hypomagnesemia.

Diagnosis of GS is distinguished by high plasma renin activity with normal aldosterone secretion rates, normal urinary prostaglandin excretion, hypocalciuria and usually marked hypomagnesemia.

Gitelman's is more common than Bartter's but is still a rare disorder. There is no racial predisposition for either BS or GS and both are inherited as autosomal recessive syndromes. Besides that, there is no gender preference and GS is often not easily diagnosed until adolescence or early adulthood.

The exact pathogenic mechanism of hypocalciuria and hypomagnesemia in GS is unclear. However, know that GS is an autosomal recessive kidney disorder caused by loss of function mutations of the thiazide sensitive sodium-chloride symporter (also known as NCC, NCCT or TSC) located in the distal convoluted tubule. This failure is associated to inactivating mutations in the *SLC12A3* gene. Until the distinct genetic and molecular bases of these disorders were identified Gitelman's syndrome was formerly considered a subset of Bartter's syndrome.

GS presents a great variability among patients. These phenotypic variations can be associated to genetic background and express specifics amino acid changes in the TSC mutated protein, which normally reabsorbs about 7% of the filtered NaCl load. This failure function cause defective Na and Cl reabsorption in the DCT.

Treatments to GS can be combine magnesium and potassium supplementation in association to spironolactone, amilioride and triamterene.

3. Glomerular diseases

3.1. Fabry Disease (FD)

Fabry disease (FD) is a lysosomal storage disorder caused by the deficient α-galactosidase A (α-gal A) activity. Fabry nephropathy typically progresses throughout the fifth decade to ESRD requiring hemodialysis and/or kidney transplantation. Except for ESRD development, a milder phenotype "renal variant" type is characterized with low plasma α-gal A activity.

FD low prevalence expresses the importance of this investigation among ESRD patients without known cause. Routine screening of male hemodialysis patients would enable earlier identification of other family members who might benefit from specific clinical treatment. The analysis of other epidemiological characteristics of regular FD could be used for the screening and detection of other kindred who might benefit from specific therapy as well as their offspring.

FD beginning in childhood, common symptoms include chronic or intermittent numbness; burning, tingling pain that can occur daily, usually in the fingers and feet; episodic pain that is incapacitating and may be brought on by stress, exercise, or temperature changes; recurring fever with elevated erythrocyte sedimentation rate; angiokeratomas that may appear in adolescence and increase as an adult; opacity of the corneal lens; inability to perspire; severe abdominal pain; and an intolerance to temperature (heat or cold) and exercise. The condition then progresses in adulthood to include renal, cardiovascular, cerebrovascular, and pulmonary complications that may lead to ESRD, stroke, myocardial infarction, breathing problems and obstructions, and more.

FD is a rare inborn error with a recessive X-linkage inherited pattern. The estimated FD incidence is between 1:40,000 and 1:117,000 in general population. The prevalence of end stage FD males on dialysis was estimated between 0.22% and 1.2% in several populations.

The enzymatic defect in FD results from the deficient activity of the α-galactosidase A (α-gal A), a lysosomal hydrolase encoded by a gene (*GLA*) localized to Xq22. The *GLA* gene is 12 kb long and consists of 7 exons encoding 429 amino acids including a 31-amino acid signal peptide. The mature form of α-gal A is a homodimeric glycoprotein with molecular weight of ~46kDa synthesized from that point on cleavage of the signal peptides with ~50kDa.

In FD this leads to progressive intracellular accumulation of glycosphingolipids, mainly in the form of globotriaosylceramide (Gb-3), in many cells, particularly in renal epithelial cells, endothelial cells, pericytes, vascular smooth muscle cells, cardiomyocytes, and neurons of the autonomic nervous system.

The genetic defect occurs in all cell types, but involvement differs greatly among different organs and cell types. This heterogeneity likely reflects different rates of sphingolipid metabolism. Thus the minimum threshold requirement for α-gal A activity to prevent Gb-3 accumulation varies across cell types due to the type and amount of substrates that are recycled by the different cells.

Clinical onset of the disease typically occurs during childhood or adolescence with recurrent episodes of severe pain in the extremities, characteristic cutaneous lesions know as angiokeratomas and a distinctive but asymptomatic corneal dystrophy. Proteinuria and chronic renal disease occur with increasing age. Severe renal impairment leads to hypertension and uremia. Without dialysis, transplantation or enzyme replacement therapy (ERT), progressive renal failure is the main cause of death in the 4^{th} decade of life in most hemizygous males with FD. However, a number of variants with residual α-gal A activity with late-onset manifestations primarily limited to the heart or kidney have been described.

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The 'classical phenotype' includes the pain and paresthesias in extremities, diffused angiokeratoma and hypohidrosis during childhood or adolescence, and also corneal opacities and renal failure. Fabry nephropathy typically progresses throughout the fifth decade of life to ESRD requiring hemodialysis and/or kidney transplantation. In view of this fact, hemodialysis patients represent an important target group for FD screening. Death usually occurs due to renal failure, cardiac or cerebrovascular disease. In addition, milder variants with residual α-gal A activity have been described. The cardiac and renal variants present with either late-onset manifestations primarily limited to the heart or kidney. The 'renal variant', a milder FD phenotype, can present late-onset manifestations primarily limited to the kidney.

While in an epidemiological point of view FD occurrence is low, on the other hand the FD diagnosis is very important for detection of family members. In view of this fact, dialysis patients represent an important target group for FD screening because they permit to identify FD patients and therefore others carriers among your family members. Each screened confirmed patient could allow early diagnosis of others related subjects, who can get treatment before or in the earlier symptoms manifestations. In these terms, FD screening among ESRD patients consists of an important tool for detection of FD patients and it could be followed by FD screening between family members of the index case. Both pedigree and population screening studies have been described and it can be carried out in subpopulations thought to be at higher risk of disease than the general population.

FD patients with proteinuria or CRI should have aggressive treatment of hypertension is present and should probably be treated preferentially with angiotensin antagonist therapy; the latter recommendation is based on theoretical considerations, as definitely proof of efficacy has not been obtained yet.

Two different recombination α-galactosidase-A preparations are in use for treating FD. One enzyme is produced by Chinese hamster ovary (CHO) cells with classic recombinant technology (agalsidase β, Fabrazyme – Genzyme Corporation), and the other enzyme is produced by cultured human skin fibroblast with an activated promoter of the α-gal A gene (Agalsidase α, Replagal – Shire Human Genetics Therapies). Both recombinant enzymes are quite comparable in properties and differ only alightly in glycan composition. The two enzyme preparations have independently been examined in clinical investigations. Although both enzyme therapies were found to result in the desired Gb-3 from endothelium, the clinical effects are not robust as anticipated. In some patients, stabilization of renal function and improvenment in cardiac hypertrophy occurs upon therapy.

3.2. Alport's Syndrome (AS)

Alport syndrome (AS) or hereditary nephritis was first identified in a British family by Dr. Cecil Alport in 1927. It is a genetic disorder characterized by glomerulonephritis, ESRD and hearing loss. AS can also affect the eyes (lenticonus). Hematuria is almost always found in this condition.

This disorder is caused by mutations in COL4A3, COL4A4 and COL4A5 genes and/or in collagen biosynthesis genes. Mutations in any of these genes prevent the proper production

or assembly of the type IV collagen network, which is an important structural component of basement membranes in the kidney, inner ear and eye. Basement membranes are thin, sheet-like structures that separate and support cells in many tissues. When mutations prevent the formation of type IV collagen fibers, the basement membranes of the kidneys are not able to filter waste products from the blood and create urine normally, allowing blood and protein into the urine.

The abnormalities of type IV collagen in kidney basement membranes cause gradual scarring of the kidneys, eventually leading to kidney failure in many people with the disease. Progression of the disease leads to basement membrane thickening and gives a "basket-weave" appearance from splitting of the *lamina densa*. Single molecule computational studies of type IV collagen molecules have shown changes in the structure and nanomechanical behavior of mutated molecules, notably leading to a bent molecular shape with kinks.

AS can have different inheritance patterns that are dependent on the genetic mutation. The pattern most common is X-linked, due to mutations in the COL4A5 gene. Mutations in both copies of the COL4A3 or COL4A4 genes, located on chromosome 2, confer an autosomal recessive pattern to mutation bearer. On the other hand, in rare situations (about 5%), some patients can have clinical features associated to AS autosomal dominant transmission. In these specific cases, renal failure tends to occur slowly.

The diagnosis of AS can be made according following observations:

1. family history of nephritis of unexplained hematuria in a first degree relative of the index case or in a male relative linked through any numbers of females;
2. persistent hematuria without evidence of another possibly inherited nephropathy such as thin Glomerular Basement Membrane (GBM) disease, polycystic kidney disease or IgA nephropathy;
3. bilateral sensorineural hearing loss in the 2000 to 8000Hz range. The hearing loss develops gradually, is not present in early infancy and commonly presents before the age of 30 years;
4. Mutation in one of the genes associated to disease (COL4A3, COL4A4 or COL4A5);
5. immunohistochemical evidence of complete or partial lack of the Alport epitope in glomerular, or epidermal basement membranes, or both;
6. widespread GBM ultrastructural abnormalities, in particular thickening, thinning and splitting;
7. ocular lesions including anterior lenticonus, posterior subcapsular cataract, posterior polymorphous dystrophy and retinal flecks;
8. gradual progression to ESRD in the index case of at least two family members;
9. macrothrombocytopenia or granulocytic inclusions, similar to the May-Hegglin anomaly and
10. diffuse leiomyomatosis of esophagus or female genitalia, or both.

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Do not have a specific treatment to AS. In this case, treatments are symptomatic and patients are advised on how to manage the complications of kidney failure and the proteinuria that develops is often treated with ACE inhibitors, although they are not always used simply for the elevated blood pressure.

4. Conclusions

Many aspects can be considered in analysis of rare inherited diseases. In this chapter, we described only five different rare inherited disorders possible to observe among hemodialysis patients. However, is important to comment that other diseases with few population frequencies should be analyzed in patients with uncommon signals. Besides that, infection diseases and drugs dependent diseases also should be investigate in some cases. Genetic and molecular analysis also can be a relevant tool to use in situations of rare clinical presentations. A multidisciplinary approach, including the nephrologists and the geneticists besides others professionals, is the most important strategy to investigate any rare inherited disorder. For these specific uncommon conditions, the linkage between clinical and research staffs can be improve the diagnosis strategy.

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Chapter 4

Bleeding Diathesis in Hemodialysis Patients

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Additional information is available at the end of the chapter

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1. Introduction

End-stage renal disease patients, particularly those treated with hemodialysis (HD), suffer from complex hemostatic disorders. Patients with uremia may experience two opposite hemostatic complications: bleeding diathesis and thrombotic tendencies. Bleeding diathesis in uremic patients is primarily seen due to abnormalities in primary hemostasis, particularly platelet function disorder and impairment of the platelet-wall interaction. Anemia, abnormal nitric oxide production and some drugs employed also contribute to bleeding diathesis.

In addition to bleeding diathesis, thrombotic complications are also frequently seen in uremic patients. Thrombotic complications play a significant role in cardiovascular events, the main cause of mortality in this patient group. Thrombotic hemostatic changes include increased platelet aggregability, increased plasma fibrinogen, factor VIII:C and vWF levels, a decrease in protein C and protein S anticoagulant activity, changes in fibrinolytic system activity and a rise in plasma lipoprotein and homocysteine levels.

In addition to hemostatic changes caused by uremia in the HD patient group, HD therapy itself leads to various hemostatic changes. These include coagulation cascade activation as a result of contact between the dialysis membrane and blood elements, the effect of anticoagulants used to prevent coagulation developing due to this cascade activation and a decrease in the negative effects on platelet functions of middle molecule uremic toxins, thought to be eliminated during HD.

Both hemorrhagic and thrombotic changes in this patient group can give rise to life-threatening consequences. For that reason, research is still continuing into identification and treatment of hemostatic abnormalities in this patient group. Here, we shall be discussing the pathogenesis and treatment of hemorrhagic and thrombotic complications in the light of new research.

2. Normal hemostasis

A knowledge of normal hemostasis is needed in order to understand hemostatic disorders in uremic patients. The normal hemostatic process establishes blood viscosity inside the vessel and rapid plaque formation as a result of vascular injury. Hemostasis consists of three phases; primary hemostasis, coagulation and fibrinolysis (Galbusera et al., 2009). Platelets assume the main role in primary hemostasis. Under normal conditions, it prevents vascular endothelium platelet aggregation and adhesion. In the event of vascular injury, platelet-mediated hemostatic plaque formation begins (Stassen et al., 2004). Two main platelet receptors, glycoprotein Ib (GPIb) and activation-dependent glycoprotein IIb–IIIa (GPIIb–IIIa) complex, and the adhesion molecule von Willebrand factor (VWF) and fibrinogen are involved in the adhesion process in hemostatic plaque formation. Various modifications take place in the platelets after the adhesion phase, and molecules assisting platelet activation and adhesion, such as ADP, serotonin, epinephrine, fibrinogen, thromboxane and VWF, are released from the platelet granules (Ruggeri et al., 2003). The coagulation phase consists of intrinsic and extrinsic coagulation pathways. A number of coagulation proteins are involved in these coagulation pathways, including Tissue Factor (TF), and factors VII, IX, X, V, VIII, XI and XIII. Natural inhibitors of the coagulation cascade are protein C, Tissue factor (TF) pathway inhibitor and antithrombin III (Stassen et al., 2004). The fibrinolytic system leads to plasmin-mediated dissolution of fibrin. Molecules serving in this system are the plasminogen activator inhibitors PAI-1 and PAI-2, the plasmin inhibitor alpha-1-antiplasmin, alpha-2-macroglobulin and thrombin activatable fibrinolysis inhibitor (TAFI) (Fay et al., 2007).

3. Bleeding diathesis in uremic patients

The relation between uremia and bleeding diathesis has been known for many years. Uremic patients used to be lost from bleeding from vital organs. Despite today's improvement in anemia with modern HD techniques and erythropoietin therapy, bleeding diathesis continues to represent a significant problem. There may be serious, life-threatening bleeding, and surgical procedures may be delayed or not performed at all out of concern over bleeding diathesis. This causes a rise in patient morbidity. The most common cause of uremic bleeding diathesis is impaired primary hemostasis. The most frequent complications seen as a reflection of primary hemostasis disorders are petechiae, purpura, and bleeding in the arteriovenous fistula puncture site and regions where the HD catheter is inserted (Galbusera et al., 2009; Remuzzi et al., 1989). In addition, bleeding in vital organs may also be seen in uremia, leading to less frequently observed but fatal complications. In HD patients in particular, various HD therapy-related factors mean that bleeding complications to be seen more frequently. Although various rates have been citied in HD patients in different publications, the bleeding diathesis rate is around 10%-15%, and bleeding-associated morbidity around 15% (Davenport et al., 1994, Martin et al., 1994; van de Wetering et al., 1996). Gastrointestinal (GIS) bleeding, particularly upper GIS bleeding, is seen in one third of uremic patients (Galbusera et al., 2009). Kutsumi et al. showed that 17% of patients presenting to the emer-

gency department with GIS bleeding received HD therapy (Kutsumi et al., 1998). Other examples of vital organ bleeding include hemorrhagic stroke, subdural hematoma, spontaneous retroperitoneal hemorrhage, hepatic subcapsular hematoma intraocular hemorrhage and hemorrhagic pericarditis leading to cardiac tamponade (Galbusera et al., 2009; Remuzzi, 1989). Of these, hemorrhagic stroke and subdural hematoma are widely observed in HD patients. Incidence of hemorrhagic stroke is 5-10 times greater than in the normal population. (Seliger et al., 2003; Toyoda et al., 2005), while that of subdural hematoma has been put at 20 times greater. Mortality in this patient group has been determined at above 40% (Power et al., 2010). van de Wetering et al. observed 48 hemorrhagic complications in 78 HD patients. Forty of the patients with hemorrhagic complications had major bleeding and 8 minor bleeding. Six of the 40 major hemorrhages were intra-abdominal, 18 involved bleeding around the catheter, 3 were GIS bleeding, 12 were oronasopharyngeal and 1 intracerebral. One intracerebral case, 1 intra-abdominal case and 1 with gastrointestinal bleeding died (van de Wetering et al., 1996). As seen in all these studies, a not inconsiderable level of hemorrhagic complications with high mortality is seen in HD patients. It is therefore important to understand the pathogenesis of and treatment approaches toward bleeding diathesis in the HD patient group. While bleeding diathesis in HD patients is associated with uremia-related factors, HD therapy itself also creates a tendency to bleeding.

3.1. The pathogenesis of uremia-associated bleeding diathesis

Predisposition to bleeding in uremic patients has been known for years. While the pathogenesis of bleeding diathesis is not fully established, multifactorial causes are thought to be responsible. The most important of these factors are structural and functional defects in platelets. Other factors are abnormal platelet-vessel wall interaction, anemia, abnormal Nitric oxide (NO) production, drug use and HD therapy itself.

3.1.1. Platelet dysfunction

3.1.1.1. Thrombocytopenia

Moderate level platelet function disorder not sufficient to cause life-threatening bleeding is frequently seen in uremic patients (Galbusera et al., 2009). The cause of thrombocytopenia is generally decreased platelet production or an increase in consumption (Boccardo et al., 2004; Panicucci et al., 1983). Thrombocytopenia may be related to HD therapy itself or develop due to primary renal disease or various accompanying comorbid conditions. These conditions include systemic lupus erythematosus, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and disseminated intravascular coagulation (Barbour et al., 2012; Boccardo et al., 2004; Loirat et al., 2012). HD-related thrombocytopenia may be related to the membrane and anticoagulant used in dialysis therapy. Studies investigating the effect of HD on platelet numbers have generally looked at platelet numbers 15-30 min before HD and after HD (Daugirdas & Bernardo, 2012). Studies investigating the effect of type of HD membrane on platelet number have shown that greater thrombocytopenia develops in non-biocompatible cellulose membranes compared to biocompatible synthetic polymer

membranes. Thrombocytopenia observed in non-biocompatible membranes has been associated with complement activation (Gutierrez et al., 1994; Hoenich et al., 1997; Verbeelen et al., 1991). Few studies have investigated the effect of membrane sterilization technique on platelet number. One such study, by Miller et al. analyzed the biocompatibility of the high-flux membrane steam sterilized F60S and ethylene oxide sterilized F60 and the low-flux membrane ethylene oxide sterilized F6, in other words, their effect on platelet and leukocyte numbers. The three different membranes had no different effects on platelet numbers, while the steam-sterilized membrane was shown to reduce leukocyte numbers less (Müller et al., 1998). Another effect of HD therapy on platelet number concerns the heparin used during therapy. Because of its low cost and short half-life, heparin is a frequently used anticoagulant in HD therapy. However, heparin-induced thrombocytopenia (HIT) is a complication that may limit its use and cause mortality. HIT is classified into types I and II. Type-I HIT is a widely seen form. It arises as the result of a direct reaction between heparin and thrombocytes. There is generally a slight fall in platelet numbers soon after heparin administration, and platelet numbers return to normal despite repeated administrations of heparin. Type-II HIT is less common, with an incidence of between 0.5% and 5% (Jang & Hursting, 2005). Etiology is attributed to platelet factor 4 and antibodies developing against heparin complex (Suranyi & Chow, 2010; Visentin et al., 1994). HIT generally appears with the development of thrombocytopenia, thrombosis, skin necrosis and gangrene accompanied by acute systemic reactions 5-30 min after administration of bolus unfractionated heparin (Syed & Reilly, 2009). HIT diagnosis is established by scoring the following criteria: thrombocytopenia appearing 5-10 days after commencement of heparin therapy, the presence of any thrombotic event, a normal platelet number before heparin, a 50% fall in platelet numbers compared to basal values in the absence of any other cause of platelet decrease and platelet numbers returning to normal when heparin therapy is stopped (Warkentin, 2004). The first procedure in treatment is cessation of heparin until HIT antibody results are obtained and the use of alternative anticoagulant methods to heparin. The use of warfarin as an alternative anticoagulant until platelet numbers return to normal is not recommended (Syed & Reilly, 2009). Saline flush, citrate anticoagulation, the direct antithrombin inhibitors lepirudin and argatroban or the Factor Xa inhibitor danaparoid can be used in heparin-free dialysis (Matsuo & Wanaka, 2008, Syed & Reilly, 2009). In conclusion, in the light of current knowledge, generally, although uremia and HD-associated thrombocyte numbers may decline slightly, no fall in platelet numbers that might cause fatal bleeding is observed in association with uremia itself or in association with HD therapy (excluding HIT2).

3.1.1.2. Platelet function disorder

3.1.1.2.1. Structural and functional platelet disorder

Structural and functional disorders have long been known in uremic patients. One structural impairment is a decrease in mean platelet volume, and this contributes to bleeding diathesis by leading to a decrease in platelet mass (Galbusera et al., 2009; Michalak et al., 1991). There are three main types or granule in platelets; dense granules, α granules and lysosomes (Kaplan & Owen., 1986). Various substances in these granules are involved in the hemostatic

process by being released from platelets with activation. In uremic patients, both the content of these granules and defects in secretion during platelet activation contribute to bleeding diathesis. There are various studies of platelet granule content in uremic patients. Eknoyan et al. showed that a low level of adenosine diphosphate (ADP) and serotonin in chronic kidney disease patients parallels platelets' functional defects, and that these defects can be reversed with hemodialysis or transplantation (Eknoyan and Brown., 1981). Di Minno et al. determined a low platelet ADP level in uremic patients compared to normal individuals, and a decrease in thrombin-stimulated thromboxane B2 and adenosine triphosphate secretion (Di Minno et al., 1985). Vlachoyannis et al. determined a higher cyclic-AMP level in uremic patients compared to healthy individuals (Vlachoyannis & Schoeppe., 1982). There is a rise in cyclic-GMP (c-GMP) in uremic patients. The rise in c-GMP level is associated with increased production of NO, produced by platelets (Noris et al., 1993). A rise in platelet Ca content and abnormal Ca release as a response to stimuli is another structural defect (Gura et al., 1982; Ware et al., 1989). There are contradictory findings regarding defective arachidonic acid in uremic platelets (Boccardo et al., 2004). Remuzzi et al. reported defective arachidonic acid metabolism in uremic platelets and a decrease in thromboxane A2 production as a reflection of this (Remuzzi et al., 1983). Bloom et al. reported no cyclooxygenase defect in uremic patients, but determined a decrease in thrombin-stimulated thromboxane synthesis (Bloom et al., 1986). These structural and functional defects in uremic patients contribute to impairment in adhesion and aggregation and facilitate bleeding diathesis. In addition to these structural and functional defects, various uremic toxins are known to lead to platelet aggregation defect. The uremic toxins guanidosuccinic acid and phenolic acid lead to platelet aggregation defect by inhibiting ADP-induced platelet aggregation (Hedges et al., 2007).

3.1.1.2.2. Platelet-vessel wall interaction defect

Platelet-vessel wall interaction defect is one of the significant causes of bleeding diathesis, in addition to platelet morphology and function disorder. As discussed in the section on normal hemostasis, defective platelet adhesion to the vascular endothelium is mediated by two important proteins; fibrinogen and von Willebrand factor (vWF). Additionally, two important proteins on the platelet surface, GP Ib (vWF receptor) and activation-dependent GPIIb–IIIa complex (fibrinogen receptor), are also involved in adhesion. Platelet glycoprotein (GP) content is divided into the membrane and intracellular component. Studies of uremic patients have produced different results regarding GP content (Moal et al., 2003). Nomura et al. determined decreased GP Ib expression and normal GPIIb-IIIa expression in uremic patients (Nomura et al., 1994). In complete contrast, Sreedhara et al. determined normal GP Ib expression and a decrease in GPIIb–IIIa expression (Sreedhara et al., 1996). Salvati et al. determined low GP Ib expression and high GPIIb–IIIa expression (Salvati et al., 2001). Moal et al. determined low GP Ib expression in platelets at rest. They also reported higher GP Ib expression in stimulated platelets in the HD patient group compared to the control and CKD groups, while GPIIb–IIIa expression was lower in the CKD and HD patients compared to the controls (Moal et al., 2003). We think this may be attributed to the technique for measuring these differences in results, whether the patient group is pre-dialysis or dialysis, if dialy-

sis, then whether it is HD or Peritoneal dialysis (PD) and when blood specimen is collected (before or after HD). However, the majority of studies suggest that these two platelet GPs decrease in uremic patients or that there is a decrease in response to stimulation. This leads to platelet-wall interaction defect and bleeding diathesis.

vWF is one of the main important proteins in platelet adhesion. For that reason, there have been many studies on both vWF level and function in uremic patients. However, these have produced controversial results in terms of both levels and functions. One such study was that by Zwaginga et al., which showed that platelet adhesion defect was not associated with abnormal vWF (Zwaginga et al., 1990). Escolar et al. reported platelet adhesion defect in uremic patients and that the defect may stem from defective interaction between vWF and the receptor (Escolar et al., 1990). Despite these conflicting results, the fact that no response is obtained to cryoprecipitate and desmessoprin in uremic bleeding diathesis suggests defective vWF involvement (Boccardo et al., 2004; Galbusera et al., 2009). vWF defect in uremia arises because of reduced interaction with GPIIb–IIIa receptor or reduced expression of this receptor (Mohri et al., 1988). Defective vWF GPIIb–IIIa receptor interaction reduces TXA2 and ADP production by leading to defects in phosphatidylinositol bisphosphate breakdown and cytosolic calcium concentration. As a result, it leads to impaired adhesion (Hedges, 2007).

3.1.2. Anemia

Anemia is known to be widely seen in chronic kidney failure patients and to lead to morbidity and mortality. The most important reason why it leads to morbidity and mortality stems from its negative effect on myocardial functions. Another negative effect of anemia is that it contributes to bleeding diathesis. It is thought to do this in two ways. The first is that under normal conditions in a non-anemic individual the flow of formed elements of blood inside the vessel is regular. Therefore, in the event of injury, in order for the platelets to be quickly able to form a clot, they act in the periphery near the vascular endothelium. In anemic individuals, however, this rheological order is defective. And this leads to bleeding diathesis (Hedges et al., 2007). Another reason is that erythrocytes release ADP and TxA2. But this secretion decreases in anemic individuals. Decreased levels of ADP and TxA2 lead to a reduction in platelet aggregation (Valles et al., 1991). Another mechanism concentrated on is the effect of anemia on NO. Erythrocytes are known to have a high affinity for NO. In anemia, however, the NO scavenger role declines because the erythrocyte mass decreases. An increase in NO level, on the other hand, leads to a rise in cGMP level and a decline in platelet aggregation (Martin et al., 1985, Galbusera et al., 2009). Improvement of anemia with both blood transfusion and erythropoietin therapy reduces bleeding time. And these are findings that support the hypothesis that anemia has an effect on bleeding diathesis (Livio et al., 1982; Moia et al., 1987, Viganò et al., 1991).

3.1.3. Abnormal NO production

There is an accumulation of uremic toxins as well as guanidosuccinic acid in uremic patients. Guanidosuccinic acid accumulation is associated with guanidine transfer from L-arginine to aspartic acid. L-arginine is the most important precursor of NO. NO has a modulator effect on

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vascular tonus. In addition, NO prevents platelet adhesion to the endothelium, lowers cAMP-mediated platelet aggregation and reduces platelet-platelet interaction by increasing cGMP levels. (Noris & Remuzzi, 1999). The administration of inhale has led to a prolongation of bleeding time in studies on healthy individuals (Högman et al., 1993). Abnormal NO production is therefore thought to contribute to bleeding diathesis in uremic patients.

3.2. Evaluation of bleeding diathesis

Evaluation of bleeding diathesis in uremia begins with the taking of a detailed history. The presence of other systemic disease, drugs used, if renal replacement therapy is administered whether this is HD or PD, and if HD what kind of membrane and which anticoagulant in what doses are used must all be established. At physical examination, petechiae, purpura, epistaxis and bleeding from the catheter or AVF puncture site, generally a reflection of platelet function effect, may all be seen. In addition, physical examination findings secondary to GIS bleeding or intracranial or subdural bleeding may also be encountered. Platelet numbers are generally normal or slightly low at laboratory analysis. The most frequently used clinical finding in evaluation of uremic bleeding diathesis is bleeding time (Steiner et al., 1979).

3.3. Treatment of bleeding diathesis

3.3.1. Hemodialysis

As previously discussed, while the HD process itself facilitates bleeding diathesis, in renal failure patients it is used as a therapeutic approach that reduces bleeding diathesis. HD's reductive effect on bleeding diathesis comes about through the removal of uremic toxins from the blood. More than 90 uremic toxins are known today. These are classified as small, middle or large molecular toxins based on their molecular weight. Large and/or protein-bound molecules in particular cannot be removed with HD techniques using classic low-flux membranes, but they can with high-flux membranes (Vanholder et al., 2005; Weissinger et al., 2004). Daily and long-term dialysis may be needed for the removal of uremic toxins and to reduce bleeding diathesis using traditional HD techniques (Hedges et al., 2007). Studies have shown that dialysis therapy produces an improvement in platelet functions by removing uremic toxins (Boccardo et al., 2004; Galbusera et al., 2009; Hedges et al., 2007). However, another point here that must not be forgotten is that HD therapy can lead to bleeding diathesis, due to both membrane interaction and to the anticoagulants used. Therefore, heparin-free dialysis must be performed, especially with patients with active bleeding or who have recently undergone major surgery. Various methods are currently applied for heparin-free HD. These include HD using low-dose heparin, regional heparinization with protamine, intermittent saline flush, regional citrate anticoagulation, prostacyclin infusion and other alternative techniques. Swartz et al. showed that regional heparinization had a lower bleeding reduction effect than low-dose heparinization (Swartz & Port, 1979). However, in another study by Swartz, a bleeding level as high as 26% was observed in patients with an active risk of bleeding using low-dose controlled heparinization (Swartz, 1981). In addition, there are studies showing that regional heparinization with protamine neutralization has an

increasing effect on bleeding, probably associated with the delayed heparin effect (Hampers et al., 1966). Nagarik et al. investigated the effects on bleeding diathesis episode of dialysis performed with intermittent saline flush and anticoagulant dialysis in patients administered intermittent renal replacement therapy in intensive care. They observed fewer bleeding episodes in patients administered intermittent saline flush (Nagarik et al., 2010). Sagedal et al. showed that intermittent saline flush did not reduce clot formation in dialyzers and intravascular coagulation in stable HD patients (Sagedal et al., 2006). Citrate has been used as an anticoagulant for many years because of its Ca-binding effect. Several studies have shown that citrate anticoagulant can be used safely in uremic patients with bleeding (Davies et al., 2011; Jarraya et al., 2010 Kreuzer et al., 2010; Park et al., 2011). However, it must not be forgotten that severe metabolic alkalosis may develop in patients receiving citrate anticoagulation, especially continuous renal replacement therapy (Alsabbagh et al., 2012). Additionally, there are various difficulties and side-effects in citrate anticoagulation beyond continuous renal replacement. Two reliable pumps are needed for citrate and Ca infusion, and these difficulties and side-effects are that serious metabolic alkalosis and hypocalcemia may result. Prostacyclin administration is another heparin-free dialysis technique. However, this technique is not much used, because it leads to headache, flushing and hypotension (Sagedal et al., 2006). Because regional anticoagulation with heparin-protamine or citrate-calcium infusion or intermittent saline flush lead to a loss of personnel time and have a number of side-effects, new techniques are under development. One of these is the use of citrate-enriched dialysate. Cheng et al. showed that citrate-enriched dialysate is more effective than intermittent saline flush (Cheng et al., 2011). However, studies showing efficacy in patients with bleeding are needed. Yixiong et al. showed that effective and safe anticoagulation is provided in high-risk bleeding patients with low-dose argatroban (direct thrombin inhibitor) saline flush (Yixiong et al., 2010). Providing effective dialysis in HD patients with bleeding continues to be a major problem. Techniques permitting safe and effective HD need to be developed with technological advances.

3.3.2. Desmopressin

Desmopressin (1-deamino-8-d-arginine vasopressin [DDAVP]) is a drug frequently used in HD patients with bleeding diathesis. While its reductive effect on bleeding diathesis is not fully understood, it is thought to function by increasing Factor VIII levels through release from where it is stored and by reducing the effect of vWF on dysfunction (Prowse et al., 1979). DDAVP's reducing effect on bleeding time starts within 1 h and continues for 4-8 h. Bleeding time returns to normal in 24 h (Mannucci et al., 1983; Galbusera et al., 2009). DDAVP has been shown to effectively reduce bleeding time when administered intravenously (0.3 microg⁄kg) by the subcutaneous and intranasal routes (Mannucci et al., 1983; Shapiro & Kelleher, 1984; Ulusoy et al.,2004; Viganò et al., 1989). One of the things that must not be forgotten in desmopressin therapy is that efficacy may decline with increasing use, probably in association with a decline in endothelial vWF stores (Canavese et al., 1985). Flushing, headache and tachycardia may be observed during desmopressin use. But not at such a level as to prevent its use in uremic bleeding diathesis.

3.3.3. Cryoprecipitate

Cryoprecipitate is a blood product rich in factor VII, vWF and fibrinogen. Use takes the form of 10 bags of American-Red-Cross-prepared cryoprecipitate infusion in 30 min. Its effect begins in 4-12 h. The effect mechanism is not fully understood, though it is thought to be associated with its concentrated coagulation factor content (Janson et al., 1980; Triulzi et al., 1990). Its advantage is that its effect appears early, the disadvantage that it involves a risk of transferring transfusion-related diseases. Hypocalcemia may also develop during cryoprecipitate transfusion, as with the transfusion of other blood products. Additionally, it may rarely lead to pulmonary edema and anaphylactic reaction. Factors requiring attention during blood and blood product transfusion, must also therefore not be forgotten in cryoprecipitate transfusion (Galbusera et al., 2009; Hedges et al., 2007; Spinella & Holcomb, 2009). Although cryoprecipitate works very quickly, other approaches are preferred because of the risk of transference of transfusion-related diseases.

3.3.4. Conjugated estrogen

The bleeding diathesis-reducing effect of conjugated estrogen emerged on the basis of observational data (Liu et al., 1980). Following these observational data, the effect on uremic bleeding diathesis began being investigated. It has been shown that use of 0.6 mg/kg IV (4-5 days) in uremic patients lowers bleeding time (Viganò et al., 1988). Twenty-five milligrams of oral conjugated estrogen for 3-20 days has been shown to safely reduce bleeding time (Viganò et al., 1988). In addition, low-dose transdermal administrations two times a week (50–100 microg/24 h) have also been shown to effectively reduce bleeding (Sloand & Schiff., 1995). The bleeding diathesis-reductive effect is thought to come about by preventing NO synthesis (Zoja et al., 1991). In the light of these studies, since there is greater research into reducing uremic bleeding diathesis, iv administration of conjugated estrogen is recommended over the subcutaneous and transdermal routes (Hedges et al., 2006).

3.3.5. Erythropoietin

We have already discussed the effect of anemia on bleeding diathesis. Based on these data, researchers have investigated the effect on bleeding diathesis of erythropoietin (EPO), an indispensible element in anemia treatment in chronic kidney patients. Several studies have shown that correction of anemia with EPO therapy reduces uremic bleeding diathesis. EPO's bleeding diathesis-reductive effect may come about through several mechanisms. The first of these is that the erythrocyte mass that increases with EPO therapy serves as an NO scavenger and reduces NO's negative effect on platelet adhesion. Another is the disappearance of blood rheology impairment brought about by anemia (Martin et al., 1985; Viganò et al., 1991). EPO therapy is thought to reduce bleeding diathesis by increasing the number of reticulated platelets in bone marrow, with its greater metabolic efficacy, by increasing platelet aggregation and interaction with the vascular endothelium and, finally by increasing platelets' response to stimuli (Diaz-Ricart et al., 1999; Hedges et al., 2007; Tàssies et al., 1995; Zwaginga et al., 1991). In conclusion, anemia treatment brings about a significant improve-

ment in bleeding diathesis, especially Htc, at a level of 27%-32% (Galbusera et al., 2009; Viganò et al., 1991)

In conclusion, despite advances in technology, bleeding diathesis continues to be a life threatening condition in HD patients. Although bleeding diathesis is not fully understood, it is thought to be associated with primary hemostasis, in other words, platelet structure and functions. Anemia should be corrected with EPO therapy and, most important of all, effective dialysis must be performed in order to prevent bleeding diathesis in these patients. Since its effect starts quickly, we think that the use of DDAVP will be appropriate in acute, life-threatening bleeding; and because its effect is long-lasting, conjugated estrogen may be used in patients without life-threatening bleeding but requiring long-term monitoring.

4. Hypercoagulability in uremia

Thrombotic complications are encountered as frequently as bleeding diathesis and are life-threatening in uremic patients. Thrombotic complications lead to mortality giving rise to cardiovascular events and can also cause morbidity by leading to AVF thrombosis. Understanding the pathogenesis of thrombotic events in uremic patients and the treatment is therefore of vital importance. A rise in platelet hyperactivity, adhesion and aggregation, coagulation cascade activation and a decrease in fibrinolysis are held responsible in the pathogenesis of the thrombotic process.

4.1. Increased platelet activation, aggregation and adhesion

The findings of studies analyzing platelet activation in HD patients are inconsistent. These inconsistent results may stem from differences in the patient population and sampling techniques or from differences in the platelet activation markers used. Various molecules expressed on the surface of activated platelets or various substances known to be released into plasma in the event of platelet activation are today used as platelet activation markers. Platelet surface markers are generally evaluated using flow cytometry and monoclonal antibody-based measurement. CD41 is a flow cytometric marker of activation-dependent GPIIb/IIIa receptor. PAC-1 is used to determine this receptor in its activated state. CD42b or GPIb are used in the determination of vWF receptor. CD62P is used in the determination of p selectin found in the membrane of platelet alpha granules and given off during platelet activation. CD63 is used similarly to CD62P in the determination of degranulation of platelet dense granules (Daugirdas & Bernardo., 2012; Michelson, 1996). Many studies to date have evaluated the effect of the HD procedure on platelet activation using one or more of these markers. These studies have also evaluated the effects on activation markers of the membrane used in the HD procedure, the site of blood collection (where blood enters or leaves the HD membrane) and time of collection. Studies showing differences depending on blood collection site and time and that activation markers are higher in blood samples collected at the HD membrane exit are in the majority (Aggarwal et al., 2002; Daugirdas & Bernardo., 2012; Reverter et al., 1994;). Additionally, these studies have also shown higher platelet acti-

vation markers in patients using cuprophan membrane (Cases et al., 1993; Daugirdas & Bernardo., 2012; Reverter et al., 1994). Today, in addition to the analysis of platelet activation using flow cytometry, various markers found in platelet alpha granules and released into plasma during platelet activation are determined using ELISA. One such marker is sCD40L. This is a transmembrane protein structurally related to the tumor necrosis factor-α (TNF α) family. sCD40L is a form of CD40L released into plasma from the active thrombocyte surface (Henn et al., 1998). There are studies showing that sCD40L is correlated with platelet activation in both the normal population and HD patients. In a study of 103 HD patients in our clinic we determined a significantly higher predialysis sCD40 L level compared to healthy individuals. There was a rise in sCD40 L level in blood specimen taken at the end of HD, though this was not statistically significant. Our study supported the presence of platelet activation independent of the HD procedure and that the procedure had an enhancing effect on that activation (Ulusoy et al., 2012). Signal peptide-CUB (signal peptide–CUB (complement C1r/C1s, Uegf, and Bmp1)-EGF(epidermal growth factor)- domain-containing protein 1 (SCUBE1) is a cell surface protein belonging to the SCUBE gene family. SCUBE1 has been shown to rise in parallel to platelet activation in acute ischemic events (Tu et al., 2006). However, the number of studies on this novel molecule is rather limited. The first of these limited studies in the HD patient group was performed in our clinic. We determined that a high SCUBE 1 level in HD patients, in a manner correlated with sCD40L, regarded as a platelet activation marker in HD patients. SCUBE 1 levels were significantly high in predialysis blood specimens and exhibited a significant rise in post-dialysis specimens. Gender, blood pressure, BUN, creatinine, hematocrit and high-sensitivity C-reactive protein (hsCRP) levels, hemodialysis membrane surface area, amount of ultrafiltration, blood flow rate, dialysis flow rate and carnitine use also significantly affected elevated SCUBE 1 in our study (Ulusoy et al., 2012). In conclusion, there are several studies showing platelet activation in HD patients, and it is a fact that the HD process affects this activation. Studies on the subject are continuing today. In addition to the effect of the HD procedure on platelet activation, there are also evaluating the effect on adhesion. Platelet adhesion during the HD procedure can be analyzed using the level of lactate dehydrogenase (LDH) released from the platelets (Daugirdas & Bernardo., 2012). Researchers have particularly evaluated membrane-specific platelet adhesion using this technique. One such study analyzed platelet adhesion in different membrane types by investigating LDH levels, and reported the lowest adhesion in a polysulfone membrane (Asai) (Hayama et al., 2004). In conclusion, HD therapy leads to an increase in platelet adhesion and degranulation. There is also an increase in platelet-platelet and platelet-leukocyte interaction during HD. For these reasons, as with uremic bleeding diathesis, platelets primarily involved in the hemostatic phase in the hypercoagulable process are held responsible for function defects.

4.2. Coagulation cascade activation and a decrease in fibrinolysis

A number of coagulation abnormalities associated with the HD procedure and uremia appear in HD patients. The effect of the HD procedure on coagulation cascade is by two routes. The first is blood passing through blood tubing sets and dialyzers coming into contact with the foreign surface during the procedure. The second is the anticoagulation used

during the procedure. As already discussed, a rise in platelet activation and adhesion comes about during the passage of blood through blood tubing sets and contact with the dialyzer during the HD procedure (Sabovic et al., 2005). The HD procedure also leads to neutrophils adhering to the dialysis membrane and release of granular content. The most important molecule in granular content is TF, one of the natural initiators of the coagulation cascade (Fischer, 2007). Endothelial damage may occur in chronic kidney patients due to uremia, elevated homocysteine, oxidative stress, inflammation and a number of traditional risk factors (HT, DM, hyperlipidemia, cigarettes, etc.). Endothelial damage or dysfunction may cause coagulation activation by leading to a rise in TF in particular, vWF and thrombomodulin (Gris et al., 1994; Gordge & Neild, 1991; Hergesell et al., 1993; Ishii et al., 1991) There are also studies showing a rise in plasmin and thrombin formation in uremic patients (Mezzano et al., 1996; Mezzano et al., 2001). The presence of endothelial damage in uremic patients has been evaluated using various markers. These include intracellular adhesion molecule-1 (ICAM-1), thrombin–antithrombin complex (TAT), prothrombin fragment 1+2 (F1+2), plasmin–antiplasmin complex (PAP), fibrin degradation products (FDP), vWF and soluble thrombomodulin (Rios et al., 2010). A great many studies have shown a rise in these markers of endothelial dysfunction and coagulation cascade and alterations in the fibrinolytic system in uremic patients (Rabelink et al., 1994). One such study was performed by Kushiya et al., who demonstrated increased plasma levels of fibrinogen, plasmin-plasmin inhibitor complex (PIC), thrombomodulin (TM), and D-dimer pre-HD and decreased plasma levels of protein C (PC), antithrombin (AT), TAT and tissue plasminogen activator (tPA)-plasminogen activator inhibitor-I (PAI-I) complex (tPA-PAI-1 complex) (Kushiya et al., 2003). Vaziri et al. determined a decline in coagulation activities even though Factor XII, IX, X and II levels were normal or elevated. Additionally, they determined a significant increase in hyperfibrinogenemia and D-dimer, VWF, factor VII, and factor XIII antibody levels and a pronounced decrease in antithrombin III, free protein S, plasminogen and tissue-type plasminogen activator concentration in end-stage kidney failure patients (Vaziri et al., 1994). Sagripanti et al. determined TAT, fibrinopeptide A (FPA), D dimer, vWF, tumor necrosis factor alpha (TNF), beta-thromboglobulin (beta TG) and serotonin (5HT) levels in predialysis and HD patients compared to the controls. Erdem et al. determined high F1+2, TAT, t-PA, urokinase-plasminogen activator (u-PA), PAP, plasminogen and α2-antiplasmin and α2-macroglobulin levels in HD patients (Erdem et al., 1996). Studies have analyzed the clinical reflections of this coagulation cascade activation and decrease in fibrinolysis. One such determined high levels of fibrinogen, CRP, factor VIII, antiphospholipid antibody and anti-factor 4 platelet-heparin levels in patients with recurrent vascular access thrombosis (O'Shea et al., 2003). Knoll et al. showed that presence of FV Leiden and increased FVIII, Lp(a) and homocysteine levels were associated with vascular access thrombosis (Knoll et al., 2005). In conclusion, in addition to bleeding diathesis in HD patients, a decrease in fibrinolysis and Hypercoagulation, a diametrically opposed condition, is a fact that must not be ignored and continue to give rise to significant morbidity and mortality.

4.3. Treatment

As we have already discussed, in chronic kidney patients the HD procedure itself creates a tendency to thrombus formation due to formed elements in blood making contact with a foreign surface (blood tubing sets and dialyzers). Anticoagulant is used during HD in order to prevent clot formation and ensure the procedure can be completed. Anticoagulant has been used in HD for many years. Selection and dose adjustment of anticoagulant must be based on the patient's clinical condition. Classic unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the most commonly preferred anticoagulant techniques. Direct thrombin inhibitor (danaparoid) can be used in some selected cases, but the cost is very high (Fischer et al., 2007). UFH and LMWH provide effective anticoagulation in patients with no contraindication in the HD procedure.

Thrombotic complication of vascular access is a frequently encountered condition in the HD patient group. Thrombotic complication is more common in patients using graft as vascular access route in particular. Studies low dose aspirin, sulfinpyrazone and ticlopidine in the prevention of vascular access thrombosis have produced good results (Fiskerstrand et al., 1985; Harter et al., 1979; Kaegi et al., 1975) But these drugs are not frequently used, both because of a lack of sufficient studies and out of a concern they may increase bleeding diathesis in this patient group with a tendency to bleeding. Another important thrombotic complication and main cause of mortality is cardiovascular thrombotic complications (myocardial infarction, cerebrovascular event). Preventive measures against these possibly fatal thrombotic complications in the HD patient group resemble those in the normal population. However, we think that the most important means of preventing various risk factors that facilitate the development of cardiovascular events particular to the HD patient group (hyperhomocysteinemia, inflammation, uremic toxins, Ca-P metabolism disorder) is with adequate dialysis. The provision of effective HD and that this effectiveness is being maintained should be checked at regular intervals.

In addition, as well as the contribution of uremia in HD patients, bleeding diathesis and thrombotic complications are associated with the HD procedure itself. Reduction of these complications with advances in HD technology (biocompatible membranes, new anticoagulant methods, etc.) will contribute to a decrease in mortality and morbidity in HD patients. As with complications of all kinds in HD patients, adequate dialysis plays a key role in this area.

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Chapter 5

Pathogenesis and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder

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Additional information is available at the end of the chapter

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1. Introduction

The prevalence of chronic kidney disease (CKD) is increasing, and CKD patients are at risk for severe adverse outcomes such as progressive loss of kidney function, cardiovascular (CV) disease, and premature death [1]. CKD-Mineral and Bone Disorder (CKD-MBD) is the clinical syndrome that develops as a systemic disorder of bone and mineral metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism [1]. Alterations in calcium and phosphate metabolism that are frequently observed in secondary hyperparathyroidism of uremia (SHPT), particularly in patients with maintenance hemodialysis, contribute to ectopic calcification, CV disease, and the risk of death [2].

SHPT is associated with various bone diseases including osteitis fibrosa caused by excessive secretion of parathyroid hormone (PTH), osteomalacia, adynamic bone disease, and combinations thereof; these diseases are collectively called renal osteodystrophy (ROD). In addition, ectopic calcifications such as soft-tissue and vascular calcifications are observed in patients with long-standing CKD. These patients are characterized by calcification of the vascular media, which is called Mönckeberg medial calcific sclerosis, and vascular intima, which is typically triggered by abnormal calcium and phosphorous metabolism due to SHPT [3]. Calcification of the vascular media is a particularly important factor for predicting CV mortality in dialysis patients. Elevation of the serum calcium × phosphate product also increases the relative mortality risk. The abovementioned facts suggest that the pathology of CKD-MBD should be fully elucidated to prepare an appropriate treatment plan.

2. Calcium and phosphate homeostasis

Small changes in extracellular fluid calcium concentration have major effects on muscle contraction and neuronal excitability, as well as numerous cellular functions such as cell division, cell adhesion, plasma membrane integrity, and coagulation. However, the changes in serum phosphate concentration are asymptomatic in normally functioning kidneys. Severe chronic depletion may cause anorexia, muscle weakness, and osteomalacia. Hyperphosphatemia is also asymptomatic, although symptoms of hypocalcemia, including tetany, can occur when concomitant hypocalcemia is present.

Parathyroid hormone (PTH), the active form of vitamin D (1,25-dihydroxyvitamin D; 1,25-$(OH)_2D$), and fibroblast growth factor (FGF)-23, are the principal physiologic regulators of calcium and phosphate homeostasis in humans [4,5] (Figure 1). Feedback loops exist between ionized calcium (Ca^{2+}), phosphate, 1,25-$(OH)_2D$, FGF-23, and PTH.

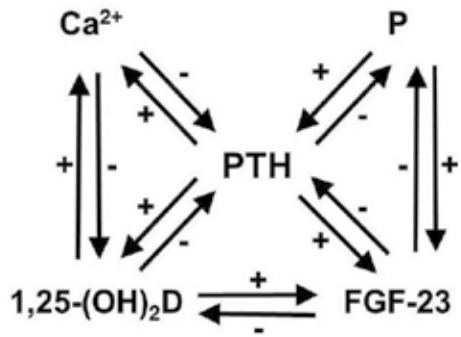

Figure 1. Feedback loops in calcium ion (Ca^{2+}) and phosphate (P) homeostasis [4,5], modified from a previous report [8]. Feedback loops exist between Ca^{2+}, P, 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$), fibroblast growth factor 23 (FGF-23), and parathyroid hormone (PTH). Ca^{2+}, 1,25-$(OH)_2D$, and FGF-23 suppress PTH secretion, whereas P overload accelerates it. P overload does not always cause the elevation of serum phosphate, with the exception of some conditions such as chronic kidney disease.

2.1. Parathyroid Hormone (PTH)

The extracellular fluid Ca^{2+} concentration is the primary regulator of the rapid (in minutes) synthesis and secretion of PTH. An inverse relationship was observed between the extracellular fluid Ca^{2+} concentration and PTH secretion from parathyroid cells *in vitro* [6] (Figure 2). Hypersecretion of PTH causes hypophosphatemia due to hyperphosphaturia in normally functioning kidneys; however, it leads to hyperphosphatemia by mobilization of phosphate from skeletal tissues in CKD, particularly in hemodialysis patients.

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2.2. 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D)

In contrast to the rapid action of PTH, 1,25-$(OH)_2$D contributes to long-term calcium homeostasis. 1,25-$(OH)_2$D also elevates serum phosphate concentration by promoting incremental intestinal phosphate absorption.

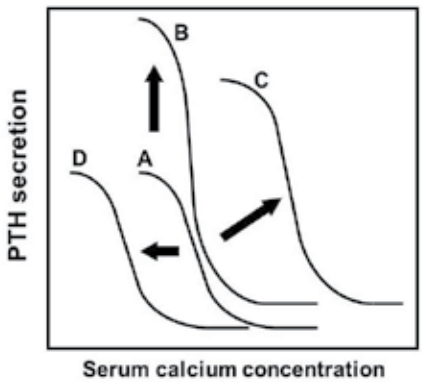

Figure 2. Pathogenesis of secondary hyperparathyroidism of uremia (SHPT) [56], modified from a previous report [26]. The analyses of PTH secretions inhibited by extracellular calcium in vitro revealed the sigmoidal relationship of the PTH –calcium relationship. Setpoint, the calcium concentration causing half-maximal inhibition of PTH secretion, is an indicator of sensitivity of parathyroid cells to extracellular calcium by CaR. (A) The relationship in healthy subjects was fitted to a symmetrical sigmoidal curve. (B) The normal sigmoidal curve will shift upward when the secretory cell number is increased, without changing its setpoint. (C) An altered sigmoidal curve is observed in human parathyroid adenomas, refractory SHPT, by changing the setpoint to the right. In the case of severe setpoint shift, PTH secretion is persistent even at high calcium concentration: so-called 'autonomous' PTH secretion. An altered PTH–calcium relationship was also observed in PTH-cyclin D1 transgenic mice [4, 52]. (D) Administration of cinacalcet or activating mutation of CaR observed in autosomal dominant hypocalcemia increases the CaR sensitivity to serum calcium. Activations of CaR result in the PTH–calcium relationship curve moving to the left.

2.3. Fibroblast Growth Factor 23 (FGF-23)

FGF-23, a member of the FGF family, is a major phosphaturic factor in the development of hypophosphatemic rickets/osteomalacia, including X-linked hypophosphatemic rickets (XLH) and oncogenic osteomalacia [7]. FGF-23 suppresses both PTH secretion and its expression in parathyroid cells [8]. PTH also stimulated FGF-23 expression and its secretion in bone [9], suggesting that a negative feedback loop exists between PTH and FGF-23 [4,5] (Figure 1).

3. Receptors in parathyroid cells

The 3 parathyroid cell receptors that are important in calcium and phosphate homeostasis include the calcium-sensing receptor (CaR) and the FGF receptor (FGFR)-Klotho complex located on the cell surface and nuclear vitamin D receptor (VDR) (Table 1). CaR

and VDR are target molecules for the treatment of hyperfunctioning parathyroid diseases in CKD patients.

Receptor	Location
1. Vitamin D receptor; VDR	cell nucleus
2. Calcium-sensing receptor; CaR	cell membrane
3. FGFR-Klotho complex	cell membrane

Table 1. Receptors in parathyroid cells

3.1. Calcium-Sensing Receptor (CaR)

CaR contains a characteristic G protein-coupled receptor 7 membrane-spanning motif with an unusually large N-terminal extracellular domain, which was cloned in 1993 [10]. Positional cloning approaches have clarified that loss-of-function mutations in the *CaR* gene cause familial hypocalciuric hypercalcemia (heterozygous mutations) and neonatal severe hyperparathyroidism (homozygous mutations) [11].

Heterozygous *CaR* knockout mice exhibited a phenotype that was similar to that of familial hypocalciuric hypercalcemia [12]. Serum PTH levels were inappropriately elevated; however, the parathyroid glands were not enlarged in the heterozygous knockout mice. Homozygous knockout mice demonstrated markedly elevated serum calcium and PTH concentrations, retarded growth, and premature death [12]. These symptoms are similar to those of human neonatal severe hyperparathyroidism.

Synthetic allosteric modulators of CaR have been developed that act as either positive modulators (calcimimetics) or negative modulators (calcilytics). These ligands do not activate the wild-type receptor directly, but rather shift the PTH-calcium sigmoidal curves to the left or right, respectively (Figure 2).

3.2. Vitamin D Receptor (VDR)

1,25-$(OH)_2$D is the major steroid hormone that plays a crucial role in calcium and phosphate homeostasis, and its actions are mediated by VDR. Hereditary hypocalcemic vitamin D-resistant rickets (HVDDR) is an autosomal recessive disorder that is caused by inactivating mutations in the *VDR* gene, resulting in target tissue insensitivity to 1,25-$(OH)_2$D [13].

VDR knockout mice exhibit hypocalcemia, hypophosphatemia, rickets, alopecia, and hyperparathyroidism with enlarged parathyroid glands, similar to HVDDR [14,15]. Tissue-specific ablation of *VDR* in parathyroid tissue results in decreased parathyroid CaR expression and moderately increased basal PTH levels; however, no significant abnormalities in PTH-calcium sigmoidal curves were observed [16], suggesting limited roles of *VDR* in parathyroid pathophysiology.

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3.3. FGF Receptor (FGFR)-Klotho complex

Klotho, which is expressed in kidney and pituitary and parathyroid glands, converts FGFR1, a canonical receptor for various FGFs, into an FGF-23-specific receptor [17]. *FGF-23* null mice exhibit various senescence-like phenotypes such as a short lifespan, infertility, atrophy of the lymphopoietic and reproductive organs, decreased bone mineral density, and ectopic calcification. This phenotype is similar to that of Klotho-deficient mice [18], suggesting that FGF-23 signaling is Klotho dependent.

4. Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD)

It is widely known that the progression of CKD increases mortality risk and the incidence of CV events [19]. Hyperphosphatemia is a critical electrolyte abnormality in patients with CKD-mineral and bone disorder (CKD-MBD) [20]. Even though hemodialysis or peritoneal dialysis is given to hyperphosphatemia patients with advanced CKD, these therapies are ineffective due to insufficient phosphorus-removal ability.

4.1. Calcium and phosphate metabolism in CKD-MBD

FGF-23 is involved in abnormal calcium and phosphate metabolism in CKD patients as the disease progresses. A cross-sectional study of 80 CKD patients revealed decreases in estimated GFR (eGFR), serum calcium, and 1,25-$(OH)_2$D levels as well as increases in serum P, fractional excretion of phosphate, PTH, and FGF-23 [21].

Further study of the abovementioned data revealed an increase in serum FGF-23 level (eGFR 45~60 mL/min), which is an independent predictor of the fractional excretion of phosphate, far earlier than the increase in serum phosphate levels (eGFR <30 mL/min). The increase in FGF-23 level is one of the greatest independent predictors of decreased 1,25-$(OH)_2$D level, independent of serum phosphate and eGFR. This suggests that the increase in FGF-23 level is the main reason for the decrease in 1,25-$(OH)_2$D level in CKD progression. Thus, the increase in FGF-23 level compensates for the increase in the serum phosphate levels caused by the decrease in nephrons associated with CKD progression by increasing the fractional excretion of phosphate. However, the increase in FGF-23 level also decreases the level of 1,25-$(OH)_2$D, which promotes PTH secretion and accelerates the progression of SHPT.

4.2. Vascular calcification in CKD-MBD

In an experiment using human vascular smooth muscle cells, inorganic phosphate transport into the cells via type III Na-Pi co-transporter (Pit-1) increased as the extracellular phosphate concentration increased. The increase in the intracellular phosphate concentration induced the expression of marker genes of apoptosis and osteogenic/chondrogenic cells in the vascular wall cells, which resulted in calcification [22]. This finding also implies a relationship between blood vessel calcification and phosphate levels *in vitro*.

Maintenance hemodialysis patients often develop blood vessel calcification, which is directly proportional to the duration of dialysis, irrespective of their age; this condition is characterized by calcification of the vascular media called Mönckeberg sclerosis rather than calcification of the vascular intima. The onset of blood vessel calcification in dialysis patients is mainly caused by abnormal calcium and phosphate metabolism due to SHPT [3], which is one of the signs of CKD-MBD. Calcification of the iliac artery [23] and abdominal aorta [24] are critical predictors of CV mortality in dialysis patients.

4.3. Renal Osteodystrophy (ROD)

ROD is a mineral and bone disorder that occurs as a complication of CKD, which exacerbates bone fragility and fracture [1]. The serum phosphorus concentration was significantly related to hospitalization for fracture [2]. Old age, dialysis vintage, female gender, white race, and lower body weight were significantly associated with an increased risk of fracture-related hospitalization.

In CKD patients, ROD manifests as alterations in bone morphology, such as osteitis fibrosa cystica, mild hyperparathyroid-related bone disease, osteomalacia, adynamic bone disease, and mixed uremic osteodystrophy. ROD represents histopathologic changes observed in bone and is typically characterized by changes in bone turnover, volume, and mineralization (TMV) (Table 2). The TMV classification, assessed by histomorphometry, provides a clinically relevant description of the underlying bone pathology and helps define the pathophysiology of the disease.

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Abnormal	Normal
High		High

TMV: bone turnover, mineralization, and volume

Table 2. TMV classification for renal osteodystrophy (ROD) [1]

5. Pathogenesis of Secondary Hyperparathyroidism of uremia (SHPT)

PTH secretion increases when the glomerular filtration rate (GFR) of CKD patients decreases to 40–50 mL/min or less [25]. Renal impairment decreases urinary phosphate excretion, gradually leading to hyperphosphatemia. Phosphate accumulation in the body reduces 1α hydroxylase activity in the kidneys and suppresses vitamin D activation, which results in decreased serum active vitamin D (1,25-$(OH)_2$D) levels [26] (Figure 3). Hyperphosphatemia causes hypocalcemia by directly affecting the parathyroid glands; moreover, impaired vitamin D activation promotes PTH synthesis and secretion [27], which induces the proliferation

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of parathyroid cells and parathyroid hyperplasia. This change stimulates excessive PTH activity and allows phosphates of the bone to move into the blood, exacerbating the hyperphosphatemia. Even though hemodialysis or peritoneal dialysis is given to hyperphosphatemia patients with advanced CKD, these therapies are ineffective due to the patients' insufficient phosphate-removal ability.

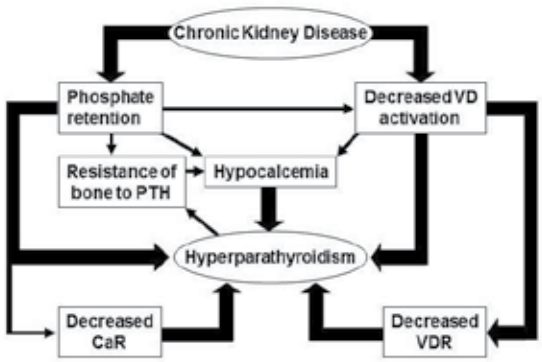

Figure 3. Pathogenesis of parathyroid tumorigenesis [4]. (A) A set of somatic mutations (hits) confers a growth advantage to an affected cell. Monoclonal growth renders the cells susceptible to more somatic mutations (hits), which leads to clonal evolution. (B) A uremic status such as chronic hypocalcemia, decreased levels of serum 1,25-$(OH)_2D$, and hyperphosphatemia stimulates parathyroid cell growth and leads to multi-glandular polyclonal hyperplasia. These hyperplastic parathyroid cells are susceptible to somatic mutations (hits), resulting in monoclonal growth.

In the earliest stages of CKD, the parathyroid glands undergo multi-glandular generalized hyperplasia, presumably a true polyclonal expansion, in response to stimuli that may include chronic hypocalcemia, decreased levels of serum 1,25-$(OH)_2D$, and hyperphosphatemia. However, in the late stage of this disease, usually after many years of dialysis treatment, a subset of patients develop refractory SHPT in which excessive PTH secretion no longer responds to physiological influences or standard medical therapy. Therefore, medically refractory SHPT is quite different from the readily managed SHPT, which is characterized by an abnormal PTH-calcium secretory relationship [28,29], is "autonomous," and is typically treated by surgical parathyroidectomy. *VDR* [30] and CaR [31] expression was reduced in the parathyroid tumors of these patients.

The majority of surgically removed uremic parathyroid glands were confirmed to be monoclonal neoplasms by X-chromosome inactivation analysis [32]. This monoclonality implies that somatic mutation of certain genes controlling cell proliferation occurred in a single parathyroid cell, conferring a selective growth advantage upon it and its progeny (Figure 4). Distinct chromosomal abnormalities in sporadic parathyroid adenomas [33] and uremia-associated parathyroid tumors [34] revealed that the molecular pathogenesis of tumorigenesis in these 2 categories of parathyroid tumors was different. However, the major genes involved in the pathogenesis of SHPT remain unknown.

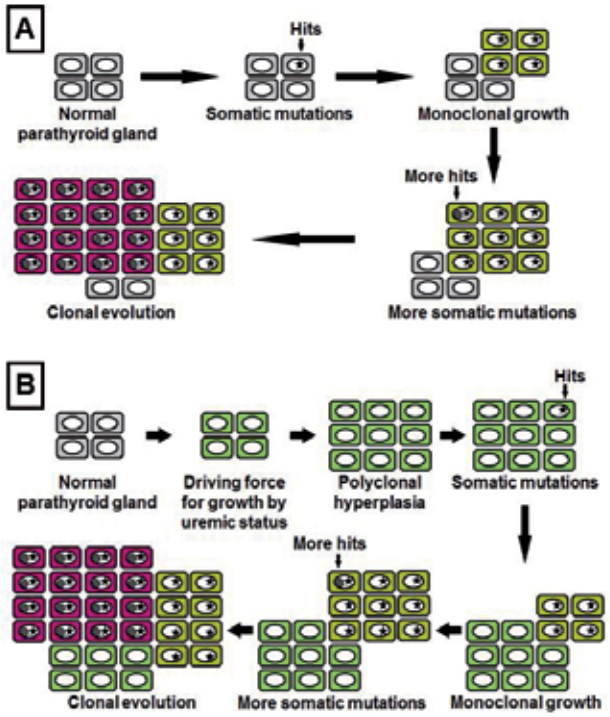

Figure 4. The sigmoidal curve of the PTH-calcium relationship [56]. The analyses of PTH secretions inhibited by extracellular calcium *in vitro* revealed a sigmoidal PTH-calcium relationship [6]. The setpoint, the calcium concentration causing half-maximal inhibition of PTH secretion, is an indicator of sensitivity of parathyroid cells to extracellular calcium by the calcium receptor (CaR). (A) This relationship in healthy subjects was fitted to a symmetrical sigmoidal curve. (B) The normal sigmoidal curve will shift upward when secretory cell number is increased without changing its setpoint. (C) An altered sigmoidal curve is observed in human parathyroid adenomas, refractory secondary hyperparathyroidism of uremia, with the setpoint shifting to the right. In the case of severe setpoint shift, PTH secretion is persistent even at high calcium concentrations, due to so-called "autonomous" PTH secretion. An altered PTH-calcium relationship was also observed in PHPT model mice [4,52]. (D) Administration of calcimimetics or the presence of an activating mutation of CaR in autosomal dominant hypocalcemia (ADH) patients [57] increased the sensitivity of CaR to serum calcium concentration in parathyroid cells. Activations of CaR result in a shift of the PTH-calcium relationship curve to the left.

Reduced expression of Klotho and FGFR1 was noted in the hyperplastic parathyroid glands of SHPT patients [35], suggesting that reduced FGF-23 signaling in parathyroid cells plays a role in the development of SHPT. However, some studies of Klotho expression in uremic animals reported conflicting results [36-38]. Further studies are necessary to clarify the role of FGFR-Klotho signaling in uremic parathyroid glands.

6. Guidelines for CKD-MBD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI, USA) published the "K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease" in 2003 as evidence-based clinical practice guidelines [39]. In

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2005, according to "Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO)," the term CKD-MBD was proposed, stating that the importance of bone and mineral metabolism in CKD should be conceptualized in terms of prognosis [20]; this means that bone and mineral metabolism in CKD can be considered a systemic disease. In 2009, KDIGO proposed the current clinical practice guidelines [40], which have been adopted in clinical settings.

7. Treatment of CKD-MBD

The risk of all-cause mortality and CV events in patients with CKD-MBD on maintenance hemodialysis is well established. A greater mortality risk associated with phosphate, followed by calcium and PTH levels, was reported [41]. These 3 parameters are not only the best surrogate markers but also the best targets for CKD-MBD treatment.

7.1. Phosphate-binding agents

All-cause mortality increased regardless of whether serum phosphate levels were higher or lower than the reference value, exhibiting a U-shaped distribution [42]. However, maintenance dialysis patients in stable condition are likely to develop hyperphosphatemia, indicating that hyperphosphatemia treatment should be a primary target. Diet therapy is the first-line therapy that can sufficiently control serum phosphate levels. If it is insufficient, phosphate binders are administered orally. Calcium-containing phosphate binder (e.g., calcium carbonate) have been used for a long time. However, concomitant use of active vitamin D products can lead to the development of hypercalcemia and increase serum calcium × phosphate product levels. Therefore, non-calcium-containing phosphate binder such as sevelamer hydrochloride and lanthanum carbonate are widely used.

Although hyperphosphatemia is a risk factor for mortality in dialysis patients, the effects of restricting phosphorus intake in these patients are unclear. When oral phosphorus intake is controlled, serum phosphate levels decrease, but poor nutritional status occurs as well. Thus, it is difficult to judge the true effect of the restriction of phosphorus intake, although studies using phosphate binders have been performed.

The Accelerated Mortality on Renal Replacement (ArMORR) study is a 1-year observational cohort study of 10,044 hemodialysis patients in 1,056 medical institutions in the US. According to this study, the 1-year survival rate of 3,555 patients prescribed phosphate binders before or within 90 days of initiating dialysis was higher than that of 5,055 patients who were not treated with these agents during the same period [43]. That study also compared survival in a subcohort of patients treated and not treated with phosphate binders matched by their baseline serum phosphate levels (i.e., a propensity score matched cohort study) and concluded that the survival rate was greater in the treated group, demonstrating the positive effect of these agents on the survival rate (Figure 5).

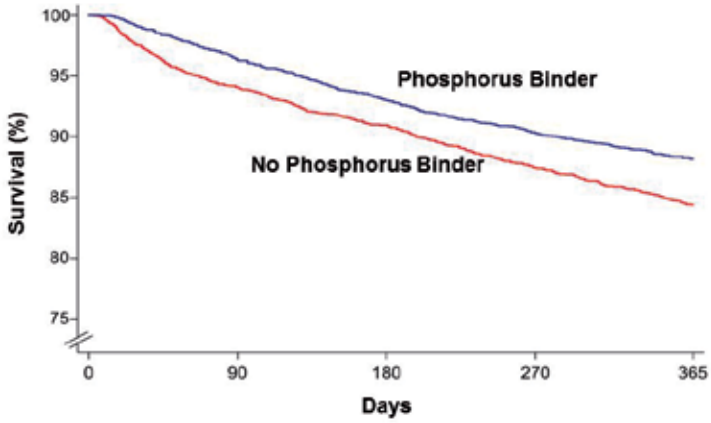

Figure 5. Survival of treated and untreated patients of the overall propensity score-matched cohort in the Accelerated Mortality on Renal Replacement (ArMORR) study [43]. A 1-year observational cohort study involving 10,044 dialysis patients in 1,056 medical institutions in the US studied the relationship between the effect of phosphate binders before and within 90 days of initiating dialysis and 1-year survival rate. The survival rate was greater in the group treated with phosphate binders. The subcohort study of patients treated and untreated with phosphate binders, matched by their baseline serum phosphate levels (i.e., the propensity score matched cohort), also demonstrated that the treated group had a better survival rate, demonstrating the positive effect of these agents on survival.

Many studies on maintenance dialysis patients have been performed. What about studies on patients who have just started dialysis? The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study is a prospective cohort study of patients who just started hemodialysis or peritoneal dialysis [44]. That study included 1,007 subjects, 98% of whom were enrolled in the study within 4 months. The study was started at a median of 45 days after the patients started dialysis. The results obtained 2.5 years later indicated that higher serum phosphate levels were an independent predictor of all-cause mortality. In addition, the relative risk of all-cause mortality was also high in subjects whose serum phosphate levels were high at the start of dialysis but decreased 6 months later. The abovementioned results suggest that the serum phosphate level at the start of dialysis is an important prognostic factor.

7.2. Vitamin D Receptor Activators (VDRAs)

Active vitamin D products inhibit PTH gene transcription and secretion as well as parathyroid cell proliferation in the parathyroid glands. Daily oral administration of 1α-(OH)D_3 (alfacalcidol), 1,25-$(OH)_2D_3$ (calcitriol), and/or 26,27-hexafluoro-1,25-$(OH)_2D_3$ (falecalcitriol) is performed to prevent the progression of SHPT. However, the effect of this treatment is insufficient, because the expression of vitamin D receptor (VDR) decreases in uremia-associated parathyroid tumor.

A rapid increase in serum 1,25-$(OH)_2$D levels due to intravenous administration of calcitriol can partly inhibit the synthesis and secretion of PTH in parathyroid cells, which express less VDR. Furthermore, 1,25-dihydroxy-22-oxavitamin D_3 (maxacalcitol, OCT), an analog in

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which the carbon of calcitriol at position 22 is replaced with an oxygen atom, is characterized by a weaker intestinal calcium absorption capacity than that with the inhibition of PTH secretion. Therefore, it is unlikely to cause hypercalcemia.

Among the subjects in the ArMORR study who were not treated with active vitamin D analogs, 25OHD level, which exhibits individual nutritional vitamin D status, was elevated, while both all-cause mortality and CV mortality decreased (Figure 6). Furthermore, all-cause mortality and CV mortality decreased significantly in the subjects administered VDRA, regardless of 25OHD level, indicating that the prognosis of VDRA improved in the maintenance dialysis patients [45].

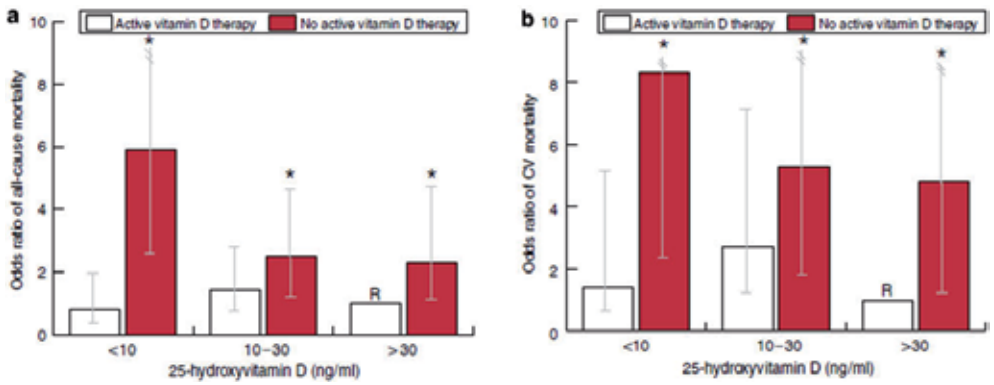

Figure 6. Multivariate-adjusted ORs of 90-day all-cause and cardiovascular (CV) mortality in the ArMORR study [45]. The ArMORR study involved 825 maintenance dialysis patients who were not treated with active vitamin D before or within 90 days of initiating dialysis to evaluate the effect of active vitamin D products on prognosis. 25OHD, which indicates the individual nutritional vitamin D status, was high in the subjects who were not treated with active vitamin D, while all-cause mortality and CV mortality decreased. Furthermore, all-cause mortality and CV mortality decreased significantly in the subjects administered with VDRA regardless of 25OHD levels.

7.3. Calcimimetics

Information on extracellular Ca^{2+} levels is transferred to parathyroid cells via CaR in the parathyroid glands, which control PTH secretion. Multivalent cations including Ca^{2+}, Mg^{2+}, and Gd^{3+} act on CaR as agonists. However, calcimimetics do not act as agonists but allosterically increase the sensitivity of CaR to multivalent cations [46].

Calcimimetic cinacalcet suppressed PTH secretion in cultured human pathological parathyroid cells obtained from primary hyperparathyroidism (PHPT) and SHPT patients, which exhibit reduced expression of CaR, the target molecule of cinacalcet [47]. These data support the clinical application of cinacalcet for PHPT and SHPT treatment.

Calcimimetic cinacalcet suppressed not only PTH secretion but also parathyroid cell proliferation, which prevented parathyroid hyperplasia *in vivo* in 5/6-nephrectomized rats, the animal model of SHPT [48]. Calcimimetic tecalcet also reversed the development of osteitis fibrosa in the SHPT rats [49]. In a relative hypocalcemic to normocalcemic environment, cal-

cimimetics effectively suppress PTH secretion and parathyroid cell proliferation. Interestingly, cinacalcet suppressed aortic calcification in SHPT rats by decreasing serum PTH, calcium, and phosphate concentrations [50], suggesting that cinacalcet may be beneficial for the prevention of ectopic calcification as well as the improvement of morbidity and mortality in patients with CKD.

Cinacalcet also suppressed PTH secretion in *PTH-cyclin D1* transgenic mice [51]. *PTH-cyclin D1* transgenic mice are an animal model of PHPT that overexpress the *cyclin D1* oncogene in the parathyroid glands, which was accomplished by using a transgene that mimics the human *PTH-cyclin D1* gene rearrangement [52]. Tissue-specific overexpression of the *cyclin D1* oncogene not only resulted in abnormal parathyroid cell proliferation but, notably, also led to the development of biochemical hyperparathyroidism with characteristic bone abnormalities.

Hypercalcemia may stimulate considerable CaR activity, as the expression of CaR was suppressed in the parathyroid glands of these mice [52]. These conditions are compatible with the status observed in refractory SHPT patients undergoing maintenance hemodialysis. Although older transgenic mice exhibited advanced hyperparathyroidism caused by severely decreased CaR expression, cinacalcet suppressed both serum calcium and PTH concentrations [51] and parathyroid growth [53]. CaR is a potentially useful target for a therapeutic agent such as cinacalcet to suppress PTH secretion, despite the reduction in CaR expression observed in the parathyroid glands of patients with advanced PHPT and SHPT.

A meta-analysis of 8 randomized, double-blind, placebo-controlled trials (total number of subjects, 1,429) revealed that calcimimetics significantly decrease serum PTH, serum calcium, and serum phosphate levels, in turn significantly decreasing the serum calcium × phosphate product [54] (Figure 7). The improvements in the abovementioned serum parameters due to calcimimetics were clarified in the analysis. However, no improvement in all-cause mortality or decreased parathyroidectomy was observed, and the incidence of bone fracture was not studied.

An observational study was performed using the United States Renal Data System to determine all-cause and CV mortality. Time-dependent Cox proportional hazards modeling found that all-cause and CV mortality rates were significantly reduced in cinacalcet-treated patients relative to those that did not receive cinacalcet treatment. Although this study revealed a significant survival benefit associated with cinacalcet, randomized clinical trials are needed to confirm a survival advantage associated with calcimimetics [55].

7.4. Percutaneous Ethanol Injection Therapy (PEIT)

Percutaneous ethanol injection therapy (PEIT) is performed by directly injecting ethanol into a parathyroid tumor under ultrasound guidance to necrotize parathyroid tumor cells. Its merits include minimal invasiveness and multiple sessions. However, the technique sometimes induces recurrent laryngeal nerve paralysis, making it inapplicable in the presence of recurrent laryngeal nerve paralysis in the contralateral parathyroid gland.

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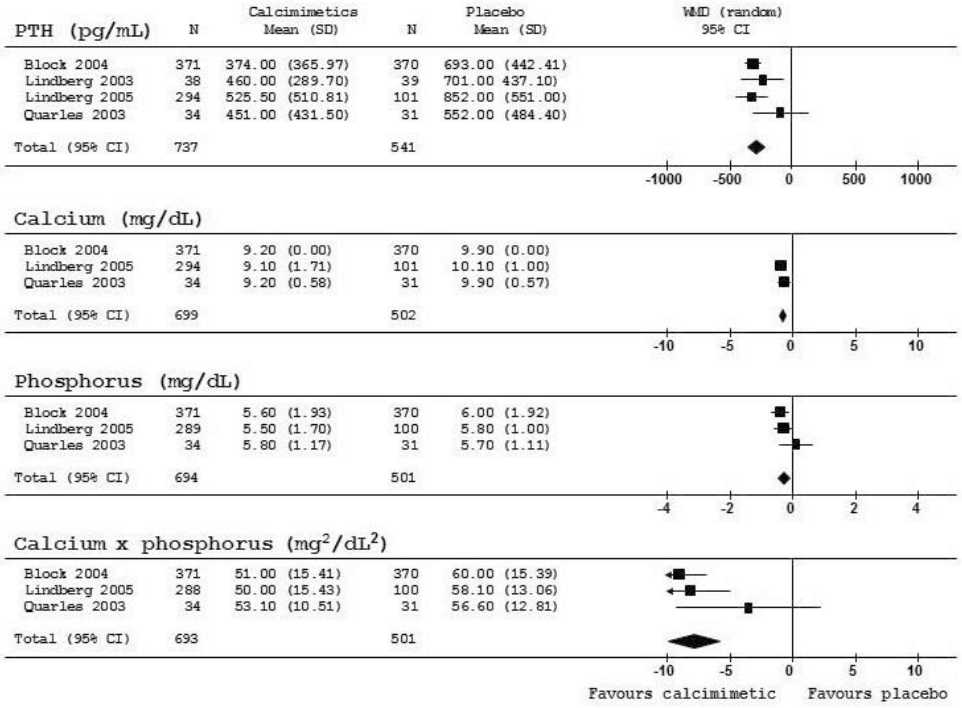

Figure 7. Positive effect of cinacalcet on serum parameters in the meta-analysis of 8 randomized, double-blind, placebo-controlled trials (total number of subjects, 1,429) [54] Cinacalcet significantly decreased serum PTH, calcium, and phosphate levels, thereby significantly decreasing the serum calcium × phosphate product; WMD: weighted mean difference, SD: standard deviation, CI: confidence interval

7.5. Parathyroidectomy (PTX)

PTX is recommended for the treatment of SHPT that is resistant to medical management. Isolation of the parathyroid glands always decreases serum PTH levels. However, there are often 5 or more parathyroid glands, and mediastinal or intrathyroid ectopic parathyroid tumors sometimes develop. Therefore, pre- and intraoperative detection of parathyroid glands is essential. The techniques for detecting them include subtotal extirpation, total extirpation, and total expiration followed by autotransplantation.

8. Conclusion

Clinical evidence regarding CKD-MBD is reported in the literature, and guidelines have been developed accordingly. Well-controlled serum phosphate, calcium and PTH levels improve the prognosis of dialysis patients. Many pharmaceuticals aiming to achieve this goal have been developed and launched. As the pathology of CKD-MBD is elucidated, the prognosis of dialysis patients and their quality of life will improve.

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Chapter 6

Lipid Abnormalities in Hemodialysis Patients

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Additional information is available at the end of the chapter

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1. Introduction

Approximately 50% of hemodialysis (HD) patients die from cardiovascular events. One of the main risk factors for cardiovascular events is hyperlipidemia. Progressive renal failure is associated with lipoprotein abnormalities and dyslipidemia. However, dyslipidemia may not appear as hyperlipidemia (a rise in plasma cholesterol and/or low-density lipoprotein (LDL)) in the majority of HD patients. Uremic dyslipidemia has an abnormal apolipoprotein profile and composition. It is characterized by reduced concentrations of apo A-containing lipoproteins in high-density lipoprotein (HDL) and increased concentrations of intact or partially metabolized triglyceride-rich apo B-containing lipoproteins in very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and LDL.

Common lipid abnormality in HD patients is hypertriglyceridemia. Other lipid abnormalities seen in HD patients are high serum lipoprotein levels and a decrease in HDL levels. Hypertriglyceridemia is caused by increased production of Apo B protein and a marked decrease in the metabolism of VLDL, primarily as a result of decreased endothelial cell debilitation of VLDL.

The lipoprotein abnormalities in HD patients are thought to be a significant factor in increased atherosclerosis. Serum total cholesterol, and particularly LDL-cholesterol, is known to be correlated with increased cardiovascular mortality in the general population. A similar correlation has also been reported in dialysis patients. However, it is today generally agreed that in the HD patient group, a low LDL cholesterol level is correlated with malnutrition and increased mortality.

Until recently, the treatment of hyperlipidemia in the HD patient group was based on adult hyperlipidemia guidelines, and it was generally thought that the approach to treatment and results in the general population would yield similar results in the HD patient group. However, in the same way that lipid abnormalities in the HD patient group differ from the gen-

eral population, there are also various differences in terms of medical treatment. Treatment of hypertriglyceridemia, the most frequently observed lipid abnormality in this patient group, is advised since at above 500 mg/dl it can give rise to complications such as pancreatitis. Lifestyle changes plus fibrate or nicotinic acid are recommended for treatment of hypertriglyceridemia. However, medical treatment must be provided on the basis of a profit and loss calculation, bearing in mind the side-effects (myositis and rhabdomyolysis). The calculation of non-HDL cholesterol, used to measure the level of remnant lipoproteins, is useful in situations where LDL cholesterol is normal and triglyceride levels high. Studies have been published suggesting that this can initially reduce the frequency of cardiovascular events associated with the use of statin in the treatment of a high LDL cholesterol level. However, the AURORA study, a large prospective, randomized study published in 2009, showed that although rosuvastatin lowered LDL cholesterol in the HD patient group it did not lead to a decrease in cardiovascular mortality. From this important study and other similar research, different approaches may be expected in both the adult hyperlipidemia guideline and in guidelines regarding the HD patient group from those in the general population.

1.1. Vascular calcification

Cardiovascular diseases are the principal cause of death in HD patients. Widespread vascular calcification especially in the coronary arteries is one of the main causes of cardiovascular disease (Braun et al., 1996; London et al., 2003, Sigrist et al., 2007). Vascular calcification can be observed in two regions of the arterial structure, the intima and the media (Shanahan et al., 1999). Arterial intimal calcification (AIC) is generally associated with atherosclerotic lesions, and with plaque formation and the development of occlusive lesions (Shanahan et al., 1999). AIC may also be observed in patients with normal renal function, and calcification of the atherosclerotic plaque increases the frequency of MI and thrombotic complications. Arterial medial calcification (AMC) is seen in muscular arteries and leads to a reduction in vascular wall elasticity more than to occlusive lesions (London et al., 2003). AMC is more associated with uremia. Both AIC and AMC may be observed in HD patients.

Although vascular calcification was determined in uremic patients many years ago, research into its etiopathology is still on-going. Factors held responsible in the etiopathology today include a rise in osteogenic proteins such as osteocalcin, osteonectin, alkaline phosphatase and collagen-I, low levels of calcification inhibitors such as matrix Gla-protein, osteopontin, fetuin, pyrophosphate and osteoprotegerin, genetic factors, use of high-dose vitamin D, high Ca-P levels, hyperparathyroidism, inflammation and hyperlipidemia (Fukagawa & Kazama, 2007; Rutsch et al., 2011; Shantouf et al., 2009; Slatopolsky et al., 1980; Tamashiro et al., 2001; Tukaj et al., 2000).

As previously discussed, while classic cardiovascular risk factors are more associated with development of AIC, uremia and associated factors are more involved in the development of AMC. London et al.'s study on the subject determined that high phosphorus and low albunim levels and excessive Ca consumption represented risk factors for AIC, in addition to classic risk factors such as advanced age, a history of atherosclerotic disease, cigarette use and a history of DM and high LDL and CRP levels. They also showed that in addition to

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these classic risk factors, parameters more associated with HD and prolonged HD were influential in the development of AMC. In addition, in contrast to AIC, AMC may also be observed at early ages (London et al., 2003)

While definitive diagnosis of vascular calcification is made with histopathological examination, since this is not possible in clinical practice, the K-DIGO guideline recommends x-ray imaging and echocardiographic examination in the diagnosis of vascular and valvular calcification (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. 2010). In conclusion, the term vascular calcification is used for two different entities in HD patients, AIC and AMC. The reason why the term vascular calcification is used to refer to both these clinical conditions is that both AIC and AMC can frequently be seen in the HD patient group and that differentiation cannot be performed with routine examinations. However, what must not be forgotten is that although they appear to be similar, there are various differences in the etiology, clinical reflections and approaches to treatment in these two clinical conditions. While improvement of atherosclerotic risk factors (hyperlipidemia, etc.) and sufficient dialysis may be beneficial in AIC, sufficient dialysis is of particular benefit in the treatment and prevention of AMC

2. The relation between dyslipidemia and cardiovascular events

Chronic kidney disease (CKD) is a significant health problem, the prevalence of which is increasing all over the world. The main cause of death in this patient population is cardiovascular disease (CVD)-related mortality (K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients, 2005; Silva et al., 2012). As with the normal population, CVD can also be treated in CKD patients, representing a potentially preventable disease group. In 1998, the National Kidney Foundation (NKF) reported that CKD patients are a high-risk group for CVD. That report stated that a high prevalence of CVD had been determined in CKD patients, leading to mortality 10-30 times greater in the dialysis patient group in particular compared to the normal population. (Levey et al., 1998; Sarnak et al., 2003). Kidney function disorder is therefore a traditional risk factor held responsible in the development of CVD.

CVD risk factors in chronic kidney patients are divided into traditional and non-traditional (Sarnak et al., 2003). Traditional and non-traditional risk factors are given in the table. The main traditional risk factors are advanced age, diabetes mellitus, kidney disease, hypertension, family history, cigarette use, male gender, obesity, left ventricular hypertrophy and a sedentary lifestyle (Anderson et al., 1991; Mallamaci et al., 2002). However, there are studies showing that of the traditional risk factors known to be correlated with mortality in the normal population, the relationship between the mortality and HT and Hyperlipidemia in HD patients do not linear (Sarnak &Levey, 2000). The correlation between mortality and HT and elevated total cholesterol in this patient group is U-shaped (Lowrie & Lew, 1990; Zager et al., 1998). For this and similar reasons, a large number of studies have shown that traditional risk factors are inadequate in determining CVD risk in CKD (Cheung et al., 2000; Longe-

necker et al., 2002; Sarnak et al., 2003). Other studies have therefore investigated whether other factors may influence the development of cardiovascular events in the CKD patient group, and non-traditional risk factors have been developed. Hyperhomocysteinemia is the main non-traditional risk factor thought to affect the development of CVD in CKD. Several clinical studies have shown elevated homocysteine levels in the HD patient group and that hyperhomocysteinemia increases cardiovascular mortality (Bostom et al., 1997; Mallamaci et al., 2002; Manns et al., 1999; Sirrs et al., 1999). It is generally accepted today that oxidative stress and a progressive atherosclerotic process are correlated with development of cardiovascular events. Studies have also shown that this correlation also applies in the HD patient group. Oxidative stress may therefore be regarded as a non-traditional risk factor in the HD patient group (Boaz et al., 1999; Boaz et al., 1999). Inflammation (a rise in CRP) has been shown to be correlated with cardiovascular events in healthy individuals in prospective studies (Ridker et al., 1997). Studies also exist showing this relationship in the HD patient group (Zimmermann et al., 1999). As shown in the table 1, uremia-associated factors (anemia, impaired calcium-phosphorus metabolism, fluid electrolyte metabolism imbalance and dyslipidemia) may be added to the non-traditional risk factors in the HD patient group. As shown, dyslipidemia appears among both the traditional and non-traditional risk factors in the HD patient group. The reason is that, in contrast to the normal population, there are various lipid metabolism abnormalities in uremic patients and their being referred to as uremic dyslipidemia.

Traditional Risk Factors	**Nontraditional Risk Factors**
Advanced age	Hyperhomocysteinemia
Diabetes mellitus	Oxidative stress
Kidney disease	Inflammation
Hypertension	Anemia
Family history	Impaired calcium-phosphorus metabolism
Cigarette use	Fluid electrolyte metabolism imbalance
Male gender	Malnutrition
Obesity	Altered nitric oxide/endothelin balance
Left ventricular hypertrophy	Elevated fibrinogen level
Sedentary lifestyle	Other thrombogenic factors
Dyslipidemia (Higher LDL cholesterol, Lower HDL cholesterol)	Dyslipidemia
Family history of CVD	

Table 1. Traditional and Nontraditional Cardiovascular Risk Factors in Hemodialysis Patients

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3. Uremic dyslipidemia

Severe lipid metabolism disorders arise in patients with kidney failure, and the lipid metabolism disorder peculiar to this patient group is known as uremic dyslipidemia (Tsimihodimos et al., 2011). However, both the pathogenesis of uremic dyslipidemia and its relationship with the atherosclerotic process that leads to the development of cardiovascular events are debatable. Studies have shown that there is abnormality in all lipoprotein fractions in uremic patients. Factors influencing these abnormalities include the degree of kidney function impairment, primary disease, presence of nephrotic syndrome, whether renal replacement therapy is administered, and if so whether HD or peritoneal dialysis (PD), drugs used (antihyperlipidemic drugs, sevelamer, calcineurin inhibitors, steroid, etc.), and the presence of malnutrition and inflammation (Attman et al., 2011; Kaysen 2009; Tsimihodimos et al., 2008; Tsimihodimos et al., 2011; Vaziri and Moradi., 2006). Abnormality in lipid metabolism commences in the early stages of CKD and contributes to the development of cardiovascular complications by initiating the atherosclerotic process. Factors contributing to lipid metabolism in stage 1-4 CKD are known to include type of primary kidney disease, degree of proteinuria and use of drugs affecting lipid metabolism. The main lipid metabolism abnormalities seen in renal patients in these stages are hypertriglyceridemia, a rise in triglyceride remnant-rich lipoproteins and lipoprotein a (Lp (a)) levels, and a decline in HDL-cholesterol levels. Moreover, with the exception of nephrotic syndrome, Total (T) cholesterol and LDL-cholesterol levels are generally at normal limits in stage 1-4 CKD patients (Tsimihodimos et al., 2008; Vaziri & Moradi., 2006; Vaziri, 2006) A rise in LDL-cholesterol levels has been determined in patients with nephrotic syndrome (Tsimihodimos et al., 2008; Vaziri, 2006).

4. Dyslipidemia in hemodialysis patients

Before discussing specific lipid metabolism disorders in HD patients, some general information about lipid metabolism will assist understanding of dyslipidemia in this patient group.

Lipids are transported in plasma by means of water-soluble molecules known as lipoproteins. In addition to their transport characteristics, various enzymes in the lipid metabolism also serve as chemical reaction platforms converting transported lipids into one another. Lipoproteins possess a core consisting of non-polar lipids such as triglyceride and cholesterol and a surrounding structure consisting of polar lipids such as apolipoprotein and phospholipid. Thanks to the structural and catalytic functions of apolipoproteins in the structure of lipoprotein, by interacting with one another or various receptors they permit specific lipid species to be added to or removed from this lipoprotein. The main plasma lipoproteins are known as HDL, LDL, IDL and VLDL, depending on their functions and molecular structures (Dominiczak&Caslake., 2011; Vaziri, 2006).

Various changes take place in uremic dyslipidemia with the start of HD therapy. However, the lipoprotein and apolipoprotein profile in HD patients resembles that in pre-dialysis patients (Attman et al., 1993). The main lipid abnormality in this patient group is a rise in tri-

glyceride and triglyceride-rich remnant lipoprotein levels. Other lipid abnormalities are a rise in Lp (a) levels and a decrease in HDL. LDL levels are generally within normal limits. However, as with other lipoproteins, LDL is not homogeneous and there are variations in size, density and composition (Tsimihodimos et al., 2008; Wiemer et al., 2002).

Studies have shown that HD therapy has various effects on lipid profile. This gives rise to various differences, even though pathogenesis and lipid profile phenotype in HD patients are similar to the pre-dialysis period. One factor associated with HD therapy is membrane type. In one study, six weeks after transition from low flux membrane to high flux membrane, Blankestijn et al. observed a decrease in triglyceride and VLDL levels and an increase in HDL levels (Blankestijn et al., 1995). Docci et al. showed that polysulfone membranes have a more positive effect on lipid profile compared to cuprophan membranes (Docci et al., 1995). There are also studies showing that high flux polysulfone membranes reduce oxidized LDL (Wanner et al., 2004). Schiffl and Lang analyzed the effect of dialysate purity on dyslipidemia. They showed that ultrapure dialysis fluids brought about an improvement in dyslipidemia (Schiffl & Lang, 2010). Apart from dialysate purity, the effects of acetate or bicarbonate use on lipid profile have also been evaluated. It has been shown that use of bicarbonate dialysate can have positive effects on lipid profile (Jung et al., 1995). Another parameter thought to affect lipid profile during HD is heparin use. Heparin is known to cause lipoprotein lipase to be released from the endothelial surface. Chronic heparin use therefore leads to a decrease in lipoprotein lipase. Lipoprotein lipase is known to serve in the catabolism of triglyceride-rich lipoproteins such as chylomicrons and VLDL. The decrease in lipoprotein lipase in chronic heparin use gives rise to impairment in triglyceride-rich lipoprotein catabolism (Tsimihodimos et al., 2008). Studies analyzing the effect of unfractionated (UF) heparin on lipoprotein metabolism have produced controversial results. Mahmood et al. reported that heparin use during HD has no effect on lipoprotein lipase levels (Mahmood et al., 2010). However, there are also studies reporting that use of heparin has negative effects on both lipoprotein lipase and on lipid parameters (Daubresse et al., 1976; Schrader et al., 1990; Shoji et al., 1992). Another contentious issue is whether there is a difference in the use of unfractionated (UF) heparin and low molecular weight heparin (LMWH) in the effect on lipid parameters. Leu et al. determined a significant fall in T. cholesterol, LDL and Apo B levels after a transition from UF heparin to LMWH in hyperlipidemic HD patients (Leu et al., 1998). Yang et al., on the other hand, showed that the use of LMWH in diabetic hyperlipidemic HD patients caused a decrease in triglyceride and VLDL levels (Yang et al., 1998). Wiemer et al. showed that the use of LMWH brought about a decrease in oxidized LDL and triglyceride levels (Weimer et al., 2002). However, in an evaluation of the effects on lipid parameters of type of HD membrane and heparin type used, Katopodis et al. showed that both membrane and type of heparin have no effect on lipid parameters (Katopodis et al., 2004). Today, the effect of both heparin use and type of heparin on lipid parameters is debatable. We think that there is a need for studies analyzing the effect of HD therapy on lipoprotein metabolism in the HD patient group.

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4.1. Triglyceride and triglyceride-rich lipoprotein metabolism disorders

As previously mentioned, hypertriglyceridemia is the most commonly seen lipid abnormality in both pre-dialysis and dialysis patients. Triglyceride-rich lipoprotein metabolism disorders give rise to an increase in triglyceride in CKD patients. The main triglyceride-rich lipoproteins are chylomicron and VLDL. Chylomicron and VLDL transport cholesterol from the intestine and liver to regions where it will be stored (adipose tissue) or used for energy (muscle cells). However, in order for chylomicron and VLDL to be able to do this they are exposed to various maturation processes. One of these is taking Apo E from HDL 2. Apo E enables binding to lipoprotein lipase and VLDL receptors. Another maturation process is taking Apo C-II from HDL 2. Apo C-II is a lipoprotein lipase activator. Apo C-III is a lipoprotein lipase inhibitor. Lipoprotein lipase enables the hydrolysis of chylomicron and VLDL and the fatty acids in them to be used by tissues (Tsimihodimos et al., 2011; Vaziri & Moradi., 2006; Vaziri, 2006). Through lipoprotein lipase, VLDL leads to a 70% decrease in hydrolyzed triglyceride content and the formation of remnant VLDL (IDL). IDL transfers Apo E and Apo C-II in plasma to HDL. After the transfer of the remaining triglycerides to HDL through the mediation of cholesteryl ester transfer protein (CETP), they are lipolyzed through mediation of hepatic triglyceride lipase.

Triglyceride metabolism defects emerge because of a rise in synthesis and/or a decrease in clearance. Lipoprotein lipase is very important in triglyceride and triglyceride-rich lipoprotein clearance. Vaziri et al. showed a decrease in lipoprotein lipase gene expression in several tissues in uremic patients (Vaziri & Moradi., 2006). There may be several causes of a decrease in lipoprotein lipase levels and efficacy in HD patients. One is the heparin use discussed in detail above (Daubresse et al., 1976; Schrader et al., 1990; Shoji et al., 1992). UF heparin use leads to a decline in lipoprotein lipase levels. Another cause is a reduced lipoprotein lipase activator (Apo C-II) and inhibitor (Apo C-III) ratio in HD patients (Chan et al., 2009; Moberly et al., 1999). Studies have shown that impaired Ca-P metabolism and secondary hyperparathyroid lead to a decrease in lipoprotein lipase activity (Akmal et al., 1990; Vaziri et al., 1997). In addition, physical inactivity, insulin resistance and an abnormal T4 (thyroxin) to-tri-iodothyromin (T3) conversion contribute to a decrease in lipoprotein lipase activity (Vaziri & Moradi., 2006). Another cause of reduced clearance is a decrease in hepatic lipase activity. Studies have shown a decrease in hepatic lipase activity in uremic patients. A decrease in hepatic lipase activity causes a decrease in the clearance of chylomicron remnants and IDL and a rise in plasma levels (Klin et al., 1996). Down regulation of VLDL receptor in various tissues is one cause of increased VLDL in plasma (Vaziri & Liang., 1997). Apart from decreased clearance, a rise in synthesis from the liver also contributes to hypertriglyceridemia. Insulin resistance is thought to be one of the factors leading to hypertriglyceridemia in HD patients by increasing hepatic VLDL production (Tsimihodimos et al., 2011). Another reason for increased triglyceride synthesis is the use of acetate dialysate, even though this is not used today. The acetate in the dialysate represents the source for fatty acid synthesis by passing into the blood (Vaziri, 2006). In addition to the use of heparin in HD therapy, various therapy-related factors are thought to cause modifications in triglyceride and triglyceride-rich lipoproteins. Use of a high flux membrane has been shown to re-

duce triglyceride levels in some studies, and to have no effect in others (Ottosson et al., 2001; Wanner et al., 2004).

4.2. High density lipoprotein metabolism impairment

Another frequently seen impairment of lipid metabolism in the CKD patient group, which includes HD patients, is a reduction in HDL cholesterol and impaired HDL metabolism. Impairments in HDL metabolism appear in the form of decreased Apo AI, impaired HDL maturation, increased HDL triglyceride and a rise in plasma pre β HDL (Pahl et al., 2009; Quaschning et al., 2001; Vaziri, 2006). The main function of HDL is to collect excess cholesterol from peripheral tissues and transport it to be metabolized in the liver (Genest et al., 1999). In addition, the fact that HDL levels decrease as a response to information suggests that it has an inhibitor effect on inflammation (Quaschning et al., 2001; Vaziri 2006). This inhibitor effect also occurs on platelet adhesion and LDL oxidation (Navab et al., 2001). As previously mentioned, another function of HDL is to represent a source for Apo CII and Apo E, which occupy an important place in the metabolism of triglyceride-rich lipoprotein. The most important proteins in the structure of HDL are Apo AI and Apo AII. Apo AI is an activator of lecithin cholesterol acyl transferase (LCAT), which occupies an important place in HDL metabolism. LCAT performs an important function in HDL maturation and in the mediated uptake of HDL from the peripheral tissue to be metabolized in the liver (Kaysen, 2009; Guarnieri et al., 1978; McLeod et al., 1984). Apo AII is a hepatic lipase activator permitting the metabolism of HDL-origin triglyceride (Vaziri, 2006). Okuboet al. showed that the level of Apo AI and Apo AII is low in uremic patients, and that the fall in Apo AI is related to a rise in catabolism and the fall in Apo AII to a decrease in production (Okubo et al., 2004). Low levels of Apo AI and Apo AII are one of the causes of low HDL in HD patients (Attman et al., 2011; Attman et al., 1993) Another reason for lowered HDL and impairment in its metabolism is LCAT deficiency (Guarnieri et al., 1978; Kaysen 2009; McLeod et al., 1984). A decrease in hepatic lipase activity in uremic patients has already been discussed. The role of hepatic lipase in the metabolism of HDL is to assist the hydrolysis and removal of HDL triglyceride content. When it is deficient, a rise in HDL triglyceride takes place (Klin et al., 1996). Cholesterol ester transfer protein (CETP) takes triglycerides by transferring cholesterol esters from HDL to LDL (Davidson and Toth, 2007; Madeleine et al., 2009; Vaziri, 2006). Kimura et al. showed a high CTEP level in HD patients (Kimura et al., 2003). Elevated CTEP may cause a rise in HDL triglyceride in this patient group (Vaziri, 2006). Studies have shown that the HD procedure itself has an effect on HDL-cholesterol levels in HD patients. One such study was performed by Jung et al. Those authors evaluated the effect of citrate and bicarbonate dialysate use on HDL-cholesterol levels and showed that bicarbonate dialysate use increased HDL-cholesterol levels (Jung et al., 1995). Another parameter affecting HDL-cholesterol level is the use of a low flux or high flux dialyzer. Studies have shown that use of a high flux membrane increased Apo AI and HDL-cholesterol levels (Blankestijn et al., 1995; Docci et al., 1995). In conclusion, with both its relation with CKD and the effect of HD therapy, the level of HDL-cholesterol, which has antiatherogenic, anti-inflammatory and antiplatelet functions, declines in the HD patient group, and various impairments arise in the metabolism.

4.3. Low density lipoprotein (LDL) and cholesterol metabolism impairment

LDL is the major source of extracellular cholesterol. In HD patients, as with CKD patients without pre-dialysis proteinuria, cholesterol and LDL levels are normal or low (Kharrat et al., 2012; Shoji et al., 1992; Vaziri, 2006). Although the LDL level is normal or low, the level of small dense LDL with its atherogenic potential is high (Alabakovska et al., 2002; Kaysen, 2009). Additionally, there is an increase in oxidized LDL, thought to be correlated with atherogenic and cardiovascular mortality. As shown in several previous studies, Mahrooz et al. demonstrated high oxidized LDL levels in HD patients (Mahrooz et al., 2012, Samouilidou et al., 2012). However, the findings from studies regarding the relation between oxidized LDL levels and mortality and morbidity are controversial. Asamiya et al. showed that the oxidized LDL/LDL-cholesterol ratio is higher in patients with coronary artery calcification (Asamiya et al., 2012). Sevinç ok et al. reported that neither oxidized LDL nor non-oxidized LDL values are correlated with mortality (Sevinc ok et al., 2012). Pawlak et al. reported low oxidized LDL in HD patients but high antibodies against oxidized LDL, and that the oxidized LDL/oxidized LDL antibody ratio might be a new marker for cardiovascular events (Pawlak et al., 2012). Mention has already been made of studies showing that LDL is small and dense in HD patients. Noori et al. determined no correlation between conventional lipid parameters and mortality, but showed that very small LDL particle concentration is correlated with mortality (Noori et al., 2011). Kimura et al. showed that small size LDL is correlated with coronary artery disease (Kimura et al., 2011). In conclusion, LDL levels are normal or low in the HD patient group while LDL fractions (oxidized LDL, small dense LDL) with their atherogenic potential are higher in this patient group.

4.4. Lipoprotein(a) metabolism impairment

Lipoprotein (a) (Lp (a)) is a LDL-like particle. It is distinguished from LDL by the presence of apolipoprotein (a) (Apo (a)). Apo a binds to Apo B-100 with disulfide bonds. Because of Apo (a)'s similarity to plasminogen it is thought to contribute to thrombogenesis by inhibiting fibrinolysis of Lp (a) (Milionis et al., 1999; Tsimihodimos et al., 2011). There have been many studies regarding the correlation between elevated Lp (a) and cardiovascular events in the normal population (Rader &Brewer., 1992; Schaefer et al., 1994). There have also been several studies on the subject in HD patients, with high levels being shown in these (Dieplinger et al., 1993; Hirata et al., 1993; Kronenberg et al., 1995). Several clinical studies have evaluated the relation between Apo (a) size and Lp (a) level. Correlations have been determined between Apo (a) low molecular-weight (LMW) isoforms and elevated Lp (a) levels, and also between high-molecular-weight (HMW) isoforms and low Lp (a) levels (Boerwinkle et al., 1992; Kraft et al., 1992). The relationship between Apo (a) phenotype and elevated Lp (a) in HD patients is questionable (Hirata et al., 1993; Kronenberg et al., 1995). One of these studies, by Milionis et al., determined elevated Lp (a) and Apo (a) levels in HD patients (Milionis et al., 1999). Kronenberg et al.'s study supported these findings (Kronenberg et al., 1995). However, Kronenberg et al.'s 1999 study showed that LMW Apo (a) phenotype is an independent predictor for CAD (Kronenberg et al., 1999). The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study showed that Lp (a) levels are high in young,

white patients and correlated with cardiovascular events. However, that study also stated that Apo (a) size is not correlated with elevated Lp (a) and cardiovascular events (Longenecker et al., 2002). In conclusion, while the correlation between elevated Lp (a) and Apo (a) size in the HD patient group is still unclear, elevated Lp (a) in particular is thought to be a cardiovascular risk factor.

4.5. Reverse epidemiology in hemodialysis patients

Hyperlipidemia is known to be one of the most important cardiovascular risk factors in the normal population (Gordon et al., 1977). However, the relationship between dyslipidemia and mortality in HD patients is controversial. Cheung et al. determined that several traditional risk factors, including T. cholesterol, were not correlated with mortality in HD patients (Cheung et al., 2000). A cross-sectional study by Stack et al. produced similar results (Stack & Bloembergen). However, some studies have reported a correlation between dyslipidemia and mortality (Hahn et al., 1983; Nishizawa et al., 2003). As already discussed, whether renal replacement is performed with CRD patients, and whether that replacement is HD, modifies lipid metabolism disorders. No dyslipidemia-mortality correlation has been determined in certain patient populations (cancer patients, hospitalized patients, etc.) including the HD patient group (Shoji et al., 2011). This reverse relationship is therefore known as 'reverse epidemiology' (Kalantar-Zadeh et al., 2004). Hypercholesterolemia, high body mass index (BMI) and hyperhomocysteinemia lead to shortening in long-term survey in the normal population. But in the HD patient these factors lead to an increase in short-term survey. Researchers have described this to malnutrition inflammation (MIA) syndrome (Stenvinkel et al., 1999). MIA syndrome is known to be correlated with atherosclerosis and mortality in HD patients. Presence of hypercholesterolemia, high BMI and hyperhomocysteinemia in this patient group shows that nutrition status may be good. Improvement in MIA in these patients may cause a decrease in mortality (Nurmohamed &Nubé, 2005). In conclusion, these traditional risk factors for HD patients should be reviewed and new treatment objectives set out.

4.6. Treatment

It is today recognized that there is a correlation between hyperlipidemia and cardiovascular events in individuals with normal renal functions and that cardiovascular mortality can be reduced by treating hyperlipidemia. It has been shown in several randomized, controlled meta-analyses that reducing LDL cholesterol with statin therapy brings about a significant decrease in CAD and myocardial infarction (MI) in the normal population (Baigent et al., 2005). However, in the same way that impairments in lipid metabolism in HD patients differ from those in individuals with normal renal functions, so there are various differences in dyslipidemia treatment in these patients. This section discusses dyslipidemia treatment and its effect on mortality and morbidity in the light of major studies.

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4.6.1. The use of statin in dyslipidemia treatment

The use of statin has been shown to have a lowering effect on mortality and morbidity in hyperlipidemic patients without renal function disorder. Statin use in pre-dialysis CKD patients is known, with its LDL-cholesterol reducing effect and an effect independent of the lipid lowering effect known as pleotropic effect, to reduce mortality and morbidity and to slow renal progression (Deshmukh & Mehta., 2011; Olyaei et al., 2011). Statins' pleotropic effects may be listed as a decrease in endothelial cells' permeability to LDL, an increase in vasodilator response, a decrease in endothelial adhesion molecules and an antioxidant effect (Vaughan et al., 2000). The use of statin in HD patients is controversial. One study on the subject by Saltissi et al. showed that simvastatin significantly reduces non-HDL cholesterol levels (Saltissi et al., 2002). Chang et al. determined that simvastatin has an anti-inflammatory effect as well as a lipid-reducing one in HD patients (Chang et al., 2002). These and similar studies have shown that statins have a lipid-reducing effect in HD patients, as well as the presence of pleotropic effects (Nishikawa et al., 1999; Soliemani et al., 2011; van den Akker et al., 2003). One piece of research to investigate the effect on mortality of statin therapy was the Deutsche Diabetes-Dialyse-Studie (4D) study. This was a prospective, randomized study involving 178 HD centers. It included more than 1000 diabetic HD patients and observed 21% MI -associated mortality in the group receiving atorvastatin and the control group. However, sudden cardiac death-related cardiac mortality levels approaching 50% developed in both groups. The researchers suggested that sudden cardiac deaths might be related to arrhythmia and were not reduced by the use of statin (Wanner et al., 2005). Another major piece of research, the AURORA study published in 2009, included 2776 HD patients. That study showed that despite a significant fall in LDL cholesterol with rosuvastatin, there was no significant decrease in cardiovascular mortality (Fellström et al., 2009). Finally, the SHARP study was conducted with 9270 patients with CKD (3023 dialysis patients). In that study, simvastatin + ezetimibe (4193 simvastatin plus ezetimibe from the start, 457 beginning with simvastatin alone and then plus ezetimibe after one year) was administered to one arm, and placebo (4191 plus at the beginning, 429 plus one year after) to the other. Average duration of monitoring was 4.9 years. Major cardiovascular events (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or arterial revascularization) were observed in 11.3% of the simvastatin plus ezetimibe group, and in 13.4% of the placebo group. A 17% fall in major atherosclerotic events was observed with a decrease of 0.85 mmol/L in LDL. In addition, this decrease in risk did not alter depending on whether the patients enrolled received dialysis therapy or not. In other words, in contrast to the 4D and AURORA studies, a decrease in major cardiovascular events was brought about with statin therapy in that study (Baigent et al., 2011).

4.6.2. The use of ezetimibe in the treatment of dyslipidemia

Ezetimibe is a selective intestinal cholesterol absorption inhibitor. Prevention of cholesterol absorption in addition to inhibition of cholesterol synthesis has been shown to reduce cardiovascular mortality in recent years. For that reason, studies have begun being performed regarding the use of ezetimibe alone in patients with a high risk of side-effects from ezetimibe

plus low-dose statin combinations or statin for the purpose of reducing side-effects frequently observed with statins, particularly at increased doses (myopathy/myositis, hepatitis, etc.). In the HD patient group, in which the effect of statin on mortality and morbidity is controversial, studies with low patient numbers have shown that ezetimibe produces a reliable and effective fall in cholesterol (Hattori & Hattori., 2010; Ahmed & Khalil., 2010). Finally, the SHARP study showed that simvastatin plus ezetimibe produced a significant decrease in atherosclerotic cardiovascular events (Baigent et al., 2011).

4.6.3. The use of fibrate in the treatment of dyslipidemia

Fibrates have been used for many years, particularly in the treatment of hypertriglyceridemia. In the HD patient group, hypertriglyceridemia exhibits a pronounced impairment of lipid metabolism. HD would therefore seem to represent a potential patient group for fibrate use. However, since fibrate metabolites are eliminated by the kidney, and since these metabolites give rise to serious side-effects such as myopathy and rhabdomyolysis by accumulating with a decrease in glomerular filtration rate, use in this patient group is limited. However, one study including some 9000 patients published in 2012 showed that fibrate use is quite safe and effective in diabetic patients with moderate renal damage. Patients with a GFR above 30 were included in that study, however (Ting et al., 2012). There are not many studies concerning the use of fibrate in HD patients. One such study is that by Makówka et al. The study included 27 chronic HD patients and lasted for 63 days. It determined a significant fall in T cholesterol, LDL and triglyceride with fenofibrate therapy and a significant rise in HDL. AST and ALT levels remained normal in patients receiving fenofibrate, while CPK levels rose significantly compared to basal values but then remained stable (Makówka et al., 2012). Prospective randomized studies involving large patient numbers evaluating the reliability and efficacy of fibrate use in the HD patient group are now needed.

4.6.4. Use of nicotinic acid in the treatment of dyslipidemia

Nicotinic acid is a water-soluble vitamin B complex (vitamin B3) that has been used in the treatment of hypertriglyceridemia for many years. It produces a fall in triglyceride, LDL and VLDL levels and a rise in HDL. However, hepatoxicity and flushing are side-effects that limit its use. While there have been pharmacokinetic studies in HD patients, studies showing its effectiveness in the treatment of dyslipidemia are restricted to a very small number of cases (Reiche et al., 2011). There are no studies showing its effect on mortality and morbidity. Restrepo Valencia and Cruz reported a fall in T. cholesterol and triglyceride levels and a rise in HDL after nicotinic acid therapy in 3 HD and 6 PD patients (Restrepo Valencia &Cruz., 2008). Shahbazian et al. reported a rise in HDL cholesterol in 48 HD patients after 8-week nicotinamide therapy (Shahbazian et al., 2011).

4.6.5. The use of sevelamer in the treatment of dyslipidemia

Sevelamer hydrochloride is a non-calcium containing phosphorus-binding resin used in the treatment of hyperphosphatemia in HD patients. The Dialysis Clinical Outcomes Revisited (DCOR) and Renagel in New Dialysis (RIND) studies showed that it provides a better sur-

vey that calcium-containing phosphorus-binders (Block et al., 2007; Suki et al., 2007). Sevelamer prevents the absorption of intestinal cholesterol. Studies have shown it has positive effects on lipid parameters in HD patients (Yamada et al., 2005; Qunibi, 2005). Iimori et al. showed that dyslipidemia improved significantly with treatment with sevelamer and that mortality declined (Iimori et al., 2012). However, the use of sevelamer in the treatment of dyslipidemia in HD patients has not been accepted due to the lack of wide-ranging and long-term studies.

4.6.6. The use of carnitine in the treatment of dyslipidemia

Also known as trimethyl-aminobutyric acid, carnitine is a naturally-occurring vitamin-like substance. Carnitine serves in several important metabolic pathways. One of the most important of these is that it lowers the level of free fatty acid necessary for triglyceride synthesis and beta-oxidation of fatty acids (Guarnieri et al., 2001). Since the kidneys are an important site of carnitine synthesis, that synthesis decreases in the event of kidney failure (Bellinghieri et al., 2003). Studies exist showing that carnitine therapy has a positive effect on lipid parameters in HD patients, while others report no positive effect (Emami Naini et al., 2012; Naini et al., 2012; Hurot et al., 2002; Guarnieri et al., 2007). For that reason, carnitine is not definitively accepted in the treatment of dyslipidemia in HD patients.

4.6.7. Heparin-induced extracorporeal LDL precipitation

Heparin-induced extracorporeal LDL precipitation (HELP) is a form of lipid apheresis particularly used in the treatment of familial hyperlipidemia. The number of case reports in the literature is limited, although a significant lipid decrease has been observed with HELP. One of this limited number of studies in the literature is that by Bosch et al. A pronounced fall in LDL was observed with 29 sessions of HELP in 5 HD patients (Bosch et al., 1993). Another study by Bosch et al. reported quite good results with HELP in 3 HD patients (Bosch et al., 1993). Eisenhauer et al. achieved a significant fall in LDL cholesterol with HELP in 6 HD patients (Eisenhauer et al., 1991). In the light of these case reports, we think that HELP may be a useful form of treatment, especially in HD patients with familial hyperlipidemia and with no response to drug therapy.

4.6.8. Guideline

The K-DOQI treatment of hyperlipidemia guideline was published in 2003 because of the variation in dyslipidemia in HD patients (Kidney Disease Outcomes Quality Initiative (K/DOQI) Group, 2003) Until then, there had been recommendations resembling an adult hyperlipidemia guideline in the studies performed. In essence, the recommendations of that guideline are as follows;

In order to prevent serious complications such as pancreatitis in patients with a triglyceride level above 500 mg/dl, primary focus must be on triglyceride-lowering therapy. Diet, fibrate and nicotinic acid can be used in treatment.

If the triglyceride level is below 500 mg, treatment should be adjusted according to LDL levels. If LDL is above 100 mg/dl, LDL-lowering therapy (diet and statin) is recommended.

If LDL is normal while triglyceride is elevated, there is generally a rise associated with lipid remnants. The amount of remnant lipoprotein can generally be estimated with a calculation of non-HDL cholesterol. Non- HDL cholesterol is calculated as the difference between T. cholesterol and HDL cholesterol. Treatment is recommended in patients with non-HDL cholesterol above 130 mg/dl.

As already stated, because of the insufficient number of studies, the dyslipidemia treatment guideline in chronic kidney patients was adapted to the adult hyperlipidemia treatment guideline. However, it is clear that treatment in HD patients requires a different approach. We therefore think that this guideline published in 2003 should be updated in the light of more recent studies.

5. Conclusion and recommendations

The pathogenesis of dyslipidemia in the HD patient group, which has various impairments in lipid metabolism, has not yet been fully clarified. New studies regarding that pathogenesis are therefore needed. In addition, new studies regarding what the aim of treatment in dyslipidemia and the parameter to be targeted should be (triglyceride, LDL, IDL, VLDL or non-HDL cholesterol?). Finally, treatment adapted to the adult hyperlipidemia treatment guideline because of a lack of sufficient studies must clearly be turned into a lipid guideline aimed at HD patients in the light of newly published studies.

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Chapter 7

Remnant Proteinuria in Chronic Hemodialysis

Hernán Trimarchi

Additional information is available at the end of the chapter

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1. Introduction

Patients with end-stage renal disease are at high risk of developing cardiovascular events. In addition to the major traditional risk factors for cardiovascular disease (ie, advanced age, hypertension, diabetes mellitus, dyslipidemia, and smoking), recent studies suggest that chronic kidney disease is an independent risk factor [1]. Several groups have reported that coronary artery disease severity and lesion complexity are associated with a decrease in the estimated glomerular filtration rate [2,3]. Recent epidemiological studies and clinical trials have demonstrated that chronic kidney disease is associated with increased mortality rate in patients with cardiovascular disease [4,5]. Notwithstanding the deep deleterious effects chronic renal disease itself plays in endothelial and medial arterial wall, renal failure leads to both significant increases in morbidity and decreases in life survival, particularly in hemodialysis patients, who represent the most severe and advanced expression of renal disease.

The mechanisms that underlie the association between renal dysfunction and coronary artery disease have not been elucidated fully. Previous studies have shown that renal dysfunction is associated with low-grade inflammation and activation of the sympathetic nervous system and of the renin-angiotensin aldosterone system [6-8]. Other factors such as calcium-phosphate disbalance, oxidative stress, hyperglycemia, advanced glycosylated end-products, and abnormal apolipoprotein levels also were shown, among others, to promote renal dysfunction [9,10]. As such, these factors could also contribute to the pathogenesis of atherosclerosis.

As renal function deteriorates at early stages, the different organ systems start to experience subtle alterations. These initial disturbances that develop at the molecular level, encompass mainly chronic inflammatory pathways mediated by cytokines secreted by leukocytes and uremic retention toxins. In turn, and with different degrees of clinical and biochemical mani-

festations, the many culprits interact and cause systemic impacts. The most important, albeit not the one, harmful effect is evident at the cardiovascular level. This is due to the fact that the endothelium is a direct target of plasmatic toxins, free radicals and altered synthesized molecules, abnormal platelets, short-live erythrocytes and malfunctioning leukocytes, hyperglycemia, dyslipidemia and hypertension. The damaged endothelium interacts with both the plasmatic and cellular constituents of blood and the inner vessel wall cells, particularly smooth muscle cells, circulating monocytes and tissular macrophages and fibroblasts. The direct consequences are vascular thrombosis, calcification and lipid deposition, and tissue hypoxia. Although these mentioned vascular alterations exist in all organ systems, the central nervous system, the heart and the kidneys are the most important clinically involved organs. This situation finds its most critical exponent when kidney function reaches stage 5 and uremia is present [11]. At this stage, renal replacement therapy is mandatory. Among the therapeutic options, hemodialysis, peritoneal dialysis and kidney transplantation are available. These options are far from ideal, albeit transplantation offers the best results. With respect to the dialysis procedures, hemodialysis is the most frequent modality employed worldwide to treat end-stage renal disease. Among the factors that add morbidity and mortality to hemodialysis individuals are -as mentioned- comorbid conditions as diabetes mellitus, hypertension, aging, endocrine and electrolyte derangements, oxidative stress, volume overload, hyporexia and nutrient losses during the dialysis process, dialysis devices and vascular access-blood interactions, the predisposition to infections, and water quality. All these main factors will definitively result in a vicious cycle in which protein energy wasting, malnutrition, uremic toxins retention, inflammation, and a hypercatabolic state with grim and most frequently irreversible consequences harmfully interact. Cardiovascular disease, malnourishment and inflammation are the main roads that can merge or independently lead to premature death, the reality dialysis patients still face nowadays [11,12].

As mentioned before, many clinical, nutritional, and biochemical parameters may be indicating a chronic inflammatory state in these individuals. Conventional and non-traditional risk factors and metabolic alterations observed in the uremic milieu may contribute to the excessive risk of cardiovascular disease [12]. Both Framingham and the so called *non-traditional* risk factors as inflammation, endothelial dysfunction, sympathetic activation, protein-energy wasting, oxidative stress, vascular calcification, and volume overload may play relevant roles in the development of vascular disease in dialysis patients [13-15]. However, it has recently demonstrated that the addition of multimarker scores (including markers of inflammation and volume overload) to conventional risk factors resulted only in small increases in the ability to grade risk, at least in the general population [16,17].

An important factor in hemodialysis that is linked to survival is residual renal function, clinically assessed as the amount of daily urinary output. Many factors conspire against this important variable: Lifetime on dialysis, aging, the etiologies of end-stage renal disease and higher degrees of ultrafiltration. However, proteinuria, an important marker of progression of renal disease that is associated in time with decreased renal function and oliguria, is not assessed routinely in hemodialysis.

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The aim of the present chapter is to consider remnant proteinuria as an active marker of inflammation and cardiovascular disease, and also as a cause of decrease of residual renal function and urinary output in hemodialysis. Although not yet assessed, it is reasonable to presume that also in hemodialysis patients, proteinuria should be associated with increased cardiovascular events, inflammatory processes and decreased life survival.

2. Residual renal function in dialysis

In recent years, there has been a greater focus on residual renal function of patients on chronic dialysis therapy. Although residual renal function is often used to indicate remaining glomerular filtration rate, it also reflects remaining endocrine functions such as erythropoietin production [18], calcium, phosphorus and vitamin D homeostasis [19,20], volume control, and removal of "middle molecules" or low molecular weight proteins [21,22]. It is assumed by some authors that an estimated urine volume < 200 ml/24 h should be considered as a cut-off to consider loss of residual renal function. However, several of the significant associations with residual renal function loss have generated testable hypotheses regarding potential therapies that may preserve renal function among dialysis patients that may be independent of the urinary volume, even at less than 200 ml daily. Renal replacement function is clinically important in that it can account for major differences in dialysis requirements, since it contributes to measures of adequacy, both Kt/V urea and creatinine clearance [23,24]. As mentioned before, residual renal function has also been shown to be associated with mortality. Analysis of the CANUSA study [25] has shown that every 0.5 ml/min higher glomerular filtration rate was associated with a 9% lower risk of death in subjects with renal disease but not still in dialysis [26]. It has been shown that clinically important and statistically significant decreases in nutritional parameters occur with residual renal function loss [25]. Furthermore, it has been demonstrated that small increments in it may account for major differences in quality of life [27,28]. It is therefore very important to determine and understand the predictors of loss of residual renal function in the dialysis patient. The importance of identifying factors that protect and preserve renal function has been recognized among patients with chronic renal failure and pre-end-stage renal disease (stages 3 and 4). Control of blood pressure, angiotensin-converting enzyme inhibition, decreasing proteinuria, dietary modification, avoidance of nephrotoxins, and glucose control have all been considered integral parts of the pre-stage 5 care [29]. However, few studies have comprehensively evaluated whether these or other factors are important in preserving residual renal function after initiation of dialysis. Also on a clinical level, evaluating and monitoring factors that preserve it in patients who have just started dialysis has not received the same level of care as among the chronic renal failure population. It is also probable that subjects with stage 5D (under dialysis) may be treated differently than stage 5 subjects not still in dialysis: In stage 5 not in dialysis, individuals may be under pharmacologic regimes to control proteinuria, that may be left aside when dialysis is started, or the beneficial effects of which are not carefully assessed or even considered.

Several authors have observed that preservation of residual renal function is prolonged with peritoneal dialysis compared to hemodialysis [30-32]. Others have noted a more rapid decline in renal function among patients on automated peritoneal dialysis versus continuous ambulatory peritoneal dialysis [33]. For hemodialysis patients, there has been debate in the literature about whether the type of dialyzer membrane has an effect on remnant renal function. Some have suggested that biocompatible membranes preserve renal function for a longer time period [34-36]. Cause of end-stage renal disease, level of blood pressure, rate and profile of fluid removal, contrast materials as iodide and gadolinium, and also various medications have all been implicated as having an effect on renal function [29,37,38]. However, the current knowledge about the factors that preserve renal function in end-stage renal disease is still very limited. Daily urinary volume recollection may be cumbersome and imprecise, but has proved to be a useful measure of residual renal function. It is interesting that patients are more likely to have the outcome variable, urine volume, reported if they are on peritoneal dialysis or if they are female. It has been recognized that residual renal function is important in continous ambulatory peritoneal dialysis due to its contribution to small solute clearance, and more attention may be paid to monitoring it in this population. The reason for the gender difference is not clear. Several studies about the progression of chronic renal disease have reported that the decline in renal function is either linear or exponential [29,39]. Thus, it is assumed that longer follow- up and lower levels of renal function at the start of dialysis would be associated with a greater likelihood of loss of residual renal function. It is therefore necessary to control for these factors when evaluating the effect of other potential predictors. Duration of time on dialysis is indeed a significant predictor of renal function loss in the overall population and among the peritoneal dialysis population, but, interestingly, not among the hemodialysis population. Among the peritoneal dialysis patients, there is an increasing risk of loss of residual renal function over time, suggesting that time on dialysis is an important variable. Likewise, higher estimated glomerular filtration rates at dialysis initiation is associated with lower risk of loss of residual renal function at follow-up among peritoneal dialysis-treated patients but not among hemodialysis-treated patients.

Increasing age may not be associated with residual renal function loss. This is consistent with data from the Modification of Diet in Renal Disease (MDRD) study [29], in which age was not an independent predictor of progression of renal disease among patients with chronic renal failure. Female gender independently predicted renal function loss loss in the overall analysis and in the analysis limited to peritoneal dialysis patients. This gender effect could not be explained by differences in body mass index, mean arterial pressure, albumin, estrogen use, or menopausal status because the effect remained despite controlling for these variables [40]. However, other studies have shown the opposite, in which a slower rate of progression of renal function decline was reported in females with chronic renal failure [41-44]. Data from the MDRD study indicated a slower mean glomerular filtration rate decline in women compared to men with chronic renal failure. However, gender differences were reduced and no longer significant after controlling for baseline proteinuria, mean arterial pressure, and HDL cholesterol [29]. Non-white race was associated with residual renal function loss in the overall analysis; however, this effect was found to be limited to peritoneal dialysis patients only. This was true of both blacks and the category “other non-white

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race." These relationships were independent of cause of renal disease and blood pressure at dialysis initiation, and also could not be explained by reported differences in pre-dialysis care. African-Americans are known to have a faster rate of progression of renal failure in the chronic renal failure population [29,45]. This analysis suggests that, at least among peritoneal dialysis-treated patients, this race effect may persist after dialysis initiation. The presence of diabetes predicts renal function loss particularly in both dialysis populations. Diabetic patients with hypertension and proteinuria have been shown to have an increased rate of loss of renal function in the chronic renal failure community. A history of congestive heart failure may also predict renal function loss, likely due to decreased blood flow to the compromised kidney. However, this statement has not been assessed properly in hemodialysis patients.

Several comparative studies of peritoneal dialysis and hemodialysis mortality have shown that the relative mortality risk favors peritoneal dialysis to the greatest degree early after end-stage renal disease start and the relative mortality risk increases for peritoneal dialysis with time on dialysis [46-49]. One reason that peritoneal dialysis may offer this early advantage may be the greater preservation of residual renal function. Higher postdialysis blood pressure at baseline appears to correlate with a lower risk of renal function loss loss in the hemodialysis-only population but may be an insignificant predictor in the peritoneal dialysis subjects. Several studies have observed a relationship of higher mortality associated with low predialysis blood pressure [50-52]. A similar phenomenon may exist for residual renal function. Previous studies have shown that use of cellulose dialyzer membranes among hemodialysis patients hastens residual renal function loss [34,36] due to blood and cellulose dialysis membrane interactions, which may induce potentially nephrotoxic inflammatory mediators [53].

Comparing peritoneal dialysis patients to hemodialysis patients using biocompatible membranes revealed that peritoneal dialysis patients are still significantly less likely to lose residual renal function than hemodialysis patients. Preservation of residual renal function is an important goal. In addition to identifying demographic groups at risk, it is also important to identify other potentially modifiable factors as calcium and phosphorus metabolism, blood pressure, hyperglycemia, PTH and vitamin D levels, dose of erythropoietin, use of iron, and therapies (dialysis modality, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, statins and aspirin) that are involved in residual renal function. There appear to be substantial differences in both the actual loss of residual renal function and the contributing risk factors among peritoneal dialysis compared to hemodialysis patients. Additional prospective studies, ideally clinical trials, are necessary to determine whether these possible interventions are efficacious. Proteinuria has not been assessed in any of both modalities as a marker of progression of residual renal function loss, and as a cause of cardiovascular disease and inflammation [40].

In peritoneal dialysis, the best means for assessing adequacy remain ill defined [54]. The concept of adequate dialysis should include some defined level of solute removal, adequate fluid removal to achieve normal volume homeostasis and blood pressure control, maintenance of adequate nutrition, normal acid–base balance, normal mineral metabolism, mini-

mal anemia, normal lipid metabolism, and prevention of atherosclerosis. Small solute clearance has traditionally been an integral part of the overall definition of peritoneal dialysis adequacy; most other measures appear to parallel solute removal. The importance of small solute clearance in peritoneal dialysis has been confirmed by a variety of studies [55,56], most notably CANUSA, which showed that Kt/V and corrected creatinine clearance independently predict patient survival. All these studies have been confounded by residual renal function. Solute removal by peritoneal dialysis may not be clinically equivalent to an equal quantitated solute removal by residual renal function. For example, the increased fractional secretion of creatinine during declining glomerular filtration rate can be extremely misleading if other solutes do not show a fractional increase in excretion. Conversely, the increased secretion of organic solutes during chronic renal failure may far exceed the diffusive losses of the same solute during peritoneal dialysis. Hence, the relative effects of renal versus peritoneal clearance on survival remain to be elucidated. There is consensus that residual renal function has a major impact on the ability to achieve small solute clearance targets [57]. Residual renal function contributes to approximately 25% of total Kt/V and 40% of total weekly creatinine clearance. This numerical contribution is even greater for high and middle molecular weight solutes. As residual renal function deteriorates, failure to compensate for this loss will result in an increasing frequency of inadequate dialysis. Even with increasing dialysis prescription, as many as 40% of continuous ambulatory peritoneal dialysis patients fail to meet the target [58,59]. Small changes in residual renal function with time on peritoneal dialysis may account for major differences in quality of life and dialysis outcome. Data from the CANUSA study showed that the overall outcome was worse for patients who lost their residual renal function [60,61]. The adverse impact of loss of residual renal function on outcome in peritoneal dialysis patients could be due partly to loss of residual diuresis and difficulty in managing fluid status, hypertension, and left ventricular hypertrophy, all of which contribute to cardiovascular mortality [62].

Residual renal function has also been shown to have a greater influence on dietary protein intake and nutritional status than peritoneal clearance [63-65]. Following the initial observation of Rottembourg et al., a number of studies have shown that the decline in residual renal function is more protracted in patients on peritoneal dialysis than those on hemodialysis [31,66-69]. However, the changes in residual renal function with time are not uniform in all patients. The issue of which factors affect preservation of residual renal function in patients with chronic renal failure once dialysis is started has received very little attention [70-74]. There appears to be a gradual deterioration of residual glomerular filtration rate with time on peritoneal dilaysis, with 33% of patients developing anuria at a mean of 20 months after the start of dialysis, according to Singal et al data [75]. In that study, on comparison between patients in the highest and lowest quartiles of slope for residual glomerular filtration rate, male gender, presence of diabetes, higher grades of left ventricular dysfunction, and glomerular filtration rate higher 24-hour urine protein excretion corresponded with faster decline of residual renal function. Singal et al could not show a good correlation between the decline of urine volume and renal glomerular filtration rate. Urine volume was well maintained until 30 months after start of peritoneal dialysis. This was in contrast to previous studies, where the decline in creatinine clearance and urine volume in individual patients

was significantly correlated [76]. A number of studies have shown that residual renal function is better preserved in peritoneal dialysis patients than in those on hemodialysis. However, all these comparisons were made between hemodialysis using conventional bioincompatible membranes and peritoneal dialysis. The advent of newer dialytic techniques such as automated peritoneal dialysis and biocompatible hemodialysis membranes may alter this relationship. It has also been suggested that peritoneal dialysis patients with rapidly falling residual renal function depart from therapy at a high rate, leaving those with better preservation of residual renal function on peritoneal dialysis after many months [77]. Previous studies have not clearly defined the factors that affect the rate of residual renal function loss in patients on dialysis. In hemodialysis patients, Iest et al. reported that the mean rate of decline of residual renal function was unaffected by weight, gender, age, hypertension status or medications, and by the original disease [78]. Lutes et al. also reported in 32 peritoneal dialysis patients no influence of age, diabetes, mean arterial pressure, peritonitis rate, and initial creatinine clearance at the start of peritoneal dialysis, on the rate of residual renal function loss [70]. Davies et al. looked at the half-life of loss of residual renal function in 303 patients started on peritoneal dialysis between 1990 and 1997 [32]. Patients with interstitial nephritis, renovascular disease and hypertensive nephrosclerosis had slower decline of residual renal function. Comorbid conditions did not influence rate of loss of residual renal function. Moist et al. studied predictors of loss of residual renal function in new dialysis patients [40]. As partially mentioned before, increasing age, female gender, and nonwhite race predicted faster loss, whereas peritoneal dialysis and use of angiotensin converting enzyme inhibitors and calcium channel blockers was associated with slower loss of residual renal function. However, the primary outcome variable was urine volume, not residual glomerular filtration rate, in that study. Singal et al evaluated the risk factors assumed to be associated with residual glomerular filtration rate [75]. There was no effect of age, race, or primary renal disease on the rate of decline of residual renal function. Presence of diabetes as a cause of renal disease or as a comorbidity was significantly associated with the rate of decline. Presence of peripheral vascular disease and higher degrees of left ventricular dysfunction on echocardiography may have a significant effect in patients in upper and lower quartiles of slope of residual glomerular filtration rate. Considering the 105 patients with diabetes, 38% had peripheral vascular disease and left ventricular dysfunction of grades I to IV in 60%, 13%, 15%, and 12% of patients respectively; compared to 137 patients with no diabetes where 12% had peripheral vascular disease and left ventricular dysfunction of grades I to IV in 77%, 13%, 7%, and 3% respectively. Similarly, 24-hour urinary protein excretion may also be associated with diabetic nephropathy as a cause of end-stage renal disease.

Therefore, residual renal function may contribute significantly to total solute clearance and fluid balance in patients on continuous peritoneal dialysis. Changes in residual renal function with time are not uniform in all patients. Faster decline of residual renal function corresponds with male gender, large body mass index, presence of diabetes mellitus, higher grades of congestive heart failure and higher 24-hour proteinuria. Higher rates of peritonitis and use of antibiotics for the treatment of peritonitis are also associated independently with faster decline of residual renal function. Whether the type of peritoneal dialysis and use of

larger dialysate volume are associated with faster decline of residual renal function remains speculative [75]. In summary, loss of residual renal function and urinary output is an important risk factor of morbidity and mortality in dialysis patients. In predialysis patients, proteinuria is clearly associated with renal and cardiovascular disease progression. However, the link between proteinuria and residual renal function in dialysis is to be discussed next.

3. Proteinuria and chronic kidney disease

The incidence of end-stage renal disease is dramatically increasing worldwide [80]. Most patients with kidney problems visit their physicians in the late stages of the disease. Progression from mild to moderate kidney disease to end-stage renal disease may be halted or slowed when kidney damage is detected and appropriate treatment is started during the early stages. Kidney damage is frequently asymptomatic but can be suspected in the presence of proteinuria, hematuria, or a reduced glomerular filtration rate [81]. Due to increased awareness of people about chronic kidney disease and early detection and prevention programs implemented in developed countries, the incidence of end-stage renal disease has shown a small downward trend [82,83]. However the total number of individuals worldwide with chronic kidney disease is still high and estimated at 500,000,000 people [82-84].

Proteinuria is a major risk factor for renal disease progression [85-87]. Among the main causes that lead to dialysis, diabetes, hypertension and glomerular diseases account for more than 70% of the most frequent described etiologies in the adult population. All these entities display a marker of disease progression: Proteinuria. In this setting, proteinuria can be due to primary glomerulopathies, which is the third cause of end-stage renal disease in the adult population and an important cause of secondary hypertension, or could be the result of secondary glomerular damage due to primary hypertension, diabetes mellitus, hyperfiltration, metabolic syndrome, reduced renal mass, autoimmune or infectious diseases, vesicoureteral reflux, etc.

Proteinuria is another predictor of increased cardiovascular risk in the general population [88]. Numerous studies have shown that treating proteinuria in patients with diabetic or non-diabetic chronic kidney disease and proteinuria slows the progression of renal disease. It can also be stated that the greater the decrease in proteinuria, the greater the clinical benefit [89-91]. In addition to predicting kidney disease progression, proteinuria is a well-established risk marker for cardiovascular disease [86,92-94]. In chronic kidney disease individuals, reduction in proteinuria confers a significant decrease in cardiovascular events. For example, the RENAAL study showed that albuminuria is the most important factor in predicting the cardiovascular risk in patients with type 2 diabetic nephropathy, and at 6 months for every 50% reduction in albuminuria, a 18% reduction in cardiovascular risk and a 27% reduction in heart failure was reported[16]. It is evident that proteinuria presents an important predictive value in cardiac failure, both as a marker of future events and also as a therapeutic target. Patients with diabetic nephropathy and proteinuria greater than 3 g/g have a 2.7-fold higher risk for heart failure when compared with patients with low proteinu-

ria (<1.5 g/g) [95]. A coexistent diagnosis of hypertension and diabetes increases the risk of adverse cardiovascular and renal outcomes. This increased risk extends to a diastolic blood pressure of 83 mmHg and a systolic of 127 mmHg [96,97]. Reduction of proteinuria by >30% within the first 6 to 12 months of treatment in patients with chronic kidney disease has also been shown to predict long-term renal and cardiovascular outcomes [86,88,98]. Moreover, the management of albuminuria in normotensive or hypertensive patients with diabetes may slow progression of diabetic nephropathy [99], and microalbuminuria itself, an early marker of kidney vascular dysfunction, is a strong prognostic indicator of mortality and cardiovascular disease in hypertension and diabetes mellitus [100,101]. Therefore, one of the main goals to slow the progression of renal disease is an adequate and not unusually aggressive control of blood pressure and the reduction of proteinuria to its lowest possible level [102]. Moreover, proteinuria has been shown to be the strongest predictor of cardiovascular outcomes, including hospitalization for heart failure. Extinguishing proteinuria by decreasing blood pressure, hyperfiltration states, sodium intake, and tight glycemia control are generally accepted potential strategies to reduce cardiovascular risk events [89]. Although the nature of the links between proteinuria and vascular disease may partly be due to endothelial dysfunction, persistent low-grade inflammation also plays a role. Indeed, inflammation is associated with both endothelial dysfunction and albuminuria [11,102-104].

4. Residual renal function and proteinuria

The past 20 years of research in nephrology have yielded substantial information on the mechanisms by which persisting dysfunction of an individual component cell in the glomerulus is generated and signaled to other glomerular cells and to the tubule. Spreading of disease is central to processes by which nephropathies of different types progress to end stage renal disease. Independent of the underlying causes, chronic proteinuric glomerulopathies have in common a sustained or permanent loss of selectivity of the glomerular barrier to protein filtration. Glomerular sclerosis is the progressive lesion beginning at the glomerular capillary wall, the site of abnormal filtration of plasma proteins. Injury is transmitted to the interstitium favoring the self-destruction of nephrons and eventually of the kidney. The underlying mechanisms of tubulointerstitial injury that are activated by ultrafiltered protein load of tubular epithelial cells continue during the entire process of the disease, which is accompanied by several clinical markers, as fluid and toxins retention, edema, hypertension, proteinuria, creeping creatinine and a continuous decrease in urinary output. It needs to be emphasized that this field is relevant to interpret clinical findings and to improve treatment of patients with non-diabetic or diabetic nephropathies.

The opinion among nephrologists that proteinuria could be a marker only of injury largely has been challenged. The strong predictive value of proteinuria in chronic nephropathies now is firmly established. Baseline proteinuria was an independent predictor of renal outcome in patients with type 1 diabetes and nephropathy [105]. and in patients who did not have diabetes and entered the MDRD study [86]. In the Ramipril Efficacy In Nephropathy (REIN) trial [92], urinary protein excretion was the only baseline variable that correlated sig-

nificantly with glomerular filtration rate decline and progression of non-diabetic chronic proteinuric nephropathies to end-stage renal disease. Similar evidence was provided recently in patients with type 2 diabetes and overt nephropathy [87]. Other studies corroborated these data and extended the predictive value of proteinuria to risks for overall or cardiovascular mortality [106,107]. Clinical trials consistently showed renoprotective effects of proteinuria reduction and led to the recognition that the antiproteinuric treatment is instrumental to maximize renoprotection [86,92,94,108]. The MDRD study revealed tight association between reduction of proteinuria and decrease in rate of glomerular filtration rate decline [86]. Protection that was achieved by lowering blood pressure depended on the extent of initial proteinuria. The renoprotection that was conferred by angiotensin-converting enzyme inhibition in the REIN study was mediated by the drug's action of reducing urinary protein levels, to the extent that patients who were on ramipril had a better outcome paralleled by more reduction in proteinuria, whereas blood pressure was comparable to that of control subjects [92]. Angiotensin converting enzyme inhibitor–induced reduction in proteinuria was the strongest time-dependent covariate predicting slower progression to uremia. Finding that the rate of glomerular filtration rate decline correlated negatively with proteinuria reduction and positively with residual proteinuria provided further evidence for a pathogenetic role of proteinuria [109]. Likewise, trials in type 1 [94,110] and type 2 diabetes [111,112] documented that whenever proteinuria is decreased by treatments, progression to end-stage renal disease is reduced. As already mentioned, the Reduction of Endpoints in type 2 diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study [111] in 1513 patients with type 2 diabetic nephropathy confirmed that more reduction in proteinuria by losartan invariably was associated with more renoprotection at comparable levels of blood pressure control. Beneficial cardiovascular effects of losartan also were driven by effects on urinary protein and largely depended on the amount of residual proteinuria. Similar results were found in the Irbesartan Diabetic Nephropathy Trial [112]. Finally, the Angiotensin-Converting-Enzyme Inhibition and Progression of Renal Disease study [113,114] confirmed that proteinuria is a strong risk factor for progression of chronic renal disease and that patients with more severe renal disease benefit most from angiotensin converting enzyme inhibitor therapy. Importantly, in no case from a was there a worsening in proteinuria that subsequently was associated with an improved outcome [115].

In progressive nephropathies, severe dysfunction of the glomerular capillary barrier to circulating proteins causes protein overload of tubular epithelial cells and intrarenal activation of complement that is responsible for spreading of injury to the tubulointerstitium. Drugs that block angiotensin II limit the abnormal passage of plasma proteins and are renoprotective. The podocyte is the primary site of antiproteinuric action through stabilization of podocyte–podocyte contacts and prevention of permselective dysfunction at the slit diaphragm. Although the abnormal passage of plasma proteins across the glomerular capillary wall is likely to be a factor that is responsible for further podocyte injury and progression to glomerulosclerosis [116], most of the available data highlight the mechanisms underlying proximal tubular cell activation and interstitial inflammation and fibrosis. The toxicity of albumin seems to be mediated by its initial endocytic uptake, although the importance of albumin itself *versus* protein-bound molecules in the induction of irreversible tubular dam-

age is not clear. Other molecules, including ultrafiltered transferrin and immunoglobulins, and the intrarenal complement and ammonium interactions could play relevant roles. Developments in these areas yield further support to design protocols in which drugs against secondary pathways of injury should be tested in association with drugs that limit the abnormal passage of proteins across the glomerular capillary barrier [117]. This statement must be borne in mind when considering treatment of proteinuria as the patient enters dialysis, as the already triggered pathologic pathways are perpetuated.

In this regard, the pathophysiological process that leads to end-stage renal disease where proteinuria is a hallmark is crucial to be followed and treated. As long as urinary output is present, all the severely damaged nephron structures may be still abnormally working, as hypertension and proteinuria are two clinical evident markers of renal disease virtually present in the vast majority of dialysis individuals.

5. Hemodialysis: Is there a role of proteinuria as a marker of disease?

Noteworthy, despite this active attempt to reduce proteinuria in pre-dialysis patients to delay disease progression, proteinuria appears to be forgotten or even ignored by nephrologists once a patient enters dialysis. However, its existence may certainly continue conferring the well-known inflammatory, catabolic, fibrinolytic and toxic effects on the endothelium that has been exerting in the pre-dialysis period [104,118,119]. Our group determined that the higher degrees of proteinuria in chronic hemodialysis patients are associated with inflammatory and cardiovascular markers of disease [120]. These results may also be related to the nutritional status and mortality rates.

In chronic kidney disease patients, proteinuria is a common event, irrespective of cause, and virtually all patients with chronic kidney disease present variable degrees of proteinuria [121]. However, in dialysis patients, the prevalence of proteinuria is unknown. In the present study, proteinuria was present in 87% of the hemodialyzed population. Noteworthy, despite significantly differences in proteinuria among the three groups, these changes were not accompanied by significant alterations in albuminemia or in cholesterolemia. This phenomenon could be attributed to the similar nutritional status the three groups displayed and to the use of statins in virtually all patients. In patients with proteinuria > 3/day, the two main causes of end-stage renal disease were diabetes nephropathy and primary glomerulonephritis, although no significant differences in the amount the proteinuria could be observed between both subpopulations. However, there was a significant increase in diabetic patients with heavy proteinuria in comparison to the other two groups, and a relative increase in the diabetic population was observed as proteinuria augmented. Proteinuric levels did not correlate with body mass index, the type of vascular acceses, and could not be attributed to hypertension or to hemodynamic fluctuations, as Pro-Brain natriuretic peptide (Pro-BNP) measurements were not different among the groups. There was a significant difference in the ultrafiltration rates, but we could not associate it to any of the variables under consideration, particularly with Pro-BNP or adiponectin, between which important

feedback regulations exist. Interestingly, as proteinuria worsened, a significant correlation developed between Troponin T, a cardiovascular biomarker, and C-Reactive Protein (CRP), an inflammatory marker. This interrelationship may suggest that proteinuria could interact as a covert and ignored culprit in the complex and chronic protein energy wasting syndrome dialysis patients live in, contributing to a higher risk of cardiovascular disease and inflammation as proteinuria rises.

In our own experience, in a one-year recruitment cross-sectional study where 265 chronic kidney disease patients were classified into the 5 stages according to K/DOQI guidelines, proteinuria was present in 204 subjects (76.98%) [122]. Interestingly, proteinuria significantly worsened as kidney function declined, and the highest rates of proteinuria were encountered in the most advanced stages of the cohort: Stage 3, 1.39±3.2 g/day (range: 0-21.6) in 80% of the 90 cases included vs stage 4, 1.87±0.99 g/day (range 0-5.1), which represented the 95% of the 37 individuals included in this group. In Stage 5D, proteinuria was present in 85% of the 60 patients included, and the mean level of proteinuria was 2.48±3.72 g/day (range 0-21.5). This level of proteinuria was significantly higher and different from stages 3 ($p=0.001$) and 4 ($p=0.013$). These findings underscore previous findings that demonstrated that proteinuria is associated with chronic kidney disease, that worsens renal function, and that it is highly prevalent in end-stage renal disease [89-91,121].

Cardiovascular disease in the main cause of death in the chronic population. However, cardiovascular disease can be the final pathophysiological pathway where many different entities may converge: Framingham factors, malnutrition, oxidative stress, calcium-phosphate metabolism, anemia, infections, inflammation. Although we have included many of the traditional Framingham risk factors in our study, only diabetes mellitus was significantly more frequent in patients with proteinuria > 3 g/day compared to the other groups. In chronic kidney disease, the main causes that lead to renal replacement therapies are diabetic nephropathy, hypertension and glomerulonephritis. In all these entities, cardiovascular disease is a major cause of morbidity and mortality, and proteinuria again plays a key role in these pathophysiological processes. In our study, higher degrees of proteinuria (> 3 g/day) significantly correlated with Troponin T and CRP, markers of cardiovascular stress and systemic inflammation. Which is the relationship among CRP, Troponin T and proteinuria in hemodialysis, if any?. Both CRP and Troponin T have been employed as markers of highly prevalent complications as inflammation and cardiovascular disease in dialysis subjects. CRP has been reported to be elevated in 30 to 60% of dialysis patients, and can be employed as a predictor of cardiovascular mortality in hemodialysis [123]. In addition, it has been established that troponin T levels are increased in subjects with renal failure, even in the absence of myocardial ischemia [124-125]. In fact, approximately 53% of patients with chronic kidney disease present with elevated troponin T without acute myocardial necrosis [126] As troponin T is normally cleared by the kidneys, it could be elevated in chronic kidney disease owing to delayed clearance [127]. However, other reasons could also explain the high troponin T levels, as left ventricular hypertrophy, congestive heart failure, and sepsis [125,126,128]. The combination of increased levels of CRP and troponin T levels are associated with an increased risk of death in chronic kidney disease [129]. Finally, Wong et al state that the posi-

tive correlation between Troponin T and CRP could be due to an inflammatory process that could induce a sub-clinical myocardial damage resulting from endothelial injury and atherosclerosis [130]. How does proteinuria fit into this process?: In dialysis, proteinuria could be an important cause of inflammation and of endothelial dysfunction and atherosclerosis and peripheral vascular disease as in previous stages of chronic kidney disease [91, 117, 131], triggering CRP and troponin T elevations. This situation could justify that as proteinuria worsens, the correlation we found between troponin T and CRP rises significantly. It has recently been published that in a murine model of spontaneous albuminuric chronic kidney disease, the systemic endothelial glycocalyx is altered in its glycosylated components due to proteinuria itself. Therefore, it becomes reasonable to speculate that as this meshwork of surface-bound and loosely adherent glycosaminoglycans and proteoglycans modulates vascular function, its loss could contribute to both renal and systemic vascular dysfunction in proteinuric chronic kidney disease, including dialysis patients [132].

Therefore, it ought to be reasonable to focus on proteinuria as a target to treat, as its decrease may portend a better care of residual kidney function and cardiovascular status in stage 5D subjects. However, once patients are started on dialysis, proteinuria generally appears to be ignored and forgotten as a potential factor of morbidity and mortality, as it occurs in predialysis subjects. Proteinuria may contribute to the burden of cardiovascular disease and should be a parameter to pay attention to in dialysis individuals. Finally, despite being on dialysis, proteinuria should be controlled as its persistence may hasten the loss of residual renal function, a relevant item to preserve at any price in this population.

Moreover, proteinuria is not only important as a marker of progression of renal disease, but it is also associated with catabolic processes, protein-energy wasting, hypoalbuminemia, and inflammation. All these processes are prevalent in the dialysis community [11,12,17]. However, the data relating proteinuria and hemodialysis is more than scant. In a work published by Goldwasser et al in 1999, in which they observed a rise in albumin and creatinine in those patients who entered dialysis after six months of treatment, they hypothesized that this phenomenon could be attributed, in part, to a better nutritional status, a gain in muscle mass, and to a decline in residual renal function [121]. This decrease in urinary output could consequently result in lower losses of protein in the urine. Finally, it is well known that as proteinuria progresses, and more importantly without any medical intervention focused specifically on it, parenchymal fibrosis ensues and residual renal function rapidly deteriorates.

One question that needs to be addressed for dialysis patients is the threshold above which proteinuria would be implicated in inflammatory processes and could have any implication or contribution in the development of cardiovascular disease. Should the levels of proteinuria be interpreted in the same way as in pre-dialysis subjects?. Our study suggests that as proteinuria increases, cardiovascular stress and inflammatory processes are more prone to be encountered. No data exists whether proteinuria should be treated in dialysis and, if that were the case, the level to pursue. Our data suggest that proteinuria should be treated, considering its association with inflammation and cardiovascular stress. Although, as mentioned above, angiotensin converting enzyme inhibitors or angiotensin II

receptor blockers could have modified the results, these drugs were employed homogeneously in the three groups.

Finally, we have observed (data not published) that at higher degrees of proteinuria, urinary output deteriorates faster. At similar initial urinary output rates, patients with proteinria > 3 g/day performed differently from those < 3 g/day: After three years of follow-up, patients with proteinuria > 3 g/day when entering hemodialysis were anuric and therefore had no residual renal function. Patients with proteinuria < 3 g/day still had residual renal function, and proteinuria did not worsen significantly during the time of follow-up. Whether this was be due to a higher proportion of diabetic patients, to higher degrees of proteinuria, or to other cofactors as previous administration of contrast agents or exposure to nephrotoxic drugs cannot be concluded from our data. Besides, in patients with heavy proteinuria a shorter time on hemodialysis trend was observed. Again, whether this phenomenon should be ascribed to diabetes mellitus itself, or to proteinuria could not be concluded. Interestingly, as mentioned before, in non-dialysis patients proteinuria in diabetics is associated with an increased risk of cardiovascular events and mortality [85-87,95-97]. However, we underscore the critical importance proteinuria may play on hemodialysis as a forgotten, overlooked marker of cardiovascular and inflammation.

Our experience, albeit limited, calls the attention of nephrologists to take proteinuria into account when a hemodialysis patient is assessed. Due to the small number of cases included in our recently published study, conclusions must be drawn cautiously. In this respect, the significant correlation found between CRP and Troponin T may be associated with heavy proteinuria, but other factors not assessed in this study may also be involved. We were unable to measure other inflammatory molecules as interleukin-6 and Tumor Necrosis Factor, or endothelial and procoagulant molecules as Plasminogen Activator Inhibitor-1, which are more sensitive than CRP and would have certainly added more information to the data presented in this study. Finally, no vascular arteriosclerotic parameters as pulse wave velocity were evaluated in our patients, which would have certainly enriched our primary findings. Moreover, as an observational study in a cross-sectional cohort, no follow-up with regard to patient prognosis, to the evolution of proteinuria and its correlation with other biomarkers, and to mortality rates could not be obtained. All these results require validation [120]. However, we believe this work is a call of attention to nephrologists regarding another important aspect of the characteristics of urinary output and residual renal function in dialysis patients.

6. Conclusions

Proteinuria is a strong predictor of chronic kidney disease progression. It is also an important marker of cardiovascular disease, both in patients with or without kidney disease. In hemodialysis individuals, urinary output is associated with morbidity and mortality. At higher levels of diuresis, there is a trend to lesser rates of hospitalization and a higher mortality. Most of renal functions are better preserved if associated with higher volumes of

urine. In this regard, proteinuria plays a critical role in renal fibrosis, stimulating sclerosis in the glomerular and in the interstitial compartments. This sclerosis causes in turn local ischaemia and further deterioration of kidney function, which can be clinically assessed with creeping of serum creatinine and a final decline in urinary output. This phenomenon is observed throughout the chronic kidney disease process, even at the dialysis setting. We have found that in chronic hemodialysis patients, at higher degrees of proteinuria, systemic markers of cardiovascular disease and inflammation are elevated. Albeit not proven yet, as proteinuria causes an eventual decline in renal function, and preservation of residual renal function is associated with higher survival rates in dialysis patients, proteinuria may be also associated with a decrease in urinary output and an increase in morbidity events and mortality in chronic hemodialysis.

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Chapter 8

Glycemic Control in Diabetic Patients on Long-Term Maintenance Dialysis

Pornanong Aramwit and Bancha Satirapoj

Additional information is available at the end of the chapter

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1. Introduction

The epidemiology of end-stage renal disease (ESRD) varies considerably worldwide. In Thailand, the incidence of ESRD on renal replacement therapy (RRT) increased from 78.9 per million populations in 1999 to 552.8 per million populations in 2009. The yearly incidence of all RRT modalities increased by an average of 34.8% from 2007 to 2009 [1]. According to the estimation by the International Diabetes Foundation, by the year 2025 the frequency of diabetes is expected to increase threefold worldwide [2]. Diabetic nephropathy is the most common cause of ESRD [3], representing 30-47% of the United States and Asian populations undergoing long-term maintenance hemodialysis [4, 5]. Disparities in the incidence of ESRD due to diabetes among ethnic groups have existed for many years, but the magnitude may be increasing.

In the United States, from 1990 to 1996, the age-adjusted diabetes-related ESRD incidence increased from 299.0 to 343.2 per 100,000 diabetic patients. However, from 1996 to 2006, the age-adjusted diabetes-related ESRD incidence decreased by 3.9% per year from 343.2 to 197.7 per 100,000 diabetic patients [6]. Diabetes-related ESRD incidence in the diabetic population has declined in all age-groups, probably because of a reduction in the prevalence of ESRD risk factors, improved treatment and care, and other factors. An alternative explanation for the decline in diabetes-related ESRD incidence in the diabetic population might be that the patients are not surviving long enough to develop ESRD, which occurs typically between 10 and 15 years after the onset of the disease. Premature mortality among ESRD patients with diabetes as a result of the increasing prevalence of coronary heart disease and stroke by tenfold could reduce the number of people who ultimately develop ESRD [7, 8]. Even though diabetes-related ESRD incidence in the population with diabetes has decreased since 1996, diabetes-related ESRD incidence in the general population and the number of persons initiating

treatment for kidney failure each year who have diabetes listed as a primary cause continue to increase [5, 9]. In Europe, data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry shows an 11.9% annual increase in patients with type 2 diabetes entering RRT [10]. The most recent report of the Thailand RRT Registry shows a prevalence of diabetes among patients with ESRD of 47.6% and an incidence of 47.7%. The majority of patients with ESRD secondary to diabetes (51.0%) are treated by hemodialysis, 45.1% by peritoneal dialysis, and 3.9% have functioning renal transplants [1].

Diabetes-related ESRD is a costly and disabling condition with a high mortality rate. These patients are at a higher risk of mortality, mostly from cardiovascular complications, than other patients with diabetes. Apart from cardiac complications, the patients are subject to a wide range of vascular (e.g., peripheral vascular disease, stroke) and infectious complications. Patients with ESRD due to diabetes challenge the nephrologists because they have the greatest number of comorbid conditions, and the greatest dependency during daily activities. The goal of therapy is to improve quality of life, as well as reduce mortality. Attention to several basic principles helps to guide therapy: control of hypertension, control of hyperglycemia, control of lipid abnormalities, treatment of malnutrition, and attention to the effects of erythropoietin. Current cardio- and renoprotective treatment for diabetic nephropathy without ESRD includes optimization of glycemic control. Early intensive glycemic interventions reduce cardiovascular events as well as nephropathy by about half when compared with a conventional glycemic treatment. However, hypoglycemia is common because of impaired renal gluconeogenesis, malnutrition, chronic inflammation, decrease renal insulin clearance and the increased half-life of hypoglycemic agents [11]. Therefore, data are scarce on how diabetes should best be treated in patients in ESRD. In this chapter, we summarize the current evidence for glucose metabolism and glycemic control in diabetic patients on dialysis.

2. Glucose metabolism in dialysis

Hyperglycemia is an important factor in the progression of diabetic nephropathy. Early functional changes in diabetic nephropathy include glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy, and the development of microalbuminuria, followed by the development of glomerular basement membrane (GBM) thickening, accumulation of mesangial matrix, and overt proteinuria, eventually leading to glomerulosclerosis and ESRD. Hyperglycemia-induced metabolic and hemodynamic pathways are recognized to be mediators of kidney injury [4].

Glucose transport activity is an important modulator of extracellular matrix formation by mesangial cells. Glucose transporter-1 (GLUT-1) regulates glucose entry into renal cells. Glucose and its metabolites subsequently activate metabolic pathways, and these pathways contribute to mesangial expansion and mesangial cell matrix-production, mesangial cell apoptosis and structural changes [12]. This may result from a similar increase in the mesangial cell glucose concentration, since similar changes in mesangial function can be induced in a normal glucose milieu by over-expression of GLUT1 [13]. Multiple biochemical pathways have

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been postulated that explain how hyperglycemia causes tissue damage including: non-enzymatic glycosylation that generates advanced glycosylation end products (AGE); activation of protein kinase C (PKC); and acceleration of the polyol pathway. Oxidative stress also seems to be a common theme. These pathways ultimately lead to increased renal albumin permeability and extracellular matrix accumulation, resulting in increasing proteinuria, glomerulosclerosis and ultimately renal fibrosis.

In ESRD, both uremia and dialysis can complicate blood glucose control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin. The abnormal glucose homeostasis in patients with dialysis is postulated to be multifactorial issues as Figure 1.

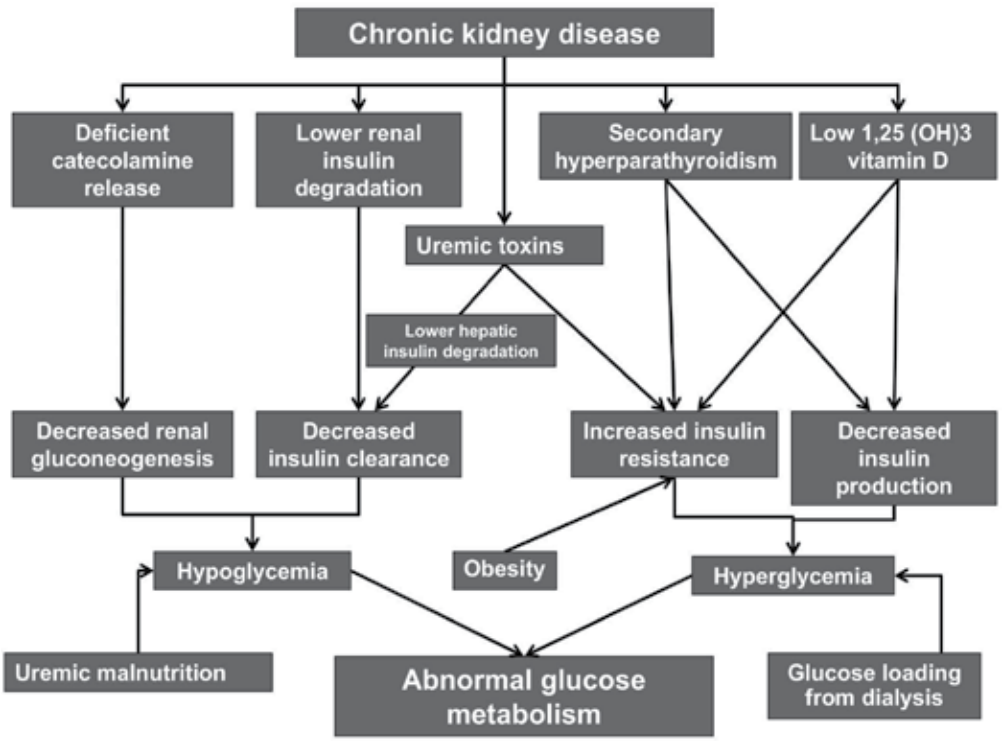

Figure 1. Contribution factors for the abnormal glucose metabolism in dialysis patients.

2.1. Hyperglycemia: Increased insulin resistance and decrease insulin production in dialysis

Advanced-stage chronic kidney disease (CKD) or ESRD can show mild fasting hyperglycemia and abnormal glucose tolerance, suggesting that the uremic state alters glucose homeostasis [14]. Insulin resistance is also frequently recognized in uremic patients and is a predictor of cardiovascular mortality in ESRD patients [15]. Impaired insulin sensitivity in the absence of overt diabetes play a central role in the development of atherosclerotic vascular disease [16]. Several clinical studies have noted impaired tissue sensitivity to insulin in diabetic nephrop-

athy [17], and non-diabetic patients exhibit only mild to moderate reductions in renal function [18-20] and in ESRD [21, 22]. However, impaired insulin sensitivity in both dialysis groups after long-term dialysis was still higher than that of the non-dialysis ESRD group while no significant differences were noted between peritoneal dialysis and hemodialysis treatments [23]. The mechanism of increased insulin resistance in patients with kidney disease is not fully understood. Several factors, including uremic toxins, may increase insulin resistance in ESRD, leading to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose utilization. In addition, in non-diabetic CKD patients, an independent factor for insulin resistance was the amount of total body fat and body mass index [20]. This change occurs in ESRD because of concomitant metabolic acidosis, deficiency of 1,25 dihydroxy-vitamin D, and secondary hyperparathyroidism. In addition, in uremic patients, previous studies have reported that treatment with hemodialysis, active vitamin D, erythropoietin and angiotensin receptor blocker can improve insulin insensitivity [21, 24-26].

Further complicating the effect of dialysis is the glucose load provided by both dialysis modalities. The dextrose concentration in the dialysate can also affect glucose control. In hemodialysis population, dialysates with lower dextrose concentrations are used and may be associated with hypoglycemia. Conversely, dialysates with higher dextrose concentrations are occasionally used in hypoglycemic patients on hemodialysis and low ultrafiltration patients on peritoneal dialysis (PD), but this can lead to hyperglycemia and insulin resistance [27].

2.2. Hypoglycemia: Decreased insulin clearance and renal gluconeogenesis in dialysis

Decreasing insulin requirements and frequent hypoglycemia also occur in diabetic patients on dialysis. Renal insulin clearance decreases as glomerular filtration rate decreases to less than 15 to 20 mL/min/1.73 m^2 [14]. Hepatic clearance of insulin is also decreased in patients with uremia. In addition, deficient gluconeogenesis along with malnutrition, deficient catecholamine release, and impaired renal insulin degradation and clearance, can contribute to frequent hypoglycemia in patients with CKD [28, 29].

Thus, advanced CKD and ESRD on dialysis exert opposing forces on insulin secretion, action, and metabolism, often creating unpredictable serum glucose values. Some patients who have insulin resistance would need more supplemental insulin. In contrast, the reduced renal gluconeogenesis and insulin clearance seen in ESRD may result in less requirement for insulin treatment. Together, all of these factors contribute to wide fluctuations in plasma glucose levels and increase the risk of both hyperglycemic and hypoglycemic events. Both of these abnormalities are at least partially reversed with the institution of dialysis. As a result, the insulin requirement in any given patient will depend upon the net balance between improving insulin secretion and insulin sensitivity, and restoring normal hepatic insulin metabolism.

3. Glycemic control in dialysis

Glycemic therapy in patients with diabetes has been shown to improve outcomes, especially microvascular complications in patients without kidney disease [30, 31]. The efficacy of

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glycemic control depends in part upon the stage at which it is begun and the degree of normalization of glucose metabolism. Glycemic control can partially reverse the glomerular hypertrophy and hyperfiltration that are thought to be important pathogenic pathways for diabetic nephropathy, and decrease the incidence of new-onset microalbuminuria in retrospective [32] and prospective studies of patients with diabetes [31, 33]. Progression of established overt nephropathy can also be stabilized or retarded through strict glycemic control. However, proving the efficacy of this treatment is difficult, and previous studies examining outcomes of glycemic control in dialysis patients gave conflicting results [34]. The benefit of glucose control on progression in patients with CKD who have advanced kidney disease is less well studied.

Interestingly, benefits of glycemic control after pancreas transplantation in patients with type 1 diabetes were observed: mesangial matrix volume, thickening of glomerular and tubular basement membranes, and nodular glomerular lesions were significantly decreased and/or returned to normal compared to the same measurements at zero and ten years [35, 36].

Effects of intensive glycemic control on prevention of macrovascular complications (e.g., coronary artery disease, peripheral artery disease, cerebrovascular disease) are less certain, particularly in type 2 diabetes. The 10-year follow-up study of patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated risk reduction for myocardial infarction and death from any cause [37]. More recent studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VA-DT) that targeted even lower hemoglobin A_{1c} (HbA_{1c}) goals (<6–6.5%), failed to show cardiovascular disease risk reduction with more intensive glycemic control regimens [38-40].

Several observational studies showed that higher levels of hemoglobin A_{1c} were associated with higher mortality rates in patients with diabetes on long-term dialysis and CKD [41-44]. A previous study demonstrated that a paradoxically lower unadjusted mortality associated with greater hemoglobin A_{1c} levels were found in 23,618 dialysis patients with diabetes. However, after adjusting for markers of malnutrition and inflammation, hemodialysis patients with hemoglobin A_{1c} levels <5% or >7% became associated with greater mortality [45]. The data indicate that competing risk factors related to malnutrition, muscle wasting, and anemia may confound the association between glycemic control and survival in diabetic patients with long-term dialysis. In the study by Williams, hemoglobin A_{1c} levels >11.0% in type 1 diabetes on hemodialysis were required to observe a statistically significant higher mortality risk, but few subjects had hemoglobin A_{1c} levels in this category [46]. In a recent cohort of 54,757 diabetic hemodialysis patients, poor glycemic control (hemoglobin A_{1c} ≥8% or serum glucose ≥200 mg/dL) appears to be associated with high all-cause and cardiovascular death and very low glycemic levels (hemoglobin A_{1c} <7%) are also associated with high mortality risk [47]. In a single interventional study in 83 dialysis patients, patients in the intensive intervention group experienced improved quality of life and a decreased need for amputations and hospitalizations [48]. Larger clinical trials are needed to conclusively prove the concept that better glycemic control is beneficial in patients with advanced CKD. To date, there are no data

available from randomized clinical trials targeting different hemoglobin A_{1c} levels and powered for cardiovascular events or mortality in ESRD populations. Careful evaluation of the relationship of hemoglobin A_{1c} with these outcomes in ESRD patients should be a high priority for future research to determine the risks and benefits of different hemoglobin A_{1c} targets.

The Kidney Disease Outcomes Quality Initiative (KDOQI) foundation state that target hemoglobin A_{1c} for people with diabetes should be <7%, irrespective of presence or absence of CKD. This recommendation is in line with diabetes management in the general population [11]. However, very few studies have addressed the benefits and risks of intensive glycemic control in late stages of CKD and ESRD. Recent evidence from randomized studies has highlighted the potential risks of aggressive glycemic control in non-ESRD diabetic populations [38, 39]. Moreover, because many dialysis patients are wasting, malnourished, and non-ambulatory, they may be less able to respond appropriately to hypoglycemia. Current evidence suggests that aggressive glycemic control cannot be routinely recommended for all diabetic hemodialysis patients on the basis of reducing mortality risk. Physicians are encouraged to individualize glycemic targets based on potential risks and benefits in diabetic ESRD patients.

The guidelines of the 2012 American Diabetes Association recommend lowering hemoglobin A_{1c} to below or around 7% for many adults, and to implement this soon after the diagnosis of diabetes that is associated with long-term reduction in macrovascular disease [49]. Providers might reasonably suggest more stringent hemoglobin A_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life-expectancy, and no significant cardiovascular disease. Less stringent hemoglobin A_{1c} goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life- expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain [49]. Therefore, providers should be vigilant in preventing severe hypoglycemia in patients with advanced kidney disease or ESRD and should not aggressively attempt to achieve near-normal hemoglobin A_{1c} levels in patients in whom such a target cannot be reasonably easily and safely achieved.

4. Monitoring of glycemia in dialysis

Glucose homeostasis is altered significantly in patients with uremia. Glycated hemoglobin (expressed as a percentage of total hemoglobin) or hemoglobin A_{1c} measurement is used as an indicator of integrated glucose control. Glycated hemoglobin is formed by the non-enzymatic reaction between glucose and the N-terminal amino group on the beta chain of hemoglobin. The good correlation between hemoglobin A_{1c} and blood glucose in non-CKD type 1 diabetic patients has been documented in the Diabetes Control and Complications Trial (DCCT) [50]. At present, this test is the most accurate method to assess chronic glycemic control based on

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clinical outcomes associated with certain hemoglobin A_{1c} levels in diabetic patients with normal kidney function [31]. The validity of glycated hemoglobin and hemoglobin A_{1c} has not been rigorously studied in patients with ESRD. These tests may be unreliable in dialysis patients because of assay interference due to the elevated blood urea nitrogen. Glycated hemoglobin tests, such as column- and ion-exchange chromatography and agar gel electrophoresis, are affected by uremia. This is due in part to analytical interference from carbamylated hemoglobin formed in the presence of elevated concentrations of urea, leading to false elevations in the hemoglobin A_{1c} level. Use of agarose affinity chromatography or the thiobarbituric acid method for analyzing hemoglobin A_{1c} can be used reliably in patients with ESRD. Other factors such as shorter life span of red blood cells, iron deficiency anemia, and recent transfusion may also cause underestimation of glucose control in diabetic hemodialysis patients (Table 1). In addition, patients treated with erythropoietin could lead to underestimation of glycemic control by using hemoglobin A_{1c} level, because of the greater proportion of young erythrocytes in the circulation of patients [51]. Therefore, hemoglobin A_{1c} levels tend to underestimate glycemic control in diabetic patients undergoing long-term maintenance hemodialysis [52, 53].

Falsely increased hemoglobin A_{1c}	**Falsely decreased hemoglobin A_{1c}**
Carbamylated hemoglobin for charge-dependent chromatography assays	Erythropoiesis supplement
Increased glycosylation rate	Shortened life span of red blood cells
Uremia	Blood transfusions
Metabolic acidosis	Hemoglobinopathy

Table 1. Glycated hemoglobin levels in dialysis patients

Despite anemia and shortened RBC lifespan in ESRD patients, hemoglobin A_{1c} in the range of 6% to 7% estimates glycemic control similarly to patients without severe renal impairment. Hemoglobin A_{1c} above 7.5% may overestimate hyperglycemia in patients with ESRD [43]. It is important to be aware of the specific assay used and the other factors affecting the accuracy of hemoglobin A_{1c} measurements in ESRD on hemodialysis and peritoneal dialysis.

Another potential method to monitor glycemic control in patients with uremia is glycated albumin. Some studies suggest that glycated albumin more accurately reflects glycemic control in diabetic hemodialysis patients than hemoglobin A_{1c} [54, 55]. However, falsely increased glycated albumin values have been measured in the presence of lipemia, hemolysis, and high bilirubin and uric acid concentrations. In addition, use of glycated albumin is hampered by conditions that alter protein metabolism including ESRD, their lack of availability in routine practice and the lack of established reference levels [56].

Despite the limitations in using hemoglobin A_{1c} in the dialysis population, this test is considered a reasonable measure of chronic glycemic control in this group. Patient self-monitoring of blood glucose is also available for patients to assess the effectiveness of the management

plan on glycemic control. It provides real-time assessments of glycemic control and results of self-monitoring of blood glucose can be useful in preventing hypoglycemia and adjusting medications (particularly prandial insulin doses), and physical activity. There are some limitations of this method, because it is subject to errors from poor technique, problems with the meters and strips, and lower sensitivity in measuring low blood glucose levels. However, hemoglobin A_{1c} does not provide a measure of glycemic variability or hypoglycemia. Thus, for patients prone to glycemic variability (especially type 1 patients, or type 2 patients with severe insulin deficiency), glycemic control is best judged by the combination of results of self-monitoring of blood glucose testing and the hemoglobin A_{1c} assay [49]. Hemoglobin A_{1c} may also serve as a check for the accuracy of the patient's meter and the adequacy of the self-monitoring schedule of blood glucose testing.

5. Insulin therapy in dialysis

Insulin regulates glucose homeostasis at many sites, reducing hepatic glucose output by decreasing gluconeogenesis and glycogenolysis, and increasing the rate of glucose uptake, primarily into muscle and adipose tissue. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. The stimulated insulin receptor phosphorylates itself, and several substrates including membranes of the insulin receptor substrate family and initiate downstream signaling events [27].

In healthy non-diabetic people, the pancreatic β-cells secrete half of the daily insulin requirement (approximately 0.5 units/kilogram/day) at a steady basal rate independent of glucose levels and the other half is secreted in response to prandial glucose stimulation [57]. Insulin is secreted into the portal system, it passes through the liver where approximately 75% is metabolized with the remaining 25% metabolized by the kidneys. About 60% of the insulin in the arterial bed is filtered by the glomerulus and 40% is actively secreted into the nephric tubules [58]. Most of the insulin in the tubules is metabolized into amino acids, and only 1% of insulin is secreted intact.

Interestingly, endogenous insulin is substantially degraded by the liver but exogenous insulin is eliminated mainly by the kidney. For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver. Insulin is freely filtered at the glomerulus and extensively reabsorbed in the proximal tubule after enzyme degradation into smaller peptides. As renal function starts to decline, insulin clearance does not change appreciably, due to compensatory peritubular insulin uptake [59]. However, once the glomerular filtration rate drops below 20 mL/min, insulin clearance decreases and the half-life of insulin increases, an effect compounded by a decrease in the hepatic metabolism of insulin that occurs in uremia [25]. Glucose and insulin homeostasis are altered in CKD patients even in the early stages of CKD, leading to insulin resistance by various pathways. Studies even in the 1980s showed that, although insulin secretion in CKD is normal, a decreased tissue sensitivity to insulin is responsible for the abnormal glucose uptake [60]. In advanced CKD, particularly in stages 4 and 5, significant metabolic derangements in insulin

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metabolism occur. Several factors have been implicated in the pathogenesis of insulin resistance including anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, metabolic acidosis, and increase in plasma free fatty acids and proinflammatory cytokines. Thus, despite the increase in insulin resistance caused by renal failure, the net effect is a reduced requirement for exogenous insulin in ESRD patients [61]. Despite similar duration of disease and clinical characteristics, patients with type 2 diabetes with ESRD often show marked heterogeneity in terms of insulin requirement and dosages [62]. However, predictors for exogenous insulin requirement in patients with type 2 diabetes undergoing continuous ambulatory peritoneal dialysis (CAPD) have not been defined. Possible factors include β-cell function, endogenous metabolism and elimination of insulin, insulin resistance, body size, carbohydrate intake, and extra glucose absorbed from dialysate fluid [27].

Recent evidence showed that insulin is a anti-inflammatory hormone that suppresses several proinflammatory transcription factors such as nuclear factor κB (NF-κB), early growth response protein 1 and activating protein 1, which all mediate inflammation. An impairment of the action of insulin because of insulin resistance would therefore result in the activation of these proinflammatory transcription factors and in an increase of the expression of the corresponding genes. Derangements in other biologic effects of insulin could be associated with certain pathologic states in CKD such as hypertension and insulin resistance [63, 64].

Previous studies have shown that uremia was associated with an insulin-resistant state, mainly because of decreased insulin-stimulated uptake of glucose by muscle [65]. However, in clinical practice, with progressive renal failure, the insulin requirements of patients with diabetes for glycemic control often tend to decrease [66]. The determinants of insulin requirements in patients with diabetes with ESRD remain uncertain. This can be influenced by factors such as insulin resistance, production and metabolism of endogenous insulin, oral intake, extra carbohydrate absorbed from dialysis solution, and reduction of body weight in uremic patients [27, 67]. Possible factors for this reduction in insulin requirement include reduced renal clearance of both endogenous and exogenous insulin and progressive loss of appetite and body weight in uremic patients. However, several studies have shown similar fasting insulin levels between patients with renal failure and those with normal renal function [27, 68].

In PD patients, the development of insulin resistance after a initial improvement is generally attributed to a high glucose load absorbed from dialysis fluid, contributing to a wide spectrum of metabolic abnormalities including hypertriglyceridemia, poor glycemic control, new-onset diabetes, hypertension and central obesity. An amplifying loop in the process of glucose absorption appears to be a consequence of the modifications in the peritoneum associated with a loss of ultrafiltration capacity [69]. Disturbances of carbohydrate metabolism seem to be even more intense in non-diabetic PD patients than in hemodialysis patients. After PD initiation, a large number of patients developed new-onset hyperglycemia because of their exposure to hypertonic glucose solutions [27, 70, 71]. In fact, glucose absorption through the peritoneum results in significantly higher serum glucose levels than are produced by an equivalent dose of oral dextrose. Wong et al. show considerable variations in the need for insulin treatment and dosages in patients with type 2 diabetes undergoing CAPD despite similar disease duration, dialysis regimens, renal function, and glycemic control [67]. Duration of diabetes,

hemoglobin A_{1c} level, and body weight were independent determinants of insulin requirement of patients with type 2 diabetes with ESRD patients undergoing CAPD. Dialysis regimen with estimated amount of glucose absorbed and Kt/V did not predict insulin requirement in these patients. Insulin resistance, insulin requirement, and fasting C-peptide levels, a crude measurement of basal pancreatic β-cell function in patients with diabetes with normal renal function, were not affected by dialysis dosage, reflected by a similar value of Kt/V [67]. Insulin-treated patients had lower C peptide concentrations than non-insulin-treated patients, and insulin dosage required was correlated with duration of diabetes mellitus, implying the significance of β-cell function in determination of insulin requirement in patients with type 2 diabetes with ESRD.

Insulin injection therapy remains the mainstay treatment to achieve good glycemic control in diabetic patients receiving hemodialysis therapy [72]. In hemodialysis patients, the insulin sensitivity normally improves on both an acute and chronic basis [66], mainly by clearing circulating urea, and also insulin clearance. The concentration of glucose and insulin is frequently affected by the dialysis procedure itself. Changes in glucose will vary with the concentration of glucose (dextrose) in the dialysis fluid, to which the patient's blood is indirectly exposed. Because glucose transfers to the dialysate according to its concentration gradient, dialysate lacking glucose is associated with significant decreases in plasma glucose levels in poorly and well-controlled diabetic patients as well as in some non-diabetic patients, and is no longer used. Plasma insulin levels also are decreased during the hemodialysis treatment, due to clearance by dialysis which varies among membranes and with the fall in glucose. Additional metabolic effects of dialysis include improvement in sensitivity to insulin and decrease in some cases of counter-regulatory hormones (e.g., growth hormone). In poorly controlled patients, hemodialysis-induced clearance of plasma immunoreactive insulin levels may result in hyperglycemia in the post-dialysis period [63].

Various insulin preparations are available in the market. In ESRD patients, insulin doses will need to be reduced, especially after dialysis has been initiated [63]. Sobngwi et al. show that the daily insulin needs on the day after hemodialysis should be decreased approximately 15% compared with the daily insulin needs before hemodialysis, with a significant reduction of basal hourly insulin requirement by 25%, unchanged boluses, and unchanged body weight-indexed total insulin dose in a group of type 2 diabetic patients on maintenance hemodialysis [73]. However, no evidence for the benefit of neutral protamine hagedorn (NPH) insulin or other long-acting insulin in patients with ESRD is available. On the other hand, insulin lispro which has a short onset of action and a short duration of action shows the benefit not only facilitate the correction of hyperglycemia but may also decrease the risk of late hypoglycemic episodes, which is of increased relevance in hemodialysis patients [64] because its pharmacokinetics is less affected in renal failure [74]. Long-acting insulin such as insulin glargine or NPH insulin can be widely used as basal requirements, along with a rapid-acting insulin analogue such as lispro or insulin aspart before meals two or three times daily [57]. When the glomerular filtration rate drops between 10 and 50 mL/min, the total insulin dose should be reduced by 25%. Once the filtration rate is below 10 mL/min, as in ESRD patients, the insulin dose should be decreased by 50% from the previous amount [75].

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Unexpected hypoglycemia often occurs in dialysis patients during basal-bolus insulin therapy despite careful adjustment of their insulin dose which may due to 3 main factors: (1) prolongation of the elimination half-life of insulin associated with decreased renal degradation and excretion [68]; (2) impairment of gluconeogenesis by the kidneys and (3) weak gastric peristalsis in diabetic patients on dialysis, with prolongation of stomach food retention, resulting in delays in glucose absorption [76]. It is important to note that the signs and symptoms of hyperglycemia are modified in patients with ESRD [63]. Signs and symptoms of hyperglycemia may involve thirst, fluid overload, and hyperkalemia rather than polyuria. Lacking polyuria, patients experience volume expansion, not contraction; excessive thirst will result in large weight gains, which correlate with poor glycemic control between dialysis treatments. Severe hyperglycemia may result in hyperkalemia and complicate management further. Other findings may be pulmonary edema, hypertension, anorexia, altered mental status, nausea, vomiting, and gastroparesis, although symptoms are frequently nonspecific or lacking.

6. Oral antihyperglycemic drugs in dialysis

Therapeutic options for patients with diabetes with CKD and ESRD are limited because a reduced glomerular filtration rate results in the accumulation of certain drugs and/or their metabolism [77]. Most of oral antihyperglycemic drugs include the insulin secretagogues such as sulfonylureas and meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors are contraindicated in ESRD patients. However, some agents have been used in patients with CKD and were found to be effective and safe even in those on dialysis. Therefore, some medications may be useful therapeutic options for the management of diabetes in CKD.

As shown in Table 2, insulin secretagogues can be classified as sulfonylureas and meglitinides while alpha-glucosidase inhibitors are modifiers of glucose absorption and thiazolidinediones are insulin sensitizers. Incretin-related therapies include dipeptidylpeptidase-4 (DPP-4) inhibitors and incretin mimetics. DPP-4 inhibitors are oral antidiabetic agents, whereas incretin mimetics are used by subcutaneous injection.

Since many drugs bind to serum protein, primarily albumin and plasma concentration of albumin in patients with renal impairment is commonly decreased, the concentrations of unbound drugs are increased.

Sulfonylureas

Insulin secretagogues increase endogenous insulin levels. These agents work by binding to sulfonylurea receptors or nearby sites, resulting in closure of ATP-sensitive potassium channels of the pancreatic β-cell, depolarization of the cell membranes, calcium influx, and subsequently insulin release [72]. They have a wide volume of distribution and are highly protein-bound. However, only the unbound drug exerts a clinical effect. Because of high protein binding property, dialysis cannot effectively clear elevated levels of sulfonylurea drugs. As these agents increase endogenous insulin levels, they are associated with an increased risk of hypoglycemia. This risk is mitigated when shorter-acting agents are used. Furthermore, many ESRD patients take drugs such as sulfonamides, vitamin K antagonists,

beta-blocker, salicylates and fibric acid derivatives which may displace sulfonylureas from albumin, thus increasing the risk of severe hypoglycemia.

Category	Action	Group	Medication	Medication	Medication	Dosing recommendation CKD stage 3, 4 or kidney transplant	Dialysis dose recommendation
Insulin	**Sensitizers**	**Biguanides**	Metformin			Contraindicated with kidney dysfunction defined as sCr≥1.5 mg/dL in men or≥1.4 mg/dL in women	Avoid
Insulin	**Sensitizers**	**TZDs (PPAR)**	Pioglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**TZDs (PPAR)**	Rivoglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**TZDs (PPAR)**	Rosiglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**Dual PPAR agonist**	Aleglitazar			Use with caution	Use with caution
Insulin	**Sensitizers**	**Dual PPAR agonist**	Muraglitazar			Use with caution	Use with caution
Insulin	**Sensitizers**	**Dual PPAR agonist**	Tesaglitazar			Use with caution	Use with caution
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Acetohexamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Carbutamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Chlorpropamide	Reduce dose by 50% when GFR<70 and 50³mL/min/1.73m² and avoid when GFR<50 mL/min/1.73 m²	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Metahexamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Tolbutamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Tolazamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glipizide	Preferred, no dose adjustment needed	Preferred, no dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Gliclazide	Preferred, no dose adjustment needed	Preferred, no dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glyburide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Nateglinide		Initiate at low dose, 60 mg before each meal	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Repaglinide		No dose adjustment needed, initiate at 0.5 mg dose when GFR<40 mL/min/1.73 m²	No dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Mitiglinide		No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**GLP-1 analogs (Incretin Mimetics)**	Exenatide			Not recommended in patients with GFR<30 mL/min/1.73 m² and caution should be applied when GFR>30 and< 50 mL/min/1.73 m², No dose adjustment needed when GFR>50 and <80 mL/min/1.73 m²	Avoid
Insulin	**Secretagogues**	**GLP-1 analogs (Incretin Mimetics)**	Liraglutide			No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Alogliptin			Reduce dose by 50% (12.5 mg/day) when GFR<50 and 30 ³ mL/min/1.73 m² and by 75% (6.25 mg/day) when GFR<30 mL/min/1.73 m²	Reduce dose by 75% (6.25 mg/day)
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Linagliptin			No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Sexagliptin			Moderate to severe kidney impairment should receive<2.5 mg/d	Moderate to severe kidney impairment should receive<2.5 mg/d
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Sitagliptin			Reduce dose by 50% (50 mg/day) when GFR<50 and 30³mL/min/1.73 m² and by 75% (25 mg/day) when GFR<30 mL/min/1.73 m²	Reduce dose by 75% (25 mg/d)
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Vildagliptin			Initiate at low dose	Initiate at low dose

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Category	Action	Group	Medication	Medication	Medication	Dosing recommendation CKD stage 3, 4 or kidney transplant	Dialysis dose recommendation
Insulin	**Analogs/other insulins**	**Rapid-acting**	Regular			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Rapid-acting**	Lispro			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Rapid-acting**	Aspart			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Long-acting**	NPH			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Long-acting**	Glargine			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Long-acting**	Determir			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Premixed**	70/30 human mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Insulin	**Analogs/other insulins**	**Premixed**	70/30 aspart mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Insulin	**Analogs/other insulins**	**Premixed**	75/25 lispro mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Others	**Alpha-glucosidase inhibitor**		Acarbose			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Alpha-glucosidase inhibitor**		Miglitol			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Alpha-glucosidase inhibitor**		Vogibose			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Amylin analog**		Pramlintide			No dose adjustment needed for GFR 20-50 mL/min/1.73 m^2	No data available
Others	**SGLT2 inhibitor**		Canagliflozin			No data available	No data available

* Modify from Masanori Abe, Kazuyoshi Okada and Masayoshi Soma "Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice" Current Drug Metabolsim Volume 12, January 2011, with permission.

Table 2. Oral anti-diabetic drugs and insulin analogs

The first-generation sulfonylureas-chlorpropamide, acetohexamide, tolbutamide, and tolazamide are almost exclusively excreted by the kidney and are therefore contraindicated in ESRD patients [78]. Second-generation agents include glimepiride and glyburide which are metabolized in the liver. However, their active metabolites are excreted in the urine and so these medications should be avoided in ESRD patients as well [72] but low-dose initiation can be used in patients with CKD [79]. Glipizide and gliclazide are the preferred agents and no dose adjustment has been necessary in a dialysis population [11].

Most sulfonylureas are not suitable for ESRD patients due to the risk of prolonged hypoglycemic; furthermore, metformin is contraindicated [80]. From all medications in this group, the only sulfonylurea recommended in ESRD patients are glipizide and gliclazide which are also metabolized in the liver but has inactive or weakly active metabolites excreted in the urine [57]. Glipizide is eliminated primarily by hepatic biotransformation; < 10% of a dose is excreted as unchanged drug in urine or feces while approximately 90% is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation that have no hypoglycemic activity. A minor metabolite which accounts for < 2% of a dose, an acetylamino-ethyl benzene derivative, is reported to have 1/10 to 1/3 of the hypoglycemic activity compared to the parent compound. The suggested dose of glipizide is 2.5 to 10 mg/day. In ESRD patients, sustained-release forms should be avoids due to the concerns of hypoglycemia [81].

Meglitinides

Repaglinide, nateglinide and mitiglinide are insulin secretagogues that stimulate pancreatic β-cells. They are currently in clinical use because of their rapid onset of action resulting in improvement in hyperglycemia. Like sulfonylureas, nateglinide is hepatically metabolized, with renal excretion of active metabolites. On the other hand, repaglinide is almost completely converted to inactive metabolites in the liver, and less than 10% is excreted by the kidneys [82, 83]. Nateglinide still pose a risk of hypoglycemia especially in ESRD patients. Because of that, this drug is not recommended to use in patients on hemodialysis [82, 83]. However, mitiglinide shows selective action on the ATP-sensitive potassium channel of pancreatic β-cells and the order of affinity is mitiglinide > repaglinide > nateglinide [84]. This result suggests that mitiglinide induces insulin secretion by specifically acting on pancreatic β-cells and has few unwanted effects on the cardiovascular system. Because mitiglinide is rarely accompanied by hypoglycemia, it may be an attractive therapeutic option for patients undergoing dialysis [85]. However, the optimal daily dose of mitiglinide is suggested to be lower in the diabetic hemodialysis patients than that in the diabetic patients with normal kidney function. Mitiglinide has the potential to reduce the number of type 2 diabetics on hemodialysis who ultimately require insulin injection therapy. The daily dose of mitiglinide (23 mg) was adequate, as evidenced by the fact that it was able to induce significant reductions in glycemic parameters such as fasting plasma glucose, hemoglobin A_{1c}, glycated albumin, and homeostasis model assessment for insulin resistance (HOMA-IR) levels [86]. This suggests that appropriate blood glucose levels can be maintained even at a low dose of mitiglinide, not only during the postprandial period but also before meals, due to the prolonged half-life of mitiglinide in patients on

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dialysis compared with the half-life in those with normal renal function. Abe et al. reported that mitiglinide significantly improved glycemic control, triglyceride levels and interdialytic weight gain even when administered for only a short duration [87]. Thus, mitiglinide not only improved hemoglobin A_{1c} and glycated albumin, the overall index of glycemic control in type 2 diabetes, but also effectively improved fasting plasma glucose in dialysis patients [72, 85].

Biguanides

Metformin, the drug of choice for many patients with type 2 diabetics, is a biguanide that reduces hepatic gluconeogenesis and glucose output. Metformin does not cause increase insulin levels, but rather decreases hepatic glucose output by suppressing fasting gluconeogenesis. It is absorbed via the small intestine and the absolute bioavailability is approximately 50-60%. Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion [88]. Renal clearance of metformin is approximately 3.5-fold greater than creatinine clearance, which indicates that tubular secretion via human organic cation transporter 2 is the major route of metformin elimination [89]. Single-dose and steady-state pharmacokinetics of metformin were compared between patients with normal renal function (CrCl > 90 mL/min), mild impaired renal function (CrCl 61-90 mL/min) as well as moderate (CrCl 31-60 mL/min) and severe impaired renal function (CrCl 10-30 mL/min). The results show that in patients with moderate to severe impaired renal function, C_{max} and AUC are increased 173% and 390%, respectively, compared to the patients with normal renal function [89]. In patients with decreased renal function, based on the measurement of CrCl, the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in CrCl [89]. Therefore, metformin should be avoided in patients with moderate to severe CKD including those on dialysis since the risk of metformin accumulation and lactic acidosis increases in line with the degree of impairment of renal function [90].

Thiazolidinediones

Rosiglitazone and pioglitazone are highly potent, selective agonists that work by binding to and activating a nuclear transcription factor, specifically, peroxisome proliferator-activated receptor gamma (PPAR-gamma) which improves insulin resistance in type 2 diabetic patients [91, 92] as well as increase glucose uptake in muscles and adipose tissue, and decrease hepatic glucose production [92, 93]. Both rosiglitazone and pioglitazone have an adequate oral bioavailability and are extensively metabolized by the liver. Rosiglitazone is mainly metabolized by CYP2C8 into inactive metabolites and < 1% of the parent drug appears in the urine in unchanged form [80, 94]. The half-life of rosiglitazone is similar in patients with ESRD and in healthy individuals, and can therefore be administered to ESRD patients without dose adjustment or risk of causing hypoglycemia [95-97]. Pioglitazone is metabolized by CYP3A4 and CYP2C8/9 [98]. Metabolites of pioglitazone are more active than those of rosiglitazone and are excreted predominantly in bile. The pioglitazone metabolites do not accumulate in CKD. The pharmacokinetics profile of pioglitazone was found to be similar in healthy subjects and patients with moderately or severely impaired renal function who did not require dialysis [98]. Moreover, in patients who did require dialysis, pioglitazone was found to have a T_{max} of 1.8 h

and a half-life of 5.4 h [98]. Therefore, a post-dialysis supplementary dose is not required, and pioglitazone can be administered irrespective of the time of dialysis. Due to the high molecular weight (392 Da), high protein-binding capacity (> 98%) and predominant hepatic metabolism of pioglitazone, its pharmacokinetics is similar in patients with normal renal function and CKD, and in those undergoing dialysis therapy. The main adverse reaction of these agents is edema, especially when they are used in combination with insulin. Because of that, a joint statement of the American Diabetes Association and the American Heart Association recommends avoiding thiazolidinediones in patients in New York Heart Association class III or IV heart failure [99]. Moreover, caution is required in patients in compensated heart failure (New York Heart Association class I or II) or in those at risk of heart failure such as patients with history of myocardial infarction or angina, hypertension, left ventricular hypertrophy, significant aortic or mitral value disease, age greater than 70 years, or diabetes for more than 10 years [99].

Thiazolidinediones have been reported to (1) reduce insulin requirements, (2) ameliorate albuminuria (3) have various roles in lipid metabolism, fibrinolysis, platelet aggregation and coagulation, (4) protect against impairment of endothelial function and (5) have an anti-inflammatory effect [100-103]. When used for the clinical management of type 2 diabetes and ESRD, thiazolidinediones are primarily metabolized in the liver and will not accumulate in patients with CKD. They might also improve uremia-associated insulin resistance and confer benefits at the metabolic, inflammatory, vascular, and hemodynamic levels [100]. The efficacy of this drug in patients with normal renal function is similar to the efficacy in those with mild to moderate renal impairment [104]. Administration of pioglitazone is also associated with mean decreases in triglyceride levels and mean increases in high-density lipoprotein (HDL)-cholesterol without consistent changes in the mean levels of total cholesterol or low-density lipoprotein (LDL)-cholesterol in non-uremic patients [105].

Thiazolidinediones are known to reduce HOMA-IR and levels of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α), and increase adiponectin levels in patients not undergoing dialysis [72]. In patients undergoing PD, thiazolidinediones have been reported to reduce hs-CRP levels, but levels of interleukin-6 (IL-6) and TNF-α were not reduced [91, 102]. In a short-term study of dialysis patients, thiazolidinediones are reported to reduce the levels of hs-CRP but not adiponectin [106]. It has been reported that pioglitazone treatment reduced the levels of hs-CRP, IL-6 and TNF-α and increased the high-molecular weight adiponectin level even in hemodialysis patients [107]. Moreover, the dosage of erythropoiesis-stimulating agents was significantly reduced during pioglitazone treatment with improvement in insulin resistance and a decrease in the levels of inflammatory cytokines [107].

It can be concluded that even though ESRD and dialysis do not affect the metabolism of thiazolidinediones, the medications in this group are not recommended in ESRD patients due to the associated risk of fluid accumulation and precipitation of heart failure.

Alpha-glucosidase inhibitors

Enzyme alpha-glucosidase is located in the gut and hydrolyzed oligosaccharides, trisaccharides and disaccharides into glucose in the brush border of the small intestine. The antihyper-

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glycemic action of alpha-glucosidase inhibitors results from the reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. Alpha-glucosidase inhibitors decrease the rate of breakdown of complex carbohydrates so that less glucose is absorbed and postprandial hyperglycemia is lowered but they do not enhance insulin secretion. The main side effects are gastrointestinal including flatulence and diarrhea.

Acarbose and miglitol slow carbohydrate absorption from the intestine. The levels of these drugs and their active metabolites are higher in patients with renal failure [80], and since data are scarce on the use of these drugs in ESRD, they are contraindicated in ESRD patients [11].

Acarbose is metabolized by intestinal bacteria and digestive enzymes exclusively within the gastrointestinal tract. Within 96 h of ingestion, 51% of an oral dose was excreted in the faces and unabsorbed drug-related radioactivity. Because acarbose acts locally within the gastrointestinal tract, low systemic bioavailability of the parent compound is therapeutically desirable. A fraction of these metabolites (about 34% of the dose) was absorbed and subsequently excreted in urine. The major metabolites have been identified as 4-methylpyrogallol derivatives (such as sulfate, methyl, and glucuronide conjugates). Moreover, one metabolite (formed by cleavage of a glucose molecule from acarbose) also has alpha-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for < 2% of the total administered dose. Although < 2% of an oral dose of acarbose was absorbed as active drug, patients with severe renal impairment (CrCl < 25 mL/min) attained increases about 5-fold higher for peak plasma concentration of acarbose and 6-fold higher for AUC values than subjects with normal renal function [108]. Because long-term clinical trials in diabetic patients with significant renal dysfunction have not been conducted, treatment of these patients with acarbose is not recommended [108].

Miglitol is not metabolized in humans or other animal species [109]. No metabolites have been detected in plasma, urine, or feces indicating a lack of either systemic or presystemic metabolism. Miglitol is eliminated by renal excretion as unchanged drug [109]. Patients with CrCl < 25 mL/min taking the miglitol 25 mg 3 times daily exhibited a greater than 2-fold increase in miglitol plasma levels when compared to subjects with CrCl > 60 mL/min [109]. Dose adjustment to correct for the increased plasma concentrations is not feasible because miglitol acts locally. However, treatment of patients with CrCl < 25 mL/min with miglitol is not recommended because the safety of miglitol in these patients has not yet been elucidated [109].

Glucagon-like peptide-1 analogues

The intestinal hormone glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin release from pancreatic β-cells in a glucose-dependent manner and inhibits inappropriate postprandial glucagon release. It also shows gastric emptying and reduces food intake. However, its meal-induced secretion is generally decreased in patients with type 2 diabetes, and this may contribute to the amplification of postprandial hyperglycemia [72]. GLP-1 is rapidly inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4) [110].

Therefore, an effective way to potentiate postprandial GLP-1 response is the use of selective DPP-4 inhibitors [111, 112].

Table 2 shows some of the medications in this group.

Sitagliptin is a highly selective, oral, once-daily administration DPP-4 inhibitor approved for the treatment of patients with type 2 diabetes [113]. DPP-4 inhibitors slow the degradation and the inactivation of the incretins, GLP-1 and glucose-dependent insulinotropic polypeptide [110]. These two incretins regulate glucose homeostasis by stimulating insulin release, while GLP-1 also suppresses glucagon release [72]. Sitagliptin can be used as initial pharmacologic therapy for type 2 diabetes, as a second agent in those who do not respond to a single agent such as a sulfonylurea [114], metformin [115-117], or a thiazolidinedione [118] and as an additional agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control [114]. CYP3A4 is the major CYP isozyme responsible for the limited oxidative metabolism of sitagliptin, with some minor contribution from CYP2C8. Sitagliptin is primarily renally eliminated with approximately 80% of the oral dose excreted unchanged in the urine [119, 120]. Excretion is thought to be via active secretion and glomerular filtration [119, 121]. Following single oral doses of sitagliptin, plasma level increases with decreasing renal function, as determined by 24 h CrCl. Relative to subjects with normal or mildly impaired renal function, patients with moderate renal insufficiency (CrCl 30-50 mL/min), severe renal insufficiency (CrCl < 30 mL/min, not on dialysis) or ESRD on dialysis have approximately 2.3-fold, 3.8-fold, or 4.5-fold higher plasma sitagliptin exposures, respectively, and the C_{max} increased by 1.4-fold to 1.8-fold [122]. T_{max} is significantly increased in patients with ESRD, and the terminal half-life increased with decreasing renal function [72]. Compared with values in subjects with normal renal function, the terminal half-life values of sitagliptin in those with mild, moderate, and severe renal impairment, and ESRD were raised to 16.1, 19.1, 22.5 and 28.4 h, respectively, compared to 13.1 h in normal renal function patients [122]. The fraction of dose removed by dialysis was low with 13.5% and 3.5% for dialysis initiated at 4 and 48 h post dose, respectively. Plasma protein binding of 38% was not altered in uremic plasma from patients with renal impairment. Based on these data, in order to achieve plasma sitagliptin concentrations comparable to those in patients with normal renal function, sitagliptin dose adjustments are recommended for patients with type 2 diabetes and moderate to severe renal insufficiency, as well as for those with ESRD requiring dialysis [123]. The usual dose of sitagliptin is 100 mg orally once daily, with reduction to 50 mg for patients with a glomerular filtration rate of 30-50 mL/min, and 25 mg for patients with a glomerular filtration rate less than 30 mL/min [122]. Sitagliptin may be used at does of 25 mg daily in ESRD patients, irrespective of dialysis timing. However, some side effects have been found after administration of sitagliptin such as anaphylaxis, angioedema and Steven-Johnson syndrome. Moreover, the risk of hypoglycemia increases when sitagliptin is used with sulfonylureas.

Vildagliptin is not a CYP enzyme substrate and does not inhibit or induce CYP enzymes, it is unlikely to interact with co-medications that are substrates, inhibitors, or inducers of these enzymes [124, 125]. The efficacy of vildagliptin in humans against the DPP-4 enzyme also

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shows a low *in vivo* IC_{50} (4.5 nM), which suggests a higher potency than that reported for sitaliptin (IC_{50} 26 nM) [119, 126]. Elimination of vildagliptin mainly involves renal excretion of unchanged parent drug and cyano group hydrolysis with little CYP involvement, suggesting a low potential for drug-drug interaction when co-administered with CYP inhibitors/inducers.

In patients with mild, moderate and severe renal impairment and ESRD patients on hemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 32-134%) compared to subjects with normal renal function [72]. However, changes in exposure to vildagliptin did not correlate with the severity of renal function. In contrast, exposure of the main metabolite increased with increasing severity of renal function (AUC 1.6- to 6.7-fold), but this effect has no clinically relevant consequences because the metabolite is pharmacologically inactive. The elimination half-life of vildagliptin is not affected by renal function and it is well-tolerated in this population [127]. According to the label, no dosage adjustment of vildagliptin is required in patients with mild renal impairment. In clinical practice, special precautions are advised for the use of this drug in patients with moderate to severe renal impairment, including those on dialysis [72].

Alogliptin was rapidly absorbed and slowly eliminated primarily via urinary excretion in healthy subjects. In patients with type 2 diabetes, alogliptin is also primarily excreted renally with a renal clearance rate of 165-254 mL/min which is slightly higher than the normal glomerular filtration rate, suggesting the occurrence of some active renal secretion. The results of a single-dose (50 mg) pharmacokinetics study in patients with renal impairment showed an increase in alogliptin exposure compared with healthy volunteers; approximately 1.7-, 2.1-, 3.2- and 3.8-fold increase in patients with mild, moderate, and severe renal impairment, and in patients with ESRD, respectively [127, 128]. According to this data, to achieve plasma alogliptin concentrations comparable to those in patients with normal renal function, alogliptin dose adjustments are recommended for patients with type 2 diabetes and moderate to severe renal insufficiency, including those with ESRD requiring dialysis [72].

Saxagliptin is another DPP-4 inhibitor and its metabolite is pharmacologically active which makes saxagliptin difference from other medications in this group. The metabolism of saxagliptin is primarily mediated by CYP3A4/5 and its major metabolite is also a selective, reversible, competitive DPP-4 inhibitor which is 50% less potent than saxagliptin [129]. Saxagliptin is cleared by both metabolism and renal excretion. However, the degree of renal impairment does not affect the C_{max} of saxagliptin or its major metabolite [127]. In subjects with mild renal impairment, AUC from time 0 to infinity (AUC_{∞}) values of saxagliptin and its major metabolite are 1.2- and 1.7-fold higher than mean AUC_{∞} in controls, respectively, while they are 1.4- and 2.9-fold higher in subjects with moderate renal impairment. Corresponding value are 2.1- and 4.5-fold higher in those with severe impairment [127]. A 4-h dialysis section removes approximately 23% of saxagliptin dose, AUC_{∞} values for saxagliptin and its major metabolite are correlated with the degree of renal impairment, whereas C_{max} values are not well correlated. Renal function should be assessed before initiating saxagliptin therapy and patients with moderate to severe kidney impairment should receive less than 2.5 mg of saxagliptin/day and this drug can still be taken after dialysis in patients with ESRD.

Linagliptin is extensively protein bound (> 80% at the therapeutic dose) which is unlike other DPP-4 inhibitors. Because DPP-4 is expressed in various tissues but soluble DPP-4 is also present in plasma, binding to soluble DPP-4 may influence the pharmacokinetics of linagliptin. High-affinity but readily saturable binding of linagliptin to its target DPP-4 primarily accounted for the concentration-dependent plasma-protein binding at therapeutic plasma concentrations of linagliptin [130]. Fecal elimination is the dominant excretion pathway of linagliptin with 84.7 and 58.2% of the dose whereas renal excretion accounted for 5.4 and 30.8% of the dose administered orally or intravenously, respectively [131]. Renal excretion of unchanged linagliptin is < 1% after administration of 5 mg [132]. As absolute bioavailability is determined to be around 30%, renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels (compared to other DPP-4 inhibitors) and accordingly, a dose adjustment in patients with renal impairment is not anticipated for linagliptin [72].

Incretin mimetics

GLP-1 belongs to the incretin class of hormones which exert an influence over multiple physiologic functions, including a rapid blood glucose-lowering effect in response to enteral nutrient absorption [72]. Native GLP-1 is rapidly metabolized by DPP-4 which is found in many tissues and cell types, as well as in the circulation [133]. Clearance of native GLP-1 and its metabolites is largely mediated by the kidneys [133]. Incretins, such as GLP-1, enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. Exenatide and liraglutide are GLP-1 receptor agonists that enhance glucose-dependent insulin secretion by pancreatic β-cells, suppress inappropriately elevated glucagon secretion and slow gastric emptying [72].

Exenatide is one of the drugs in this group. The amino acid sequence of exenatide is partially homologous to that of human GLP-1. Exenatide binds and activates the human GLP-1 receptor which leads to an increase in both glucose-dependent synthesis of insulin and secretion of insulin from pancreatic β-cells. Exenatide is a naturally occurring GLP-1 analogue that is resistant to degradation by DPP-4 and has a longer half-life. The kidney provides the primary route for elimination and degradation of exenatide [134]. Given subcutaneously, exenatide undergoes minimal systemic metabolism. In subjects with mild to moderate renal impairment (CrCl 30-80 mL/min), exenatide exposure is similar to that of subjects with normal renal function and no dose adjustment is required. However, in subjects with ESRD receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function. Exenatide is contraindicated in patients undergoing hemodialysis, ESRD or in patients who have glomerular filtration rate less than 30 mL/min and it should be used with caution in patients undergone renal transplantation [135]. In patients with ESRD receiving dialysis, single dose of 5 μg exenatide are not well tolerated due to gastrointestinal side effects. Due to the side effects of exenatide such as nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution is required when initiating or escalating doses of exenatide from 5 μg to 10 μg in patients with moderate renal impairment (CrCl 30-50 mL/min) [72].

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Liraglutide is a once-daily human GLP-1 analog and has a high degree of sequence identity to human GLP-1 [136, 137]. The half-life of liraglutide is approximately 13 h after subcutaneous injection [138] and its metabolism is similar to that of large peptides which is fully degraded in the body [137]. There is no evidence that kidney is a major organ for elimination. Its pharmacokinetics parameters are essentially independent of renal function [139]. Renal dysfunction is not found to increase exposure of liraglutide and patients with type 2 diabetes and renal impairment can be treated with standard regimens of liraglutide [72].

Amylin analogs

Currently, pramlintide is the only drug in this group which is administered by subcutaneous injection and it is a naturally occurring neuroendocrine hormone co-secreted with insulin by pancreatic β-cells [140]. Amylin regulates gastric emptying [141], suppresses inappropriate postprandial glucagon secretion [142] and reduces food intake [143]. Through the mechanism similar to those of amylin, pramlintide reduces postprandial glucose, improving overall glycemic control [144, 145] and increases satiety resulting in reduced food intake and weight loss [146-148]. The half-life of pramlintide in healthy subjects, which is metabolized primarily by the kidney, is approximately 48 min. Its primary metabolite has a similar half-life and is biologically active. Patients with moderate or severe renal impairment (CrCl > 20 to < 50 mL/min) do not show increased pramlintide exposure or reduced pramlintide clearance when compared with subjects with normal renal function. However, no data is available for dialysis patients and further clinical studies are warranted in this population.

Sodium glucose co-transporter 2 (SGLT2) inhibitors

The plasma glucose level below which nearly all filtered glucose is reabsorbed by the kidneys, and above which glucose is excreted in urine, is designated as the renal threshold for glucose (RT_G) [149]. In healthy individuals, virtually all filtered glucose is reabsorbed up to a plasma glucose level of approximately 10 mmol/L (180 mg/dL), thus defining RT_G [150, 151]. At plasma glucose levels higher than RT_G, the renal glucose reabsorptive capacity is saturated and the amount of glucose in urine increases proportionately to plasma glucose concentration [152]. By inhibiting the proximal renal tubule glucose transporter responsible for the majority of glucose reabsorption, sodium glucose co-transporter 2 (SGLT2) inhibitors are predicted to lower RT_G, thereby increasing urinary glucose excretion [149]. In patients with diabetes, reduction of RT_G is expected to increase urinary glucose excretion and lower plasma glucose concentrations. Unlike other antidiabetic agents which often cause weight gain, the glucose-lowering effect with SGLT2 inhibitors is accompanied by urinary loss of calories, potentially resulting in weight loss. Moreover, SGLT2 inhibitors do not target the major pathophysiological defects in type 2 diabetes mellitus-namely insulin resistance and impaired insulin secretion-they represent a potentially promising new option in the treatment of diabetes [153]. One of the drug in this category is canagliflozin. In preclinical studies, a single oral administration of 3 mg/kg of canagliflozin decreased plasma glucose levels independent of food intake in mice on a high-fat, hyperglycemic diet [153]. In normo-glycemic mice, canagliflozin

administration led to a minimal change in plasma glucose levels. Sha et al. show that canagliflozin was well tolerated in healthy men across the range of single does studied up to 800 mg. By inhibiting SGLT2, canagliflozin treatment dose dependently decreased RT_G, leading to a dose-dependent increase in urinary glucose excretion [149]. However, no data on its safety and efficacy is available for CKD or dialysis patients and further clinical studies are warranted in this population.

7. Combination therapy

Saxagliptin plus metformin

In order to obtain the better control of plasma glucose level and decrease the side effect of some medications in renal patients, combination therapy has been used. Scheen reviewed the use of metformin plus saxagliptin in renal impairment patients [154]. Since saxagliptin's license was recently extended to include diabetic patients with moderate or severe renal impairment while metformin is still widely prescribed in patients with some degree of renal impairment in real life even though it is contraindicated, the pro and contra of using this combination in type 2 diabetic patients with renal impairment need to be reviewed. Some recent data suggested that both metformin and saxagliptin may be used safely in type 2 diabetic patients with mild-to-moderate renal impairment, provided that dose reduction is made appropriately according to individual CrCl [154]. Because of the absence of pharmacokinetics interactions between the two drugs, this should be also the case with the saxagliptin-metformin combination. In this population, DPP-4 inhibitors offer advantages compared with sulfonylureas, especially because of the absence of hypoglycemia [155, 156]. A retrospective subgroup analysis of data from five randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase III trials showed that saxagliptin 5 mg once-daily monotherapy and as add-on therapy are associated with clinically relevant and significant efficacy for reducing hemoglobin A_{1c} in older patients (≥ 65 years; CrCl: 80±20 mL/min) versus younger patients (< 65 years; CrCl: 119±40 mL/min) [157]. Furthermore, saxagliptin was well-tolerated in older patients with a low incidence of hypoglycemia and no weight gain. Normally, patients with type 2 diabetes and renal impairment are exposed to a higher risk of cardiovascular disease. Therefore, reducing cardiovascular risk in this population should be considered as a main objective and drugs that have proven their efficacy and safety in this regard should be preferred. Treatment with metformin in type 2 diabetic patients is associated with a lower cardiovascular morbidity and mortality, compared with alternative glucose-lowering drugs [158]. It has also been suggested that metformin might exert direct protective effects on the heart [159]. Since both metformin and saxagliptin are excreted via the kidney, dose adjustment is required in case of moderate-to-severe renal impairment (ca. half dose of saxagliptin). Due to major discrepancies exist between guidelines (metformin excluded in case of renal impairment because of the risk of

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lactic acidosis) and real life, physicians should weigh the benefit/risk ratio carefully before deciding to prescribe or withdraw this combination in renal patients.

DDP-4 inhibitor plus thiazolidinedione

Thiazolidinediones are currently considered as the most efficacious class of oral anti-diabetics [160]. However, they carry the burden of weight gain and hemodilution which may lead to cardiovascular complications. It has been considered that the use of a low dose thiazolidinedione in combination with DPP-4 inhibitor may reduce the risk of dose dependent side effects of thiazolidinediones such as weight gain and hemodilution while, simultaneously, this combination may be more effective owing to different mechanisms of action of thiazolidinediones and DPP-4 inhibitors. Roy et al. demonstrated that in aged *db*/*db* mice, a combination therapy of low dose rosiglitazone and vildagliptin is safer and equally efficacious when compared to the therapeutic dose of rosiglitazone [160]. The combination therapy (1 mg/kg/day of rosiglitazone plus 5 mg/kg/day of vildagliptin) showed similar efficacy as that of 10 mg/kg/day rosiglitazone in lowering random blood glucose. GLP-1 and insulin levels were found to be elevated significantly in both vildagliptin and combination treated groups following oral glucose load. Vildagliptin alone had no effect on random glucose and glucose excursion during oral glucose tolerance test in severely diabetic *db*/*db* mice. The combination treatment showed no significant increase in body weight as compared to the robust weight gain by therapeutic dose of rosiglitazone. Rosiglitazone at 10 mg/kg/day showed significant reduction in hematocrit, red blood cell count, hemoglobin pointing towards hemodilution associated with increased mRNA expression of Na^+, K^+-ATPase-α and epithelial sodium channel gamma in kidney. The combination therapy escaped these adverse effects. The results suggest that combination of DPP-4 inhibitor with low dose thiazolidinedione can interact synergistically to represent a therapeutic advantage for the clinical treatment of type 2 diabetes without the adverse effects of haemodilution and weight gain associated with thiazolidinediones.

DDP-4 plus metformin

The retrospective analysis by Banerji et al. found that the combination of vildagliptin and metformin in type 2 diabetic patients with mild renal impairment is safe and tolerable, similar to that in patients with normal renal function [161]. Furthermore these results were similar to those in patients receiving a combination of thiazolidinedione and metformin. Higher incidence of headache and rash was noted in both vildagliptin groups, whereas those with mild renal impairment receiving thiazolidinedione experienced a higher incidence of peripheral edema.

Mitiglinide plus voglibose

Unlike typical sulfonylurea agents, mitiglinide, a benzylsuccinic acid derivative, is a rapid- and short-acting insulinotropic sulfonylurea receptor ligand with rapid hypoglycemic action. It alleviates postprandial hyperglycemia and, as a result, improves overall glycemic control [162]. The blood concentration of mitiglinide rapidly increases after oral administration and the drug quickly disappears subsequently; therefore, it is unlikely to exert hypoglycemic

effects early in the morning and between meals. Abe et al. demonstrated that add-on therapy of mitiglinide with voglibose may be a therapeutic option for achieving good glycemic control in type 2 diabetic hemodialysis patients with otherwise poor glycemic control [86]. The daily dose of mitiglinide is suggested to be lower in the diabetic hemodialysis patients than that in the diabetic patients with normal kidney function. At low dose (23 mg), mitiglinide was adequate to induce significant reductions in glycemic parameters such as fasting plasma glucose, hemoglobin A_{1c}, glycated albumin levels and HOMA-IR. Mitiglinide also significantly improved glycemic control, triglyceride level and interdialytic weight gain even when it was administered only for a short duration [86].

8. Effects of high-flux dialyzer membranes on plasma insulin

Nowadays, several types of high-flux dialyzer membranes are on the market. The normally used ones are made from polysulfone, polyethersulfone, cellulose triacetate, polymethylmethacrylate or polyester-polymer alloy. The mechanism of plasma insulin clearance by hemodialysis is mainly by adsorption rather than diffusion or convection since no insulin is not normally detected in either the dialysate or the ultrafiltrate fluid during hemodialysis [163]. Furthermore, the amount of insulin adsorbed differed depending on the dialyzer membrane used. The insulin levels during a dialysis session depend not only on insulin removal by dialysis but also on the secretion of insulin from the pancreatic β-cells; this in turn is determined by the changes in plasma glucose induced by dialysis and the ability of the β-cells to respond to these glucose changes [163]. Therefore, it was suggested that an increase in endogenous insulin secretion may occur in response to hemodialysis treatment, in particular with the polysulfone membrane. On the other hand, plasma glucose levels at the post-dialysis stage were mainly determined by the glucose concentration in the dialysate; this is because the molecular weight of glucose is very small, and glucose rapidly transmigrates across the membrane during hemodialysis treatment. Therefore, plasma glucose levels at the post-dialysis stage should be similar in the case of polysulfone, cellulose triacetate and polyester polymer alloy membranes, regardless of the type of high-flux membrane. However, in the insulin-dependent diabetes mellitus (IDDM) subjects, who lack endogenous insulin secretion, the insulin reduction rate was significantly higher when the polysulfone membrane was used compared with the cellulose triacetate and polyester-polymer alloy membranes. This is because these patients have no residual β-cell function, which is responsible for insulin secretion; therefore, if plasma insulin was removed by hemodialysis, these cells could not have maintained the patients' insulin levels. Hence, plasma insulin removal is highly significant in the case of diabetic hemodialysis patients with low C-peptide levels, particularly those with type 1 or 2 diabetes with a deteriorated β-cell function [164]. Higher doses of injected insulin or antidiabetic agents might be added in order to achieve good glycemic control in such patients, because the surplus insulin is removed by hemodialysis, particularly when the polysulfone dialyzer is used [163]. Therefore, patient monitoring of blood glucose on the day that hemodialysis is

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performed could be useful for self-assessment of glycemic state, and if hyperglycemia was recognized, and additional dose of injected insulin after hemodialysis should be considered.

Due to the development in dialyzer technology, it was found that the biocompatible dialyzer membrane used in hemodialysis patients not only causes less hemodialysis-induced inflammation but also achieves better clearance of uremic toxins and medium- to large-sized molecules [165]. Moreover, high-flux dialyzers have been shown to be superior in terms of attenuating hyperlipidemia and alleviating oxidative stress [166, 167]. There is a significant reduction in patients' plasma insulin at different time point with each type of membranes, because various biological reactions can occur in the course of contact between artificial materials and blood components in the extracorporeal circulation [163]. The clearance of plasma immunoreactive insulin (IRI), a biologically active molecule, is significantly higher in patients used polysulfone membrane than by other membranes such as polyethersulfone, cellulose triacetate, polymethylmethacrylate or polyester-polymer alloy [168]. Moreover, no clinical difference has been found in the reduction rate of IRI between hemodialysis treatments when using either polysulfone, polyethersulfone, cellulose triacetate or polymethylmethacrylate except for polyester-polymer alloy [168]. From these results, it suggests that hemodialysis patients with residual β-cell function, the course of treatment for diabetic control would be unaffected by the differences resulting from the type of membrane used. However, in diabetic hemodialysis patients, particularly in type 1 and type 2 with deteriorated β-cell function, these differences might be very significant. Higher doses of injected insulin might be required to achieve good glycemic control in hyperinsulinemic patients because the surplus insulin is removed by hemodialysis, specifically by polysulfone, polyethersulfone, cellulose triacetate or polymethylmethacrylate, excluding polyester-polymer alloy membrane dialyzer. Polysulfone membrane dialyzer may worsen glycemic control and switching to the polyester-polymer alloy membrane dialyzer which shows a lower IRI clearance rate might improve the glycemic control in hemodialysis patients.

9. Conclusion

Although diabetes is the most common cause of ESRD and diabetic control is considered as one of the most important factor to prolong patients' life and improve their quality of life, data are scarce on how diabetes should be best treated in patients with CKD or ESRD. Since the glycemic control and monitoring in CKD and ESRD patients is complex, patient education is also one of the key factors for successful treatment. Moreover, patients with diabetic nephropathy are especially susceptible to hypoglycemia and diabetic drug therapy requires special caution. Adjustment of the type of drugs used or dosage regimen should be individualized based on self-monitored blood glucose patterns.

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Chapter 9

Epidemiology of Chronic Dialysis Patients in the Intensive Care Unit

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Additional information is available at the end of the chapter

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1. Introduction

The incidence and prevalence of end-stage renal disease (ESRD) is rising worldwide, in part due to increasing rates of diabetes, hypertension and an ageing population [1,2]. Incidence rates of patients commencing renal replacement therapy (RRT) are estimated at 109 and 354 per million population (pmp) per year in the UK and US respectively [1,2], with the highest incidence seen in patients over 75 years of age.

Shifting demographics over the past two decades have resulted in an older and sicker long-term dialysis population, burdened with multiple and significant co-morbid conditions. ESRD patients experience higher rates of hospitalisation, cardiovascular events and all cause mortality when compared to patients with normal renal function, and are more likely to require admission to the intensive care unit (ICU) [3,4]. It has been estimated that 2% of all dialysis patients will require admission to ICU every year [5]. The presence of pre-existing end-stage organ failure, and often numerous co-morbidities, can impact on medical decisions regarding appropriateness of escalation of care and ICU admission. For a long time, it was thought that patients requiring long-term dialysis would have similarly poor ICU outcomes to those with acute kidney injury (AKI), however emerging evidence suggests otherwise.

This chapter aims to review the epidemiology, patient characteristics and short and long-term outcomes of critically unwell chronic dialysis patients, who require admission to ICU. Risk factors for early mortality, ICU prognostic scoring systems and end of life care planning will also be discussed in relation to the critically ill hemodialysis patient.

2. Characteristics on admission to ICU

Chronic dialysis patients have higher critical care admission rates than the general population; however there is a significant variation in estimates between published studies. This may reflect differences in referral rates, ICU admission policy and resource availability on a national and local level as well as the demographics of the surrounding population.

The largest cohort of critically ill ESRD patients studied derives from the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database which records data of patients admitted to more than 200 ICUs across England, Wales and Northern Ireland. Analysis of this database showed that from 1995 to 2004 there were 270,972 admissions to ICU, of whom 1.3% were chronic dialysis patients [4]. The authors of the study projected that this was equivalent to six ICU admissions or 32 ICU bed days per 100 dialysis patient-years. When compared to annual ICU admission rates of 2 per 1,000 of the general population, this represents a 30-fold difference in critical care requirements. A more recent study using the same UK ICNARC database with data from 1995-2008, similarly found that ESRD patients accounted for 1.4% of all ICU admissions [6].

Other studies have proposed much higher estimates for admission rates of chronic dialysis patients to the ICU; however these are mostly single centre and involve significantly smaller study cohorts than Hutchinson et al [4]. A French prospective observational single-centre study admitted 92 chronic dialysis patients over a 3 year period, which gives a calculated admission rate of 8.6%, significantly higher than the UK database study [7]. Of note, this study was based at a teaching hospital which served as the sole critical care unit able to provide RRT to its large surrounding population.

Strijack and colleagues [8] report that 3.4% of all admissions to 11 adult ICUs in Winnipeg, Canada over a 6 year period were chronic dialysis patients, with crude admission rates for the ESRD population significantly higher than for those without ESRD (15.6 admissions per 100 prevalent patients with ESRD per year vs. 0.58 per 100 prevalent patients without ESRD per year). An American single-centre study conducted in Pittsburgh, and involving medical, surgical, trauma, neurological/neurosurgical, coronary and cardiothoracic ICUs found a similar admission rate for chronic dialysis patients of 3.6% [9]. In contrast to the 30-fold increase in critical care admissions for ESRD patients reported by Hutchinson et al [4], a multi-centre Australian study based on 3 months of data demonstrated a significantly lower 4-fold annual risk of ICU admission in dialysis patients compared to the general population [5].

Although ICU admission rates for the ESRD population vary from 1.3% - 8.6%, it is evident that patients with chronic renal disease are at higher risk of requiring critical care than the general population. Whether this is related to the underlying renal disease or associated co-morbidities remains to be seen. The decision to admit a patient to critical care is based on multiple factors, including the patient's and relatives' wishes, local admission policy, judgement of the clinicians involved and capacity.

Epidemiological data has shown that ESRD patients admitted to ICU are younger and more likely to be male in comparison to the general population [4,6-8,10]. The proportion of male

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admissions to the ICU is in keeping with the male preponderance in the dialysis population; however the reason for the lower mean age seen in critically ill ESRD patients requires further analysis.

3. Characteristics of critically ill dialysis patients

3.1. Severity of illness scores

Chronic dialysis patients requiring intensive care admission are more critically unwell and have a greater number of co-morbidities than the general population. Strijack et al [8] found they had significantly higher rates of diabetes (52.3% vs. 21.7%, $p<0.0001$) and peripheral arterial disease (29.7% vs. 12.3%, $p<0.0001$) than those without ESRD on admission to the ICU. Rates of coronary artery disease, stroke and cancer were comparable between the two groups.

Several studies have used ICU mortality and prognostication models such as the Acute Physiology and Chronic Health Evaluation II (APACHE) score [11] to attempt to quantify the severity of illness of dialysis patients admitted to critical care. Hutchinson et al [4] reported that both the APACHE II (24.7 vs. 16.6, $p < 0.001$) and Simplified Acute Physiology Score (SAPS) (17.2 vs. 12.6, $p < 0.001$) were significantly higher in dialysis patients when compared to those not requiring long-term renal replacement. Both scoring systems include physiological variables assessing cardiovascular, respiratory, biochemical, haematological and neurological status, within the first 24 hours of admission to ICU; however the APACHE II score places more emphasis on age and medical history than the SAPS. Strijack and colleagues [8] found a similar trend in their Canadian historical cohort study where patients with ESRD had a higher APACHE II score than those without ESRD (24 vs. 15, $p < 0.0001$), a finding that persisted even after removal of the renal component (serum creatinine and presence of AKI) of the score (20 vs. 14, $p < 0.0001$).

The fact that ESRD patients are more critically unwell on admission to ICU than the general population is an interesting concept. Certainly, this cohort is not being denied treatment based on illness severity, and it may reflect the differing admission diagnoses between the groups. However it does raise the possibility of whether there exists a higher threshold for seeking intensive care intervention in chronic dialysis patients, resulting in delayed referral, or whether patients need to be more critically unwell before being accepted into the ICU. It is also possible, that the commonly used scoring systems to assess severity of illness are not valid in chronic dialysis patients.

3.2. Reasons for admission to ICU

Dialysis patients are more likely to be admitted to ICU with a medical diagnosis than the general population (66.7% vs. 56.2%) [4]. Data shows that whilst there is a significant difference in critical care admissions after elective surgery (7.4% vs. 19%, $p< 0.0001$) between the two groups, with ESRD patients much less commonly admitted post operatively, the figures for admission after emergency surgery are comparable [8].

Interestingly, among patients with ESRD, admission after cardiopulmonary resuscitation (CPR) is a more frequent reason for ICU admission compared to other patient populations (13.6% vs. 7.3%, $p < 0.001$) [4]. Senthuran and colleagues [12] similarly found that 12% of their cohort of chronic dialysis patients were admitted to a single Australian ICU having survived a cardiac arrest. Epidemiological data from the US suggests that hemodialysis patients have a 10-fold increased risk of dying from cardiac arrest than the general population [2]. The fluid and electrolyte shifts experienced during and in between dialysis sessions may contribute to this increased risk in conjunction with left ventricular hypertrophy/dysfunction, ischaemic heart disease, autonomic dysfunction, hypertension, diabetes, and being male [13]. The fact that dialysis patients are more likely to have had CPR in the 24 hours prior to ICU admission is consistent with the finding that these patients are more critically unwell when they arrive in the ICU. Again whether this is an indirect consequence of delayed referral or acceptance or a direct consequence of the unphysiological fluid and electrolyte shifts experienced during hemodialysis is uncertain.

Cardiovascular disease and sepsis are the leading causes of death in patients with ESRD [1,2], and it is therefore not unexpected that these constitute two of the most common reasons for admission to ICU. Dialysis patients are particularly susceptible to infections due to uraemia related immune deficiency, defective phagocytic function, older age, and co-morbidities including diabetes mellitus. In addition, repeated vascular access for the purpose of hemodialysis increases the risk of bacteraemia. The annual percentage mortality rates secondary to sepsis for dialysis patients have been estimated at 100- to 300-fold higher than rates seen in the general population [14]. Between 5.6%-46% of chronic dialysis patients are admitted to ICU with a diagnosis of sepsis [4,7,8,10,12,15-18]. Strijack et al [8] found that significantly more ESRD patients were admitted to ICU with a diagnosis of sepsis compared to those without renal failure (15.8% vs. 6.5%, $p< 0.0001$), however the source of sepsis was not detailed, and whether this was related to vascular access infections cannot be determined. A small Brazilian study reported that the lung was the most frequent source of sepsis in the critically ill dialysis population, followed by soft tissue, catheter related/blood-stream and abdominal sources [17].

As well as having traditional cardiovascular risk factors, chronic kidney disease patients have associated non-traditional risk factors such as increased levels of inflammatory markers, left ventricular hypertrophy, anaemia, endothelial dysfunction, increased arterial calcification and stiffness, abnormal apolipoprotein levels, high plasma homocysteine and enhanced coagulability [3]. These factors are thought to put patients with renal dysfunction at a higher risk of adverse cardiac events including myocardial ischaemia, pulmonary oedema, cardiogenic shock, arrhythmias and sudden cardiac death. Studies have estimated that the proportion of ESRD patients admitted to ICU with a cardiac diagnosis (including pulmonary oedema) ranges from 5.1%-31% [4,7,8,10,12,15-17].

A recent study conducted in a single French ICU specifically analysed chronic dialysis patients admitted to their unit with acute pulmonary oedema [19]. Out of 102 patients with ESRD and pulmonary oedema admitted to ICU over an eight year period, they reported 41% could be attributed to an underlying cardiac cause, 26% to bronchopneumonia, 25% to excessive interdialytic weight gain and 23% secondary to an inappropriate dialysis prescription and

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incorrect assessment of dry weight. Interestingly they noted a distinct pattern to the ICU admissions related to patients‘ dialysis schedules; those dialysed on Monday-Wednesday-Friday were commonly admitted on Sunday and those on a Tuesday-Thursday-Saturday timetable were more likely to be admitted on Monday. The authors speculated that this may reflect a reduced tolerance to fluid overload in patients‘ with cardiac dysfunction and/or poor compliance with salt and water restriction over the weekend.

Gastrointestinal bleeding is the third most common reason for chronic dialysis patients to require critical care. Dara et al [10] report that between 1997 – 2002, 20% of their ESRD cohort had an ICU admission and the most common ICU admission diagnosis was gastrointestinal haemorrhage. However other studies have slightly lower estimates of 2.7%-15% [7,16,17].

It is difficult to ascertain precisely how often ESRD patients require critical care intervention for hemodialysis related complications, including pulmonary oedema, arrhythmias, hyperkalaemia or vascular access related septicaemia. Hutchinson and colleagues [4] report from their large UK database analysis that the most common ICU admission diagnosis for long-term dialysis patients is ‘chronic renal failure' (8.6%), which they define as volume overload or electrolyte disturbance. Hyperkalaemia was recorded as the admitting diagnosis for 4.3% [7] and 3% [12] of ESRD patients admitted to single ICUs in France and Australia respectively. Clearly, these statistics depend not only on patients’ severity of illness but also ICU admission policy, capacity, patients’ wishes and whether a renal unit is on-site or not.

In summary, patients admitted to critical care on long-term dialysis are more likely to have multiple co-morbidities and have a higher severity illness score on admission than the general population. They more frequently present having had a cardiac arrest and CPR prior to admission and are more commonly admitted for medical rather than surgical reasons [18].

4. Short term outcomes of chronic dialysis patients admitted to ICU

4.1. Mortality

During the last ten years, numerous studies have focussed on the outcomes of critically ill long-term dialysis patients admitted to ICU (Table 1). Prior to this, it was believed that ICU mortality in this population was high, and comparable to those admitted with AKI. Reliable data on prognosis are necessary to enable patients and clinicians looking after critically ill dialysis patients to make well-informed and timely decisions regarding escalation of care.

Clermont et al [9] were among the first to attempt to evaluate ICU outcomes in ESRD patients admitted to eight American ICUs over a 10 month period. They reported an observed ICU mortality of 11% for ESRD patients compared to 5% in patients without renal failure. Numerous other studies have reported ICU mortality rates of 9-44% for chronic dialysis patients [4,5,7,9,10,12,15-18,20-22].

Study	Country	Type of RRT	No of patients (n)	Mean age (years)	Mean severity score	ICU mortality (%)	Hospital mortality (%)	30-day mortality (%)	ICU LOS (days) Mean±SD or Median [range]	ICU readmission rate (%)
Clermont [9] 2002	USA	IHD, CVVHD	57	58	64 (APACHE III)	11	14	-		-
Uchino [5] 2003	Australia	CRRT	38	45	22 (APACHE II)	22	38	-	6	-
Dara [10] 2004	USA	N/A	93	66	64 (APACHE III)	9	16	22	2	-
Manhes [7] 2005	France	IHD	92	63	49.4 (SAPS II)	28	38	-	6.2±9.9	-
Bagshaw [22] 2006	Canada	IHD, CRRT	92	66	29.7 (APACHE II)	16	34	-	-	-
Hutchinson [4] 2007	UK	N/A	3420	57	24.7 (APACHE II)	26	45	-	1.9 [0.9-4.2]	9
Ostermann [21] 2008	UK and Germany	IHD, CRRT, PD	797	55	8 (SOFA)	21	35	-	2 [1-64]	-
Senthuran [12] 2008	Australia	IHD, CVVHDF, CAPD	70	57	26.1 (APACHE II)	17	29	-	2 [1-27]	-
Strijack [8] 2009	Canada	IHD, CVVHDF	619	62	24 (APACHE II)	-	16	-	4.3	12
Chapman [20] 2009	UK	N/A	199	59	27.6 (APACHE II)	44	56	-	7.5±10.1	-
Rocha [17] 2009	Brazil	IHD, CRRT, SLED	54	66	43.9 (SAPS II)	20	24	-	5 [3-11]	-
Juneja [16] 2010	India	IHD, CRRT, SLED	73	54	27.1 (APACHE II)	27	-	41	2 [1-20]	-
Sood [18] 2011	Canada	N/A	578	61	19 (APACHE II, renal adjusted)	13	-	-	-	-

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Study	Country	Type of RRT	No of patients (n)	Mean age (years)	Mean severity score	ICU mortality (%)	Hospital mortality (%)	30-day mortality (%)	ICU LOS (days) Mean±SD or Median [range]	ICU readmission rate (%)
Walcher [24] 2011	USA	CRRT	28	58	-	36	39	39	9±8	-
O'Brien [6] 2012	UK	N/A	8991	59	24.6 (APACHE II)	24	42	-	2 [0.9-4.7]	-
Bell [37] 2008	Sweden	CRRT, IHD	245	-	-	-	-	90 day mortality 42%	-	-

Abbreviations: APACHE, Acute Physiology Assessment and Chronic Health Evaluation; SOFA, sequential organ failure assessment; SAPS, Simplified Acute Physiology Score; ICU, intensive care unit; LOS, length of stay; RRT, renal replacement therapy; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; CVVHDF, continuous hemodiafiltration; CVVHD, continuous hemodialysis; SLED, slow extended dialysis; CAPD, continuous ambulatory peritoneal dialysis; PD, peritoneal dialysis

Table 1.

Analysis of the UK ICNARC database showed an ICU mortality rate of 26.3% in patients with ESRD compared to 20.8% in those without ESRD ($p< 0.001$) [4]. This significant increase in mortality is however not surprising, given the higher illness severity scores of ESRD patients on admission to ICU. In 199 dialysis-dependent patients requiring support of two or more organ systems (including RRT) in ICU between 1999 - 2004, ICU mortality was 44% [20], which is similar to ICU mortality for patients with multi-organ failure which can range from 20-95% depending on number of organs involved and underlying comorbitdity [23].

Factors that are commonly associated with ICU mortality in chronic dialysis patients are age, number of non-renal organ system failures, an abnormal serum phosphorus level (high or low), higher mean APACHE II or SAPS II score and duration of mechanical ventilation [7,9,12]. There is clearly some overlap between these factors as confirmed by multivariate analyses [7]. The importance of abnormal serum phosphorus levels is unclear. Manhes et al [7] hypothesise that a low phosphate level can signify malnutrition and be related to severity of illness, where as hyperphosphataemia may be an indicator of inadequate renal replacement and a risk factor for cardiovascular disease in long-term dialysis patients, although the relevance of this to acute illness is uncertain.

4.2. Length of stay

Epidemiological data consistently show that chronic dialysis patients have comparable lengths of stay in ICU to the general population [4,7-9]. Mean length of stay ranged from 1.9 to 9 days [4,6-9,12,17,20,24], with Manhes [7] reporting a trend towards longer admissions in patients without ESRD. Clearly, the decision to discharge patients from ICU is influenced by the

capabilities and staffing of the receiving ward which may explain some of the discrepancies between different studies. In hospitals with renal units offering level two care, safe discharge of patients may be possible earlier compared to hospitals without dedicated step-down units.

4.3. Re-admission to ICU

Studies have shown that ESRD patients have a higher rate of readmission to ICU during the same hospital stay than patients with normal renal function [4,8], with quoted figures of 9-12% [4,8,12]. Strijack et al [8] found a significant difference in readmission rates (12% vs. 4.9%, $p < 0.0001$) between those on chronic dialysis and the general population and reported twice the frequency of readmissions to ICU within three days in the former. A recent Canadian study explored ICU readmission rates even further by evaluating the impact of dialysis modality and vascular access. They found a significant reduction in readmission rates to ICU for hemodialysis patients using arterio-venous (AV) fistulae as opposed to central venous catheters (4.7% vs. 16.4%, $p < 0.05$) [18], but acknowledged that this finding was open to confounding as central venous catheters may be simply a surrogate for poor performance status. The same group also reported that dialysis dependence was independently associated with two-fold higher odds for ICU readmission in the elderly (> 65 years) population even after adjustment for case mix and illness severity variables [25].

Therefore, the literature suggests that sicker chronic dialysis patients have shorter stays in ICU but experience almost twice the number of readmissions. Readmission to ICU is associated with poor outcomes and while many renal units have considerable experience in managing unwell dialysis patients, careful planning for a timely and safe discharge from ICU to a suitable destination is paramount.

5. Longer term outcomes of critically ill dialysis patients

Having been discharged from ICU it is essential to know how an episode of critical illness impacts on the medium and long-term outcomes of patients requiring chronic dialysis. Several studies have attempted to quantify hospital and 30-day mortality rates for this cohort and report figures of between 14-56% [4-10,12,16,17,20,24] and 32-41% [10,16,24] respectively. Hospital mortality rates were significantly higher in chronic dialysis patients compared to the non-ESRD population after ICU discharge (45.3% vs. 31.2%, $p < 0.001$) [4]. The wide range seen in these figures can in part be attributed to differences in case-mix as well as variations in illness severity between the studies.

Chapman et al [20] reported the highest hospital mortality rate of 56% for their 199 chronic dialysis patients after discharge from ICU, but emphasised that their patient cohort had a longer length of stay in ICU and higher APACHE II score than other studies, suggesting that they were a sicker group of patients. Two year survival was 29%. Interestingly they reported that a medical admission reason to ICU was associated with a relative risk of death of 2.1 when compared to patients with surgical diagnoses. 61% of medical patients died, in contrast to 19% of surgical admissions to ICU. The effect remained significant even after discharge. Age,

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dialysis vintage and APACHE II score did not appear to significantly affect mortality in this cohort. The majority of deaths in critically ill dialysis patients occurred within the first month, and Chapman calculated that if a patient survived to one month or hospital discharge, then long-term survival reverted back to that of chronic dialysis patients who had not been admitted to ICU.

A large Swedish nationwide cohort study involving 32 ICUs followed up 245 ESRD patients who had been admitted to critical care [15]. 90-day mortality of ESRD patients was 42%. Diabetes and heart failure were significant predictors of 90-day mortality in this population with age adjusted odds ratios of 1.9 and 2, respectively. The long-term mortality in critically unwell ESRD patients was 25 times higher than expected from mortality rates in the general population (Standardized mortality ratio 25; 95% Confidence Interval 20-31), with the highest number of deaths occurring in the first year after ICU discharge, as might be expected. This is in contrast to the work of Chapman and colleagues who reported that on leaving hospital, mortality rates for ESRD patients reverted back to normal [20]. This discrepancy may be explained by different statistical methods used, for instance, Bell and team [15] did not exclude patients who had died in ICU from their calculations.

Dialysis access and modality have been found to impact on long term mortality rates in ESRD patients admitted to critical care. Sood and colleagues [18] evaluated the 6 and 12 month outcomes of 619 ESRD patients admitted to 11 Canadian ICUs. More than 80% of admission diagnoses were medical, most commonly sepsis, and 6 and 12 month mortality were 38% and 48%, respectively. Interestingly they reported that hemodialysis patients with central venous catheter access had higher crude mortality rates at both 6 and 12 months than those who dialysed with AV fistulae. Central venous catheters remained independently associated with death even after adjustment for baseline and ICU admission characteristics as well as comorbidities. Again, this finding is open to confounding, given that tunnelled lines are more commonly used in patients with a poor performance status, and pose an increased risk of infection. Two additional cohort studies have reported similar 6 and 12 month survival rates for critically ill chronic dialysis patients [7,22]. Bagshaw et al [22] found that chronic dialysis patients had a similar 1-year mortality rate to those with no kidney dysfunction after adjustment for age, severity of illness and admission type, a finding confirmed by Strijack and coworkers [8]. These studies suggest that although ESRD identifies a cohort with a worse ICU outcome than the general population, the prognosis is related to illness severity and comorbidities rather than lack of renal function itself.

In addition to a medical admission diagnosis [4,20], diabetes, heart failure [15], and central venous catheter use [18], there are further factors which are associated with an increased mortality risk after discharge from ICU. Studies showed that older age, admission after emergency surgery, chronic health problems, CPR in the 24 hours preceding admission to ICU, having been in hospital for at least 7 days prior to ICU and the number of non-renal organ failures significantly affect outcome of ESRD patients post ICU [4,9,10,17]. As expected physiological and biochemical disturbances including hypotension, bradycardia, tachypnoea, hypoxia, reduced GCS, hyponatraemia, leucopenia and sepsis within the first 24 hours of ICU admission exert a significant impact on hospital mortality, too [4]. Mechanical ventilation and

need for inotropic support are also significantly associated with mortality at 30 days [16]. Whilst many of these variables are risk factors for mortality in ICU patients in general, their impact on the ESRD population appears to be greater, perhaps due to a lack of physiological reserve in this group.

An important long-term outcome after ICU admission is quality of life and functional status. Unfortunately, to date this area has not been explored in detail in chronic dialysis patients but certainly deserves attention.

6. ICU outcomes in AKI compared to ESRD

Acute kidney injury is extremely common in critically ill patients and a frequent reason for admission to the ICU. A significant proportion require RRT and have a high associated mortality rate which can vary from 25-90% depending on patient characteristics and defining AKI criteria. Several studies have compared outcomes in patients with AKI to outcomes in critically ill chronic dialysis patients.

Clermont and colleagues [9] were among the first to examine ICU mortality in patients with AKI, ESRD and those with normal renal function. In spite of similar illness severity scores in the AKI and ESRD populations, ICU mortality rates were five times higher in the dialysis-requiring AKI group than those on chronic dialysis and ten times higher when compared to those with normal renal function (57% vs. 11% vs. 5%, respectively). There was no reported difference between patients with AKI on admission to ICU and those who developed AKI during their stay in ICU.

Similarly a small case-control study conducted in Brazil compared the outcome of AKI patients on RRT with ESRD patients, two cohorts characterised by loss of renal function. They reported double the ICU and hospital mortality rates in AKI patients compared to ESRD patients when matched for age, severity of illness and number of organ dysfunctions (42% vs. 20% and 50% vs. 24%, respectively) [17]. Length of stay in both ICU and hospital was also significantly increased in the AKI group. Having excluded patients admitted to ICU for post-operative monitoring and fluid overload or electrolyte imbalance secondary to inadequate dialysis, sepsis was the main reason for admission in both cohorts. In this study however they reported that patients with AKI were more likely to require mechanical ventilation and vasopressors than those on chronic dialysis, even when matched for severity of illness.

The largest comparison of outcomes in these two groups has come from a retrospective analysis of the Riyadh Intensive Care Program database, which recorded over 40,000 ICU admissions to nineteen units in the UK and three units in Germany over a 10 year period [21]. 1847 patients with AKI on RRT were compared to 797 ESRD patients. ICU and hospital mortality in addition to ICU length of stay were significantly increased in the cohort with AKI requiring RRT. ESRD patients had approximately half the ICU and hospital mortality rates of AKI patients on RRT (20.8% vs. 54.1%, $p < 0.0001$ and 34.5% vs. 61.6%, $p < 0.0001$, respectively). As expected, increasing ICU mortality was seen with an increasing number of organ failures in both cohorts,

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however the group of AKI patients on RRT had a significantly higher proportion with more than two non-renal organ failures (75.4% vs. 25.6%) and needed mechanical ventilation more often (91.3% vs. 60.9%, $p<0.0001$). The strongest independent risk factors for ICU mortality were mechanical ventilation, maximum number of organ failures and non-surgical reason for admission.

Walcher et al [24] also reported that significantly more AKI patients were mechanically ventilated than critically ill dialysis patients, even when well matched for illness severity scores and controlled for mode of RRT (89% vs. 57%, $p = 0.0003$). Mechanical ventilation was the single factor associated with increased hospital mortality with an odds ratio of 3.1. ICU, hospital, 30- and 60-day mortality rates as well as length of stay in ICU were higher in the AKI cohort compared to ESRD patients, when both received continuous renal replacement therapy (CRRT).

Although the majority of published literature indicates that ICU and hospital outcomes are significantly worse for AKI patients requiring RRT than critically ill chronic dialysis patients, one small Australian study reported comparable ICU and hospital mortality rates for diagnosis and severity-score matched AKI and ESRD patients receiving CRRT [5].

Most outcome studies are hampered by the difficulty in assessing severity of illness correctly in patients with ESRD. The commonly used ICU prognostic scoring systems are often applied to patients with ESRD despite the fact that they are not fully validated in this patient population and may over-estimate mortality rates. What is evident from the literature is that the requirement for mechanical ventilation appears to be significantly increased in patients with AKI and that this is independently associated with an increased mortality rate.

7. Validity of ICU severity scores in ESRD

ICU illness severity and organ dysfunction scoring systems are primarily used within critical care as research and audit tools to enable comparison between observed and predicted mortality and controlled matching between study cohorts. Whilst these scoring systems have been validated in a wide variety of different subspecialties, their application and accuracy in the ESRD population remains controversial.

The Acute Physiology and Chronic Health Evaluation (APACHE II and III) [11,26], SAPS II [27] and Sequential Organ Failure Assessment (SOFA) [28] scores are commonly used in critical care literature. The first two scores assess up to 20 physiological variables within 24 hours of admission to ICU, while the SOFA score is used to track progress between subsequent 24 hour periods in ICU. As might be expected all scoring systems have a renal component, taking into account urine output, urea, serum creatinine, serum potassium and bicarbonate to varying degrees. Application of these tools to chronic dialysis patients and their accuracy in predicting mortality in this group is therefore uncertain.

Several studies have attempted to assess the validity of different scoring systems when used in the ESRD population, with differing results. Hutchinson and co-workers [4] used the

APACHE II score and reported an area under the receiver operating curve (ROC) of 0.721 for their ESRD cohort, compared to 0.805 in the non-ESRD group, indicating that it is less accurate in predicting mortality in chronic dialysis patients. When using a modified renal-adjusted APACHE II score especially for dialysis patients the ROC improved to 0.817. Uchino [5] and Juneja [16] also reported a ROC of 0.81 and 0.86 respectively for the APACHE II score, using a much smaller cohort of long-term dialysis patients. The APACHE III score is an extension of its predecessor and takes into account twenty physiological variables as well as major disease categories and treatment location prior to ICU admission to provide risk estimates for hospital mortality for individual ICU patients. Two small studies have demonstrated that this score over-estimates 30-day mortality in ESRD [9,10]. Similarly, Strijack [8] found that the APACHE II score over predicted mortality in dialysis patients by a factor of 2.5.

The SOFA score assesses degree of dysfunction of six organ systems, including respiratory, cardiovascular, renal, hepatic, neurological and coagulation system. Data on its validity in patients with ESRD are conflicting. One study reported a ROC of 0.92 (although not significantly different from the APACHE II score) [16] whereas Dara et al [10] found the SOFA score to be less accurate than the APACHE III with a ROC of 0.66. Notably the patients in the first study were sicker than those included in the latter with an increased number of organ failures and greater need for mechanical ventilation and inotropes.

Therefore at present there is limited and conflicting information regarding the validity of commonly used scoring systems in chronic dialysis patients. The majority of studies have used too small sample sizes to make any reliable claims. As mentioned previously ESRD patients have similar illness severity scores to patients with AKI on admission to ICU, but have significantly better outcomes indicating that these prognostic tools over-estimate mortality in dialysis patients. The application of these tools in their current form to a population of anuric patients with chronically deranged biochemistry on long-term RRT is at best limited.

A group in Belgium have developed a renal specific prognostic score to predict outcomes in patients with AKI [29]. The Stuivenberg Hospital Acute Renal Failure Scoring System (SHARF II) is based on eight parameters; age, serum albumin, bilirubin, prothrombin time, respiratory support, sepsis, hypotension and heart failure and consists of two scores at AKI diagnosis and 48 hours later. ROC was 0.82 at diagnosis and 0.83 at 48 hours in a cohort of 293 patients admitted to the ICU with AKI. As with other prognostic tools, this system has limited clinical application because of its complexity and remains a research and audit tool. It has yet to be assessed in critically ill long-term dialysis patients and it would be interesting to investigate whether it is a more accurate predictor of mortality than current scoring systems.

8. End of life planning in critically ill dialysis patients

Advance care planning varies widely between institutions, regions and countries. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT) was published in 1995 and highlighted the shortcomings in end-of-life decision making practices [30]. The authors described issues with communication, frequency of intensive

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interventions and the way in which patients died. Less than half of physicians knew whether their patients wanted to avoid CPR, 46% of do-not-resuscitate (DNR) orders were signed within 2 days of death, and 38% of those who died had spent at least 10 days in ICU. More recently significant efforts have been made to try and improve end-of-life care for patients with chronic and terminal disease.

Critically ill patients in the ICU frequently lack the capacity to make decisions regarding life-saving and life-prolonging interventions [31]. Instead the burden falls to the family to act as surrogate decision makers in conjunction with the multi-disciplinary team. Good communication between health professionals and relatives in this scenario is essential in order to ascertain the patient's values and beliefs, as well as impart key information regarding prognosis, probability of survival and future quality of life. Decisions to withdraw active life sustaining therapies in ICU appear to be comparable between dialysis and non-dialysis patients [4].

A large retrospective mortality study using the US Renal Data System found that chronic dialysis patients over the age of 65 years experienced very high rates of medical intervention in the last month of their lives; 76% were hospitalized, 48.9% were admitted to ICU and 29% underwent at least one intensive intervention (mechanical ventilation, CPR or feeding tube placement) [32]. Unfortunately patients' preferences related to ICU admission and interventions were not explored.

With an increasingly elderly and unwell hemodialysis population advance care planning before an episode of critical illness or ICU admission is key [33]. Nephrologists have frequent contact with their patients and are in an ideal position of trust to explore any religious or cultural beliefs and discuss limitations of treatment. Advance care planning is known to address fears, prepare patients for death, and allow them to exert some control over their life as well as strengthen interpersonal relationships. Many physicians are reluctant to initiate such important discussions either through lack of adequate training or belief that patients will initiate any discussion when they are ready. In fact qualitative research has shown that ESRD patients prefer earlier physician initiation of end-of-life discussions and would welcome more information on prognosis and potential outcomes of their disease than is currently delivered [34]. These discussions are infinitely better suited to an outpatient environment rather than on a critical care unit.

A group in Saudi Arabia carried out a survey of 100 primarily Muslim dialysis patients on their views regarding advance care planning [35]. More than 95% had little knowledge of CPR, intubation or ventilation, however interestingly more than half of those surveyed had been admitted to ICU within the last 2 years. It was generally believed that CPR was effective in 50-90% of cases and the majority of patients opted to have CPR in the event of cardiac arrest. When informed about the more realistic success rates of CPR and potential ventilator dependency, brain injury and coma, the proportion of respondents agreeing to CPR fell to 35%. This study emphasises the importance of effective doctor-patient communication regarding prognosis and quality of life, supporting patients to make informed decisions.

Similarly a British study found that 76% of hemodialysis patients surveyed wished to receive CPR in the event of an in-hospital cardiac arrest not related to dialysis [36]. The patients who opted to receive CPR were significantly younger (59 ± 16 vs. 74 ± 10 years, $p < 0.01$) and had a significantly higher albumin level than those who declined or who were undecided, perhaps indicating a better chronic health status. Gender, comorbidity, dialysis vintage, proportion of patients with adequate dialysis and mean haemoglobin level were not associated with the decision.

It is evident that a large proportion of chronic dialysis patients experience an admission to ICU before they die. End-of-life discussions often fall to the family and health professionals caring for the patient. Research indicates that dialysis patients want to be involved in advance care planning at the earliest opportunity and the onus rests on the physician to enable patients to make well informed and timely decisions regarding end-of-life care.

9. Conclusion

Critically ill patients with ESRD are frequently admitted to the ICU, and although they display worse outcomes than those with normal renal function, their prognosis is better than that of ICU patients with AKI. Mortality is related primarily to the severity of the underlying illness and their co-morbidities rather than to lack of renal function itself. Having survived an episode of critical illness, data on longer-term outcomes remains conflicting and little is currently known about quality of life and performance status after discharge from ICU. Prognostic scoring systems used in critical care appear to over-estimate mortality in the chronic dialysis population and should be used with caution. There is a need for ESRD-specific tools to score severity of illness and predict mortality in the critically ill and enabling accurate research and audit in this population. Current evidence suggests that long-term dependence on dialysis should not prejudice against prompt referral or admission to ICU.

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Chapter 10

Disturbances in Acid-Base Balance in Patients on Hemodialysis

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1. Introduction

The prevalence of metabolic acidosis increases in Chronic Kidney Disease (CKD) patients according to the fall in glomerular filtration rate (GFR). In early stages of renal dysfunction acid retention is mainly due to the reduced tubular ammonium (NH^{4+}) secretion. As GFR declines retention of organic acids (HSO^{-s}_{4}, HPO^{-}_{4}) is also observed. The acid load resultant from diet and protein catabolism was believed to be the main responsible for acidosis in hemodialysis patients, however recent studies have shown an increasingly important role of hyperchloremia in the genesis of metabolic acidosis and pathophysiological disorders associated with it [1]. This finding was made possible through the use of Stewart´s [2] physicochemical approach for diagnosis and classification of acid base disorders. This new approach not only enables the identification and classification of acid-base disorders and allows the quantification of the magnitude of each component to the disorder genesis [3,4].

The current K/DOQI recommendation for the treatment of metabolic acidosis in the patients on hemodialysis therapy is for maintaining a serum bicarbonate of at least 22 mEq/l [5]. Although consensus recommendation, the studies on metabolic acidosis in these patients showed that hemodialysis fail to raise the levels of serum bicarbonate to the desired value. Santos et al. [6] in a study of metabolic acidosis (HCO^{-}_{3} < 22 mEq/L) in dialysis patients found a 90% prevalence of metabolic acidosis. Libório et al. found an average level of serum bicarbonate in dialysis patients of 18 to 19 mEq/L in their trials [1,7].

The deleterious effects of maintaining metabolic acidosis in this population of individuals are well known, endocrine disorders and anorexia leading to catabolism of endogenous proteins and changes in bone mineral metabolism all these contributing to increased morbidity and mortality in these patients [8].

CKD related acidosis is associated with several life-threatening conditions. Adequate treatment of this condition might be associated with better outcomes in the dialysis population as shown in some studies reporting improvement in nutritional status with oral bicarbonate supplementation or higher dialysis solution bicarbonate [6]. Data on involvement of chloride as cause of acidosis and its implication on acidosis complications are scarce.

In this chapter we intend to approach the importance of metabolic acidosis for dialysis patients, discuss the possible pathophysiological mechanisms involved in the genesis of the acidosis and the consequences that this disorder brings to these individuals, using quantitative physicochemical approach. We propose to conduct a literature review about the therapeutic alternatives as well as dialysis treatment modalities that could be used for the correction of this disorder.

2. The acid–base equilibrium: Henderson–Hasselbalch

The Henderson–Hasselbalch equation is still the standard method for interpreting acid–base equilibrium in clinical practice [9]. It is based in the following equation:

$$pH = pK1' + log\ HCO^{3-} \mid (Sx\ PCO_2) \quad (1)$$

This equation describes how plasma CO_2 tension, plasma bicarbonate (HCO^{3-}) concentration, the apparent dissociation constant for plasma carbonic acid (pK) and the solubility of CO2 in plasma interact to determine plasma pH. The magnitude of the metabolic acidosis is generally quantified by the base deficit or base excess, which is defined as the amount of base (or acid) that must be added to a liter of blood to return the pH to 7.4 at a partial pressure of carbon dioxide (PCO_2) of 40 mmHg [10].

3. Stewart model for acid base disorders

The traditional approach has been criticized as being descriptive rather than mechanistic in nature and limited in scope and therefore unable to make complete diagnosis in patients with complex disorders. In contrast, proponents of Stewart's approach believe it to be mechanistic in nature and comprehensive in scope, able to detect important hidden disorders [10,11]. The fundamental underpinning of Stewart's approach is the concept of independent and dependent variables in acid-base homeostasis. According to Stewart, "Independent variables in any system are those which can be directly altered from outside the system without affecting each other" and "...dependent variables in a system can be thought of as internal to the system. Their values represent the system's reaction to the externally imposed values of the independent variables." [12].

On the basis of Stewart's definition, H^+ and bicarbonate are dependent variables whose concentrations are determined by the three independent variables, Strong Ion Difference (SID),

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PCO_2, and total concentration of weak acids (ATOT), mainly composed of albumin and phosphate [12]. In Stewart's approach, similar to the traditional approach, respiratory disorders are those that are due to a primary alteration in PCO_2. Metabolic disorders, however, are due to primary alterations in SID or ATOT and not bicarbonate. By the law of electroneutrality [4]:

$$([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) - ([HCO_3^-] + [A^-]) = 0 \quad (2)$$

This formula can be rearranged as follows:

$$([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) = [HCO_3^-] + [A^-] \quad (3)$$

Therefore,

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) = [HCO_3^-] + [A^-] \quad (4)$$

Under normal conditions, concentration of lactate and other strong ions is very low and can be ignored. The formula could therefore be simplified to

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-]) = [HCO_3^-] + [A^-] \quad (5)$$

SID therefore can be calculated as the difference between fully dissociated cations and anions or sum of bicarbonate and A^- where A^- represents total charges contributed by all nonbicarbonate buffers, primarily albumin, phosphate, and, in whole blood, hemoglobin. SID is therefore the same as buffer base concept introduced by Singer and Hasting more than five decades ago. When an abnormal anion is present, a gap will appear between SID calculated by the difference between strong ions (the so-called "apparent SID", SIDa) and calculated by the addition of bicarbonate and nonbicarbonate buffers (so called "effective SID" SIDe) (Figure 1). This difference, named strong ion gap (SIG), is a marker for the presence of an abnormal anion. Anion gap (AG) is also calculated on the basis of the principal of electroneutrality as shown as follows [4]:

$$([total\ cations] - [total\ anions]) = ([measured\ cations] + [unmeasured\ cations]) - ([measured\ anions] + [unmeasured\ anion]) = 0 \quad (6)$$

This can be rearranged as:

$$([measured\ cations] - [measured\ anions]) = ([unmeasured\ anions] - [unmeasured\ cations]) = AG \quad (7)$$

In normal state, plasma unmeasured anions reflect charges contributed by the nonbicarbonate anions (A^-), primarily albumin and phosphate. The unmeasured cations are primarily made up of calcium, magnesium, and, depending on the formula used, potassium. AG, the

difference between the abnormal and normal (or baseline) AG, represents the amount of abnormal anion(s) present in plasma. SIG, as pointed out already, also represents the amount of abnormal anion(s) present in plasma and is expected to be mathematically equal to ΔAG (Figure 1) [4].

This relationship could have been even stronger if ΔAG were calculated in a more precise manner by using actual baseline values for AG in each patient rather than the mean value of 12 [13]. It should be clear that specific components of Stewart's formulas, such as SID and SIG, are conceptually and mathematically closely related to specific components of traditional formulas such as bicarbonate, AG, and ΔAG[4].

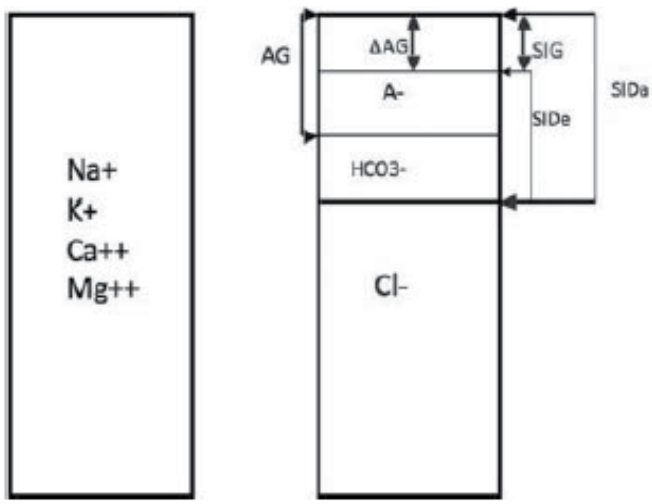

Figure 1. Relation between Strong Ion Gap (SIG) and ΔAG [4]

4. Classical X Stewart´s approach

One important goal of any method used to analyze acid base disorders is to develop a clinically useful classification. The traditional approach, using a robust body of empirical observations, has developed a classification that contains six primary disorders: Metabolic acidosis, metabolic alkalosis, acute and chronic respiratory acidosis, and acute and chronic respiratory alkalosis. Metabolic acidosis can further be classified as anion gap or hyperchloremic acidosis. In addition, by using compensatory formulas as well as ΔAG, the traditional approach is capable of diagnosing complex acid-base disorders [14].

In Stewart's approach, classification of acid base disorders is based on changes in the three "independent" variables (Table 1) [15]. Respiratory disorders, as in the traditional approach, are due to a change in PCO_2, whereas metabolic disorders are due to alterations in either SID or ATOT. SID is decreased in metabolic acidosis and increased in metabolic alkalosis. By

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calculating SIG, one can further classify metabolic acidosis. In hyperchloremic metabolic acidosis, both effective and apparent SID decrease equally, as the increase in chloride is counterbalanced by an equal decrease in the bicarbonate concentration. SIG therefore remains at or near zero. In AG metabolic acidosis, apparent SID does not change (as chloride concentration is unchanged), but effective SID decreases (as a result of a decrease in bicarbonate concentration) and SIG therefore becomes positive [15]. One major departure from the traditional approach is classification of acid-base disorders as a result of alteration in ATOT. ATOT, representing all nonbicarbonate buffers pairs ($HA + A^-$), is made up of charges contributed primarily by serum proteins (mainly albumin) with phosphate and other buffers playing a minor role. On the basis of this classification, an increase in serum protein would result in metabolic acidosis and a decrease, metabolic alkalosis [15,16].

Parameter	Acidosis	Alkalosis
Respiratory	↑PCO2	↓PCO2
Nonrespiratory (metabolic)		
Abnormal SID		
Water excess/deficit	↓SID, ↓ [Na]	↑SID, ↑[Na]
Imbalance of Strong anions		
Chloride excess/deficit	↓SID, ↑[Cl]	↑SID, ↓[Cl]
Unidentified anion excess	↓SID, SIG "/> 0	
Nonvolatile weak acids		
Serum albumin	↑[Alb]	↓[Alb]
Inorganic phosphate	↑[Pi]	↓[Pi]

Table 1. Classification of acid-base disturbances according to Stewart´s approach [4]

5. Pathophysiology of acidosis in CKD

Classical uremic acidosis is characterized by a reduced rate of NH^{4+} production and excretion because of cumulative and significant loss of renal mass [17]. Usually, acidosis does not occur until a major portion of the total functional nephron population (>75%) has been destroyed, because of the ability of surviving nephrons to increase ammonia genesis. However, there is a decrease in total renal ammonia excretion as renal mass is reduced to a level at which the GFR is 20 mL/min or less. PO_4^{3-} balance is maintained as a result of both hyperparathyroidism, which decreases proximal PO_4^{3-}absorption, and an increase in plasma PO_4^{3-} as GFR declines. In advanced renal insufficiency, including hemodialysis patients, the hyperchloremic acidosis discussed earlier converts to a typical high AG acidosis. Poor filtration plus continued reabsorption of poorly identified uremic organic anions resulting from diet and body metabolism contributes to the pathogenesis of this metabolic disturbance [17].

Libórioet al. [1] showed when using Stewart´s approach to acid–base disorders in maintenance hemodialysis that unmeasured anions are an important cause of acidosis in this population, contributing to more than 40% of reduction in serum bicarbonate. A surprising finding was the role of hyperchloremia in acidosis etiology, which had a similar quantitative effect in acidosis. Recently, a study carried out in nondialysis chronic renal failure patients disclosed the main role of hyperchloremia in acidosis [18]; however, the acidosis composition in the dialysis population is still largely unknown.

The lack of quantitative analysis has led major textbooks to the assumption that the acidosis in these patients is due to the accumulation of unmeasured anions only, leading to high anion gap acidosis. Rocktaeschelet al. [19] showed in acute renal failure, acidosis also has complex and multiple etiologies in maintenance hemodialysis.

Sevelamer hydrochloride is a known cause of acidosis in hemodialysis due to the load of hydrochloric acid (each 800 mg tablet of sevelamer hydrochloride leads to an acid load equivalent to 4 mEq hydrochloric acid) [20].Another potential culprit in the cause of hyperchloremia is the chloride levels in the dialysate bath. In a literature review,15 considerable variations were found in dialysate chloride levels: from 90 to 125 mEq/l. The elevation in chloride is accompanied by a reduction in dialysate SID. Considering this fact, the maximum level of dialysate chloride must be 105 mEq/l, allowing the dialysate SID to increase up to 40 mEq/l, a value similar to that of plasma [7].

Acidosis in maintenance hemodialysis has multiple etiologies. Unmeasured anions and hyperchloremia are the main components, and hyperphosphatemia has a minor effect. Hyperchloremia cannot be attributed to sevelamer hydrochloride therapy alone, and we speculate that high levels of chloride in dialysate constitute a potential culprit. Additional studies assessing the relationship between the nature of acidosis and its detrimental effects on bone, inflammation, and nutrition are warranted [1].

6. Consequences of metabolic acidosis

6.1. Exacerbation of bone disease and impaired growth in children

Studies indicate that metabolic acidosis can be a contributory factor to the development or exacerbation of bone disease in both adults and children and that it can impair growth in children with or without CKD. Direct effects of an acidic milieu on bone and indirect effects mediated by changes in PTH levels and/or its actions or vitamin D levels appear to contribute to these pathological effects [21].

Bone disease in CKD is mainly due to alterations in parathyroid hormone (PTH) and vitamin D levels. Certain toxins, such as aluminum may play a role [22]. However there is a substantial amount of data relating chronic metabolic acidosis as an additional important factor [23,24]. In vitro and in vivo studies have demonstrated that prolonged metabolic acidosis

can directly stimulate osteoclast-mediated bone resorption and inhibit osteoblast mediated bone formation [24-27]. Some animal and human studies have shown that metabolic acidosis can reduce vitamin D levels and stimulate PTH secretion. Metabolic acidosis also attenuates the cellular response to PTH, as measured by cAMP accumulation in rat tissues. The actions of the calcium sensing receptor might also be attenuated by a decrease in extracellular pH, perhaps contributing to an increase in PTH levels [21]. Chloride might also be related to higher PTH levels and worsening bone disease. Using Stewart´s physicochemical approach Liborio et al. [28] found a higher PTH levels in hemodialysis patients with higher chloride serum concentration and a significant relationship between chloride, PTH levels and serum markers of mineral bone disease.

In adult patients on chronic maintenance hemodialysis, amelioration of the acidosis by raising the dialysate base concentration was found to attenuate the rise in PTH, reduce bone resorption, and improve bone formation. In another study in dialysis patients, correction of the acidosis restored the normal suppression of PTH secretion in response to infused calcium [21]. Although controlled studies of the impact of correction of metabolic acidosis alone on the growth in children with CKD are not available, metabolic acidosis is considered to be a contributory factor to short stature in children with CKD prior to or after initiation of chronic maintenance dialysis. It´s recommended that it be corrected prior to the initiation of growth hormone therapy [29].

Data about chloride and SID changing in dialysis bath and bone disease outcomes are still lacking. New studies in dialysis population assessing the long term effect this measure might influence in the amelioration of bone disease must emerge.

6.2. Increased muscle wasting

Muscle wasting is increased in CKD. This is not only due nutritional deprivation or exposure to a uremic milieu. Metabolic acidosis in CKD stimulates muscle wasting and may impair growth in children [30].

The increased protein degradation was due to the increased transcription of genes encoding proteins of the ATP-dependent ubiquitin–proteasome pathway, resulting in increased activity of the ATP-dependent ubiquitin–proteasome system (UPS) [30]. Of interest, activation of muscle protein degradation requires endogenous glucorticoids [21]. Recent studies have identified the dependency on glucocorticoids to increase muscle protein wasting as a non-genomic mechanism by which the glucocorticoid receptor sequesters phosphatidylinositol-3-kinase to interrupt insulin–IGF-1 signaling [31]. Several conditions including CKD and metabolic acidosis appear to be related to the activation of the UPS. In several studies, amelioration of metabolic acidosis by the provision of base to patients with CKD before or after initiation of maintenance dialysis decreased the rate of protein degradation and urea generation, resulting in improved protein balance and increased muscle mass [30].

Similar to bone disease, some evidence suggests that a detectable fall in serum [HCO_3^-] may not be necessary to stimulate muscle degradation. [21]

6.3. Reduced albumin synthesis

Hypoalbuminemia is the most common marker of protein-energy wasting in dialysis patients and has strong association with increased morbidity and mortality. Hypoalbuminemia is associated with development and recurrent cardiac failure in hemodialysis patients [32].

Experimental induction of metabolic acidosis in normal humans for at least 7 days has in some studies caused a reduction in albumin synthesis, thereby predisposing the individual to the development of hypoalbuminemia [33,34]. Indeed, analysis of more than 1500 patients > 20 years of age who participated in the NHANES III study revealed that the age-adjusted odds ratio of serum [HCO_3^-] for hypoalbuminemia rose from 1.0 for serum [HCO_3^-] > 28 mEq/l to 1.54 for serum [HCO_3^-] ≤22 mEq/l [35]. Furthermore, in two studies of adult patients with CKD either prior to or after initiation of chronic maintenance dialysis, improvement of the metabolic acidosis by the provision of base caused the serum albumin concentration to rise and protein catabolic rate to fall [36,37].

Reduced protein synthesis, increased protein breakdown, and enhanced amino acid oxidation have all been suggested as factors contributing to a reduced serum albumin concentration with metabolic acidosis. A decrease in protein intake might also play a role, although in one study in which dietary intake was examined, no difference in protein intake was found in patients with CKD before or after correction of the acidosis [21].

6.4. Accelerating the progression of CKD

Studies in humans have supported the potential role of metabolic acidosis in the progression of CKD. In a large cohort of patients with CKD followed at a single medical center, a serum [HCO_3^-] of <22 mEq/l was associated with a 54% increased hazard of progression of CKD when compared with a serum [HCO_3^-] of 25–26 mEq/L [38]. In two separate studies, one in patients with hypertensive renal disease [39]and another in patients with CKD of diverse etiology [40], the administration of base slowed the progression of CKD. In the latter study, the rate of decline in GFR in those given bicarbonate was less than half that in the control group. Moreover, the bicarbonate group was less likely to experience a rapid decline in GFR or develop end-stage renal disease [21].

Three mechanisms have been postulated to explain the acceleration of progression of CKD in response to metabolic acidosis. First, it has been suggested that the increase in renal medullary ammonia concentration resulting from the stimulation of ammonia production by metabolic acidosis activates the alternative complement pathway and causes progressive tubulointerstitial injury [41]. Second, it has been suggested that new bicarbonate synthesized by the kidney in response to acidosis alkalinizes the interstitium and encourages precipitation of calcium in the kidney [42]. Finally, evidence in both animals and humans has been accrued to suggest that increased endothelin production may mediate the tubulointerstitial injury and decline in GFR noted with the metabolic acidosis of CKD [43].

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6.5. Impaired glucose homeostasis

Studies in patients with CKD demonstrated impaired glucose tolerance and insulin resistance, both prior to and after the initiation of chronic maintenance dialysis. The effect of uremia on insulin resistance appeared to be related, in part, to metabolic acidosis, because the administration of base to stable hemodialysis patients improved, although it did not normalize, insulin sensitivity. The insulin resistance and glucose intolerance of uremia per se are generally not severe, but it is possible that they contribute to the development of other clinical abnormalities [21].

6.6. Accumulation of β2-microglobulin

The accumulation of β2-microglobulin in individuals with CKD contributes to the development of amyloidosis. Amyloid infiltration can cause the carpal tunnel syndrome, bone cysts and, possibly, cardiomyopathy [44]. This accumulation of β2-microglobulin is primarily related to the number of years on dialysis, which has been interpreted as suggesting that the predilection to amyloidosis is due to reduced excretion of β2-microglobulin and, in the case of hemodialysis, also to chronic exposure of blood to the dialysis membrane [44].

Metabolic acidosis has been suggested as a possible additional factor in promoting β2-microglobulin accumulation. First, there is an inverse correlation between serum [HCO_3^-] and β2-microglobulin levels in patients with CKD. Furthermore, β2-microglobulin concentrations have been found to be higher in patients dialyzed with acetate who have a lower serum [HCO_3^-] than those dialyzed with bicarbonate [44].

6.7. Abnormal thyroid function

Individuals with uremia have low basal metabolic rates. This could be related in part to the associated metabolic acidosis affecting thyroid hormone levels, since ammonium chloride-induced metabolic acidosis has been found to be associated with reduced triiodothyronine (T3) and thyroxine (T4) and elevated thyroid-stimulating hormone levels [21]. Correction of metabolic acidosis in patients with CKD causes T3 levels to rise towards normal [45].

6.8. Stimulation of inflammation

Exposure of macrophages to an acidic environment leads to the increased production of tumor necrosis factor α (TNFα) [46]. In one study, the correction of metabolic acidosis in a small number of patients maintained on chronic ambulatory peritoneal dialysis was associated with a reduction in TNFα levels [21]. Thus, it has been suggested that metabolic acidosis is associated with the stimulation of inflammation and, therefore, that it represents a chronic inflammatory state. However, no significant difference was observed in the serum levels of C-reactive protein and interleukin-6 (two biomarkers of inflammation) among three separate groups of dialysis patients with a mean serum [HCO_3^-] of 19.2, 24.4, and 27.5 mEq/L, respectively [47].

6.9. Development or exacerbation of cardiac disease and increase in mortality

Low serum bicarbonate level is related to higher mortality in CKD patients both prior [48] to and after initiation of chronic maintenance dialysis [21]. A retrospective analysis of laboratory data obtained from more than 12,000 hemodialysis patients showed an increased risk of death in patients with a serum [HCO_3^-] <15–17 mEq/L [49]. Also, patients with CKD not on dialysis had a greater risk of death when their serum [HCO_3^-] was <22 mEq/L [50]. Navaneethanet al. [48]found a higher mortality rate in the group of patients with lower serum bicarbonate ([HCO_3^-] < 23 mEq/L) level in a trial of 41.445 stage 3 and 4 CKD patients. An interesting finding of this trial was that higher level ([HCO_3^-] > 32 mEq/L) was also associated with poor outcome and higher mortality rate. The DOPPS study [51] showed better outcomes in maintenance hemodialysis patients with midweek bicarbonate serum level of 21,1 to 22 mEq/L. In this study both low ([HCO_3^-] < 17 mEq/L) and higher (>24 mEq/L) were related to higher hospitalization and mortality rate. These data point to the importance of a strict control of metabolic acid base disturbances in CKD patients and the harmful effect of overcorrection of acidosis.

Cardiovascular disease is the most common cause of death in patients with CKD. There are strong evidence that inflammation plays an important role in the genesis and progression of atherosclerotic heart disease. As discussed earlier in this text acidosis is a chronic inflammatory state and it is reasonable to speculate that metabolic acidosis could be related to increased prevalence or severity of cardiovascular disease [21].

6.10. Renal replacement therapy and liver failure

Anticoagulation with heparin might be a problem in patients with increased bleeding risk specially critically ill patients and cirrhotic patients requiring continuous renal replacement therapy (CRRT). There is increasing evidence questioning the safety of heparin in such patients and there are accumulating data on a potential better alternative, regional anticoagulation with citrate. Sodium citrate administered before the filter inhibits the generation of thrombin. For anticoagulation the citrate dose is adjusted to blood flow to attain low ionized calcium (< 0,4 mmol/l) concentration in the filter, the lower the calcium concentration the higher the degree of anticoagulation. Citrate is partially removed by the filter and the remaining amount is metabolized in citric acid cycle predominantly in the liver. The chelated calcium is than released and the lost calcium is replaced after filter. The systemic coagulation is unaffected [52].

Buffer strength of citrate depends on the proportion of strong cations in the fluid counterbalancing citrate concentration. Assuming the citrate is completely metabolized, one micromole of trisodium citrate provides the buffer as 3 mmol sodium bicarbonate. The Stewart Concept provides an easier way to understand the buffering effect of citrate: after metabolized in the liver the remaining sodium increases serum SID. Increased SID produces alkalosis. Sodium citrate has a SID of zero until citrate is metabolized, so in conditions where citrate metabolism is grossly impaired, such as severe liver dysfunction the citrate alkalinizing effect might be compromised. Citrate accumulation decreases the SID leading to a metabolic acidosis [52]. For this reason anticoagulation free or low heparin regimens have been

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used for patients with severe liver dysfunction requiring continuous renal replacement therapy. This strategy reduces bleeding risk however lowers the procedure efficiency and thefilter patency.

Recent studies have emerged showing protocol using sodium citrate as a safe alternative for anticoagulation even in patients with liver dysfunction. In a prospective randomized open label crossover trial of regional citrate anticoagulation vs. anticoagulation free liver dialysis by the Molecular Adsorbents Recirculating System (MARS) Meijers et al. [53] demonstrated that citrate anticoagulation significantly increased the likelihood of completed MARS treatment (P = 0,04), higher bilirubin reduction ratio when citrate was applied and improvement in systemic ph levels. In this study, systemic ionized calcium concentrations were significantly reduced during citrate anticoagulation but remained within a safe range even using standard protocol for extracorporeal calcium levels. There were no major adverse events in the citrate group. Other study in early post liver transplantation patients requiring CRRT showed efficacy and safety of regional citrate anticoagulation without severe decrease in calcium concentration and acidosis [54]. Another study applied anticoagulation with sodium citrate in patients with severely impaired liver dysfunction (mean Child-Pugh score: 10,5) under renal replacement therapy with sustained low efficiency dialysis (SLED) after repeated filter clotting (filter lifetime < 2h) under heparin free or low dose heparin therapy. The dialysis time with citrate anticoagulation was 17,3 h, filter lifetime increased to 23,3 h. No major bleeding episodes related to dialysis therapy were observed, total calcium, ionized calcium, calcium gap, electrolytes and base excess were maintened at stable levels during therapy and thereafter. There were no significant hypotensive episodes and norepinephrine dose was reduced during therapy. This protocol used lower citrate infusion rate with higher post-filter ionized calcium levels and absence of routine calcium supplementation at venous line and the use of high-flux dialyser for reducing the risk of accumulating calcium citrate complexes [55].

These data show increasing evidence that citrate might be used for anticoagulation even in patients with impaired liver function. However clinicians should be alert when using this strategy, measuring the citrate levels and use of high-flux dialyser must be applied for warranting safety of maintaining low citrate concentrations. Data showing safety of citrate regional anticoagulation and recommendation of its use in patients with liver impairment under CRRT are scarce and don´t warranty recommendation of its application for this modality of treatment.

7. Treatment of metabolic acidosis in hemodialysis patients

The standard recommendation for correction of metabolic acidosis in CKD patients is for reaching a bicarbonate level at least 22 mEq/L in dialytic and conservative management patients [5]. Reaching this level may be a challenging schedule [1,6,7]. Current dialysate base standards appear to be somewhat arbitrarily chosen. Standard concentrations of bicarbonate in dialysates (33–35 mEq/L) do not completely correct the acidosis [56].

Alkali therapy has been shown to retard the progression of CKD in patients with reduced GFR not in dialysis therapy [57]. Benefits of correcting this disturbance in hemodialysis patients have already been reported in this chapter.

Routine measuring bicarbonate serum levels and the application of one of the following strategies might be of utility for maintaining bicarbonate target concentration and improving outcomes.

7.1. Oral supplementation

In CKD patients in conservative management acidosis should be treated by administering base in the form of oral bicarbonate or organic anions that are metabolized to bicarbonate such as citrate. Once serum bicarbonate reaches the desired level, the amount of base administered can be reduced to the minimal necessary to maintain this level [21]. A Systematic review on treatment of metabolic acidosis in non-dialysis patients showed improvement in kidney function, which may afford a long term benefit in slowing the progression of CKD [57]. Papadoyannakis et al. [58]found that ingestion of sodium bicarbonate corrects metabolic acidosis and increases appetite and body mass of the end-stage renal failure patients.

In dialysis patients oral administration of calcium carbonate at a dosage of 3–6 g/daily raises pre-dialysis plasma bicarbonate [59]. Calcium carbonate induces positive nitrogen balance due to correction of metabolic acidosis. Furthermore, calcium carbonate serves as a phosphate binder [60]. Instead of ingestion of the bicarbonate, calcium salts of organic acids could also be used as phosphate binders, i.e. acetate, citrate, gluconate or ketogluterate, which all could be metabolized into bicarbonate [61].

7.2. Bicarbonate based dialysis solution

Whichever dialysis therapy is used, there is a similar need for correcting the acid-base balance. The most important tool for this aim is the buffer in the dialysis fluid. Bicarbonate dialysis achieves much better hemodialysis stability [62]. Based on clinical and experimental studies, different side effects of hemodialysis treatment have been attributed to acetate, such as nausea, vomiting, headache, muscle cramps, hypotension, hemodynamic instability and increased cytokine release [63,64]. In contrast to acetate dialysis, bicarbonate dialysis does not interfere with gluconeogenesis and lipid synthesis [65]. The buffer source in all modern versions of these therapies should be bicarbonate. Bicarbonate is a physiological buffer, therefore in bicarbonate dialysis, plasma bicarbonate concentration and blood pH progressively increase during the dialysis session[65].

7.3. Higher bicarbonate in dialysate

Rising bicarbonate level in dialysate is effective in correcting metabolic acidosis. This correction is associated with improvement in CKD related anorexia and influencing the nutritional status [6]. Choosing dialysate bicarbonate level might be challenging. Some observations confirmed that dialysate bicarbonate concentrations of 40 mEq/L appear safe and well tolerated [66,67]. Oettinger and Oliver [68] demonstrated that high-bicarbonate dialysate (42

mEq/L) corrects pre-dialysis acidosis in 75% of hemodialysis patients without causing progressive alkalemia, hypoxia, or hypercarbia and that pre-dialysis BUN, calcium, ionized calcium and phosphorus are unaffected by high-bicarbonate dialysate. Williams et al. [69] demonstrated that bicarbonate dialysate concentrations of 40 mEq/L were safe, well tolerated and produced better control of acidosis (significantly higher pre-dialysis arterial plasma pH values as pre-dialysis serum total CO_2), with an increase in triceps skinfold thickness, compared to a bicarbonate concentration of 30 mEq/L. The amount of base transferred to the patient during dialysis depends on the patient's needs. Agroyannis et al. [70] showed a significant correlation between interdialytic weight gain and the values of pre-hemodialysis blood pH and bicarbonate, suggesting an important role of the interdialytic weight gain on acid-base equilibrium of uremic patients undergoing hemodialysis.

There is no doubt that individualized bicarbonate concentration is necessary for hemodialysis patients. Therefore, the choice of dialysate bicarbonate concentration should also be predicted on the basis of the patient's determinants (hydrogen generation, bicarbonate distribution space) and technique-related factors (membrane permeability, ultrafiltration rate, blood and dialysate flow) [71]. This can be achieved by new dialysis machines and by bicarbonate profiling.

7.4. Changing SID – The physicochemical approach

The base supply by dialysis does not seem to represent the main mechanism for acid-base correction by dialysis. Using Stewart´s physicochemical approach Liborio et al. [1], showed in that chloride might play a pivotal role in pathogenesis of metabolic acidosis in hemodialysis patients. Other study found a better correction in bicarbonate levels after dialysis with a chloride level of 107 mEq/L rather than 111 mEq/L [7]. Such correction in serum bicarbonate might be possible due to elevation in plasma SID by exposing plasma to higher SID in dialysis solution. However although not expected, correction of metabolic acidosis in this study was mainly due to reduction of unmeasured anions, represented in Stewart´s model by SIG.

This unexpected reduction in unmeasured anions can be explained by Gibbs Donnan equilibrium. The reduction in serum chloride during the post-dialysis period can facilitate redistribution from the intracellular or interstitial compartment, this decrease in intracellular chloride can improve the intracellular capacity of buffering other negative charges, reducing plasma unmeasured anions. Another possible explanation may be found in the dialysate compartment. It has been suggested that a higher dialysate chloride concentration, through Gibbs-Donnan equilibrium across the dialyzer membrane, partially prevents an adequate clearance of unmeasured anions due to a charge effect, i.e., electric repulsion of a negative charge. Moreover, based on this principle, it is not possible to exclude that an improvement in bicarbonate diffusion might have been the result of using a lower dialysate chloride concentration [7].

Diet, intestine, bone and intermediate metabolism could play a pivotal role in the acid-base status of uremic patients. Probably, more attention needs to be paid to the possible noxious effect of overcorrection of acidosis. Rapid correction of acidosis by bicarbonate dialysis may cause drowsiness, unconsciousness, hypokalemia and cardiac arrhythmia [72].

8. Conclusion

Metabolic acidosis is a detrimental condition both for CKD patients on hemodialysis therapy or conservative management. Several adverse effects of maintenance of an acidic state come with the falling in GFR and developing and worsing of acidosis. Several strategies have been employed for correction of that disturbance as listed before, some need more researches for finding consistent results of the benefits of such strategies. Stewart´s approach brought new perspectives for understanding and treating this disturbance. Studies validating changing SID, chloride or other components of the dialysate bath are still need.

Attention must be paid for the metabolic alkalosis in this population as a result of overcorrection or overtreatment of acidosis. This one brings deleterious effects like metabolic acidosis. How metabolic alkalosis impairs survival in CKD is still unknow, new researches are need in this field.

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Chapter 11

More than Half of Patients Receiving Hemodialysis with Leg Ulcer Require Amputation

Masaki Fujioka

Additional information is available at the end of the chapter

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1. Introduction

Patients receiving hemodialysis (HD) often develop leg ulcers, which are difficult to heal because of complications of other diseases, including diabetes mellitus (DM), calciphylaxis, collagen disease, peripheral arterial disorder (PAD), chronic anemia, and weakness of the skin (Figure 1) [1-3]. Especially, infection of an ulcer is associated with the risk of sepsis, which may be fatal if the blood access shunt becomes infected [4]. Some surgical treatment is usually required in these cases.

This article focuses on the prognosis and results of treating these wounds in patients receiving HD.

2. Patients and methods

We evaluated 57 patients receiving HD (male: 37, female: 20, and 32 because of diabetes mellitus, 22 because of chronic glomerulonephritis, 2 because of polycystic kidney, and 1 because of systemic lupus erythematosus) who had leg ulcers and underwent surgical treatment in our unit from 2004 through 2011. Patients ranged in age from 43 to 95 years (median age: 69 years).

Ninety-four patients with leg ulcers due to DM (male: 53, female: 41) who underwent surgical treatment in our unit from 2004 through 2011, were also investigated as a control. They ranged in age from 26 to 93 years (median age: 59.5 years) (no significant difference, Wilcoxon rank sum test).

I investigated differences in the cause of wounds, type of surgery, and their mortality to evaluate the severity of the wounds in patients receiving HD.

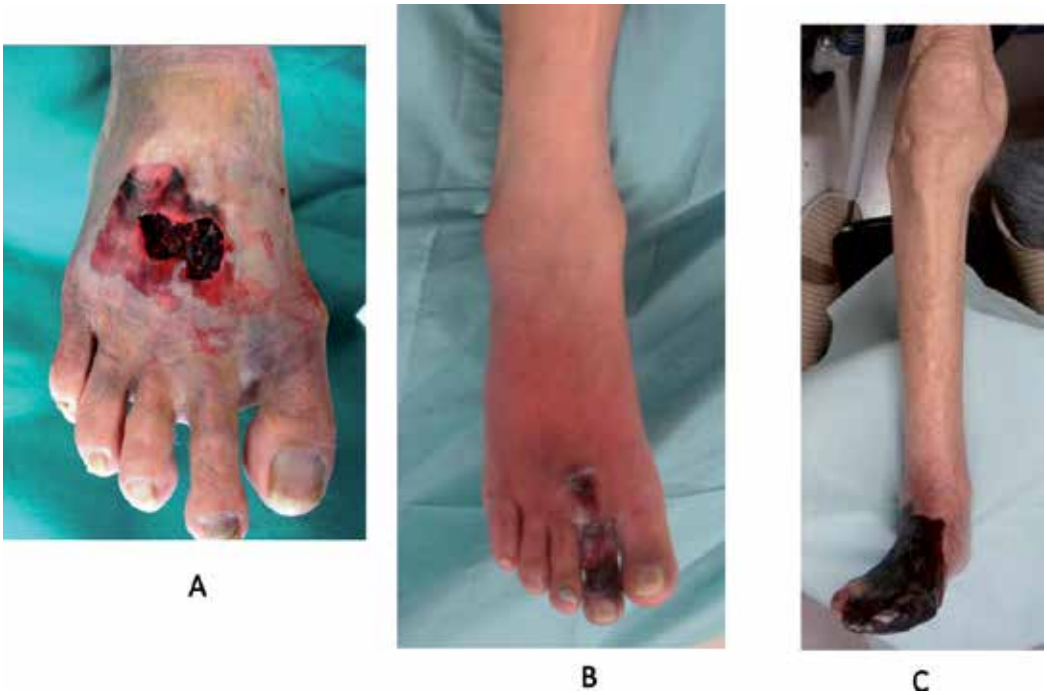

Figure 1. Patients receiving hemodialysis often develop leg ulcers due to several causes, including trauma (A: skin defect following developing a hematoma due to falling on a step), infection (B: diabetic gangrene), peripheral arterial disorder (C: leg dry necrosis due to arteriosclerosis obliterans).

3. Results

3.1. Causes of leg ulcers in patients with HD and DM

Leg ulcers in patients undergoing hemodialysis were originated due to ischemia in 34 cases (60%), infection in 13 cases (23%), and trauma in 10 cases (17%). Those in patients with DM were originally due to ischemia in 18 cases (19%), infection in 61 cases (65%), and trauma in 15 cases (16%) (Figure 2). HD-receiving patients were significantly more likely to develop leg ulcers due to PAD comparing to those with DM ($p<0.001$, Chi-square test).

3.2. Treatments for leg ulcers in patients with HD and DM

In the HD-receiving patient group, 30 patients (52%) underwent amputation surgery. Among them, 19 (33%) required major (below or above the knee) amputations, while 39 (42%) underwent amputation surgery, including 11 (12%) major amputations in the patients

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with leg ulcers due to DM (Figure 3). There was a significant differences between the groups in the frequency of amputation ($p<0.05$, Chi-square test) and that of major amputation ($p<0.001$, Chi-square test).

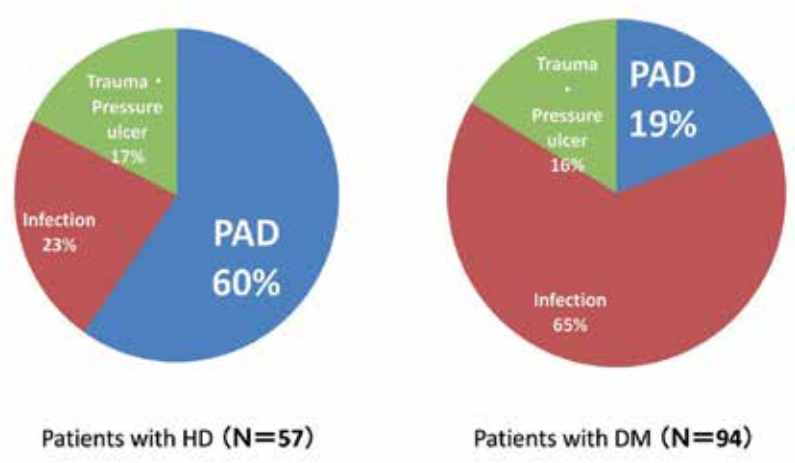

Figure 2. Causes of leg ulcers in patients with HD and DM (PAD: peripheral arterial disorder)

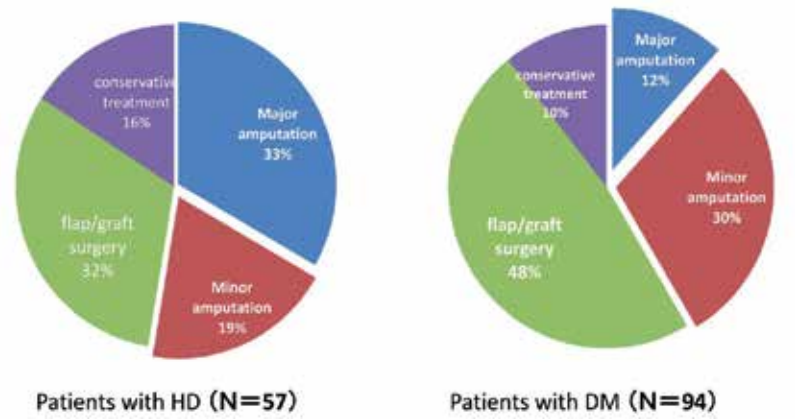

Figure 3. Treatments for leg ulcers in patients with HD and DM

3.3. Mortality of patients with leg ulcers

Three patients (5%) with HD died of contaminated foot ulcers, and 3 (3%) with DM (Figure 4). There were no significant differences in mortality between the 2 groups ($p>0.05$, Chi-square test).

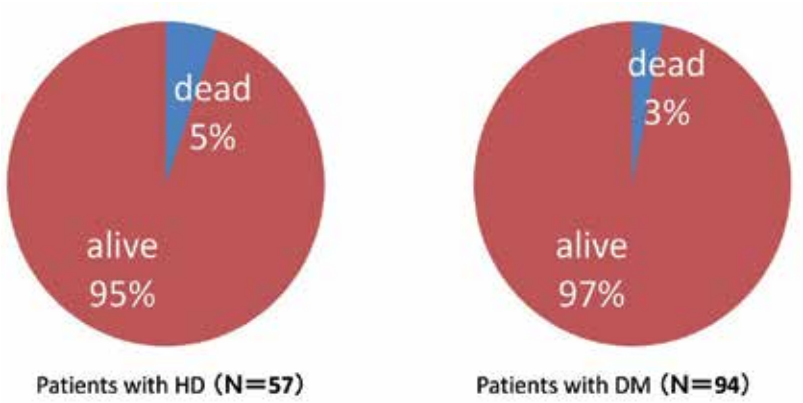

Figure 4. Mortality of patients with leg ulcers

4. Discussion

Chronic renal failure (CRF) affects all the systems of the body, causing neurological, gastrointestinal, cardiovascular, pulmonary, hematological, endocrine-metabolic, and dermatological disorders [5]. Among them, cutaneous disorders are one of the common problems in patients on long-term hemodialysis. The commonest skin disorders are xerosis and pruritus [6, 7]. The skin of patients on hemodialysis is dry, and so the skin barrier structure and function are impaired [8]. Formerly, it was believed that the impaired skin resistance and stimuli caused by scrunching because of itchy skin cause continuous inflammations, which contribute to local skin ulcers [9]. Of course, these problems may be the causes of erosion or slight ulcers in HD-receiving patients. However, my study revealed that severe leg ulcers, which may require amputation, were mainly caused by some complications such as PAD and infection[10].

Difficulty healing wounds is a frequent problem in patients on HD because of their poor general conditions, including malnutrition, inflammation, and PAD [1]. Mistrík et al. reported a significant decrease in skin blood flow during the HD procedure, and concluded that the skin blood flow may be impaired in HD patients, which leads to the development of difficulty in healing skin wounds[3]. Regarding cutaneous infection, the incidence of fungal infection in patients undergoing hemodialysis was 67%, which suggested that adequate foot care had not been performed for these patients [11]. CRF patients exhibit impaired cellular immunity due to a decreased T-lymphocyte cell count; this could explain the increased prevalence of infections [12]. Consequently, patients receiving HD were associated with higher complication rates and mortality when they developed leg ulcers [13].

Patients with severely ischemic legs due to maintenance HD often require multiple surgeries because arteriosclerosis obliterans usually progresses, which causes other ischemic ulcers (Figure 5-8). Amputations of legs or fingers are sometimes performed for these complex ulcers, because patients receiving HD are thought to present with immunocompromised con-

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ditions, and aggressive life-threatening infections such as sepsis require immediate surgical debridement in order to salvage the blood access line and save their lives (Figures 7, 9, 10). Administering antibiotics for a contaminated wound containing necrotic tissue is of no use because they cannot affect a non-vascularized or necrotic mass. Immediate surgical debridement is the only choice to improve these soft tissue infections [14, 15]. Surgical amputation is sometimes recommended to resurface these wounds, especially for some ischemic wounds including dry necrosis of toes and feet (Figure 9). My study revealed that more than half of patients underwent toe or leg amputation.

Figure 5. Case 1. Ischemic ulcer (A) The photograph shows a necrotic wound of right 2nd toe in a patient receiving HD at the initial examination. He was also diagnosed with peripheral arterial disorder. (B) He underwent amputation of the toe and the wound was healed.

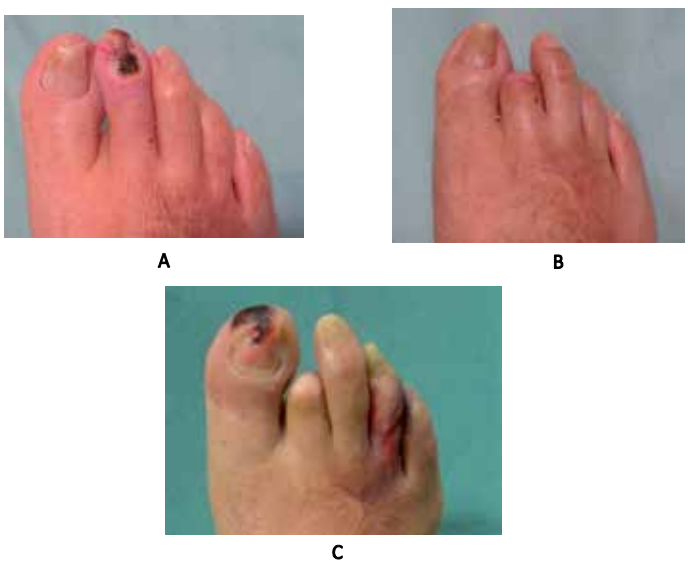

Figure 6. Case 2. Ischemic ulcer (PAD) (A) The photograph shows a necrotic wound of the right 2nd toe in a patient receiving HD at the initial examination. He was also diagnosed with peripheral arterial disorder. (B) He underwent amputation of the toe and the wound was healed. (C) However, he developed another ischemic ulcer 20 months later and required another amputation.

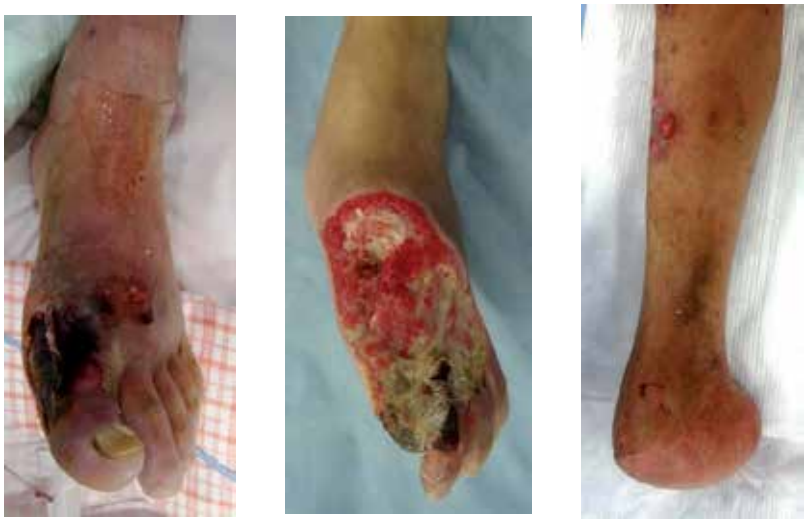

Figure 7. Case 3. Foot burn (trauma) (A) The patient was referred from an emergency unit for a complex necrotic ulcer caused by a burn to the left foot, with a high fever. As his blood access shunt in the right elbow also showed inflammation, amputation of the left big and 2nd toes was immediately performed. (B) As soft tissue necrosis progressed after debridement, and osteomyelitis occurred 1 month later, he underwent further amputation. (C) Finally, he underwent Chopart's joint amputation 2 months later.

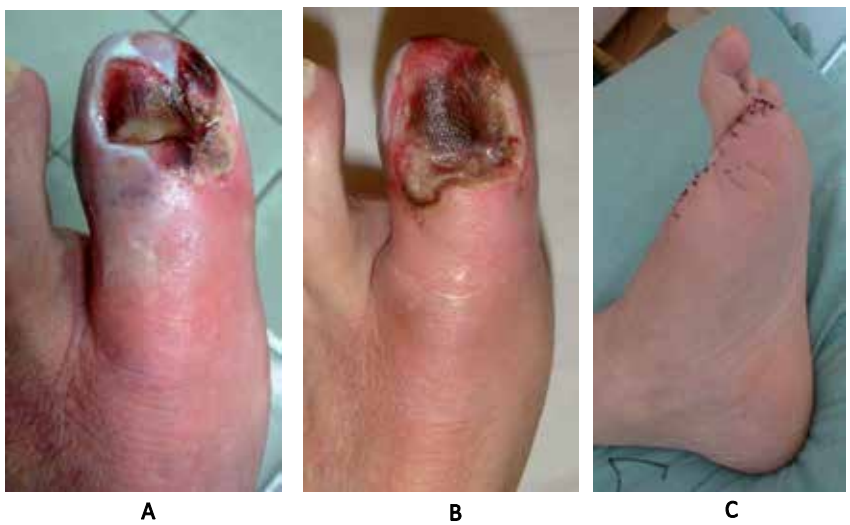

Figure 8. Case 4. Onychia periungualis (infection) (A) An HD-receiving patient developed onychia periungualis of the left 1st toe. (B) Although, he underwent the removal of the nail and antibiotic treatment, the ulcer and toe necrosis progressed. (C) The patient underwent amputation of the 1st and 2nd toes. (D) However, wound healing was unfavorable, because of the peripheral arterial disorder, thus, further amputation was required. (E) One month after the 3rd toe amputation, the wounds healed satisfactorily.

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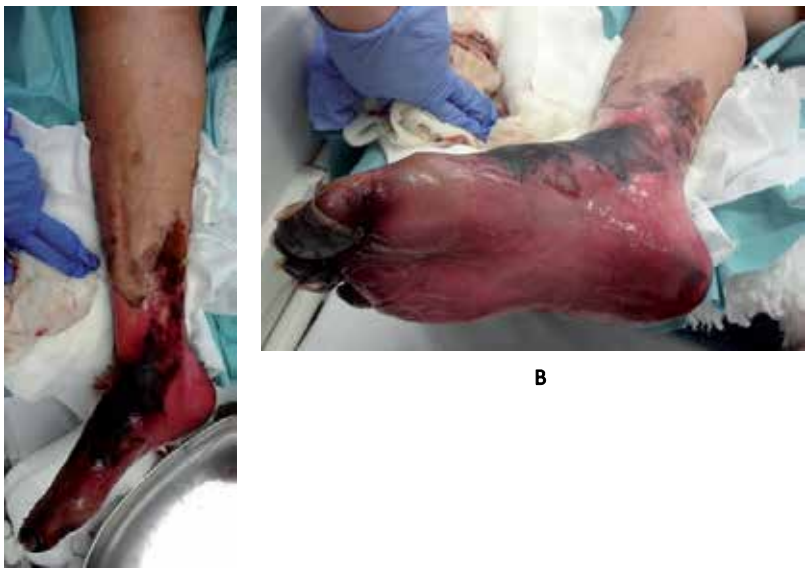

Figure 9. Case 5. Ischemic ulcer (PAD) (A) The photograph shows a necrotic wound of the right foot in a patient receiving HD at the initial examination. He was also diagnosed with peripheral arterial disorder. (B) As he developed sepsis and his blood access shunt in the right elbow also showed inflammation, he underwent below the knee amputation immediately, and the wound healed.

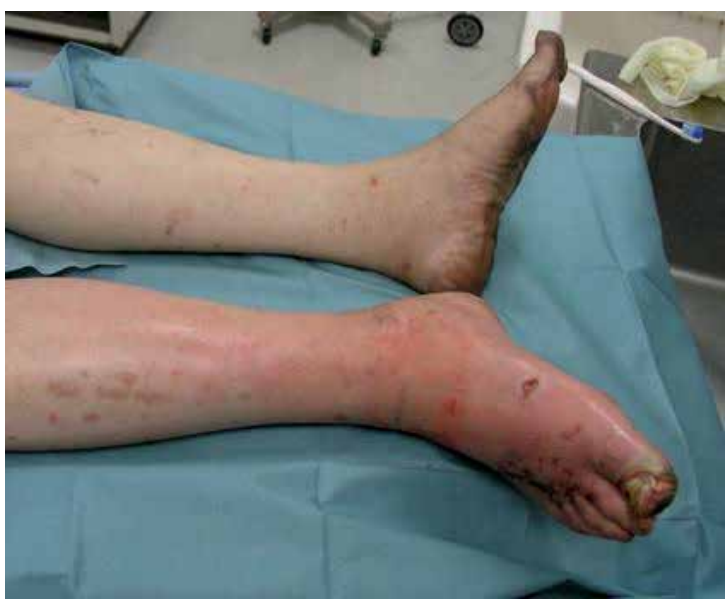

Figure 10. Case 6. Necrotizing fasciitis (infection) The photograph shows necrotizing fasciitis of the right foot in a patient receiving HD at the initial examination. He underwent below the knee amputation immediately.

I have investigated ulcers requiring surgical treatment, and the present study indicates that the development of severe leg ulcers in patients with HD is strongly influenced by ischemia due to PAD. Several investigators have reported incidences of peripheral arterial occlusive disease in patients receiving HD, ranging from 2.5 to 19.0% [16, 17].

These wounds usually develop infection, and often result in higher mortality rates because blood access shunts, especially when an artificial vessel is grafted, are easily infected. All my patients with infectious wounds (14 cases) required immediate debridement, including amputation to prevent such unfavorable general infections, because aggressive local inflammatory reactions had already developed.

On the other hand, the development of ulcers in patients with DM (control group) was mainly due to infection, which is so-called diabetic gangrene and is known to be life-threatening. My study revealed that there were no significant differences in mortality between the DM and HD groups. This suggested that the control of infection by aggressive debridement, including amputation, is the most important for the treatment of both local and general infection and saving the lives of patients. When initial debridement is insufficient and local infection recurs, further debridement should be performed. Wound infection cannot be controlled in the presence of necrotic tissue; therefore, amputation of fingers or legs is sometimes recommended, especially, when the patients show an septic status.

5. Conclusion

I conclude that patients receiving HD developed leg ulcers mainly due to PAD. They were likely to be more severe and progressive. Thus, they frequently require amputation before blood access shunts are infected.

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Chapter 12

Helicobacterpylori Infection for Hemodialysis Patients

Yoshiaki Kawaguchi and Tetsuya Mine

Additional information is available at the end of the chapter

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1. Introduction

Helicobacter pylori (*HP*) infection is reported to be closely associated with upper gastrointestinal disorders, such as gastroduodenal ulcers, chronic gastritis, and gastric cancer. Furthermore, patients with chronic renal failure receiving hemodialysis often complain of digestive symptoms. There are many possible factors causing these symptoms, including reduced gastrointestinal motility attributable to diabetes mellitus, uremia, intestinal ischemia associated with circulatory failure, and adverse reactions to many oral medications including non-steroidal anti-inflammatory drugs. Although *HP* infection is amongthe factors that may cause upper gastrointestinal disorders in patients with chronic renal failure, the association with*HP* infection has not as yet been elucidated. According to recent reports, the prevalence of *HP* infection is significantly lower in patients with chronic renal failure than in controls with normal renal function, and the prevalence is even reported to decrease with longer duration of hemodialysis. However, there are also previous reports presenting contrary findings. This chapter describes *HP* infection and eradication therapy in hemodialysis patients.

2. Is the prevalence of *HP* infection low in hemodialysis patients?

It is often reported that the prevalence of *HP* infection tends to be lower in patients with chronic renal failure receiving hemodialysis than in control groups with normal renal function [1-19]. In a study conducted in 539 hemodialysis patients, the prevalence of *HP* infection was 48.6%, whereas health check-up examinees with normal renal function showed a significantly higher prevalence of 69.4% ($P < 0.001$) [15]. Another report also showed that, compared to a 27.5% prevalence of *HP* infection in hemodialysis patients, the prevalence in patients with chronic renal failure not receiving hemodialysis was significantly higher at 56.0% [4]. Although there is a report showing the prevalence of *HP* infection to also be low in patients undergoing renal transplantation, it seems that most had received hemodialysis

before transplantation [3]. Based on the above observations, the prevalence of *HP* infection would appear to be low in hemodialysis patients, suggesting that the hemodialysis procedure itself may be involved in the low prevalence of *HP* infection.

3. Are duration of hemodialysis and prevalence of *HP* infection inversely correlated?

How are duration of hemodialysis and prevalence of *HP* infection associated? There are reports that the prevalence of *HP* infection tends to be lower with longer duration of hemodialysis [9, 15, 20, 21]. Nakajima et al. report that the prevalence of *HP* infection gradually decreases with a 2-year or longer duration of hemodialysis, and Sugimoto et al reported that the prevalence gradually decreases within 4 years of hemodialysis [15]. Moriyama et al. report that such a tendency is revealed in patients receiving hemodialysis for 8 years or longer [20]. There is also a report that the prevalence of *HP* infection in health check-up examinees with normal renal function was similar to that in patients with chronic renal failure who had received hemodialysis for less than 1 year [15]. Meanwhile, other studies have shown that there is no such association [22, 23]. However, Sugimoto et al. conducted a 4-year follow-up study in hemodialysis patients with *HP* infection and found that the prevalence gradually decreased from 51.6% at the start to 38.3% at the end [15]. Given that the spontaneous elimination rate of *HP* infection is generally reported to be 0.6% annually [24], it must be assumed from these results that the hemodialysis procedure itself contributes to the observed decrease in the prevalence of *HP* infection.

4. Is there variation in *HP* infection rates among different countries?

The gastricmucosa of approximately 50% of the world's populationis infected with *HP*, and the infectionlevels exceed 70% in some developing areas [25, 26].

There is variation in *HP* infection ratesamong different countries. It may, therefore, be important to evaluate the infection rate in various countries. In East Asian countries, the prevalence of *HP*infection in patients receiving chronic hemodialysis is44.5% (95% confidence interval (CI): 41.5–47.6%], 474/1065), which is significantly lower than in all patients with nor malrenal function [54.0% [95% CI: 50.9–57.1%], 560/1038,P <0.001] [27]. On the other hand, because the prevalenceof *HP*in other areas, such as Europe, Middle East, and South Asia has a wide variation, it isdifficult to evaluate the prevalence of *HP*infectionin those areas.

5. Why does the hemodialysis procedure reduce the prevalence of *HP* infection?

One reason is eradication of *HP*by antibiotics that are administeredas therapy for other infections experienced by hemodialysis patients. Antibiotics are the most typically prescribed

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drugs in general. In hemodialysis patients, antibiotics may be used for the treatment of bacterial infections as often as or even more frequently than in the general population. It is assumed that patients with renal failure are often prescribed reduced doses of antibiotics. However, compared to the general population with normal renal function, blood levels of antibiotics are likely to be higher after administration in patients with renal failure, and the elimination time is expected to be longer. Thus, in hemodialysis patients with a long duration of renal failure, the spontaneous elimination rate of *HP* infection might be increased by repeated administration of antibiotics. Because blood urea levels are increased in hemodialysis patients, urea levels in gastric juice are also high. The increased urea levels are considered to suppress the growth of *HP* in the stomach [28]. Another possible explanation is that up-regulation of pro-inflammatory cytokines in hemodialysis patients triggers the infiltration of inflammatory cells activated by the gastric mucosa, resulting in progression of gastric mucosal atrophy, an increase in pH, and ultimately *HP* elimination [29, 30]. While there are as yet no data clearly supporting this explanation, the prevalence of *HP* infection may be decreased by a combination of various factors.

6. What are the harmful effects of a decreased prevalence of *HP* infection on hemodialysis patients?

In general, *HP* infection is considered to be a cause of gastroduodenal ulcers, and a decrease in the prevalence of *HP* infection is favorable in this regard. It is widely known that *HP* eradication suppresses gastric acid secretion, which causes gastric erosion [31]. The frequency of endoscopically detected gastric erosion is reported to be high in hemodialysis patients [20, 32, 33], which may be associated with a decrease in *HP* infection. Because gastric erosion may cause gastrointestinal bleeding, caution is required especially in hemodialysis patients [20]. They are often receiving anticoagulant or antiplatelet drugs, and gastrointestinal bleeding can thus be fatal.

Prophylactic administration of anti-acid secretory drugs, such as proton pump inhibitors (PPI), is recommended. While long-term hemodialysis is reported to carry a high risk for reflux esophagitis [32-34], this may also be attributable to suppressedgastric acid secretion due to a decrease in *HP* infection. In patients receiving long-term hemodialysis, administration of anti-acid secretory drugs is recommended to prevent reflux esophagitis.

7. Is *HP* eradication necessary for hemodialysis patients?

While the previous section described the harmful effects of a reduced prevalence of *HP* infection on hemodialysis patients, the harmful effects of *HP* infection include the aforementioned association with gastroduodenal ulcers, chronic gastritis and gastric cancer, as well as gastric mucosa associated-lymphoid tissue lymphoma, etc. Especially in hemodialysis pa-

tients, the frequency of gastroduodenal ulcers and gastric cancer is reported to be higher than in healthy people [3, 35]. Because hemodialysis patients are often receiving anticoagulant or antiplatelet drugs, bleeding from gastroduodenal ulcers may be fatal. Thus, *HP* eradication is considered to be an important treatment for hemodialysis patients in order to prevent gastroduodenal ulcers and gastric cancer. Although spontaneous elimination of *HP* infection can be expected in hemodialysis patients, the earliest possible *HP* eradication is recommended especially in those with a history of gastroduodenal ulcer and confirmed current *HP* infection.

8. How is *HP* eradication best achieved in hemodialysis patients?

According to recent reports, the major regimen is a combination of a PPI selected from among omeprazole, lansoprazole, and esomeprazole and 2 antibiotics selected from among clarithromycin, amoxicillin, and metronidazole, which are administered for 1 or 2 weeks [1, 6, 36-40]. Although the eradication rate fluctuates slightly from 72.7 to 96.0%, it averages around 90%. There seems to be no substantial difference in comparison with the eradication rate of *HP* infection in the general population. The factors contributing to eradication failure include a history of previous eradication therapy, suggesting that the presence or absence of resistant strains to antibiotics iskey to the success of eradication therapy [6].

9. What are the precautions for *HP* eradication therapy in hemodialysis patients?

Caution should be considered in performing eradication therapy for hemodialysis patients to avoidexcessive doses of drugs. Administration of low doses results in high blood levels. However, hemodialysis removes both PPI and antibiotics, lowering their blood levels. In consideration of this fact, without adjustment of the therapy by administering the drugs after the hemodialysis session on the day of hemodialysis, the eradication rate of *HP* infection may be decreased. Safe and effective optimal dosages and administration procedures should be established. In patients with chronic renal failure before the initiation of hemodialysis, attention should be paid to the nephrotoxicity of amoxicillin, and the eradication therapy needs to be adjusted by substituting amoxicillin with metronidazole [39, 41, 42].

Moreover, hemodialysis patients often receive oral antibiotics, and the duration of circulation of these antibiotics in the body is prolonged due to delayed metabolism. Thus, it seems that *HP* often acquires resistance to antibiotics. According to a report on resistance to clarithromycin, resistant *HP* strains were detected in 36.4% of patients with renal failure and 15.2% of healthy volunteers, showing the prevalence of resistant *HP* strains to be significantly lower in the latter [43].

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10. Conclusion

This chapter has described *HP* infection in hemodialysis patients. Because the prevalence of *HP* infection is lower in these patients than in healthy people, attention should be paid to symptoms due to gastric hyperacidity. For those with *HP* infection, eradication therapy is recommended in order to prevent gastrointestinal ulcers and gastric cancer. Even after *HP* eradication, prophylaxis against gastric erosion and reflux esophagitis should be performed with anti-acid secretory drugs.

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Chapter 13

Site and Size of Vascular Calcifications Are Different in Dialysis Patients with Various Underlying Diseases

H. Suzuki, T. Inoue, H. Okada, T. Takenaka, Kunihiko Hayashi, Jyunnichi Nishiyama, Takashi Yamazaki, Yuji Nishiyama and Keiko Kaneko

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1. Introduction

Computed tomography (CT) constitutes the gold standard for quantification of vascular calcification (VC) and, being the most effective and widely available with reproducible measurements, is also useful for monitoring progression as well as assessing the effect of therapeutic strategies to modify progression [1] [2]. VC has a significant effect in cardiovascular diseases on dialysis patients. Tanne et al. [3] focused on calcification of the thoracic aorta and found that it associated with coronary and valvular calcification in hypertensive patients. In the Calcification Outcome in Renal Disease (CORD) study, abdominal aortic calcification was found to have the predictive value for the occurrence of cardiovascular events and mortality in dialysis patients [4]. Coll et al. [5] reported that VC in large, conduit arteries was prevalent in patients on dialysis patients, and that age, dialysis vintage, past medical history of cardiovascular disease, atherosclerosis and inflammation were variable significantly influencing VC. From these studies, it is suggested that VC occurs in vessels of various diameters. However, no definitive studies have determined the significance of VC in different vessels in patients receiving dialysis therapy until the present time. Moreover, there have been few studies examining a relation between semi-quantitative measures of VC and their contributing factors. The aim of this work presented here is to examine a relation between semi quantitatively measured calcification of three major vessels, the thoracic aorta, the abdominal aorta and the iliac arteries and several known contributing factors to VC such as underlying diseases, age, gender, vintage of dialysis, values of serum calcium and phosphate, use of calcium-based phosphate binders and so on.

2. Methods

All HD patients received three dialysis sessions of at least 4 h duration per week. HD was performed using low flux polysalphose dialyhsers (1.5-2.0 m2 APS Asahi Medical R Tokyo, Japan). All HD patients were dialyzed using bicarbonate-bound 1.25 mmol/L, calcium and 134 mmol/sodium containing dialysate. Patients were all dialysed at the Dialysis Unit of Irumadai Hospital.

This was an observational and cross-sectional study that included 79 hemodialysis patients at the Dialysis Unit of Irumadai Hospital, who gave their informed consent to enroll in this study. The inclusion criteria were patient providing informed consent, age ≥ 40 years and duration of dialysis ≥ 1 year. Exclusion criteria were significant fetal diseases that were estimated to reduce life expectancy to < 6 months and patients in whom it was impossible to measure CT scan.

The recorded cardiovascular history and smoking status were obtained. The following baseline biochemical data were obtained; serum calcium, phosphorus, intact parathyroid hormone, albumin, total cholesterol, low-density lipoprotein cholesterol. Data on weight, height, body mass index and duration of dialysis and use of medications: phosphate binders, vitamin D, statins, erythropoietin and antihypertensive agents. Clinical characteristics and laboratory variables including dual-energy x-ray absorptiometry and pulse wave velocity. This study complies with the Declaration of Helsinki and was in agreement with the guidelines approved by the ethics committee at the institution.

2.1. Computed tomography

CT scan of the aorta and arteries was performed with a 16-detector CT scan {Prime Purpose MDCT (GE Healthcare, Milwaukee, WI USA)}. Scanning time was 0.5 s for two contiguous 1.25 mm sections and 20±5 seconds for the entire zone of interest. Examination was performed during a single, unforced, withheld inspiration. During scanning with the tube rotating at 2 rotation/second and the table moving at 55 mm/s with a 1:1.375 scanning pitch, images were obtained with an effective section thickness of 10 mm. Scanning was performed with 120 kVp and 350 mAs, standard resolution, and a 28-36 cm field of view. The total duration of the procedure was 5min. The range of CT scan was illustrated in Fig. 1.

2.2. Evaluation of thoracic and abdominal aorta and iliac artery

Volume acquisitions were analyzed using Volume Viewer software (GE Healthcare). The thoracic and abdominal aorta were segmented manually. In order to reduce errors due to noise, a cut-off of 130 Housefield Unit (HU) was applied. The total calcification volume was calculated as the sum of all voxels in the remaining volume.

2.3. Biochemistry

Blood samples were collected at monthly intervals. The results presented here were time-averaged results from the preceding 6 months prior to the CT scan.

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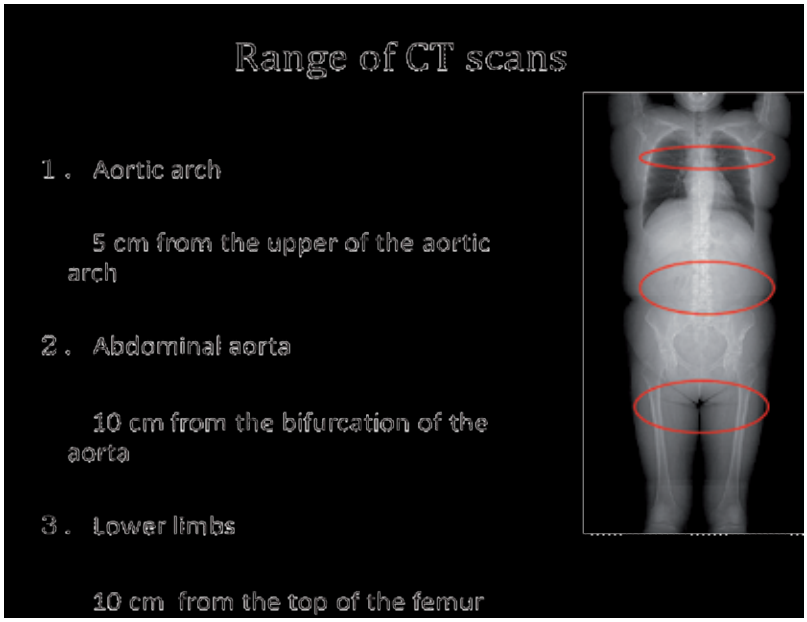

Figure 1. A range of computed tomography (CT) scan is illustrated.

2.4. Blood pressure

Three blood pressure (BP) recording were taken suing automated device.

2.5. Statistics

Data are expressed as means ± SD. Using variables found to be significant in the univariate analysis and potential confounders, we applied forward stepwise logistic regressions, in order to determine which of these variables were most significantly associated with calcification of the thoracic and abdominal aorta and the arteries of the lower limbs. F-to-Remove was set at 2.9. $P<0.05$ was considered as significance.

3. Results

3.1. Patients characteristics

The underlying kidney diseases were diabetic nephropathy [32], chronic glomerulonephritis (23), nephrosclerosis, polycystic kidney disease (3) and others (12).

Baseline demographics and laboratory and hemodynamic values of the study population are shown in Tables 1, 2 and 3 and current medications used are listed in Table 4.

Age (years)	62.3±12.8
Dialysis duration (months)	76.6±83.8
Gender (male/female)	52/27
Diabetes/non diabetes	32/47
Smoking/non smoking	36/43
Body mass index (kg/m^2)	21.9±1.6

Table 1. Characteristics of patients

Systolic Blood Pressure (mmHg)	154±122
Diastolic Blood Pressure (mmHg)	79±13
Heart Rate (beats/min)	74±12

Table 2. Hemodynamic markers

Calcium (mg/dL)	8.9±0.8
Phosphate (mg/dL)	5.6±1.2
Intact PTH (ng/mL)	125.5±65.4
Creatinine (mg/dL)	12.5±1.1
Blood urea nitrogen (mg/dL)	98.4±12.2
Uric acid (mg/dL)	6.3±0.5
Hemoglobin (g/dL)	10.7±0.6
Low density lipoprotein (mg/dL)	84.2±27.0
Albumin (g/dL)	3.7±0.4

Table 3. Serum markers

Agent	Percentage of patients
Phosphate binders	
Calcium containing	86
Sevelamer	65
Vitamin D analogues	59
Cinacalcet	72
Statins	12
Antihypertensives	96
Erythropoiesis stimulating agents	98

Table 4. Current medications of the study population

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3.2. Calcification of vessels

In Table 5, the average of calcification scores is shown.

All three lesions correlated significantly with each other. Stepwise regression was applied in which the independent variables were identified from the univariate analyses. Significant associations were seen for the following: the prevalence of calcification; the thoracic aorta with period of dialysis, elevations of both systolic and diastolic blood pressure and levels of serum albumin (Table 6); in the abdominal aorta with age, presence of diabetes, and calcium supplement (Table 7); arteries of the lower limbs with presence of diabetes mellitus, use of sevelamer and cinacalcet and serum levels of intact parathyroid hormone and albumin (Table 8).

Vessels	
Thoracic aorta	3.49 +4.65
Abdominal aorta	5.21 +7.21
Iliac artery	1.18 +1.92

Table 5. Calcification scores of thoracic aorta, abdominal aorta and iliac artery

Constant	Coefficient	Standard Error	F	P
Dialysis vintage (months)	0.011	0.006	3.401	0.050
SBP (mmHg)	0.090	0.029	9.336	0.003
DBP (mmHg)	-0.210	0.054	15.071	0.001
Albumin (g/dL)	-2.181	1.206	3.270	0.045

SBP: systolic blood pressuer, DBP: diastolic blood pressure

Table 6. Significant correlations with calcification of thoracic aorta

Constant	Coefficient	Standard Error	F	P
Age (years)	0.2445	0.68	13.156	0.001
Presence of DM	3.997	1.715	5.431	0.002
$CaCO_3$	0.001		4.066	0.048
Vitamin D	-4.89	2.231	4.802	0.032
Ca (mg/dL)	2.32	1.224	3.595	0.043

DM: diabetes mellitus, $CaCO_3$: oral administration (g/day), Vitamin D: oral administration (μg/day)

Table 7. Significant correlations with calcification of abdominal aorta

Constant	Coefficient	Standard Error	F	P
Presence of DM	1.346	0.416	10.469	0.002
Savelamer	1.403	0.430	10.632	0.002
Cinacalcet	0.882	0.482	3.353	0.072
Intact PTH	-0.006	0.003	3.446	0.048
Albumin (g/dL)	-1.414	0.473	8.944	0.004

DM: diabetes mellitus, Savelamer: oral administration (g/day), Cinacalcet: oral administration (mg/day)

Table 8. Significant correlations with calcification of lower limb

4. Discussion

In the present study, we found that the contributing factors to VC were different in the different vessels. The development and progression of VC is a multifactorial process. Potentially differing factors may exert their maximum influence at either the predisposition, initiation and continuation phases of the process. The multivariate analysis performed on these data attempt to elucidate which factors might be most significant to the development of VC. In the present study, age, duration of HD, systolic and diastolic BP, presence of DM serum levels of Ca, intact PTH, calcium modulating drugs and albumin contributed differently in the different vessels. Albumin was negatively correlated with the severity of VC. This suggests that a characteristic state of low albumin as seen in malnutrition, inflammation or atherosclerosis complex is most important, as suggested by Wang et al. [6]. Factors shown to predict VC in the current study included older age, longer dialysis vintage, diabetes, higher concentrations of serum phosphorus and calcium are associated with more extensive VC among patients on HD and result partially consistent with those reported previously [7] [8] [9] [10].

Adler et al [11] demonstrated a strong association of coronary calcification and calcification of the thoracic aorta on spiral CT. The aortic calcification signifies a higher probability of coronary atherosclerosis and ischemic stroke (Cerebrovascular disease). Also, Tanne et al. [3] found that severe calcification in descending aorta is a predictor of ischemic cerebrovascular events. Calcification of the thoracic aorta is not a direct causative factor for embolic stroke, but rather a marker of increased burden of vascular (atherosclerotic disease) disease [12]. However, Honkanen et al. [4] reported that although the duration of HD correlates with calcification in coronary [1], carotid and peripheral arteries [7], the association is less clear in the thoracic arteries [8].

In the present study, calcification of the thoracic aorta had a strong association with dialysis vintage, systolic and diastolic BP and albumin, which are a major factors contributing to cardiovascular diseases. From these data, it is possible that severe calcification of the thoracic aorta is produced by hemodynamic, malnutrition and uremia in combination.

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Abdominal aorta calcification has been well studied, has been associated with an increase risk of cardiovascular morbidity and mortality in patients with HD [13]. Hanada et al. [14] proposed that the section of the aorta chosen for measuring the semiquantitative calcification score is suitable for evaluation of the severity of VC because the site is associated with turbulent flow and is susceptible to development of atheroma. The chosen site is also simple to investigate radiologically since it is in a significant part of the aorta and is vertical to the transverse section. In the present study, VC of the abdominal aorta was correlated with the presence of diabetes, which is a well-known atherosclerotic risk factor. In addition, the factors relating with calcium-phsophate modulation, such as concentrations of calcium, PTH and so on are frequently evoked as the principal causes associated with vascular remodeling and/or arterial calcifications [15] [16]. Guerin et al. [17] reported that in HD patients, there is an association between the presence of aortic calcification and increased Ca x P products. In contrast, Arad et al. did not find the serum concentrations of calcium, 1,25-Vit D, and PTH to be associated with the presence of arterial calcifications [18]. Besides, the amount of CaO_3 prescribed as a phosphate binder was independently associated with the score of vascular calcifications. One of the adverse effects of calcium based phosphate binders is hypercalcemia, which may in turn result in arterial calcification. It is therefore likely that development of VC of the abdominal aorta is associated with calcium and phosphorus regulation in HD patients. Moreover, mineral bone disease-related factors such as serum calcium, phosphorus and PTH are thought to be strongly associated with the severity of VC in dialysis patients [19] [20].

Sigrist et al. [21] described a simple, sensitive low radiation dose technique as an alternative to coronary artery and aortic measurements to quantify a calcification score for the superficial femoral artery (SFA). The sector of artery chosen for this study is ideal as it avoids major bifurcations and arterial branching, and therefore, obvious site for turbulent flow and the development of atheroma. In the present study, factors contributing to VC of the iliac arteries are similar with those of the abdominal aorta.

In the Calcification Outcome in Renal Disease (CORD) study, 19% of patients had no visible calcification in their abdominal aorta [4]. These findings are partially in line with certain previous observations and it has been suggested that these individuals rarely develop calcification at follow-up [22] [8] [23]. In the present study, we did not find these individuals. Recently, further reports from CORD study provided a new evidence that no coronary [24] or thoracic aortic calcification at baseline, but their calcification developed during 2 years of observation and was most prevalent in those receiving calcium-containing binders. Besides, retrospective and cross-sectional data have given contradicting results with some publication showing a contribution of Vit D to VC [15], whereas others do not support this contention [25]. It is therefore unlikely that HD patients receiving calcium-containing binders and Vitamin D analogues have no VC of the vessels.

Recently Allison et al. [26] demonstrated that in terms of extent of calcification, the iliac arteries showed the strongest association for all mortality and end points, consistent with the well-known association between the severity of peripheral artery disease and both CVD and total mortality [27].

In addition, they concluded [26] that higher levels of calcium in different vascular beds are associated not only with CVD mortality but also with non-CVD and total mortality and that location of the arterial calcification appears to be relevant to the strength of the association with mortality, and the CVD risk factors appear to mediate some of this association.

4.1. Study limitations

First, the imaging methods used in this study did not distinguish the two types of VC (pathy calcification of the intima and calcification of the media). As is known, mineral metabolism disturbances link specifically with medial rather than intimal V and intima calcification associates with atherosclerosis. Second, our studies was cross-sectional, it does not directly show how detection of VC in various vessels predict incident cardiovascular events in the dialysis patients. Third, VC represents the result of long-standing atherosclerotic and calcification processes. It is unclear whether the steady-state of serum chemistry such as calcium, phosphate, intact PTH concentrations measured in this study accurately represents pathological process that occurred when VC was developing.

5. Conclusion

Presence and extension of VC in thoracic and abdominal aortas and lower limbs might be regulated in complex manner and caution should be needed to use these variables as a marker of the burden of vascular disease. The associations between calcified atherosclerosis and mortality differ by vascular bed, suggesting that the location and severity of calcification in different vascular beds provide unique information for mortality.

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Chapter 14

Colloids in Dialytic Refractory Hypotension

Guy Rostoker

Additional information is available at the end of the chapter

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1.Introduction

1.1. Definition and epidemiology of dialytic hypotension

Intradialytic hypotension is the most common complication of hemodialysis,occurring in up to 33% of patients. There are two main clinical patterns of dialysis-associated hypotension : the first is episodic hypotension (defined by a sudden drop of systolic blood pressure below 100 mmHg or at least 30 mmHg with accompanying clinical symptoms), that typically occurs during the later stages of dialysis sessions and is generally favored by excessive weight gain ; the second is chronic persistent hypotension, which affects about 10% of long-term dialysis patients [1, 2], most of whom experience frequent episodes of hypotension during dialysis sessions, whereas some patients have permanent hypotension with low predialysis systolic pressure, often less than 100 mmHg [3, 4]. Intradialytic hypotension not only causes discomfort and has a negative impact on health-related quality of life but it may also adversely affect the outcome of chronic hemodialysis, reducing patients' life expectancy and favoring underdialysis [5-10]. According to recent data, low pre-dialytic systolic and diastolic pressures, like low post-dialytic systolic pressure and the occurrence of hypotensive episodes during dialysis sessions, are associated with a significantly increased risk of death [5-9]. Moreover, a recent Japanese study has shown a link between dialysis-related hypotension and the occurrence of progressive frontal lobe atrophy [10]. The incidence of intradialytic hypotension is expected to grow with the increasing number of elderly and diabetic patients and patients with cardiovascular disease who are now starting hemodialysis, together with the use of long-term dialysis in an increasing number of hemodialyzed patients. In addition, dialysis treatment time has had a tendency to decrease over the last two decades and all these situations are known to be risk factors for this phenomenon [2,3].

1.2. Etiology and pathogenesis of dialytic hypotension

Several factors contribute to dialytic hypotension. These include too rapid fluid removal in an attempt to reach dry weight, a rapid reduction in plasma osmolality which causes extracellular water to move into cells, high interdialytic weight gain, anemia, poor nutritional status with hypoalbuminemia, autonomic neuropathy, anephric status, reduced pressor response to vasopressor agents, reduced cardiac reserve, increased arterial stiffness, impaired venous compliance, use of acetate rather than bicarbonate as a dialysate buffer, ingestion of a meal immediately before or during the dialysis session, use of low sodium or high magnesium concentrations in the dialysate, and intake before the dialysis session of anti-hypertensive medications that can impair cardiovascular stability (especially nitrate derivatives) [1-4, 11,12]. In a recent cross-sectionnal study of a cohort of 72 hemodialysis patients, 36 of whom suffered from dialysis-relatedchronic hypotension, cardiac diastolic dysfunction was found to be associated with dialysis hypotension [13]. The excessive release of several endogenous vasodilatators such as nitric oxide, adrenomedullin and adenosine, has been implicated in the pathogenesis of dialytic hypotension, together with an imbalance in the synthesis of the endogenous vasoconstrictors endothelin and vasopressin [14-17]. The immediate cause of intradialytic hypotension is acute central hypovolemia [2,4]. Frank hypotension occurs when cardiovascular mechanisms do not adequately compensate for the blood volume reduction resulting from the imbalance between the ultrafiltration rate and the plasma-refilling rate [12].

2. Management and prevention of dialytic hypotension

Management of intradialytic hypotension involves treating the acute episode and applying measures to prevent future episodes [4,11,18]. The acute management of intradialytic hypotension includes the following measures : reducing or halting ultrafiltration, use of the Trendelenburg position and often a reduction in the blood flow rate and use of volume expanders, regardless of the underlying mechanism [4,11,18]. Normal saline is the most widely used volume expander and has been advocated as first-line therapy for intradialytic hypotension [4,11,18]. Commonly used second and third-line fluids are hypertonic saline, dextran, hydroxyethyl starch (HES), mannitol, albumin and gelatin solutions [4,11,18,19]. Standard measures to prevent or alleviate intradialytic hypotension include accurate setting of the dry weight, avoidance of modifiable factors known to favor this phenomenon (e.g. excessively rapid fluid removal in an attempt to reach dry weight, anemia, poor nutritional status with hypoalbuminemia, ingestion of a meal immediately before or during the dialysis session, and intake before the dialysis session of anti-hypertensive medications) that can impair cardiovascular stability, adjustment of the dialysate sodium and/or calcium concentration and temperature, use of initial ultrafiltration followed by standard (or isovolemic) dialysis, use of sodium, and ultrafiltration modeling [1-4,14]. Among resistant patients, the most effective strategies to prevent intradialytic hypotension are to increase the dialysis time

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(for example by using either short daily hemodialysis sessions or frequent nocturnal hemodialysis) or to switch to peritoneal dialysis [1-4,14].

3. Use of colloids in refractory dialytic hypotension

Recent studies have shown that human albumin is safe in intensive care unitsand can also be useful in this setting in patients with acute renal failure secondary to sepsis or associated with profound hypoalbuminemia [20]. As central hypovolemia is the initiating factor in the pathogenesis of dialytic hypotension [2, 12], recent studies have hypothesized and analyzed the potential benefit of systematic infusion of colloids -- 20% albumin or 4% gelatin -- during dialysis sessions in hypotension-prone patients unresponsive to usual preventive measures [21, 22]. Until recently, few studies have evaluated colloids and especially albumin as a priming fluid for hemodialysis in septic patients or as preventive or curative therapy for hypotension-prone dialysis patients. Jardin and coworkers showed that infusion of 300 ml of 17.5% albumin as a priming fluid at the start of the dialysis session resulted in better ultrafiltration and hemodynamic stability than saline infusion in patients with sepsis-induced anuric acute renal failure ; these authors also showed that hypovolemia(as reflected indirectly by reduced left ventricular filling pressure), reduced cardiac output and the decline in mean arterial pressure were better corrected by 17.5% albumin than by saline [23]. McLigeyo first reported an improvement in hemodynamic parameters in four hemodialysis patients with chronic persistent hypotension receiving systematic infusions of 100 ml of 25% albumin [24]. More recently, Van der Sande and coworkers showed in nine cardiac-compromised hypotension-prone dialysis patients that 100 ml of 20% albumin and 100 ml of hydroxyethyl starch preserved systolic blood pressure and relative blood volume better than 33 ml of 3% saline during a hypotensive episode [25]. However, the side effects of hydroxyethyl starch (prolonged bleeding time, deposition of HES in various tissues and especially the liver) preclude its use in this setting and it is now forbidden in France and in numerous countries in dialysis patients [26, 27].

We recently conducted a single blind prospective cross-over study of systematic infusion of 200 ml of 20% albumin as compared to 200 ml of 4% gelatin in 10 patients on long-term bicarbonate hemodialysis with refractory permanent hypotension (despite cool dialysate associated with sodium and ultrafiltration profiling, at an ideal dry weight assessed by echocardiography) ; the study lasted 20 weeks [21]. We analyzed the effect of albumin and gelatin infusions on systolic and diastolic pressure and the number of hypotensive episodes by using the n-of-1 trial methodology and the Wilcoxon matched-pairs signed-ranks test [21]. Statistical analysis of individual data showed that 20% albumin increased systolic pressure in 6 patients ($p< 0.05$ Wilcoxon test) whereas 4% gelatin improved systolic pressure in only 2 patients ($p< 0.05$ Wilcoxon test) [21].

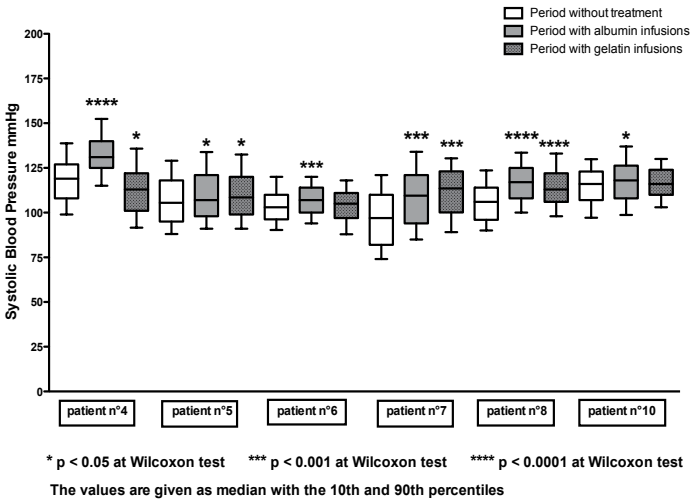

Figure 1. Evolution of systolic blood pressure with 20% albumin and 4% gelatin infusions in improved patients according toRostoker G,et al. A pilot study of routine colloid infusion in hypotension-prone dialysis patients unresponsive to preventive measures. J Nephrol 2011; 24(02) : 208-217; *p<0.5 at Wilcoxon test, ***p<0.001 at Wilcoxon test, ****p<0.0001 at Wilcoxon test; The values are given as median with the 10th and 90th percentiles

Albumin infusions increased diastolic pressure in 4 patients (p< 0.05 Wilcoxon test) whereas gelatin improved diastolic pressure in only 1 patient (p< 0.05 Wilcoxon test) [21].

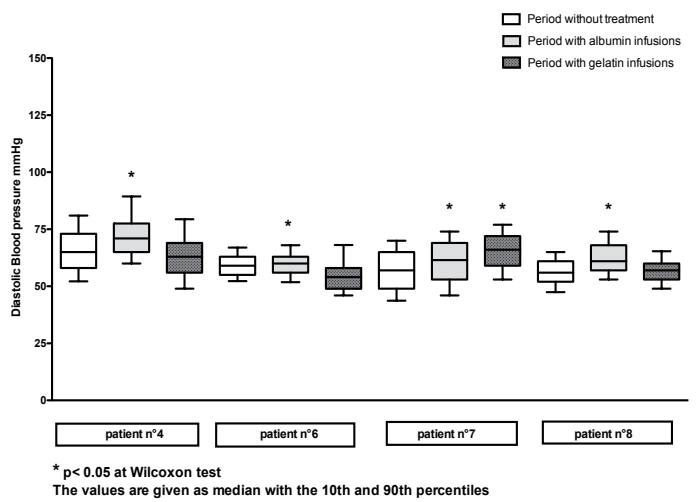

Figure 2. Evolution of diastolic blood pressure with 20% albumin and 4% gelatin infusions in improved patients accordingtoRostoker G,et al. A pilot study of routine colloid infusion in hypotension-prone dialysis patients unresponsive to preventive measures. J Nephrol 2011; 24(02): 208-217; *p<0.05 at Wilcoxon test; The values are given as median with the 10th and 90th percentiles

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The median number of hypotensive episodes (systolic pressure < 100 mmHg) fell significantly in 3 patients during 20% albumin infusion and in 2 patients receiving 4% gelatin ($p< 0.05$, Wilcoxon test) [21]. Dialysis quality assessed by the Kt/V ratio and the relative blood volume reduction were also stable, whereas ionic dialysance at the end of the dialysis session was improved by albumin but not by gelatin ($p< 0.05$, repeated measure ANOVA) [21]. Thus,in this single blind cross-over pilot study using n-of-1 methodology, we found that systematic infusion of 20% albumin or 4% gelatin during hemodialysis sessions improved hemodynamic parameters (systolic blood pressure, diastolic blood pressure and the number of hypotensive episodes) and the ultrafiltration rate in most hypotension-prone patients unresponsive to usual preventive measures [21]. Albumin was proved to be superior to gelatin; however, both colloids were ineffective in some patients, suggesting the need for careful and objective evaluation of these expensive therapeutics on an individual level [21].

4. Hemodynamic mechanisms of action of colloids in refractory dialytic hypotension

In hemodialysis sessions, during ultrafiltration, the refilling rate is dependent on colloid osmotic pressure [28]. Therefore, systematic infusion of 20% albumin during the dialysis session and, to a lesser extent, 4% gelatin, would be expected to increase colloid osmotic pressure, enhance plasma refilling and thus prevent an abrupt reduction in blood volume and acute hypovolemia. Albumin has a water binding capacity of 18 ml per gram, and 200 ml of 20% albumin solution binds 720 ml of water for 6-8 hours, whereas 200 ml of 4% gelatin binds only 200 ml of water for 4-5 hours [29, 30]. It is also tempting to postulate that colloids counteract the reduced cardiac preload with both atrial and ventricular underfilling as recently shown by Graziani and coworkers at the end of the ultrafiltration session in the subset of patients with severe dialysis-related hypotension [31]. Finally, systematic infusion of colloids could improve cardiac output in patients with diastolic dysfunction: the German nephrologic school postulated in the late 1980s, and demonstrated in the early 1990s, that left-ventricular hypertrophy was a risk factor for dialysis-related hypotension due to diastolic dysfunction [32-35]. In contrast to German nephrologists, we found no relationship between diastolic dysfunction and left ventricular mass [13]. The latter finding might be related to changes in the epidemiology of dialysis over the last two decades: patients in the eighties had left ventricular hypertrophy related to both hypertension and uremic fibrosing cardiomyopathy, promoted by a long history of chronic dialysis with cuprophane membranes, while dialysis patients are now older and have diabetes or cardiovascular diseases (especially ischemic cardiopathy), which are known to cause left ventricular diastolic dysfunction and diastolic heart failure [13]. In patients with a very long dialysis vintage left ventricular enlargement is attributable to chronic volume and flow overload associated with anemia, presence of arteriovenous fistulas, sodium, water and uremic toxins retention [36]. Several mechanisms are involved in the pathophysiology of dialytic hypotension secondary to cardiac diastolic dysfunction: first, diastolic dysfunction in hemodialysis patients induces

filling disturbances in diastole leading to systolic dysfunction especially a fall in stroke volume during hypohydratation induced by rapid ultrafiltration or when plasma refilling compensatory mechanisms are deficient resulting in central hypovolemia and abrupt hypotension: central hypovolemia in such cases could be counteracted by infusions of colloids [37,38]. Second, these hearts have a limited ability to utilize the Franck-Starling mechanism during exercise or its counterpart such as a dialysis session. Such limited preload reserve especially if coupled with chronotropic incompetence seen with advancing age limits cardiac output during exercise and dialysis sessions ; this leads to lactate accumulation and functional abnormalities of the myocardium [37,38]. Third, a substantial number of patients who have left ventricular hypertrophy with high wall thickness and a small end diastolic volume exhibit a low stroke volume and depressed cardiac output [35].

5. Modulation of oxidative stress and microinflammatory status by colloids in refractory dialytic hypotension

Data on the association between inflammatory status and dialysis hypotension are scarce: Tomita and coworkers have shown in nine patients with a history of intradialytic hypotension when compared with eight patients without dialysis associated hypotension a correlation between the levels of CRP and IL6 and the maximum percent change in mean arterial pressure over multiple dialysis sessions suggesting that dialysis hypotension may trigger inflammation [39]. This is consistent with the finding of Bergamini et al who found a significant release of TNF-alpha during hypotension episodes [40]. We recently hypothesized that frequent hypotension episodes may induce a noxious inflammatory response mediated by oxidative stress induced by ischemia-reperfusion phenomenon [22]. In a prospective cross-over study (lasting 20 weeks) of routine infusion of 200 ml of 20% albumin versus 200 ml of 4% gelatin in 10 patients with refractory intradialytic hypotension, we analyzed the effect of 20% albumin and 4% gelatin on microinflammatory status, oxidative stress, serum nitrite and nitrate levels by analysis of variance [22]. A significant decrease in serum ceruloplasmin and serum C3 was observed during the albumin period ($p < 0.05$, repeated measure ANOVA) [22]. A significant decrease in serum hydrogen peroxide was seen during albumin and gelatin administration ($p < 0.01$, repeated measure ANOVA) and a dramatic decrease in serum lipid peroxides was observed during the albumin period only ($p < 0.01$, Friedman test) [22].

Serum lactoferrin, serum proinflammatory cytokines and serum nitrite and nitrate levels remained stable during the different periods of this pilot trial [22]. These results strongly suggest that the improvement in microinflammatory status observed in hypotension prone dialysis patients may be related to the decrease in ischemia-reperfusion of noble organs by infusions of colloids together with a specific reduction of oxidative stress by 20% albumin.

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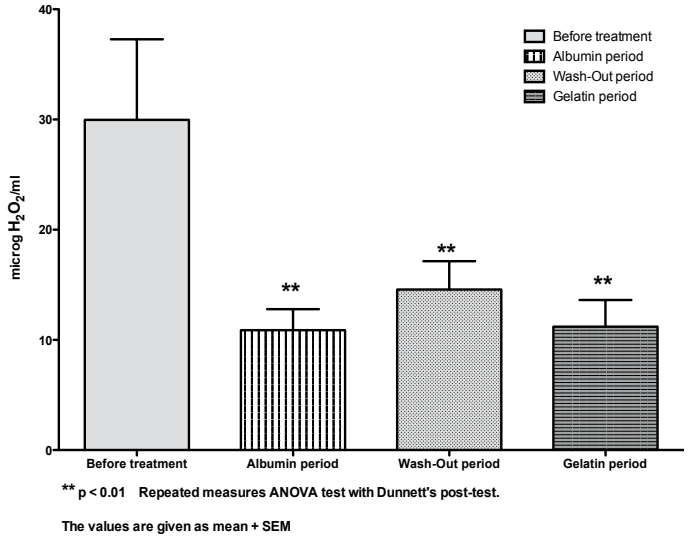

Figure 3. Concentration of serum hydrogen peroxide in patients with refractory dialytic hypotension treated by systematic infusion of colloids during dialysis sessions, according to Rostoker G et al Modulation of oxydative stress and microinflammatory status by colloids in refractory dialytic hypotension. BMC Nephrol 2011; oct 20; 12 (1): 58; **p<0.01 Repeated measures ANOVA test with Dunnett's post-test

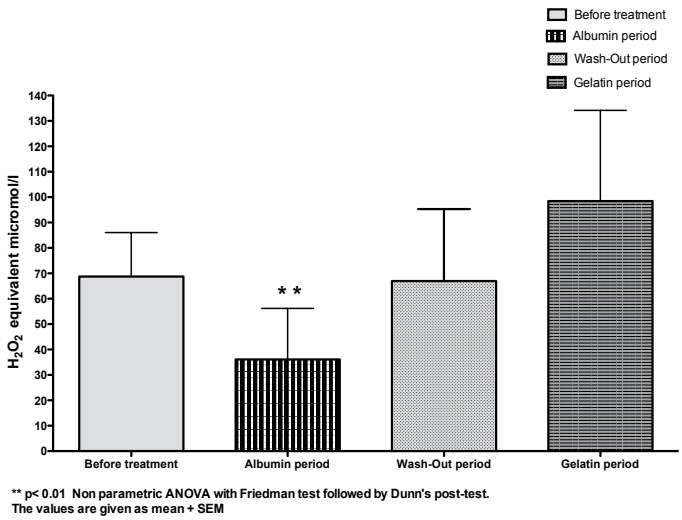

Figure 4. Concentration of serum lipid peroxides in patients with refractory dialytic hypotension treated by systematic infusion of colloids during dialysis sessions, according to Rostoker G et al Modulation of oxydative stress and microinflammatory status by colloids in refractory dialytic hypotension. BMC Nephrol 2011; Oct 20; 12 (1): 58 ; **p<0.01 Non parametric ANOVA with Friedman test followed by Dunn's post-test.; The values are given as mean + SEM

6. Anti-inflammatory mechanisms of action of colloids in refractory dialytic hypotension

In the aforementioned pilot study, C3 and ceruloplasmin were significantly lowered during the albumin period but not during the gelatin period [22]. This is consistent with recent studies using experimental models of hemorrhagic shock, which indicated that the type of resuscitation fluid greatly influences proinflammatory responses and especially neutrophil activation and nuclear factor-Kappa B gene transcription; albumin was found to be the least proinflammatory fluid [41, 42]. Conversely, ex-vivo data suggest that uremia may also increase vascular permeability [43] which may be acutely raised during dialysis–associated hypotension via released mediators such as adenosine aimed to preserve perfusion of the noble organs [17]; in this setting, albumin may itself influence vascular integrity by binding to the interstitial matrix and sub-endothelium and by altering the permeability of these layers to large molecules and solutes; these effects may be mediated by the binding of arachidonic acid to albumin and by polynitroxylated albumin, which inhibits xanthine-oxidase-mediated adhesion of human neutophils to endothelial cells [44].

In this trial, serum hydrogen peroxide levels were significantly lowered during both the albumin and the gelatin periods, suggesting that the improvement in hemodynamic parameters by colloids reduces oxidative stress related to the ischemia-reperfusion of noble organs that occurs during dialytic hypotension [22,45]. Besides this classical ischemia-reperfusion mechanism, by analogy with heart failure, it was hypothesized that entry of bacterial endotoxin during dialysis sessions might be the result of intermittent underperfusion of the intestine during dialysis-associated hypotension episodes leading to cardiac stunning and oxydative stress [46,47,48]; thus in this setting, colloids may improve both systemic and intestinal perfusion and reduce gut ischemia [22,46,47,48]. In the latter pilot study, serum lipid peroxide levels were also significantly reduced only during the albumin period. This is consistent with data showing that human serum albumin and bovine serum albumin provide protection from lipid peroxidation propagated by inorganic reactive oxygen species generated from xanthine oxidase/hypoxanthine in artificial systems [49] and that persistent hypoalbuminemia in hemodialysis patients is associated with peroxidation of erythrocyte membranes [50]. Moreover, albumin is the major extracellular source of reduced sulphydryl groups, termed thiols which are avid scavengers of reactive oxygen and nitrogen species;in-this way albumin influences redox balance [51, 52]. All these data also strongly suggest that dialytic hypotension may contribute by different ways to the overproduction of reactive oxygen species seen in end-stage renal failure patients, a multifactorial process mainly related to uremia per-se, the hemoincompatibility of the dialysis system and trace amounts of endotoxin in the dialysate, gut ischemia and that colloids may indifferent mechanisms counteract it [22, 53].

7. Conclusions

Recent studies have shown that systematic infusions of 20% albumin and 4% gelatin during hemodialysis sessions improve hemodynamic parameters and ultrafiltration rate in most hypotension prone dialysis patients unresponsive to the usual preventive manoeuvers. An improvement in microinflammatory status was observed in parallel, which might be related to the decrease in both ischemia-reperfusion of noble organs, gut ischemia and oxidative stress. Hyperoncotic 20% albumin was found to have greater anti-inflammatory and anti-oxidative properties than 4% gelatin. Moreover, in the case of a new and expensive therapy such as 20% albumin (cost of 200 ml 20% albumin : 80 Euros as compared to 4 Euros for 200 ml 4% gelatin, in France), n-of-1 trials can furnish powerful evidence for provision on an individual basis, allaying managerial and medical fears as to the cost of frequently ineffective therapies being applied to an expanding at-risk population. From a pragmatic point of view, we advise practitioners to initiate first gelatin which is much less expensive when a treatment of systematic infusion of colloids is scheduled during dialysis sessions. Owing to its high cost, hyperoncontic albumin should be considered as a second-line therapy.Further well-designed controlled trials with a sufficient number of patients, of hyperoncotic 20% albumin and 4% gelatin in hypotension-prone dialysis patients are warranted to assess the benefit of colloids infusions in dialytic refractory hypotension.

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Section 2

Pathogenesis and Management of Anemia

Chapter 15

Current Anemia Treatment in Hemodialysis Patients: The Challenge for Secure Use of Erythropoietin-Stimulating Agents

Paulo Roberto Santos

Additional information is available at the end of the chapter

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1. Introduction

Anemia is the poor capacity of blood to carry oxygen. Anemia is diagnosed by measuring hemoglobin (HB) level (g/dL) and hematocrit (HT) (percentage of erythrocytes in the blood). Normal limits vary in the general population [1]. According to the World Health Organization, normal HB is defined as 13 g/dL in men and 12 g/dL in women [2]. In clinical practice, HB lower than 11 g/dL is widely accepted as abnormal. For didactic purposes, the several causes of anemia can be placed into three groups: blood loss, increased destruction of erythrocytes or decreased production of erythrocytes.

The main regulatory mechanism for erythrocyte production is the action of the hormone erythropoietin (EPO) in the bone marrow. EPO acts in bone marrow to promote the development of red blood cells and also stimulates the synthesis of HB. In adults, EPO is mainly produced by interstitial fibroblasts in the kidneys and is secreted when specialized cells sense low oxygen level. Independently of etiology, chronic kidney disease (CKD) provokes anemia by decreasing EPO production. In clinical practice, it is useful to classify CKD in five stages according to glomerular filtration rate (GFR) [3]. Based on a normal GFR of 90 ml/min,

- stage 1 refers to CKD with normal GFR, which means GFR of 90 ml/min or higher;
- stage 2 corresponds to GFR between 60 and 90 ml/min;
- stage 3 to GFR between 30 and 60 ml/min;
- stage 4 to GFR between 15 and 30 ml/min; and
- stage 5, the most advanced, to GFR lower than 15 ml/min.

Usually anemia appears in stage 3, worsens with the further decrease of GFR and is universally present and usually symptomatic in stage 5.

In stage 5, CKD patients need some kind of renal replacement like peritoneal dialysis, hemodialysis (HD) or kidney transplantation. Each of these treatment modalities imposes particular factors contributing to anemia in addition to the main cause, decreased renal production of EPO. The focus of this chapter is anemia treatment of patients with CKD in stage 5 undergoing conventional HD.

Among HD patients, several factors besides decreased renal production of EPO contribute to anemia, such as: increased destruction of red blood cells due to chemical effects of uremic toxins; platelet dysfunction provoking blood loss, usually due to occult bleeding; blood loss due to clotting inside hemodialyzers and sets during HD sessions; hemolysis associated with contamination of dialysate water; and water-soluble losses of folate and vitamin$_{12}$ through hemodialyzer membranes, affecting red blood cell production [4]. In summary, anemia is multi-factorial in patients undergoing HD because besides the central role of decreased EPO production, HD therapy per se negatively affects production and survival of red blood cells. Moreover, typical comorbidities associated with stage 5 CKD also act as causal factors of anemia, mainly bone disease (secondary to hyperparathyroidism or aluminum intoxication) and high inflammatory activity.

Anemia must be highlighted among the main challenges of CKD treatment. In this context, anemia's effects on cardiovascular outcomes and quality of life deserve especial attention. Anemia decreases physical function and vitality, worsening quality of life [5]. Cardiovascular problems are the main causes of death among HD patient, and anemia imposes an overload on cardiac function, ultimately provoking left ventricular hypertrophy, a well-recognized marker of morbidity and mortality [6]. Nonetheless, there is no certainty about the optimal HB level in order to improve quality of life and decrease cardiovascular risk. Paradoxically, higher HB levels seem to cause side effects and, concerning quality of life, higher HB is only associated with a small and not clinically significant improvement [7,8]. Presently, there is substantial discussion about the ideal level of anemia control. This is a topic of this chapter.

Before the start of the clinical use of erythropoietin stimulating agents (ESAs) in the early nineties, anemia had been the main stigma of CKD and its treatment was based on repeated blood transfusions, which caused many HD patients to be infected with C virus. Now the use of ESAs is widespread. They can correct EPO deficiency and control anemia among HD patients. Basically, there are three generations of ESAs: epoetin (first generation), darbepoetin (second generation) and methoxy polyethylene glycol-epoetin (a long-acting EPO receptor activator of the third generation, recently introduced). Successive generations acquired longer half-lives (see Table 1, based on [9]). ESAs are able to increase HB to normal levels, but their clinical use during the past 20 years has brought unexpected questions: Why is complete anemia correction associated with worse clinical outcomes? Are ESAs toxic? And, how should patients be managed patients who do not respond to ESA?

Erythropoietin-stimulating agents	Half-lives in hours	
	Intravenous route	Subcutaneous route
Epoetin	6.8	19.4
Darbepoetin	25.3	48.8
Methoxy polyethylene glycol-epoetin	134	139

Table 1. Half-lives of erythropoietin-stimulating agents

The next sections summarize the literature evidence on "side effects" of complete correction of anemia, review the current recommendations on anemia treatment and discuss the main obstacles to efficient anemia control among HD patients, with focus on the condition of patients who do not respond to usual ESA doses.

2. Why partial and not complete anemia correction?

After 20 years of clinical use of ESAs, the question about the optimal HB target for CKD patients remains unanswered. ESAs allow complete correction of anemia, but at the end of the nineties a study indicated a higher risk of death when targeting complete anemia correction compared to partial anemia control among HD patients [7]. This study, comprising high-risk patients (either with congestive heart failure or ischemic heart disease), showed more death, more myocardial infarction and more vascular thrombosis among patients treated to reach complete anemia correction (HT of 42%) when compared to patients treated to achieve partial anemia correction (HT of 30%). In fact, bad outcomes were present even among patients assigned to the high-HT group who did not really achieve the target of 42% HT. These findings posed three questions:

Are CKD patients in general at danger when they have anemia completely corrected or only HD cardiac patients with characteristic similar to the sample studied?

Since patients in the high-HT group were submitted to high epoetin dose and were at risk even when the high-HT target was not reached, is the risk due to high HT level or high ESA dose?

Since to reach higher HT, the patients were also submitted to higher replacement of iron, is iron the villain?

At least three controlled random trials were conducted trying to answer some of these questions, using first and second ESA generations [10-12]. All three studies focused on comparing partial versus complete anemia correction among CKD patients, not only in high risk HD, like typical cardiac patients from the Besarab study [7], but also among CKD patients in stages 3 and 4 under conservative treatment (not yet undergoing HD). Two studies [10,11] were published in the same year and comprised all-cause CKD patients. One study [10] showed benefits regarding quality of life among patients under complete anemia correction when compared to partial anemia correction. However, there were more hypertensive epi-

sodes and headaches among patients under complete anemia correction. Due to the main objective of the study, if complete correction could improve cardiovascular outcomes, the result was neutral. Cardiovascular events and death rates were the same between the two groups. The conclusion was that even not showing a risk, complete anemia correction did not seem to be beneficial related to cardiovascular outcomes for CKD patients under conservative treatment. Thus, this study did not give support to the clinical practice of targeting complete anemia correction. The other study [11] showed a greater risk of death and congestive failure hospitalization among patients for whom the target was HB of 13.5 g/dL compared to patients with HB target of 11.3 g/dL. Moreover, no improvement in quality of life was found among higher-HB patients. Consequently, complete anemia correction was discouraged. The third study [12] was specifically designed to investigate the effects of different patterns of anemia correction only among diabetics. Even though high risk of death or cardiovascular events associated with complete anemia correction was found, patients treated to achieve higher HB experienced more episodes of stroke and thromboembolism. Taken together, these studies show no advantage and even potential risks of targeting higher HB/HT in CKD patients. Concerning HD patients, the safety of targeting higher HB level using higher ESA doses requires even more attention, because HD patients present more comorbidities than those under conservative treatment, with a profile closer to the high-risk patients that took part in the Besarab study [7] than the patients in the other studies [10-12]. The consequence is the current adoption in clinical practice of partial anemia correction among HD patients. These studies did not address the possible causes of adverse outcomes observed with complete anemia control, but cast doubt on the safety of high ESA doses and high iron replacement.

There are more convergent findings coming from observational studies. As known, randomized controlled trials are suitable for hypothesis-testing and observational studies work to generate hypotheses. However, in the nephrology area, observational studies are able to comprise more typical patients under regimens found in daily practice. Here I comment on three observational studies which demonstrated higher risk of all-cause mortality associated with higher ESA doses [13-15]. In North America, based on the United States Renal Data System, comprising a sample of 94,569 prevalent HD patients, the patients were stratified in four groups according to ESA dose quartiles and also according to five HT levels: < 30%, 30-<33%, 33-<36%, 36-<39 and ≥39 [13]. The finding was higher risk of all-cause death associated with the fourth quartile of ESA dose (higher ESA doses), regardless of HT level achieved. A similar result was found in another study among 139,103 patients treated in DaVita dialysis clinics in the United States [14]. In this more recent study, patients were classified in four groups according to weekly ESA dose: <10.000 IU, 10-<20.000 IU, 20-<30.000 IU, ≥30.000 IU, and also according to HB level: <10 g/dL, 10-<11g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL. The result was higher risk of death among patients submitted to more than 30.000 units of ESA for any of the five HB levels. In both studies [13,14], the group with highest mortality was that of patients using higher ESA doses and presenting lower HT/HB levels.

It must be stressed that the association between high ESA dose and high risk of death is not only found in observational studies comprising large samples. Last year in Brazil, the re-

search group I lead performed a study encompassing HD patients from a single unit [15]. In our study, we divided patients into two groups according to anemia control profile: excellent/good and moderate/bad control, taking into consideration of HT and HB levels during a period of one year. Also, patients were divided into two groups according to ESA dose: usual ESA dose and high ESA dose (=epoetin dose higher than 400 units per kg per month). Patients submitted to high ESA dose presented a five-fold risk of death, independent of anemia control profile. Again, as found in the other studies [13,14], most of the patients submitted to high ESA dose were those with worse anemia control. Unlike inconclusive results coming from randomized controlled trials, data from observational studies strongly indicate higher mortality among HD patients submitted to high ESA dose, especially those not reaching good anemia control.

A detailed discussion of the mechanisms involved in the genesis of bad outcomes related to complete anemia correction is beyond the scope of this chapter. Indeed, these mechanisms are not clear in the literature. Further knowledge of such mechanisms is essential to propose safer approaches to anemia in the future. The suggested mechanisms are: ESA toxicity, effects of hyperviscosity, iron toxicity or merely a selection bias of patients (patients submitted to high ESA are sicker). Probably there is not a single mechanism, but rather an interaction of factors leading to adverse clinical outcomes. The main points involved in the supposed mechanisms are summarized below and are shown in Table 2. High HT results in higher blood viscosity, which might explain the higher risk of thromboembolism [16]. Targeting high HB demands greater replacement of iron. High intravenous replacement of iron is linked to cardiovascular disease and susceptibility to bacterial infections [17,18]. ESAs have hypertensive effects but no studies have shown a link between arterial hypertension and bad outcomes. More attractive is the biological plausibility of ESA toxicity due to activation of extra-bone marrow receptors of EPO distributed in myocardium, brain and endothelial cells. These receptors are only activated by a high EPO concentration, as occurs with the clinical use of ESA. Theoretically, unphysiologic EPO spikes in plasma could activate extra-bone marrow receptors and be harmful [19,20]. Finally, patients submitted to high ESA dose may die more just because they are sicker, without any role of blood hyperviscosity and ESA or iron toxicity.

3. Current recommendations

The National Kidney Foundation describes the initial evaluation of anemia in HD patients, consisting of measurement of HB, HT, reticulocyte count, serum iron, total iron binding capacity, percent transferring saturation, serum ferritin and a test for occult blood in stools [21]. My opinion is that analysis of peripheral blood smears can be added to the initial evaluation. This simple analysis can give important clues on underlying factors contributing to anemia (see Table 3).

There is general consensus that the target of anemia treatment is to achieve partial anemia correction, which means HB in the range of 11 to 12 g/dL and HT between 33% and 36%

[21]. Currently this is a target for all patients, including children, CKD patients under conservative treatment, peritoneal dialysis patients and kidney transplant recipients. The data supporting partial anemia control in HD patients and CKD patients under conservative treatment were provided in the previous topic. However, less information is available on the effects of high HB level on peritoneal dialysis outcomes. A difference in the effects of a higher level in peritoneal dialysis patients could be possible due to the fact that most peritoneal dialysis patients receive lower ESA doses for the same achieved HB level when compared to HD patients. In support of this hypothesis, a recent study did not find any association between higher achieved HB and all-cause mortality among ESA-treated peritoneal dialysis patients [22]. On the other hand, it seems that among kidney transplant recipients the risks are similar to those of HD patients. There are studies suggesting that targeting HB more than 12.5 g/dL is associated with increased mortality risk in kidney transplant recipients [23,24]. In my view, it is probable that in the coming years an individualized target according to specific patient profiles will be a better way of controlling anemia. Based on this opinion, I make some suggestions of individualized approaches in the conclusion of this chapter.

Variable	Mechanism
Hyperviscosity	More episodes of thromboembolism because of platelet activation and increased proacoagulant activity
High ESA dose	Activation of hematopoietic receptors, producing highly active platelets, and/or Activation of extra-hematopoietic receptors, triggering adverse events
High iron replacement	Cardiovascular disease, and/or susceptibility to bacterial infections

Table 2. Possible mechanisms involved in bad clinical outcomes related to complete anemia correction

Finding	Factors
Microcytosis	Iron deficiency
Macrocytosis	Folate or Vitamin B_{12} deficiency
Echinocytes	Hypomagnesemia or hypophosphatemia
Stomatocytosis	Over-hydration
Heinz bodies	Acute hemolysis
Howell-Jolly bodies	Iron deficiency
Basophilic stippling	Lead toxicity

Table 3. Correlation of red cell morphology in peripheral blood smears with contributing factors of anemia

Iron depletion is found in nearly all patients undergoing HD. Thus, in order to achieve and maintain the HB/HT target, the recommended treatment is initial replacement of 100 mg of

iron intravenously at every HD session for a total of 10 doses, and then 100 mg of iron intravenously once a week for maintenance replacement [20]. In the case of patients presenting iron overload (percent transferring saturation ≥ 50% or serum ferritin ≥ 800 ng/mL) withholding of initial iron replacement is recommended until iron comes back to normal. For those who develop iron overload during the maintenance phase, re-introduction of half the previously used maintenance dose can be tried when iron levels return to normal.

After certifying iron status, HD patients presenting HB < 11 g/dL may be submitted to ESA replacement. The most used ESAs are epoetin and darbepoetin, and for both subcutaneous administration is the most efficient route for replacement in HD patients. More recently, C.E.R.A (continuous EPO receptor activator) was introduced. The usual dose for initial replacement with epoetin should be 80 to 120 units/kg/week (typically 6,000 units/week) in two to three doses per week [21]. In a monthly control, if the increase of HB is less than 2%, the epoetin dose should be increased by 50%. On the other hand, if the increase of HB is more than 8% or exceeds the target, a 25% decrease in the epoetin dose should be tried [21]. The initial dose for darbepoetin is 0.45 μg/kg once a week and 20 to 30% of the initial dose can be used as maintenance dose [25]. C.E.R.A can be started using 0.60 μg/kg each 15 days and maintained using120 to 360 μg/kg once a month [25].

The most common causes of hyporesponsiveness to ESAs are iron deficiency, infection and inflammatory states, mainly due to access infections and surgical inflammation, but also due to some primary causes of CKD like acquired immunodeficiency syndrome and systemic lupus erythematosus. The other possible causes to be ruled out in case of hyporesponsiveness are: chronic blood loss, osteitis fibrosa, aluminum intoxication, hemoglobinopathies, folate or vitamin B12 deficiency, multiple myeloma, malnutrition, and hemolysis. For didactic purposes, these various causes are grouped according categories in Table 4.

Categories	Variables
Related to dialysis therapy	Less biocompatible hemodialyzers
	Poor quality of water
	Contamination of dialysate
	Hemolysis and clotting
	Recurrent infection of vascular access
	Inadequate dialysis dose
Related to nutritional status	Iron, folate or vitamin B_{12} deficiency
	Low protein intake
Related to kidney disease	Hyperparathyroidism
	Inflammation
	Failed renal transplant graft
	Drugs (see Table 5)

Table 4. Causes of hyporesponsiveness to erythropoietin-stimulating agents related to dialysis therapy, nutritional status and kidney disease

Hyporesponsiveness to ESA is the main obstacle to anemia treatment among HD patients. Nonetheless, a consensus about the definition for resistance to ESA is lacking. The definition of resistance by the European Best Practice Guidelines can be mentioned, which is the failure to reach the target using more than 20.000 IU/week of epoetin or more than 100 μg/week of darbepoetin, or the need for consistently high doses to maintain the target HB [26]. For others, the erythropoietin resistance index (weight-adjusted dose of ESA divided by HB g/dL) is a better way to evaluate the resistance to ESA [27]. Indeed, it is not a lack of a widely accepted definition for resistance the main problem; it is the lack of efficient approaches to treat cases of resistance.

The initial approach to hyporesponsiveness may be to rule out some common and modifiable conditions, like iron deficiency, blood loss (reticulocyte count can help), catheter infection, inadequate dialysis (check Kt/V, discard access malfunction), and to search for occult malignancy, evaluate nutritional status and check drugs in use that can aggravate anemia (see Table 5, based on [28]). Routine laboratory follow-up can diagnose hyperparathyroidism. There is a strong association between hyporesponsiveness to ESA and high parathyroid hormone levels [29]. Sometimes a bone marrow examination is necessary to confirm osteitis fibrosa or aluminum toxicity. In case of absence of the previous conditions, micronutrients can be suspected. Response to folic acid replacement remains the gold-standard diagnosis if there is suspicion of folate deficiency. More controversial is the replacement of vitamin C. It leads to the release of iron from ferritin and enhances movement of iron to the erythrocytes [30]. Even without broad recommendation, some clinicians replace vitamin C in patients with poor response to ESA, using a scheme of intravenous replacement of vitamin C after each HD session [31]. L-carnitine deficiency has been extensively studied in nephrology area, but there are no conclusive recommendations about its replacement in HD anemic patients, basically because no large clinical trials have been conducted. Based on the Carnitine Consensus Conference [32], the recommended dose of L-carnitine in the context of anemia is 20 mg/kg administered intravenously after each HD session. The results of this treatment must be evaluated at 3-month interval and be discontinued if no results are reached after 9 months.

Unfortunately, most patients that are unresponsive to ESA do not present one of the conditions mentioned above that can be modified. CKD, especially in stage 5, is a chronic disease characterized by a very high activated inflammatory status. Thus, CKD itself is a central cause of hyporesponsiveness to ESA, and because it is irreversible, it cannot be significantly modified. In fact, inflammation occurs in many other chronic diseases and is responsible for the so-called anemia of chronic disease. The difference is the magnitude of inflammation in CKD, which is much higher than in other morbid conditions. The understanding of the pathophysiology of anemia due to inflammation is useful to suggest possible approaches to anemia in CKD. Basically, inflammation is a stimulus to hepatic production of hepcidin, a small cysteine-rich polypeptide that is a regulator of iron homeostasis. Hepcidin acts to suppress iron release into plasma by decreasing ferroportin and the resulting iron accumulation within the cell. Hepcidin also inhibits the small intestine's absorption of iron. A final consequence is reduced availability of iron for erythropoiesis [33]. This all corresponds to a very

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usual and well-known profile of patients found in daily activities by nephrologists: patients being supplied with iron or with iron store in the upper limits without response to ESA. It should be borne in mind that despite being a good physiological explanation, in fact hepcidin has failed to predict ESA responsiveness in HD patients [34].

Groups	Drugs
Antibiotics	Penicilins
	Cephalosporins
	Bactrim
	Furadantin
	Ciprofloxacim
	Vancomycin
Anti-hypertensive	Angiotensin-converting enzyme inhibitors
Antifungals	Amphotericin
	Fluconazole
	Ketoconazole
Antivirals	Vanganciclovir
	Didanosine
Analgesics	Aspirin
	Non-steroidal anti-inflammatory drugs
Antacids	Esomeprazole
	Ranitidine
	Cimetidine
Miscellaneous	HMG-CoA reductase inhibitors
	Lorazepam

Table 5. Drugs that can contribute to anemia

Current guidelines do not give attractive options for the treatment of patients with inadequate response to ESA. In our practice we are forced to treat hyporesponders as done in the era before ESA. Virtually all symptomatic anemic patients must be submitted to red cell transfusions, with well-known risks of blood transfusions [21]. The National Kidney Foundation guidelines [21] recommend the use of L-carnitine and androgen, but their effects are limited. In summary, there are no new or special approaches to resistance to ESA, at least in the guidelines. Practitioners will have to wait for results from studies testing novel therapeutic agents. These new potential agents are: the protein product of the growth arrest-specific gene 6, known as Gas6, only tested in an animal model [35]; a natural mixture of herbs called Juzen-taiho-to (TJ-48), which showed good results in a small HD sample [36]; and oxpentifyline, with significant results in small samples [37,38] and undergoing further testing in a multi-center randomized clinical trial [39]. In my view, among these drugs oxpentifyline

is the most promising because it works to decrease inflammation, which plays a central role in the genesis of anemia and also in the resistance to ESA.

4. Hyporesponders: The challenge

It is necessary to distinguish two groups of hyporesponders among HD patients. The first group consists of patients with an identified cause of hyporesponsiveness, like iron deficiency, infection, neoplasia, malnutrition, hyperparathyroidism, aluminum intoxication, vitamin B_{12} or folate deficiency or inadequate dialysis. For this first group, most causes of hyporesponsivennes are modifiable with well-established approaches. The second group consists of patients without a clearly defined cause for hyporesponsiveness, who are called here primary hyporesponders. This group comprises very high-risk patients. Since they do not present an identified and modifiable cause, the usual approach is to increase ESA dose, trying to reach the HB/HT target. Thus, this group of patients is usually submitted to high ESA dose whether or not they reach a minimum control of anemia. These patients were identified in the observational studies as having a high risk of death [13-15]. In the literature, it is estimated that at least 10% of HD patients are primary hyporesponders [40]. From my personal experience of nearly 20 years treating HD patients in clinical practice, I believe this figure of 10% is low.

Primary hyporesponders fit the profile of patients with normal iron reserves, but with their release for erythorpoiesis somehow being blocked, leading to failure of the actions of erythropoeisis-stimulating agents. It seems reasonable to explain primary hyporesponsiveness by the previously mentioned model where the inflammatory status interferes with iron hemostasis via hepcidin. If this is the case, the proper approach to ESA resistance would be anti-inflammatory treatment. But drugs with potent anti-inflammatory effects in the context of CKD are still lacking. Oxpentifyline (pentoxifyline), a drug used for more than 20 years in the treatment of vascular disease due to its haemorrheological properties, is a promising option for therapy. It has been proved to have potent anti-inflammatory properties mediated by inhibition of phosphodiesterase [41]. Oxpentifyline acts as anti-apoptic, anti-oxidant, anti-TNF-alpha and anti-IFN-gama [42-44] agent. In small and not randomized studies, oxpentifyline was able to significantly increase HB among HD resistant patients [34,35]. Oxpentifyline is not cited in anemia guidelines yet. It is necessary to wait for results of a multicenter double-blind randomized placebo controlled phase 3 trial in progress [36]. Meanwhile, I believe it is advisable to consider ESA resistance as a useful and powerful marker of morbidity and mortality and to avoid at all costs large increases in ESA dose for hyporesponders.

5. Conclusion

Many crucial questions about optimal anemia control among HD patients are not adequately answered yet. However, the central role of anemia in the context of morbidity of CKD

and dialytic therapy requires continuing to work with the available data. Guidelines are very general and there is an urgent need to attend to the particularities of patients. In medicine, successful treatments are usually individualized therapy. I believe it is possible to consider a few individualized approaches based on the present data. For experienced clinicians it is clear that the general target of HB between 11 and 12 g/dL is not suitable for all patients. Patients with type-2 diabetes or advanced cardiovascular or cerebrovascular disease can be treated for HB level near the lower limit or even with limits of 10-11 g/dL when concerning risks. On the other hand, for young and highly active patients, aiming better quality of life, vitality and physical functioning, the possibility should be considered of pursuing a higher hemoglobin target, but at the moment nothing allows a target exceeding 13 g/dL. When thinking about individualized HB-targets with concern for quality of life, it is advisable to perform follow-up of quality of life level using one of the several validated instruments to evaluate life quality in HD samples. Care must be taken for all patients not to exceed the upper limits of ESAs and stay below 20.000 IU/week of epoetin or 100 μg/week of darbepoetin. ESA resistance should be routinely used in dialysis units as a powerful marker of morbidity and mortality. Finally, the complexity of the management of anemia among HD patients cannot blind us to simple tasks, like routine screening for infection, evaluation of malnutrition and avoidance of sub-dialysis. Due to the characteristics of intense inflammation inherent to CKD, it will be hard to find new drugs that can reduce inflammation enough to make anemia treatment easy. Thus, anemia will continue a challenge all professionals involved in the care of CKD patients on dialysis.

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Chapter 16

rhEPO for the Treatment of Erythropoietin Resistant Anemia in Hemodialysis Patients – Risks and Benefits

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Additional information is available at the end of the chapter

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1. Introduction

Anemia is a common complication in hemodialysis (HD) patients, mainly due to the insufficient production of erythropoietin (EPO) by the failing kidneys [1]. Anemia itself can worsens cardiac function, cognitive function, exercise capacity and quality of life, and it has been independently associated with increased mortality and progression of renal disease [2, 3]. A successful management of anemia is, therefore, crucial, as it may improve clinical outcome. The introduction of recombinant human EPO (rhEPO) therapy to treat anemia of chronic kidney disease (CKD) patients reduced anemia, improving patients' quality of life [3]. There is, however, a marked variability in the response to this therapy and 5-10% of patients develop resistance to rhEPO therapy [4]. Resistance to rhEPO therapy has been associated to inflammation, oxidative stress and "functional" iron deficiency, as major causes.

EPO presents also an important protective role in other tissues, outside of the erythropoietic system. Actually, a biological response to EPO and the expression of EPO receptors, have been observed in many different cells, namely, in endothelial, neural and cardiac cells. However, HD patients requiring high rhEPO doses present an increased risk of death [5]. Recently, randomized controlled trials showed no benefit, or even increased risk of mortality and/or cardiovascular complications, in HD patients with hemoglobin (Hb) concentration higher than the target levels [6].

In this book chapter, a review of the etiological mechanisms associated with the development of EPO resistant anemia, in HD patients, will be performed. We also intend to review also the risk-benefits associated with high rhEPO doses used to achieve the target Hb levels.

2. Anemia of chronic kidney disease

CKD is a pathological condition that results from a gradual, permanent loss of kidney function over time, usually, months to years. CKD can result from primary diseases of the kidneys. However, diabetic nephropathy and hypertension have been considered as the main causes of CKD [1]. Anemia is a common complication of CKD that develops early in the course of the disease increasing its frequency with the decline of renal function. The incidence of anemia is less than 2 % in CKD stages 1 and 2, about 5% in CKD stage 3, 44% in CKD stage 4 and more than 70% in the end-stage renal disease (ESRD) [7]. This condition is associated with a decreased quality of life [3], increased hospitalization [2, 8], cardiovascular complications - angina, left ventricular hypertrophy (LVH) and chronic heart failure – and mortality [9-12].

The European Best Practice Guidelines for the management of anemia in patients with CKD recommends that a diagnosis of anemia in these patients should be considered when Hb concentration falls below 11.5 g/dL in women, 13.5 g/dL in adult men and 12.0 g/dL in men older than age 70 [13].

The anemia of these patients is, mainly, due to decreased kidney´s secretion of EPO. In CKD patients there is a failure in increasing the EPO levels in response to hypoxia, as occurs in others types of anemia. These patients present an EPO deficiency, rather than an absolute lack, as EPO remains detectable even in the most advanced stages of CKD [14]. However, other factors contribute to the anemia in these patients, as reduced red blood cell (RBC) life span, iron deficiency, uremic toxins, HD procedure, blood loss and inflammation.

3. Erythropoiesis-stimulating agents

The correction of anemia in CKD patients needs pharmaceutical intervention with erythropoiesis-stimulating agents (ESAs). An intravenous (i.v.) iron supplementation, as adjuvant therapy, should be administrated to prevent iron deficiency and minimize the dose of ESA needed to achieve the target-range of Hb levels [4, 13]. However, recently, some concerns about this treatment of the anemia were raised and questioned in several studies, namely, the need to define Hb targets, safety, benefits and costs of ESA treatments.

3.1. Pharmacology of erythropoiesis- stimulating agents

The introduction of ESAs revolutionized the treatment of anemia in CKD patients. After cloning of the EPO gene, the recombinant human technology allowed the production of ESAs that present the physiological role of EPO. Epoetin beta was the first ESA to be used. It was presented in 1987 [15] and approved by the Food and Drug Administration (FDA) in 1989. Since then, other ESAs appeared, with similar actions, differing in their half-life. Consequently, they were divided in “short-acting” and “long-acting” ESAs (Table 1). The frequency of administration and route of administration (usually, the intravenous (i.v.) administration is more convenient for HD patients) is, therefore, conditioned by their half-life.

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In humans, it seems that the rhEPO treatment increases Hb concentration, and, thus, arterial oxygen content, by increasing red cell volume and depressing plasma volume, probably through a mechanism involving the reduction of the renin–angiotensin–aldosterone axis activity [16].

The mechanisms for ESAs elimination are not well elucidated, and several hypotheses have been considered [17, 18]:

- ESAs are primarily cleared by a hepatic pathway;
- Clearance of ESAs occurs through the kidneys;
- ESAs may be cleared via EPO receptor-mediated endocytosis and subsequent intracellular degradation.

However, other mechanisms, not yet elucidated can be responsible for ESAs elimination.

ESA	Approval		Characteristics	Half-life	Frequency administration
	FDA	EMA			
Short-acting					
Epoetin beta		1989	Identical a.a. and carbohydrate composition to EPO	i.v. 4 - 12 h s.c. 12 – 28 h	3 times/week
Epoetin alpha	1989	1989	Identical a.a. and carbohydrate composition to EPO	i.v. ≈ 5h s.c. ≈ 24h	3 times/week
Epoetin zeta (biosimilar medicine)		2007	Identical a.a. and carbohydrate composition to EPO	i.v. ≈ 5h s.c. ≈ 24h	3 times/week
Epoetin theta (biosimilar medicine)		2009	Identical a.a. and carbohydrate composition to EPO	i.v.≈ 4h s.c. ≈ 34h	3 times/week
Long-acting					
Darbopoetin alpha	2001	2001	2 additional N-linked carbohydrate chains compared to EPO	i.v. 21 hours s.c. 73 hours	once/week
Methoxy polyethylene glycol-epoetin beta	2007	2007	continuous erythropoietin receptor activator	i.v. 134 hours s.c. 139 hours	once/month
Peginesatide	2012		PEGylated, homodimeric peptide with no sequence homology to rhEPO		once/month

Abbreviations: FDA – Food and Drug Administration; EMA – European Medicines Agency; a.a. – amino acid; i.v. – intravenous; s.c. – subcutaneous. rhEPO – recombinant human erythropoietin. Adapted from Food and Drug Administration (2012) [19], European Medecines Agency (2012) [20] and Green et al. (2012) [21].

Table 1. Erythropoiesis – stimulating agents.

3.2. Non-hematopoietic actions of erythropoietin and erythropoiesis- stimulating agents

ESAs are designed to treat anemia, but recent evidences points to other non-hematopoietic actions of EPO and ESAs [22]. Several pleiotropic effects have been attributed to EPO, such as cytoprotective, antiapoptotic, anti-inflammatory and angiogenic capacities.

The erythropoietic and non-erythropoietic effects of EPO appear to result from the existence of two different receptors with different affinities for EPO [23].

In erythroid cells, picomolar concentrations of EPO bind to the EPOR homodimers, whereas on other cells and tissues EPO binds to an heterodimer receptor, constituted by EPOR and CD131 (beta common receptor – βcR), and, high local EPO concentrations are needed to exert its action [23-25]. The EPO variants, including asialo-EPO, carbamylated EPO (CEPO) or carbamylated darbopoetin alpha (C-darbe), that present the protective effects of EPO in non-haematopoietic tissues, but no hematopoietic activity [26-28], suggested the presence of two types of receptors. EPOR are present in several cells and tissues, as brain (neurons, astrocytes, and microglia) [29, 30], kidney [31], female reproductive system [32], vascular endothelial cells [33], cardiomyocytes [34], lymphocytes and monocytes [35], among others.

Some of the non-hematopoietic effects of EPO are summarized:

- Cardioprotection: several studies showed that ESAs promote cardioprotection through the inhibition of cardiomyocyte apoptosis, reduction of inflammation and oxidative stress, and induction of angiogenesis [22-24, 34, 36].
- Anti-inflammatory properties: EPO and its derivates reduce the production of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, and NO (nitric oxide) via inducible NO synthase (iNOS) through the inhibition of NF-κB pathway [23, 24, 37].
- Neuroprotection: EPO seems to be important for the neural development, as it stimulates the differentiation of neural progenitor cells [29], but it also promotes angiogenesis and reduces inflammation, oxidative stress and neuronal apoptosis in some conditions, as hypoxia-ischemia (HI), stroke and neurotoxicity of glutamate [22-24, 29].
- Angiogenesis: EPO increases the number of functionally active endothelial progenitor cells (EPCs), enhancing angiogenesis, and seems to be dependent on functional endothelial NO synthase (eNOS) [24, 38]. EPO plays an important role in uterine angiogenesis, through EPOR expressed by endometrial vascular endothelial cells [33].
- Immunomodulation: EPO may have effects on dendritic cells [potent antigen presenting cells (APCs) that possess the ability to stimulate naïve T cells], presenting effects in innate immunity [39].
- Renoprotection: several studies on acute kidney injury reported that a single dose of rHuEPO reduces kidney dysfunction through an antiapoptotic mechanism, and increased NO production, but only in intact vessels [31]. However, it appears that this renoprotection is achieved only with low doses of EPO, non-hematopoietic doses, as high EPO doses cause an increase in hematocrit that is accompanied with changes in hemorheology, activation of thrombocytes and increased platelet adhesion to injured endothelium [31].

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3.3. Benefits of erythropoiesis-stimulating agents

ESAs have beneficial effects by correcting anemia and their associated symptons (fatigue, dizziness, shortness of breath, among others), improving the quality of life of these patients [40-42]. ESAs also reduce the need for transfusions, thereby reducing transfusion reactions (immunological sensitization), transmission of infectious agents and iron overload [43].

The anemia of CKD is associated with cardiovascular complications, due to increasing blood pressure and LVH. Indeed, LVH is present in many patients with CKD, even in the earlier stages of the disease (75% of patients who start HD have LVH) and may lead to heart failure, cardiac arrhythmia or both, that are considered as major causes of cardiac-related deaths in this population [44, 45]. LVH is a physiological adaption that results from long-term increase of myocardial work, from high-pressure or volume overload, which can lead to major cardiac events. Volume overload can result from anemia, as hypoxia and the decreased blood viscosity contribute to decrease peripheral resistance, and from increased venous return, both of which increase cardiac output [44, 46]. LVH is also a risk factor for the development of uremic cardiomyopathy, which is defined as congestive heart failure due to a primary disorder of the heart muscle in uremic patients, and is characterized by profound systolic dysfunction and cardiac fibrosis; however, increased sympathetic activity in response to anemia also appears to be a factor for this condition [47, 48].

Several studies report the synergy between anemia and LVH and that the use of ESAs for anemia correction (Hb target of approximately 11 g/dL) is associated with an improvement in heart failure symptoms and with a reduction in LVH [45, 49].

The effects of ESAs on the progression of renal function are controversial. Some studies demonstrated that following ESA initiation renal function declines at a slower rate and delays the dialysis initiation in pre-dialysis patients [50-52], while other studies reported that ESAs do not significantly slow renal function decline [53, 54].

3.4. Risks associated with erythropoiesis-stimulating agents

As referred, ESAs have several benefits beyond the treatment of anemia; however, its administration seems to associate some risks. Cardiovascular and thromboembolic events have been described. Some of the protective effects of EPO and ESAs, as described above, occurs upon the activation of the heterodimeric EPOR; however, as the affinity of EPO for this receptor is low, higher doses of EPO are needed to reach these effects.

One of the most described effects of ESAs is hypertension. Several mechanisms can explain the rise in blood pressure (BP) mediated by ESAs. Renal anemia is a factor predisposing to increase BP, due to the increased sympathetic activity and impaired NO availability [55]. ESAs impair the balance between vasodilating and vasoconstrictor factors, since it induces the production of vasoconstrictors as endothelin-1 (ET-1), thromboxane (TXB2) and prostaglandin 2α (PGF2α), and reduces the production of the vasodilatory prostacyclin (PGI2) [56, 57]. Chronic treatment with ESAs appears to impair the vasodilatory capacity of endothelial NO, through an increase in the asymmetrical dimethylarginine (ADMA), an inhibitor of eNOS [57]. ESAs seem to induce hypersensitivity to angiotensin II, a recognized vasoconstrictor [56, 57].

An increase in noradrenaline concentration and hypersensitivity - a vasoactive substance - may contribute also to hypertension during ESA therapy [56, 57].

Treatment with ESAs is associated with an increase in the incidence of thrombotic events [58]. EPO has the capacity of stimulating thrombopoiesis, increasing platelet count; however, EPO also increases platelet reactivity (especially on the newly synthesized ones) promoting a prothrombic effect [59]. Some other hemostatic disturbances have been described, as an increased expression in E selectin, P selectin, von Willebrand factor and plasminogen activator inhibitor-1, which may favor bleeding episodes, and increase the risk of thrombosis and thromboembolism, as occlusion of the vascular access [57].

An uncommon but serious complication associated with ESAs administration is pure red blood cell aplasia, an immunogenic side effect that results from the production of antiEPO antibodies induced by ESAs administration [60-62]. Indeed, the method used to produce ESAs may not eliminate impurities or aggregated protein that may trigger the immune response in patients [62]. Immunoprecipitation assays have shown that antiEPO antibodies are directed against the protein moiety of the molecule [61].

ESAs are also indicated in the treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. However, some evidences point that these agents can accelerate tumor growth, but data are controversial. High doses of EPO can stimulate endothelial and vascular smooth muscle cell proliferation and promote angiogenesis. The antiapoptotic pleiotropic effect of EPO can also contribute to tumor progression [57, 63].

4. Resistance to erythropoieses-stimulating agents

Although the majority of CKD patients respond adequately to ESAs, 10% of these patients develops resistance to this therapy [4]. According to the European best practice guidelines for the management of anemia in patients with chronic renal failure [13] resistance to ESAs is defined as a failure to achieve target Hb levels (11– 12 g/dl) with doses lower than 300 IU/kg/ week of epoetin or 1.5 μg/kg/ week of darbopoietin-α. For the National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI) guidelines [4], hyporesponsiveness to ESAs therapy is defined by, at least, one of these situations: a significant increase in the ESA dose required to maintain a certain Hb level, a significant decrease in Hb level at a constant ESA dose or a failure to increase the Hb level to higher values than 11 g/dL, despite the administration of an ESA dose equivalent to epoetin higher than 500 IU/kg/week.

ESAs resistance is associated with poor outcome, increasing the risk of mortality [5, 64, 65]. Hyporesponsiveness to ESAs therapy can have many underlying causes. The most common causes are iron deficiency (absolute or functional), and inflammation.

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4.1. Iron deficiency

Iron-restricted erythropoiesis is frequent in CKD patients and is due to absolute or functional iron deficiency. The latter seems to be the most common cause of hyporesponsiveness to ESAs in HD patients [66, 67]. About 25-37% of CKD patients with anemia present with iron deficiency [66]. Iron therapy is recommended, and i.v. iron supplementation is more effective than oral supplementation in HD patients [67]. It is important to distinguish between absolute and functional iron deficiency. Indeed, there is a controversy about iron supplementation when transferring saturation is lower than 20% and ferritin is higher than 500ng/mL (functional deficiency) [67, 68]. In this situation, probably associated with an inflammatory response, an excess of iron can be potentially harmful to these patients.

4.2. Chronic blood loss

Blood loss is frequent in patients undergoing HD and could be a cause to an inadequate ESA response. This condition should always be suspected in several conditions, namely, in patients who need a higher dose of ESA to maintain a stable Hb concentration, in patients whose Hb concentration is falling, and in patients who fail to increase iron stores, even after i.v. iron supplementation [13].

4.3. Inflammation

The anemia of CKD is often referred as an inflammatory anemia. Indeed, inflammation is a common feature in CKD patients, mainly, in those under HD. Inflammation is recognized as one cause to hyporesponsiveness to ESA therapy, and several studies reported an association between high levels of inflammatory markers and ESA resistance in CKD patients [5, 69-72]. Usually, HD patients present with high levels of inflammatory markers, namely, IL-6, CRP, TNF-α, INF-γ, and with lower serum levels of albumin [69-71].

A week response to ESA also appears to be associated with enhanced T cell capacity to express IFN-γ, TNF-α, IL-10, and IL-13 [70, 73]. Costa et al. [71] also reported a significant rise in neutrophil count in non-responder patients. They also found positive correlations between CRP and elastase and between elastase and rhEPO doses, suggesting that elastase, a neutrophil protease released by degranulation, could be a good marker of resistance to rhEPO therapy in HD patients under hemodialysis. Inflammation contributes to anemia through several ways:

- suppression of erythropoiesis: **directly**, by the inhibitory effects of pro-inflammatory cytokines: IL-1β and TNF-α stimulate the growth of early progenitors BFU-E, but suppresses the growth of the later stages, inducing apoptosis in CFU-E [74]; **indirectly** as IL-1β and TNF-α stimulate the production of INF-γ [75], known to mediate erythropoiesis suppression.
- accelerated destruction of erythrocytes (as referred above in the uremic toxins section) by the reticulo-endothelial macrophages activated by the inflammatory state [76];
- reduction of EPO production: in hypoxic conditions, IL-1β and TNF-α increase the expression GATA and NF-κB, both inhibitory of the transcriptional factors of EPO gene [77];

- impaired iron availability for erythropoiesis: transferrin receptors in erythroid and non erythroid cells can be down-regulated by inflammatory cytokines reducing iron uptake [76]; they can also increase the expression of lactoferrin receptors and reduce the expression of ferroportin in macrophages, increasing the iron storage in these cells and reducing the iron availability [76, 78]; inflammation is responsible for the increase of hepcidin expression, a regulatory peptide in the iron cycling that reduces iron absorption and mobilization.

Recently, it was reported the existence of a soluble form of the EPOR (sEPOR) [79, 80]. Although this soluble receptor is able to bind to EPO, the role of these circulating sEPOR in humans remains largely unknown. sEPOR seems to be increased in patients receiving high ESA doses [79, 80], and the pro-inflammatory cytokines IL-6 and TNF-α can be responsible for this increment [79]. sEPOR could, therefore, be associated with ESA resistance through the inhibition of EPO effectiveness.

4.4. Decreased hepcidin excretion

In the last years hepcidin emerged as a key regulator of iron metabolism. Hepcidin is a peptide (25 aminoacids) produced, mainly, in hepatocytes, although other sites of production have been described, such as kidney [81], adipose tissue [82], brain [83] and heart [84, 85]. Hepcidin expression is regulated by the *HAMP* gene located in the long arm of chromosome 19 [86].

An increase of hepcidin levels leads to a decrease in iron absorption (hepcidin inhibits DMT1 transcription [87] or promotes an ubiquitin-dependent proteasome degradation of DMT1 [88]) and an inhibition of iron release from its storages (macrophages and hepatocytes) as hepcidin binds to ferroportin (the only known iron exporter in the cells) promoting its internalization and degradation in lysosomes (Fig. 1) [89, 90].

Hepcidin is increased in HD patients [91, 92], and it is regulated by inflammation [93] and linked to ESA resistance. Hepcidin correlates with IL-6, the cytokine that stimulate its production [94, 95], and with ferritin reflecting high inflammation and high levels of iron stores [96]. Some authors point that hepcidin could be a marker of functional iron deficiency [86] and that ESA therapy can decrease hepcidin levels [72, 96].

The kidney appears to play a role in the excretion of hepcidin, as this peptide is found in urine [97]. Hepcidin levels are increased in HD patients, and its levels appears to be reduced after HD procedure, supporting the role of kidneys in the excretion of this peptide [91, 92].

4.5. Secondary hyperparathyroidism

The parathyroid hormone (PTH) is considered by EUTox Work Group [98] as a middle molecule uremic toxin with some biological effects. Secondary hyperparathyroidism is a condition resulting from the deregulation of calcium and phosphorus homeostasis in the kidney. It seems that PTH could be a marker of hyporesponsiveness to ESAs in dialysis patients [99, 100].

Several mechanisms have been proposed as interference with RBC production as PTH causes bone marrow fibrosis, has an inhibitory effect on BFU-E and interferes with EPO endogenous

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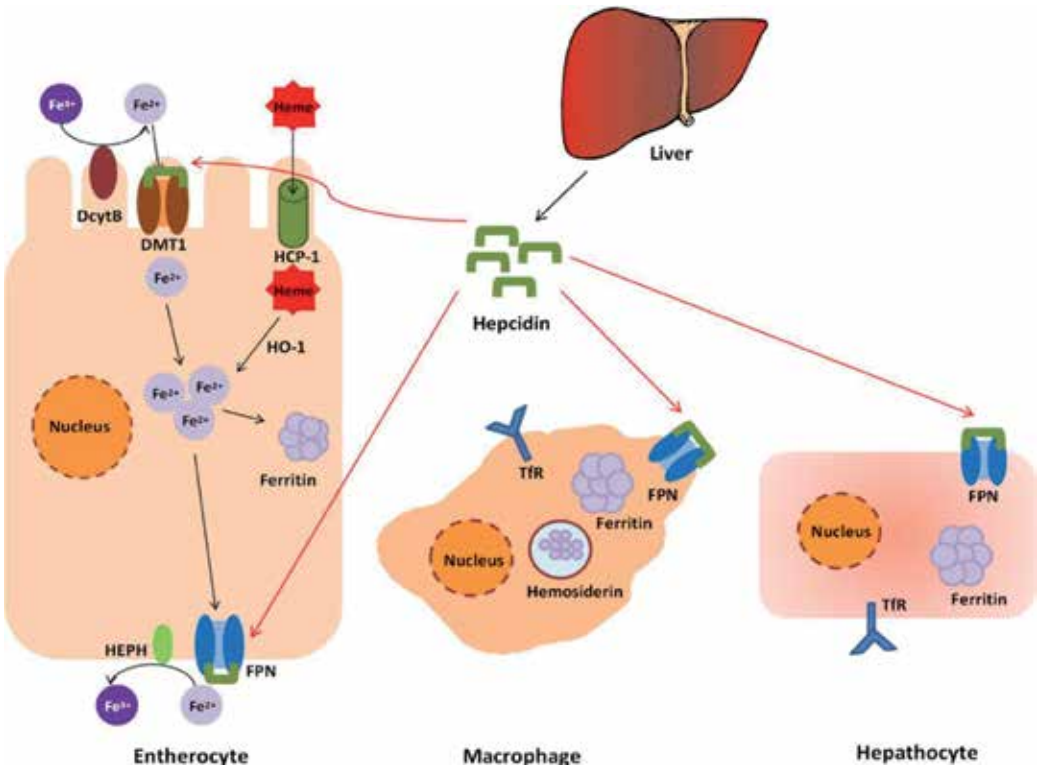

Figure 1. Iron metabolism and hepcidin. The iron is present in the diet as either heme iron (Fe^{2+}) or nonheme iron (Fe^{3+}). Nonheme iron must first be reduced to Fe^{2+}, by duodenal cytochrome B (DcytB), before it can be transported by the divalent metal iron transporter 1 (DMT1). Once inside the enterocyte, the newly absorbed iron enters the intracellular iron pool. If the iron is not required by the body, it is loaded onto the iron storage protein ferritin. Iron required by the body is transferred across the basolateral membrane by ferroportin (FPN). The export of iron also requires the ferroxidase hephaestin (HEPH). Heme carrier protein (HCP1) can transport heme; the enzyme heme-oxigenase 1 (HO-1) is required for releasing iron from heme. Hepcidin expression in the liver inhibits iron absorption from the diet and the release of iron from its storage.

production [99, 101-103]; interference with RBC survival as PTH increases osmotic fragility of erythrocytes [102, 103].

4.6. Aluminium toxicity

Although the recent progresses in the dialysis procedures, some patients present high levels of aluminium (Al) [104]. Usually, high levels of Al cause a microcytic, hypochromic or normochromic anemia that is hyporesponsive to ESA therapy, as it interferes with the enzymes necessary for the heme synthesis [67, 105]. The sources for the increase in plasma Al levels seems to be the water used for dialysis [105], medications given i.v. [104] and infections [106].

4.7. Vitamin deficiencies (e.g. folate or vitamin B12 deficiency)

The deficiency of folate or vitamine B12 is not very common in dialysis patients, but as these nutrients are water soluble and can be easily loss during dialysis, they can become a cause of ESA resistance, especially in patients with malnutrition. The supplementation of these nutrients seems to overcome ESA hyporesponsiveness [66, 67].

4.8. Malnutrition

Low body mass index (BMI) and low levels of cholesterol are related to poor outcomes in dialysis patients, increasing the risk of mortality [107]. This phenomenon, called as "reverse epidemiology", is based on the malnutrition-inflammatory complex [108]. These patients present a decreased nutritional reserve, reducing its capacity to overcome inflammation; they also present a reduced protein-calorie intake, chronic acidosis and failure of vascular access [108]. A diminished nutritional status and the enhancement of inflammation could be responsible for the requirement of higher EPO doses [69, 108].

4.9. Inadequate dialysis

Intensity or adequacy of dialysis (measured by Kt/V) is a factor that can modulate the response to ESA therapy. Inadequate dialysis is associated with the need for higher ESA doses. Some studies showed that convective treatments present benefits in ESA response, as compared with other treatments [109]. High flux HD (HF-HD) and online hemodialfiltration (OL-HDF) improve the response to ESAs, as compared to low flux HD (LF-HD), probably due to a better removal of middle and large molecules that impair erythropoiesis [67, 92, 109]. However, some studies failed to reach to these conclusions [110].

4.10. Angiotensin-converting enzyme inhibitors and angiotensin receptors blockers

These drugs, used for hypertension control, can be associated with ESA hyporesponsiveness due to its effects on angiotensin II. They can act through several mechanisms, not well understood, including inhibition of angiotensin-induced EPO release and increased plasma levels of N-acetyl-serylaspartyl-lysil-proline that impairs the recruitment of pluripotent hemopoietic stem cells [66, 67].

4.11. Testosterone deficiency

It appears that low testosterone levels may contribute to anemia in men with CKD and to ESA resistance. Testosterone stimulates erythropoiesis through the production of hematopoietic growth factors and possible improvement of iron bioavailability [111, 112].

5. Controversies in the treatment of anemia in chronic kidney disease

Since the introduction of ESAs therapy a demand exists to define the better Hb target associated with lower CV risks. Indeed, recent studies reported increased CV risk and death in patients

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treated with high doses of EPO to achieve higher Hb levels, and this led to the controversy of what is the cause of these increased risk: higher doses of EPO or higher levels of Hb?

5.1. Clinical trials

The correction of anemia to higher target Hb levels with ESAs in CKD or ESRD patients merits attention, as it may be associated with increased risk of death or of CV events, namely, stroke, hypertension, and vascular access thrombosis [6].

Only four studies assessed properly the effect of higher Hb levels on the increased risk of CV events and/or death.

5.1.1. Normal hematocrit trial (NHT) [113]

This study included patients under HD with congestive heart failure or ischemic heart disease. They were randomized to one of two groups to receive epoetin alpha, aiming to achieve and maintain a target hematocrit (Ht) of 42% or 30%. Primary end points were the length of time to death or for the first nonfatal myocardial infarction (MI). The study was interrupted due to the increased number of deaths observed in the high-Ht group and that were nearing the boundary of statistical significance. An increased rate of incidence of vascular access thrombosis was also reported in the high-Ht group. The study failed to reach statistical difference between the two groups, however, it was concluded that a target Ht of 42% is not recommended in HD patients.

5.1.2. Cardiovascular risk reduction by early anemia treatment with epoetin beta (CREATE) [53]

This study included pre-dialysis patients in stage 3 or 4 with mild-to-moderate anemia. They were randomly assigned to normalization of Hb values (13.0-15.0g/dL) or to a partial correction of anemia (10.5-11.5 g/dL), in order to investigate the effect of Hb correction on complications from CV causes. The primary endpoint was the time for the first CV event. Secondary objectives included the investigation of the effects of these treatments on the left ventricular mass index, the progression of CKD, and the quality of life. They did not find a significant difference in the risk for a first CV event between the two groups. However, this study reported a higher incidence of hypertension and headaches, and a higher risk for starting dialysis in the group aiming normalization of Hb values. But they also reported significant benefits on the quality of life for the patients with higher Hb targets.

In conclusion, they found that in pre-dialysis patients with mild-to-moderate anemia, the normalization of Hb levels to 13.0 to 15.0 g/dL did not reduce CV events.

5.1.3. Correction of hemoglobin and outcomes in renal insufficiency (CHOIR) [114]

Non-dialysis patients with CKD were included and the effect of raising Hb concentration with epoetin alpha to a target Hb value of 13.5 g/dL or 11.3 g/dL was compared. The primary end point was the time of death, MI, hospitalization for congestive heart failure (excluding renal replacement therapy), or stroke.

An increased risk of the primary end point, for the high-Hb group, as compared with the low-Hb group was found. Death and hospitalization for congestive heart failure accounted for 74.8% of the events. An increased rate of thrombotic events was also reported in the group of high-Hb. Patients in the high-Hb group had a higher (but not significant) rate of both progression to renal replacement therapy and hospitalization for renal replacement therapy. They did not find any apparent additional benefit in quality of life. In conclusion, they recommended the use of a target Hb level of 11.0 to 12.0 g/dL rather than a level of 11.0 to 13.0 g/dL, because of the increased risk, increased costs, and no quality-of-life benefit.

5.1.4. Trial to reduce cardiovascular events with aranesp therapy (TREAT) [115]

In this trial patients with type 2 diabetes mellitus, CKD and anemia were enrolled. Patients were randomized to receive darbepoetin-alfa (in order to achieve a target Hb of 13.0 g/dL) or placebo (in this group were prescribed blinded "rescue" darbepoetin for Hb level < 9.0 g/dL). The primary end point was time to death or hospitalization for myocardial ischemia. A significantly higher rate of strokes in patients treated with darbepoetin was observed. A higher rate of both thromboembolism and cancer-related deaths among patients with a history of cancer in the treatment group was also reported in the treatment group.

Higher targets of Hb levels imply the use of higher ESA doses. Therefore, the increased risk for adverse CV outcomes could also result from the higher ESAs doses and not only from the normalization of Hb [116]. In this sense, a trial has been designed to identify the potential benefits and harms of different fixed doses of ESA. The Clinical Evaluation of the DOSe of Erythropoietins (C.E. DOSE) trial [117] enrolled HD patients that were randomized 1:1 to 4000 IU/week *versus* 18000 IU/week of i.v. epoietin alfa or beta, or of any other ESA in equivalent doses. The primary outcome was death, non fatal stroke, non fatal MI and hospitalization for CV causes.

Several potential mechanisms for harm with higher Hb targets have been proposed and revised by Fishbane et al. [118]. The hypothesis is that increased viscosity and hemoconcentration, the increased BP, the toxic effect of iron and unphysiological doses of ESAs contribute to ESAs toxicity. The rise in Ht results in a higher viscosity and, consequently, higher risk of thromboembolism. It also favors platelet activation by increasing the interaction between the endothelial cells and platelets in blood vessels. Hemoconcentration is a phenomenon observed in these patients after a dialysis session that results from the removal of large amounts of fluids.

5.2. Safety advisories

Considering the results of these studies, in 2007 the FDA launched a safety advisory, recommending that patients do not exceed the Hb level of 12g/dL [119]. At the same time, the NKF KDOQI made an update on its guidelines, recommending that the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL, but should not be greater than 13.0 g/dL [120].

In 2010, the European Best Practice Guidelines Work Group published the recommendation that "Hb values of 11-12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL" [121]. In 2011, the FDA introduced warnings in the ESA label

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giving the recommendations "for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) to improve the safe use of these drugs" [122].

5.3. Hemoglobin variability

In conjugation with the optimal Hb target and ESA dose, there is a study of Hb variability (Hb-var). It was noted that during the treatment of HD patients with ESAs the level of Hb have a great fluctuation, that is, the Hb levels tends to rise or fall in a cyclic pattern, that is different for each patient [123]. However, the impact of this Hb-var is not still elucidated. Some studies show that there is an association between Hb-var and increase of death [11, 64, 65], especially if this variability is greater than 1g/dL [11]. The main factor for this variability is ESA dose; however, other factors have been pointed, as i.v. iron and other biological factors (inflammation and nutritional status) [123].

Hb-var represents an important physiological stress, as the ESA treatment involves short, intermittent burst of plasma EPO availability that do not coincide, either temporally or in magnitude with its physiological action. Under physiological conditions EPO levels are maintained in a narrow range, through several mechanisms, in order to support a constant oxygen supply to the organs. The impact of Hb-var on the organism is not fully understood, but the myocardium may be one of the most affected organs, as it has to compensate with an increased output and cardiomyocytes proliferation during the periods of reduced oxygen availability, that occur when Hb reaches lower levels, before the new ESA administration. This might result in deregulation of cardiac growth signal, leading to left ventricular dilation and hypertrophy [11, 123]. The autonomic nervous system can also suffer from this Hb-var; actually, autonomic dysfunction occurs in other pathological conditions, where Hb-var also occurs, like sickle cell anemia [11]. Fishane et al. also [123] found that better responders to ESA tend to have a higher degree of Hb-var.

6. Conclusion

Despite all the technologic advances in HD procedure and medical support, the morbidity and mortality in CKD patients remains high, particularly in hyporesponsiveness patients to ESAs therapy. The clinical trials showed that a higher Hb target is associated with increased risk of cardiovascular complications and death; however, the impact of higher ESAs doses to achieve higher Hb targets remains unclear. Some evidence points that the pleiotropic effects of ESAs can contribute to the ESAs toxicity observed with higher doses. Meanwhile, the recommendations to target Hb to a range of 11 – 12 g/dL, without exceeding the 13g/dL, with the lower doses of ESAs to accomplish this goal, can reduce the risks associated with higher Hb target and higher ESAs doses in CKD patients. More studies are needed on this field to evaluate the impact of the linkage anemia/high sustained ESAs therapeutic doses in CKD that might explain the high mortality in hyporesponsiveness patients. To accomplish these goals blood, cellular and tissue studies are need that cannot be performed in humans; therefore, the use of appro-

priate animal models could be useful to understand whether the association of moderate anemia and high sustained therapeutic doses of ESAs in non-responders is beneficial or an increasing risk; to clarify the underlying mechanisms and, eventually, to propose new therapeutic strategies to reduce mortality in HD patients.

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Chapter 17

Management of Anemia on Hemodialysis

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Additional information is available at the end of the chapter

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1. Introduction

The definition of anemia is controversial. The WHO defines anemia as hemoglobin (Hb)<13 g/dL for men and <12 g/dL for women [1]. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, which is the criteria used for Medicare reimbursement, defines anemia in adult men and postmenopausal women as Hb<12 g/dL, or <11 g/dL in a premenopausal woman [2]. Anemia represents a significant problem to deal with in patients with chronic kidney disease (CKD) on hemodialysis (HD). Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia [3]. This is a frequent complication and contributes considerably to reduced quality of life (QoL) [4-6] of patients with CKD. It has also been associated with a number of adverse clinical outcomes, increased morbidity and mortality [5, 7-13]. In general, there is a progressive increase in the incidence and severity of anemia with declining renal function. The reported prevalence of anemia by CKD stage varies significantly and depends, to a large extent, on the definition of anemia and whether study participants selected from the general population, are at a high risk for CKD. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hb levels starts to fall at an estimated glomerular filtration rate (eGFR) of less than 75 ml/min per 1.73 m^2 in men and 45 ml/min per 1.73 m^2 in women [14]. Among patients under regular care and known to have CKD, the prevalence of anemia was found to be much greater, with mean Hb levels of 12.8 ± 1.5 g/dl (CKD stages 1 and 2), 12.4 ± 1.6 g/dl (CKD stage 3), 12.0 ± 1.6 g/dl (CKD stage4), and 10.9 ± 1.6 g/dl (CKD stage 5) [15]. Although renal anemia is independent of the etiology of kidney disease, there are two important exceptions. Renal anemia in diabetic patients develops more frequently, at earlier stages of CKD, and more severely at a given level of renal impairment [16-18]. In patients with polycystic kidney disease, Hb is higher than in other patients with similar degrees of renal failure, and polycythemia may occasionally develop [19]. Many patients not yet on dialysis still receive no specific treatment for their anemia. In contrast, in

patients on dialysis,, average Hb values have steadily increased during the past 15 years, following the advent of erythropoietin (EPO) and the development of clinical practice guidelines for anemia management [16, 17]. Anemia contributes to significant healthcare costs associated with CKD [20]. The average Hb value, however, varies considerably between countries, reflecting variability in practice patterns [21]. Before the availability of recombinant human erythropoietin (rhuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and sensitization, which reduced the chances of successful transplantation. Anemia in CKD patients except from the lack of EPO [22, 23], is a multifactor process. Shorter lifespan of red blood cells, iron and vitamin deficiency due to dietary restrictions, and rarely bleeding that accompanies uremia seem to be other important factors [24, 25]. Adequate dialysis can contribute to anemia correction through many mechanisms, including the removal of molecules that may inhibit erythropoiesis using high-flux dialyzers [26-30]. It also seems that residual renal function is important in dialysis patients and its decline also contributes significantly to anemia, inflammation, and malnutrition in patients on dialysis [31, 32]. It is also affected by the underlying disease, co morbid conditions, malignancy, infection, heart failure, as mentioned above, the environment and several other factors (therapeutic treatment with angiotensin-converting enzyme(ACE) inhibitors, [33-37] increased PTH, [38-43] osteodystrophy [44, 45]) that differ among patients. Thus, anemia management in these patients needs an individualized approach. Each patient should be treated according to an Hb target with the lowest effective Erythropoiesis Stimulating Agents (ESA) dose, while avoiding large fluctuations in Hb levels or prolonged periods outside the target. This strategy may necessitate changes to the ESA dose, dosing frequency and iron supplementation over the course of a patient's treatment, and proactive management of conditions that can affect ESA responsiveness. While all ESAs effectively increase Hb levels, differences with respect to route of administration, pharmacokinetics, and dosing frequency and efficiency should be considered to maximize the benefits of ESA treatment for the individual patient [46]. Substitution of the subcutaneous route of administration for the intravenous route for epoetin-alfa can reduce drug acquisition and costs, the two largest components of healthcare costs in CKD patients [20]. Hence, treating anemia in CKD patients on HD seems to be very complex and has to be managed step by step correcting all the factors that affect this process.

2. Diagnostic approach of anemia in hemodialysis patients

The diagnosis of anemia and the assessment of its severity are best made by measuring the Hb concentration rather than the hematocrit. Hb is a stable analyte measured directly in a standardized fashion, whereas the hematocrit is relatively unstable, indirectly derived by automatic analyzers, and lacking of standardization. Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are one half and one third those for hematocrit, respectively [16]. There is considerable variability in the Hb threshold used to define anemia in CKD patients. According to the definition in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, anemia should be diag-

nosed at Hb concentrations of less than 13.5 g/dl in adult men and less than 12.0 g/dl in adult women [16].These values represent the mean Hb concentration of the lowest 5th percentile of the sex-specific general adult population. In children, age-dependent differences in the normal values have to be taken into account. Normal Hb values are increased in high-altitude residents [16]. The end of the short interdialytic period is the most appropriate timing for anemia assessment [47]. Although renal anemia is typically normochromic and normocytic, [48, 49] deficiency of vitamin B12 or folic acid may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (such as thalassemia) may produce microcytosis. Macrocytosis with leucopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins, nutritional deficit, or myelodysplasia. Hypochromia probably reflects iron-deficient erythropoiesis. An absolute reticulocyte count, which normally ranges between 40,000 and 50,000 cells/μl of blood, is a useful marker of erythropoietic activity. Iron status tests should be performed to assess the level of iron in tissue stores or the adequacy of iron supply for erythropoiesis. Although serum ferritin is so far the only available marker of storage iron, several tests reflect the adequacy of iron for erythropoiesis, including transferrin saturation, MCV, and MCHC; the percentage of hypochromic red blood cells (PHRC); and the content of Hb in reticulocytes (CHr) [50]. Storage time of the blood sample may elevate PHRC, MCV and MCHC are below the normal range only after long-standing iron deficiency. It is important to identify anemia in CKD patients because it may signify nutritional deficits, systemic illness, or other conditions that warrant attention, and even at modest degrees, anemia reflects an independent risk factor for hospitalization, cardiovascular disease, and mortality [16, 51]. Drug therapy such as ACE inhibitors may reduce Hb levels by: firstly, direct effects of angiotensin II on erythroid progenitor cells, [52] secondly, accumulation of N-acetyl-seryl-lysyl-proline (Ac-SDKP), an endogenous inhibitor of erythropoiesis, [53] and thirdly, reduction of endogenous EPO production, potentially due to the hemodynamic effects of angiotensin II inhibition [54]. Myelosuppressive effects of immunosuppressants may further contribute to anemia [55].The measurement of serum EPO concentrations is usually not helpful in the diagnosis of renal anemia because there is relative rather than absolute deficiency, with a wide range of EPO concentrations for a given Hb concentration that extends far beyond the normal range of EPO levels on healthy, non-anemic individuals. Abnormalities of other laboratory parameters should be investigated, such as a low MCV or MCHC (may indicate an underlying hemoglobinopathy), a high MCV (may indicate vitamin B12 or folic acid deficiency), or an abnormal leukocyte or platelet count (may suggest a primary bone marrow problem, such as myeloma or myelodysplastic syndrome).

3. Clinical manifestations

Due to the fact that anemia reduces tissue oxygenation, it is associated with widespread organ dysfunction and hence an extremely varied clinical picture. In mild anemia there may be no symptoms or simply increased fatigue and a slight pallor. As anemia becomes more marked the symptoms and signs gradually appear. Pallor is best discerned in the mucous

membranes; the nailbeds and palmar creases, although often said to be useful sites for detecting anemia, are relatively insensitive for this purpose. Cardiorespiratory symptoms and signs include dyspnea, tachycardia, palpitations, angina or claudication, night cramps, increased arterial pulsation, capillary pulsation, a variety of cardiac bruits, reversible cardiac enlargement. Neuromuscular involvement is reflected by headache, vertigo, light-headedness, faintness, tinnitus, roaring in the ears, cramps, increased cold sensitivity. Acute anemia may occasionally give rise to papilledema. Gastrointestinal symptoms include loss of appetite, nausea, constipation, and diarrhea. Genitourinary involvement causes menstrual irregularities, urinary frequency, and loss of libido. There may also be a low-grade fever. In the elderly, to whom associated degenerative arterial disease is common, anemia may be manifested with the onset of cardiac failure. Alternatively, previously undiagnosed coronary narrowing may be unmasked by the onset of angina [56].

In the early clinical trials of EPO performed in the late 1980s, the mean baseline Hb concentration was about 6 to 7 g/dl, and this progressively increased to about 11 or 12g/dl after treatment. Patients subjectively felt much better, with reduced fatigue, increased energy levels, and enhanced physical capacity, and there were also objective improvements in cardiorespiratory function [57]. Thus, it is now clear that many of the symptoms previously attributed to the "uremic syndrome" are indeed due to the anemia associated with CKD. Although the avoidance of blood transfusions and improvement in quality of life are obvious early changes, there are also possible effects on the cardiovascular system. The physiologic consequences of long-standing anemia are an increase in cardiac output and a reduction in peripheral vascular resistance. Anemia is a risk factor for the development of left ventricular hypertrophy in CKD patients and exacerbate left ventricular dilation. Sustained correction of anemia in CKD patients results in a reversal of most of these cardiovascular abnormalities, with the notable exception of left ventricular dilation. Once the left ventricle is stretched beyond the limits of its elasticity, correction of anemia cannot reverse this [58]. It may, however, prevent the development of LV dilation, and this leads to improved quality of life [59]. Anemia correction may improve QoL, [60, 61] cognitive function, sleep patterns, nutrition, sexual function, menstrual regularity, immune responsiveness, and platelet function [62-66].

4. Therapeutic approach

As mentioned above, renal anemia is a multifactor process and its treatment has to focus on a step by step correction of all factors which are involved in this process [67]. First of all, iron deficiency has to be treated before adding more expensive therapies such as EPO therapy.

4.1. Iron deficiency

Iron is an essential ingredient for heme synthesis, and adequate amounts of this mineral are required for the manufacture of new red cells. Thus, under enhanced erythropoietic stimulation, greater amounts of iron are used, and many CKD patients have inadequate amounts of available iron to satisfy the increased demands of the bone marrow [68]. Patients with CKD,

on HD treatments, may lose up to 3gr of iron each year because of frequent blood losses, so they are at particularly high risk of iron store depletion with subsequent iron deficiency anemia [17]. Even before the introduction of ESA therapy, many CKD patients were in negative iron balance as a result of poor dietary intake, poor appetite, and increased iron losses due to occult and overt blood losses. Losses on HD patients are up to 5 or 6 mg a day, compared with 1 mg on healthy individuals, and this may exceed the absorption capacity of the gastrointestinal tract, particularly when there is any underlying inflammation. Iron deficiency can be defined as absolute or functional [17, 68, 69]. Absolute iron deficiency develops as the body's iron stores become depleted to such a low level that not enough iron is available for the production of Hb [70, 71]. This is usually indicated by a decline in serum ferritin levels to ~<15 μg/l in patients with normal kidney function, [70, 71] or <12 ng/mL [72] according to other studies and TSAT levels below 16% [73]. Absolute iron deficiency in CKD patients has been defined as serum ferritin levels <100 ng/mL and TSAT levels <20%. The functional iron deficiency describes the state when iron cannot be mobilized from stores (despite an adequate dietary supply) to meet the demand for erythropoiesis [70]. Serum ferritin levels can appear normal (200–500 μg/l) or increased in chronic inflammatory disorders, [70] while levels of transferrin saturation (TSAT), which is serum iron divided by total iron-binding capacity, [68] will be low (typically <20%), indicating limited transport of iron to the erythron for erythropoiesis [70, 74, 75] and increased hypochromic red cells (>10%). The distinction between absolute and functional iron deficiency is crucial to understanding what constitutes adequate TSAT and serum ferritin levels on Epoetin-treated patients. The iron deficit limits the effectiveness of EPO therapy, and, to optimize the treatment, patients must receive an oral or intravenous (IV) iron supplement [76-78]. Thus, higher doses of ESAs may worsen iron depletion and lead to an increased platelet count (thrombocytosis), ESA hyporesponsiveness, and hemoglobin variability. Hence, ESA therapy requires concurrent iron supplementation [17, 79]. On the other hand, serum ferritin <200 ng/mL suggests iron deficiency in CKD patients, ferritin levels between 200 and 1,200 ng/mL may be related to inflammation, latent infections, malignancies, or liver disease. In part, this is due to the fact that, in addition to reflecting body iron stores, serum ferritin is also an acute phase reactant. As such, it can increase in the setting of either acute or chronic inflammation. Available data demonstrate that the lower the TSAT and the serum ferritin, the higher the likelihood that a patient is iron deficient, and the higher the TSAT and the serum ferritin, the lower the likelihood that a patient is iron deficient [77, 80]. A serum ferritin concentration of 100-500 ng/mL is the target during oral and intravenous (i.v.) iron therapy for pre-dialysis and peritoneal dialysis patients, but use of the i.v. route of administration and a target serum ferritin concentration of 200-500 ng/mL is recommended for HD patients by NKF [81]. Due to the fact that parenteral iron administration has potential risks that are immediate (eg, toxic effects and anaphylactic reactions) and long-term (e.g., decreased polymorphonuclear leukocyte function, increased risk of infections, organ damage), it is essential to select patients who need iron supplementation. Although oral iron administration is the primary treatment for iron deficiency, it has also disadvantages, such as poor iron absorption and adverse gastrointestinal reactions, which often lead to poor compliance. Oral iron is ineffective in many CKD patients, and parenteral iron administration is required, particularly on those receiving hemo-

dialysis [68]. Nevertheless, even with these limitations of oral iron absorption, the cheap costs of using this route, along with convenience for the patient, often persuade physicians to try oral iron supplementation first on non-dialysis patients; if, however, there is insufficient response after 2 to 3 months, intravenous iron should be administered. However, the use of IV iron reduces the risk of adverse gastrointestinal reactions and overcomes the problem of poor compliance with oral therapy [82, 83]. Another advantage of the i.v. route is that the iron will not be eliminated by first-pass effects or by high efficiency dialysis membranes and the iron can be quickly released into the reticuloendothelial system and used for erythropoiesis, thus increasing its bioavailability. Intravenous iron administration may not only decrease hemoglobin variability and ESA hyporesponsiveness, it may also reduce the greater mortality associated with the much higher ESA doses that have been used in some patients when targeting higher hemoglobin levels [84]. Other, longer term concerns about intravenous administration of iron include the potential for increased susceptibility to infections and oxidative stress. Much of the scientific evidence for this has been generated in *in vitro* experiments, the clinical significance of which is unclear. There is emerging evidence that intravenous iron may improve the anemia of CKD in up to 30% of patients not receiving ESA therapy and have a low ferritin level [85]. Abnormalities of iron metabolism and anemia in chronic renal failure seem to correlate with levels of serum Hepcidin [86]. Hepcidin is a recently discovered protein of expeditious action produced in the liver and that may play an important role in iron homeostasis [87-89]. Hepcidin limits the absorption of iron from the intestine and iron release from macrophages and hepatocytes [90]. Iron absorption capacity in patients with CKD is considerably lower than in non-uremic individuals, particularly in the presence of systemic inflammatory activity, and this is probably mediated by Hepcidin up-regulation [91, 92]. The data in CKD and particularly in ESRD is limited both in hemodialysis and in peritoneal dialysis [93]. Because of its excretion in the urine [94, 95] and regulation by the presence or absence of inflammation, it is likely that its metabolism is affected by renal function and consistently influences the absorption of iron from the intestine and the stores of iron [96-99]. Originally due to the inability to measure serum levels of Hepcidin, its role in chronic kidney disease had not been adequately studied and most studies involved hepcidin's levels in urine. It has been attempted to measure prohepcidin a precursor peptide of Hepcidin in CKD patients [100, 101]. According to our recently unpublished data Hepcidin levels were increased in hemodialysis patients in relation to normal individuals. The U.S. [16] and European [17] guidelines on renal anemia management suggest that the ferritin level be maintained in the range of 200 to500 μg/l, with an upper limit of 800 μg/l. Levels of ferritin above this threshold usually do not confer any clinical advantage and may exacerbate iron toxicity. The optimal transferring saturation is above 20% to 30% to ensure a readily available supply of iron to the bone marrow. Several studies support the maintenance of the percentage of hypochromic red cells at levels of less than 6%. Other measures of iron status, such as serum transferring receptor levels [102] and erythrocyte zinc protoporphyrin levels, are mainly research tools and have not been established in routine clinical practice. Intramuscular administration of iron is not recommended in CKD, given the enhanced bleeding tendency, the pain of the injection, and the potential for brownish discoloration of the skin. Thus, intravenous administration of iron has become the

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standard of care for many CKD patients, particularly those receiving hemodialysis [17, 68, 69, 103]. An important advantage of i.v. iron over oral iron is that it may bypass hepcidin actions by directly loading transferrin and making iron available to macrophages. Despite a reduction in the short-term risks, there is still concern about the potential for long-term toxicity of i.v. iron use (e. g. atherosclerosis development, infection and increased mortality) [104, 105] .The association of atherosclerosis with iron overload remains unclear. Alternatively, the relative risk for mortality or hospitalization from infection in patients undergoing HD and receiving i.v. iron was shown not to be higher than that observed in the overall HD population. Indeed, doses of i.v. iron up to 400 mg/month were associated with improved patient survival. There are several intravenous iron preparations available worldwide, including iron dextran, iron sucrose, and iron gluconate and Ferric carboxymaltose (table 1).

AVAILABLE IRON PREPARATIONS	IVMAXIMUM DOSE	ADMINISTRATION	TEST DOSE
Dextran Iron*	1000mg	0.0442 (Desired Hb - Observed Hb) x LBW + (0.26 x Lean body weight in kg) (For males: LBW = 50 kg + 2.3 kg for each inch of patient's height over 5 feetFor females: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet.)	A test dose of 25 mg diluted in 50 ml normal saline and infused over 5 minutes should be given. Infusion should then be stopped for 1 hour. If there is no reaction after 1 hour continue.
Gluconate Iron*	125mg	The recommended dosage of Sodium Ferric Gluconate for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron). Ferrlecit may be diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour per dialysis session	No test
Iron Sucrose*	500mg	Administer Venofer 100 mg undiluted as a slow injection over 2 to 5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes, per consecutive session. Venofer should be administered early during the dialysis session.	No test dose

AVAILABLE IRON PREPARATIONS	IVMAXIMUM DOSE	ADMINISTRATION	TEST DOSE
Ferric Carboxymaltose**	A cumulative iron dose of 500 mg should not be exceeded for patients with body weight < 35 kg. A single dose of Ferinject should not exceed 1000 mg of iron (20 ml) per day. Do not administer 1000 mg of iron (20 ml) more than once a week.	1000 mg of iron during a minimum administration time of </=15 minutes.	No test dose

Table 1. Avalaible i.v. iron preparations. *: www.globalrph.com - **: www.medicines.org.uk

All of these preparations contain elemental iron surrounded by a carbohydrate shell, which allows them to be injected intravenously. The liability of iron release from these preparations varies, with iron dextran being the most stable, followed by iron sucrose and then iron gluconate. Iron is released from these compounds to plasma transferrin and other iron-binding proteins and is eventually taken up by the reticulo-endothelial system. In hemodialysis patients, it is easy and practical to give low doses of intravenous iron (e.g., 10 to 20 mg every dialysis session) or, alternatively, 100 mg weekly. The more stable the iron preparation, the larger the dose administration rate that can be used. For example, 1gr of iron dextran may be given by intravenous infusion, whereas the maximum recommended dose of iron sucrose at any one time is 500 mg. For iron gluconate, doses in excess of 125 to 250 mg are best avoided. A 100 mg dose of iron sucrose is administered at 10 consecutive HD sessions. If after the end of the first 10-dose cycle patients remain iron deficient they complete another 10-dose cycle. If TSAT is 20-50% and SF 100-800 ng/mL, the patients start the maintenance regimen. If TSAT>50% or SF> 800 ng/mL then no further iron supplementation was deemed necessary. Iron replete patients received the iron maintenance regimen, consisting of 10 one weekly doses of up to 100 mg iron sucrose over 5 minutes. Iron repletion is defined as TSAT

20-50% and SF 100-800 ng/mL [106, 107]. Iron sucrose appears to offer the most favorable safety profile when compared to iron dextran and sodium ferric gluconate in treating hemodialysis patients. Oxidative stress and hypersensitivity reactions are common problems encountered when administering intravenous iron [108]. Therapy with dextran-free iron formulations is an essential part of anemia treatment protocols, and was not found to be associated with either short- or long-term serious side-effects [109]. Results suggest that 200 mg/FeIV/month is effective and that, of the markers tested, TSAT would be the most suitable one to the practicing nephrologist so as to optimize intravenous iron in the long run [110]. Sodium ferric gluconate is well tolerated when given by intravenous push without a test dose [111]. SFGC has a significantly lower incidence of drug intolerance and life-threatening events as compared to previous studies using iron dextran. The routine use of iron dextran in hemodialysis patients should be discontinued [112]. Nevertheless, older i.v. iron formulations have their limitations, including the potential for immunogenic reactions induced by dextran molecules (iron dextran) [113], dose limitations, a slow rate of administration (to prevent acute, labile iron-induced toxicity and vasoactive reactions) [70, 113] and the compulsory requirement for a test dose (iron dextrans in USA [114] and Europe. All-event reporting rates were 29.2, 10.5 and 4.2 reports per million 100 mg iron dose equivalents, while all-fatal-event reporting rates were 1.4, 0.6 and 0.0 reports per million 100 mg dose equivalents for iron dextran, sodium ferric gluconate and iron sucrose, respectively [115]. Recently, two new iron preparations have become available for intravenous use (ferumoxytol in the United States and ferric carboxymaltose in Europe) [116]. Both of these compounds allow higher doses of intravenous iron to be administered rapidly as a bolus injection, without the need for a test dose. Ferric carboxymaltose [FCM; FerinjectR; Vifor (International) Inc., St Gallen, Switzerland] is a next-generation parenteral, dextran-free iron formulation designed to overcome the limitations of existing i.v. iron preparations. The FCM is a macromolecular ferric hydroxide carbohydrate complex, composed of a poly-nuclear iron(III) hydroxide complexed to carboxymaltose [117]. As FCM is a strong and robust iron complex, and it can be administered in high doses, it does not release large amounts of reactive ('free') iron into the circulation and does not trigger dextran- associated immunogenic reactions [111, 117-119]. All intravenous iron preparations carry a risk for immediate reactions, which may be characterized by hypotension, dizziness, and nausea. These reactions are usually short-lived and caused by too large a dose given during too short a time. Iron dextran also carries the risk for acute anaphylactic reactions due to preformed dextran antibodies, and although this risk may be less with the lower molecular weight iron dextrans, the potential for anaphylaxis still remains. In such patients, a response to intravenous iron alone may occur within 2 to 3 weeks of iron administration. In those already receiving ESAs, there is considerable evidence that concomitant intravenous iron may enhance the response to the ESAs and result in lower dose requirements [17, 21, 68]. Ferric carboxymaltose also replenishes depleted iron stores and improves health-related quality-of-life (HR-QoL) on patients with iron-deficiency anemia. FCM is at least as effective as iron sucrose and as ferrus sulfate with regards to end point relative to serum ferritin, transferrin saturation and HR-QoL. Commonly reported drug-related adverse events include headache, dizziness, nausea, abdominal pain, constipation, diarrhea, rash and injection-site reactions. The incidence of drug-

related adverse events on patients receiving intravenous FCM was generally similar to that in patients receiving oral ferrous sulfate. In general, rash and local injection-site reactions were more common with ferric carboxymaltose, whereas gastrointestinal adverse events were more frequent with ferrous sulfate [120]. Based on the No-Observed-Adverse-Effect-Levels (NOAELs) found in repeated-dose toxicity studies and on the cumulative doses administered, FCM has good safety margins. Lastly, no evidence of irritation was found in local tolerance studies with FCM [70]. Ferric carboxymaltose may represent a cost-saving option compared with the most likely alternative existing therapies used for the management of anemia [121, 122].

4.2. Correction of vitamin B and Acid Folic

Vitamin abnormalities in patients with CKD are frequent and appear early even with mild renal failure; fat-soluble vitamin supplements (A and E) should be avoided and their dietary intake limited [123]. Deficiency and/or altered metabolism of vitamins in ESRD is caused by uremic toxins, dietary restrictions, catabolic illness, losses during dialysis and drug interaction. In patients with polyneuropathy high doses of thiamine pyrophosphate (Cocarboxylase), given i.v., can be helpful in this respect. There are conflicting reports concerning plasma level of vitamin B2 (riboflavin) in ESRD patients. Some authors recommend its supplementation. The majority of patients with ESRD exhibit biochemical and clinical signs of vitamin B6 deficiency. A univocal opinion exists that supplementation of this vitamin effects the cellular immune system and the amino acid metabolism as well. An adequate dose of vitamin B6 is still a matter of dispute. Evidence of vitamin B12 deficiency has been reported rarely, thus, only few authors recommend the supplementation of it, mainly in CAPD patients. According to most authors the losses of folic acid and ascorbic acid during dialysis require oral supplementation. Despite the divergences in opinions concerning the deficiency of water-soluble vitamins in ESRD patients, the supplementation of these vitamins is practiced in many nephrological centers. The amount and the route of vitamins, administered to ESRD patients, should be individualized [124-126]. In ESRD patients under maintenance hemodialysis, oral L-carnitine supplementation may reduce triglyceride and cholesterol and increase HDL and hemoglobin and subsequently reduce needed erythropoietin dose without effect on QoL [127]. Adjuvant therapy includes: iron, vitamin C and D, L-carnitine, folic acid, cytokines and growth factors. Vitamin C (500 mg, after every hemodialysis) is very helpful in cases of functional iron deficiency. L-carnitine stabilizes the membrane of erythrocytes and prolongs their lives. Folic acid (10 mg/day) enhances response to EPO [128]. According to other authors supplementations of pyridoxine in the dose of 20 mg/day and of folic acid 5 mg/week in hemodialyzed patients during erythropoietin treatment are necessary [129].

4.3. Erythropoiesis Stimulating Agents

Erythropoiesis is a complex physiologic process through which homeostasis of oxygen levels in the body is maintained. It is primarily regulated by EPO, a 30-kD, 165–amino acid

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hematopoietic growth factor that is produced primarily by renal tubular and interstitial cells. Under normal conditions, endogenous EPO levels change according to O2 tension. EPO gene expression is induced by hypoxia-inducible transcription factors (HIF) [130]. In the presence of EPO, bone marrow erythroid precursor cells proliferate and differentiate into red blood cells. In its absence, these cells undergo apoptosis [131]. Endogenous EPO and rHuEPO share the same amino acid sequence, with slight but functionally important differences in the sugar profile. In clinical practice, rHuEPO is typically administered as a bolus injection, and the dosage is titrated to give the desired effect [131]. There is no significant difference between once weekly versus thrice weekly subcutaneous administration of rHu EPO. Once weekly administration of rHu EPO would require an additional 12U/kg/week for patients on hemodialysis [132].

Recombinant human erythropoietin has been used for more than 20 years for the treatment of renal anemia, revolutionizing its treatment in patients with CKD when it was approved for use in the United States in 1989, [133, 134] with epoetin-alfa and -beta representing the common traditional preparations. By the modification of the molecule's carbohydrate moiety or structure a longer duration of erythropoietin receptor stimulation was achieved. The administration of darbepoetin or C.E.R.A. once or twice a month is also sufficient to achieve serum hemoglobin target levels, [135] making the treatment safer and more comfortable both for the patients and the personnel. These synthetic erythropoietin receptor stimulating molecules, along with recombinant human erythropoietin, are together called "Erythropoiesis Stimulating Agents". The recombinant human erythropoietins and allied proteins (epoetin-alfa, attempted copies and biosimilar variants of epoetin-alfa, epoetin beta, epoetin delta, epoetin zeta, epoetin theta, epoetin omega, darbepoetin-alfa, and methoxy-polyethylene glycol-epoetin beta) are among the most successful and earliest examples of biotechnologically manufactured products to be used in clinical medicine (Table 2) [136].

AVALAIBLE ESAs	DOSE REGIMEN
Prototype	
epoetin-alfa*	Correction phase: 50 IU/kg, 3 times per week. When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg, 3 times per week. Maintenance phase: Dosage adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2 - 7.5 mmol/l). The recommended total weekly dose is between 75 and 300 IU/kg.
epoetin beta*	1. Correction phase - Subcutaneous administration: - The initial dosage is 3 x 20 IU/kg body weight per week. The dosage may be increased every 4 weeks by 3 x 20 IU/kg and week if the increase of Hb is not adequate (< 0.25 g/dl per week).

AVALAIBLE ESAs	DOSE REGIMEN
	- The weekly dose can also be divided into daily doses. - Intravenous administration: The initial dosage is 3 x 40 IU/kg per week. The dosage may be raised after 4 weeks to 80 IU/kg three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals. For both routes of administration, the maximum dose should not exceed 720 IU/kg per week. 2. Maintenance phase To maintain an Hb of between 10 and 12 g/dl, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of one or two weeks individually for the patient (maintenance dose).
darbepoetin-alfa*	Correction phase: The initial dose by subcutaneous or intravenous administration is 0.45 µg/kg body weight, as a single injection once weekly. If the rise in haemoglobin is greater than 2 g/dl (1.25 mmol/l) in four weeks reduce the dose by approximately 25%.Dosing should be titrated as necessary to maintain the haemoglobin target. If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%
Methoxy-polyethylene glycol-epoetin beta*	a starting dose of 0.6 microgram/kg bodyweight may be administered once every two weeks as a single intravenous or subcutaneous injection in patients on dialysis or not on dialysis. The dose may be increased by approximately 25% of the previous dose if the rate of rise in haemoglobin is less than 1.0 g/dl (0.621 mmol/l) over a month. Further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin level is obtained.
Biosimilar	
epoetin zeta*	1. Correction phase: 50 IU/kg 3 times per week. When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg 3 times per week. 2. Maintenance phase: Dose adjustment in order to maintain haemoglobin (Hb) values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). The recommended total weekly dose is between 75 and 300 IU/kg.
epoetin delta**	For Epoetin delta it is recommended to adjust the dose individually to maintain the target haemoglobin in the range 10 to 12 g/dl. A starting dose is recommended of 50 IU/kg three times a week if given intravenously or twice a week if given subcutaneously

AVALAIBLE ESAs	DOSE REGIMEN
epoetin omega***	Starting with 20 to 50 IU / kg three times a week, with a gradual increase in dose or frequency of issuance before the impact. Beyond hemoglobin levels to 12 g / m and Hematocrit-35 %. Dose reduction or no treatment. If there Effect dose increase to 40 to 55 IU / kg three times a week for two weeks, if necessary, until 60-75 IU / kg The course continues until the level Hematocrit (35 vol. %) And hemoglobin (12 g / m); Total weekly dose should not exceed 225 IU / kg supporting-60 IU / kg per week for 2-3 reception
epoetin theta**	Correction phase Subcutaneous administration: The initial posology is 20 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 40 IU/kg, 3 times per week, if the increase in haemoglobin is not adequate (< 1 g/dl [0.62 mmol/l] within 4 weeks). Further increases of 25% of the previous dose may be made at monthly intervals until the individual target haemoglobin level is obtained. Intravenous administration: The initial posology is 40 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 80 IU/kg, 3 times per week, and by further increases of 25% of the previous dose at monthly intervals, if needed. For both routes of administration, the maximum dose should not exceed 700 IU/kg body weight per week. Maintenance phase The dose should be adjusted as necessary to maintain the individual target haemoglobin level between 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l), whereby a haemoglobin level of 12 g/dl (7.45 mmol/l) should not be exceeded. If a dose adjustment is required to maintain the desired haemoglobin level, it is recommended that the dose be adjusted by approximately 25%. Subcutaneous administration: The weekly dose can be given as one injection per week or three times per week. Intravenous administration: Patients who are stable on a three times weekly dosing regimen may be switched to twice-weekly administration. If the frequency of administration is changed, haemoglobin level should be monitored closely and dose adjustments may be necessary. The maximum dose should not exceed 700 IU/kg body weight per week

Table 2. Available ESAs worldwide. *: ww.medicines.org.uk, **: www.ema.europa.eu, ***: www.pharmabook.net

In hemodialysed patients the intravenous route is preferred, but the subcutaneous administration can substantially reduce dose requirements [137-139]. However, there are studies according to which conversion from SC to IV epoetin administration did not result in changes in Hb levels or epoetin dosage requirements in iron-replete hemodialysis pa-

tients, [140] but it seems that SC route of administration was associated with modestly higher hemoglobin variability [138].

There are ongoing clinical trials with erythropoiesis stimulating molecules that can be administered by inhalation or per os [137]. It is also known from other studies that some comorbidities like antecedents of malignant neoplasm are associated with EPO responsiveness [141]. In a pre-dialysis population, female gender, cardiovascular disease, malnutrition and inflammation are associated with ESA hyporesponsiveness [142]. EPO resistance in a pediatric dialysis cohort was predicted by nutritional deficits, inflammation, poor dialysis, and hyperparathyroidism, while iron and folic acid deficits were the major determinants in adults. Although confounded by the pattern of EPO prescription, neither age nor gender was predictive of EPO resistance in the two study groups [143]. Additionally delivered dialysis (Kt/ V(urea)) does not seem to be a significant predictor of erythropoietin responsiveness [144]. It also seems that there is difference in EPO hyporesponsiveness prevalence among different countries and different modalities [145]. The proportion of age has a limited influence on the level of anemia in pre-dialysis patients and is similar in both genders [146] There are, although, studies according to which there is higher proportion of anemia in female patients [147]. In a multicenter study with 8154 dialysis patients, females, blacks, patients between 18 and44 years old on hemodialysis less than six months exhibited significantly lower mean hemoglobin values despite being prescribed, on average, significantly higher epoetin alfa doses than males, whites and older patients, on hemodialysis more than six months. A significant regional variation in the prescribing patterns for s.c. epoetin alfa and i.v. iron has been described in this study [148]. Comparisons between patients from western and from eastern/central Europe show that patients from eastern/central Europe are less likely to receive epoetin treatment before starting dialysis, and have lower Hb concentrations at the start of epoetin treatment as well as at the start of dialysis [149]. In another multicenter study by Nissenson et al. there were wide variations in hemoglobin response rate among patients on hemodialysis, hemofiltration and hemodiafiltration [150].

Other factors such as cytokines like IL6 are induced by malignant tumors and may impair erythropoiesis. Also, TNF-α is known to inhibit this pathway [151]. Low ESA responsiveness was associated with higher mortality in both HD and PD patients [152]. In patients with persistently low Hb levels, mortality risk is strongly associated with the patient's ability to achieve a hematopoietic response rather than the magnitude of EPO dose titrations [153]. ESA dosing may be directly associated with risk of death, but the nature of the association likely varies according to hemoglobin concentration. Small doses with hemoglobin ≤12 g/dl and large doses with hemoglobin ≥10 g/dl may both be associated with poor outcomes [154].

Serum albumin concentration is an important predictor of both baseline Hb and EPO sensitivity in chronic hemodialysis patients. Factors that improve serum albumin may also improve Hb in hemodialysis patients [155]. Hyperleptinemia reflects better nutritional status and rHuEPO response in long-term HD patients. Increasing energy intake improves erythropoiesis, which may be mediated in part by an increase in serum leptin levels [156, 157]. Statin therapy may improve responsiveness to erythropoietin-stimulating agents in patients with end-stage renal disease, increasing erythropoiesis by targeting hepcidin and iron regu-

latory pathways, independent of erythropoietin [158, 159]. The initial and sustained erythropoietic responses are independent from each other and are associated with different factors. Treatment focusing on these factors may improve the response [160]. A pleiotropic effect of EPO has been shown in the kidney, the central nervous system, and the cardiovascular system, [161] such as significant slowing of progression and substantial retardation of maintenance dialysis [162, 163].

Although ESA use in patients with chronic kidney disease or/and on dialysis were studied extensively, the optimal target hemoglobin concentration as well as the required ESA dose and dosing interval to achieve this concentrations remain elusive (NHS, CREATE, CHOIR and TREAT) [164-167]. Hb can be increased with erythropoiesis-stimulating proteins (ESPs); however, 5-10% of patients respond poorly. The patient incidence of hyporesponse seems to be around 14%, and a mean 9% of patients is hyporesponsive at any given time. The most common potential causes of hyporesponse is iron deficiency (being reported in 39% of hyporesponse events), medication (immunosuppressive agents, ACE inhibitors), secondary hyperparathyroidism [168] and inflammation/malnutrition [169]. The safety profile of epoetin-alfa and darbepoetin-alfa are similar, but the longer half-life of darbepoetin-alfa permits administration on a once a week or once-monthly basis in patients with CKD and anemia. Extended dosing of CERA also appears safe and effective on dialysis patients with CKD [81].

Epoetin alfa: is a recombinant form of erythropoietin, a glycoprotein hormone which stimulates red blood cell production by stimulating the activity of erythroid progenitor cells. Intravenous and subcutaneous therapy with epoetin alfa raises hematocrit and hemoglobin levels, and reduces transfusion requirements, in anemic patients with end-stage renal failure undergoing hemodialysis. The drug is also effective in the correction of anemia on patients with chronic renal failure not yet requiring dialysis and does not appear to affect renal hemodynamics adversely or to precipitate the onset of end-stage renal failure. Epoetin alfa does not appear to exert any direct cerebrovascular adverse effects [170]. Administration of epoetin alfa at once weekly and fortnightly intervals are potential alternatives to three times per week dosing for the treatment of anemia [171-173].

Epoetin beta: is a recombinant form of erythropoietin. The drug binds to and activates receptors on erythroid progenitor cells which then develop into mature erythrocytes. Epoetin beta increases reticulocyte counts, hemoglobin levels and hematocrit in a dose-proportional manner. Increases of 15 to 54% in hemoglobin levels and 17 to 60% in hematocrit were reported after subcutaneous or intravenous epoetin beta therapy in studies of 8 weeks' to 12 months' duration. Comparative data indicate that dosage reductions of approximately 30% compared with intravenous therapy are possible when subcutaneous administration of epoetin beta is used. Hematocrit increased more rapidly in 5 multicenter studies on patients who received epoetin beta subcutaneously than on those who received the same dosage intravenously. It also causes significant improvements on quality of life, exercise capacity and overall well-being. Results of clinical studies indicate that subcutaneous administration is desirable where possible in the majority of patients [174].

Darboepoetin-alfa: It is a hyperglycosylated analog of recombinant human erythropoietin with the same mechanism of action as erythropoietin, but with a three-fold longer terminal

half-life after intravenous administration than recombinant human erythropoietin and the native hormone both in animal models and in humans. It is administered less frequently (once weekly or every other week) [175, 176]. The recommended starting dose in chronic renal failure patients is 0.45mcg/kg once weekly for both intravenous and subcutaneous administration, with subsequent titration based on the hemoglobin concentration. The adverse event profile of darbepoetin-alfa is similar to that of recombinant human erythropoietin in both settings, [177, 178] and effectively maintains hemoglobin in the target range in dialysis patients with renal anemia [179]. It also has been shown to be effective when administered once/week and once every 2, 3, or 4 weeks [180]. There are no reports of antibody formation associated with darbepoetin-alfa on chronic renal failure patients, and three cases of antibody formation, with neutralizing activity in one of the cases, reported on cancer patients [181-184].

Cera: Methoxy polyethylene glycol-epoetin beta (MPG-EPO; Mircera®, Roche, Basel, witzerland) is an agent that has a different interaction with the erythropoietin receptor than previous agents and has a long elimination half-life (approximately 130 hours) [185]. MPG-EPO is the only ESA generated by chemical modification of glycosylated erythropoietin, by the integration of one specific, long, linear chain of polyethylene glycol. The resultant molecule has a molecular weight of approximately 60 kDa, which is twice that of epoetin. The methoxy polyethylene glycol polymer chain is integrated through amide bonds between the N-terminal amino group or the ε-amino group (predominantly lysine-52 or lysine-45) with a single butanoic acid linker [186]. In ESA-naïve patients, the recommended starting dose is 0.6 μg/kg administered once every 2 weeks as a subcutaneous or intravenous injection, in order to reach a hemoglobin level of.11 g/dL. The dose may be increased by approximately 25% if hemoglobin levels increase by, 1.0 g/dL over a month. Further increases of approximately 25% may be made once per month until the individual target hemoglobin level is reached. If a hemoglobin level of.11 g/dL is reached for an individual patient, MPG-EPO may be continued once per month using a dose equal to twice the previous dose once every 2 weeks. Patients currently being treated with ESA can be directly converted to MPG-EPO administered once per month as a single intravenous or subcutaneous injection. The starting dose of this agent is based on the calculated weekly equivalent dose of DA or epoetin at the time of conversion [187]. The first injection of MPG-EPO should start at the next scheduled dose of the previously administered DA or epoetin dose. On patients receiving treatment with ESA and those naïve to ESA, the MPG-EPO dose should be reduced by approximately 25% if the hemoglobin level increases by more than 2 g/dL in 1 month or if the hemoglobin level approaches 12 g/dL. If hemoglobin levels continue to increase, MPG-EPO administration should be interrupted until these levels begin to decrease (a decrease of approximately 0.35 g/dL per week is expected). Therapy should then be resumed at a dose approximately 25% less than the previously administered dose. Dose adjustments should not be made more frequently than once per month [17, 188]. Once-monthly CERA therapy maintains stable Hb values with low intra-individual variability and few dose adaptations in hemodialysis patients when administered entirely according to local practice, and the regimen is well-tolerated [189]. C.E.R.A. can be administered to patients at any time during hemodialysis or hemofiltration without appreciable loss in the extracorporeal circuit [190].

Peginesatide (formerly known as Hematide™): is a synthetic, peptide-based erythropoiesis-stimulating agent linked to polyethylene glycol. Based on extensive preclinical and clinical data substantiating the efficacy and safety of this agent, it was approved in the U.S. in March 2012 for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. Peginesatide (Omontys®) was launched in the U.S. in April 2012 [191, 192]. A drug capable of stimulating erythropoiesis is the first ESA that bears no structural similarity to rhuEPO. Peginesatide is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). Peginesatide binds to and activates the human EPO receptor, stimulating the proliferation and differentiation of human red cell precursors in vitro in a manner similar to ESAs [193]. Peginesatide administered once monthly was as effective as epoetin alfa given thrice weekly (dialysis patients) or darbepoetin given once weekly (nondialysis patients), in correcting anemia of chronic kidney disease as well as maintaining hemoglobin within the desired target range [194-196].

4.4. Biosimilar

Epoetin zeta: Epoetin zeta is therapeutically equivalent to epoetin alfa in the maintenance of target Hb levels on patients with renal anemia. No unexpected adverse effects were seen [197-201].

Epoetin theta: Has efficacy comparable with epoetin beta (s.c.) in pre-dialysis patients with renal anemia based on Hb changes from baseline to end of treatment (non-inferiority). The safety profile was also comparable. Patients could be switched from maintenance treatment with epoetin beta to epoetin theta without relevant dose changes [202].

Epoetin omega: Epoetin-omega is a sialoglycoprotein with smaller amounts of O-bound sugars, less acidic and with different hydrophylity than the other 2 epoetins. The initial weekly dose of epoetin-omega was 90 units per kg of body weight (b.w.) divided in 3 equal portions and administered subcutaneously after each dialysis session. After correction of the hemoglobin, the dose of rHuEPO was individualized to keep Hb within target limits of 100-120 g/l. The mean dose of epoetin-omega during the correction period never exceeded 100 U/kg b.w. per week and the average maintenance dose between 50-60 U/kg b.w. per week [203, 204].

HX575: Is a biosimilar version of epoetin-α that is approved for the treatment of anemia associated with chronic kidney disease (CKD) using the intravenous route of administration [205, 206]. In a study for S.C. use two patients developed neutralizing antibodies (NAbs) to erythropoietin, which resulted in the study being terminated prematurely [207].

4.5. Adverse effects of EPO therapy

Adverse effects of EPO therapy are uncommon, apart from a moderate increase in blood pressure and an increased rate of vascular access thrombosis. In spite of the fact that, these effects are probably dependent to a large degree on the increase in Hb concentrations, there are some concerns that ESA therapy may enhance thrombogenicity and tumor growth on patients with malignant disease as well as exacerbate vascular events in CKD independently of Hb concentrations [208]. In treatment with epoetin alfa hypertension occurs in 30 to 35% of patients with

end-stage renal failure, but this can be managed successfully with correction of fluid status and antihypertensive medication where necessary, and is minimized by avoiding rapid increases in hematocrit. Although vascular access thrombosis has not been conclusively linked to therapy with the drug, increased heparinisation may be required when it is administered to patients on hemodialysis [170]. On patients who receive epoetin beta, hypertension may occur but may be minimized by avoiding rapid increases in hematocrit (> 0.5%/week), and is managed in most cases with control of fluid status and antihypertensive medication. Although clotting of the vascular access has not been conclusively linked to epoetin beta, caution is recommended on patients undergoing hemodialysis. Increased heparinisation is recommended to prevent clotting in dialysis equipment [174]. Before 1998, EPO alfa in Europe was formulated with human serum albumin, but because of a change in European regulations, this was replaced with polysorbate 80. EPO beta is formulated with polysorbate 20, along with urea, calcium chloride, and five amino acids as excipients. The importance of the formulation of the EPO products was highlighted in 2002 with an upsurge in cases of antibody-mediated pure red cell aplasia in association with the subcutaneous use of EPO alfa after its change for indicate mulation. Patients affected by this complication develop neutralizing antibodies against both rhuEPO and the endogenous hormone, which result in severe anemia and transfusion dependence [209, 210]. The cause of this serious complication in which there is a break in B-cell tolerance remains obscure, although it seems likely that factors such as a breach of the cold storage chain were relevant, and the subcutaneous application route was a prerequisite; circumstantial evidence also suggested that rubber stoppers of prefilled syringes used in one of the albumin-free EPO alfa formulations may have released organic compounds that acted as immunologic adjuvants [211].

4.6. Which target is the best for the correction of anemia on hemodialysis patients?

There has been considerable debate in recent times about the optimal target range of Hb in CKD patients [133]. The improvement in quality of life with increasing Hb concentrations supports a level above 10 to 11 g/dl in all CKD patients, [16, 17] but some studies have indicated increased risks associated with attempts to completely correct anemia. No survival benefit is evident at a higher level of anemia correction, [13, 164, 165, 167] although quality of life and exercise capacity may be greater. Thus, there is a possible tradeoff between improved quality of life and increased cost and risk for harm, so that a target level of Hb above 13 g/dl should be avoided [16]. Clinical trials of erythropoiesis-stimulating agents indicate that targeting the complete correction of anemia in patients with chronic kidney disease results in a greater risk of morbidity and mortality despite improved hemoglobin and quality of life [59, 164, 212]. Although there are studies that state the opposite [213, 214]. Relationships between hemoglobin concentration and mortality differed between African Americans and whites. Additionally, the relationship of lower mortality with greater achieved hemoglobin concentration seen in white patients was observed for all-cause, but not cardiovascular mortality [215]. Erythropoiesis-stimulating agents should be used to target hemoglobin 11-12 g/dl on patients with chronic kidney disease. However, a risk-benefit evaluation is warranted in individual patients, and high ESA doses driven by hyporesponsiveness should be avoided [216]. Intravenous iron may be beneficial for patients with hemoglobin less than

11 g/dl and transferrin saturation less than 25% despite elevated ferritin (500-1200 ng/ml) [217, 218]. TREAT and other large randomized, controlled trials of ESA treatment on patients with CKD have not demonstrated a clinical benefit in terms of mortality, morbidity, or quality of life improvement of targeting Hb levels greater than 12-13 g/dl. Some of these studies have demonstrated increased risk of stroke, vascular access thrombosis, hypertension, and other events [219]. The European Renal Best Practice (ERBP), which are issued by ERA-EDTA, are suggestions for clinical practice in areas in which evidence is lacking or weak, together with position statements on published randomized controlled trials, or on existing guidelines and recommendations. In 2009, the Anemia Working Group of ERBP published its first position statement about the hemoglobin target to aim for with erythropoietin-stimulating agents (ESA) and on issues that were not covered by K-DOQI in 2006-07. Following the findings of the TREAT study, the Anemia Working Group of ERBP maintains its view that 'Hb values of 11-12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL and that the doses of ESA therapy to achieve the target hemoglobin should also be considered. More caution is suggested when treating anemia with ESA therapy on patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). To those with ischemic heart disease or with a previous history of stroke, possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for. These recommendations are not intended to represent a new guideline as they are not the result of a systematic review of evidence [220]. The National Kidney Foundation (NKF) and the Food and Drug Administration (FDA) recommend different target levels for hemoglobin in patients with terminal kidney disease treated by hemodialysis [79, 221]. The NKF recognizes also the importance of individualizing the treatment of anemia. The optimal range of target hemoglobin levels in Kainz et al analysis of hemodialysis patients was 11 g/day. Furthermore, ESA hypo-responders showed an increased risk of mortality with higher hemoglobin levels, and ESA responders actually exhibited a decreased risk [222]. A corrected weekly ESA dose up to 16 000 units with achieved hemoglobin levels ~11 g/dL exhibited the lowest mortality risk. Hemoglobin variability as well as ESA hypo-response causing low hemoglobin levels was associated with a numerically increased risk of mortality compared with patients with stable hemoglobin levels between 10 and 12 g/dL. Furthermore, ESA response requiring more than 16 000 units per week was also associated with an increased risk of death in ESA responders [222]. The Japanese Society for Dialysis Therapy (JSDT) guideline committee presents the Japanese guidelines entitled "Guidelines for Renal Anemia in Chronic Kidney Disease." These guidelines replace the "2004 JSDT Guidelines for Renal Anemia in Chronic Hemodialysis Patients," and contain new, additional guidelines for peritoneal dialysis (PD), non-dialysis (ND), and pediatric CKD patients [223]. Values for diagnosing anemia are based on the most recent epidemiological data from the general Japanese population. To both men and women, Hb levels decrease along with an increase in age and the level for diagnosing anemia has been set at <13.5 g/dL on males and <11.5 g/dL on females. Renal anemia is identified as an "endocrine disease." It is believed that in this way defining renal anemia will be extremely beneficial for ND patients exhibiting renal anemia despite having a high GFR. We have also emphasized that renal anemia may not only be treated with ESA therapy but also with ap-

propriate iron supplementation and the improvement of anemia associated with chronic disease, which is associated with inflammation, and inadequate dialysis, another major cause of renal anemia. In Japanese HD patients, Hb levels following hemodialysis rise considerably above their previous levels because of ultrafiltration-induced hemoconcentration; and (ii) as noted in the 2004 guidelines, although 10 to 11 g/dL was optimal for long-term prognosis if the Hb level prior to the hemodialysis session in an HD patient had been established at the target level, it has been reported that, based on data accumulated on Japanese PD and ND patients, higher levels have a cardiac or renal function protective effect, on patients without serious cardiovascular disease,without any safety issues.. Accordingly, the guidelines establish a target Hb level in PD and ND patients of 11 g/dL or more, and recommend 13 g/dL as the criterion for dose reduction/withdrawal. If the serum ferritin is <100 ng/mL and the transferrin saturation rate (TSAT) is <20%, then the criteria for iron supplementation will be met; if only one of these criteria is met, then iron supplementation should be considered unnecessary [223]. Italian Society of Nephrology in its guidelines for the treatment of anemia in chronic renal failure supports that before beginning epoetin treatment, it is essential to evaluate the level of anemia by the measuring Hb concentration, Red blood cell indices (MCV, MCH, MCHC), Reticulocyte count, Iron stores and availability and C-reactive protein (CRP). The minimum target Hb concentration to be attained is 11 g/dL. The upper limit is established individually on a clinical basis. Pending further data, it is advisable to maintain and not exceed 12 g/dL for patients with cardiovascular disease, diabetes, and graft access. In the presence of adequate reserves of iron the need for higher dosages of epoetin define a state of resistance [224].

Iron deficiency (60%) measured by ferritin levels and TSAT at start of dialysis was found in Predialysis Survey on Anemia Management (21 European countries, Israel and South Africa) despite the majority of patients under nephrologist's care for more than twelve months. Only 27% of patients had started epoetin treatment before dialysis therapy. Thirteen percent had started dialysis therapy first, 33% had started epoetin and dialysis therapy simultaneously, and 28% had not been administered epoetin at any time (total n = 4,095).

[225] Difference in hemoglobin levels was found in DOPPS study and mean Hgb levels were 12 g/dL in Sweden; 11.6 to 11.7 g/dL in the United States, Spain, Belgium, and Canada; 11.1 to 11.5 g/dL in Australia/New Zealand, Germany, Italy, the United Kingdom, and France; and 10.1 g/dL in Japan. Hgb levels were substantially lower for new patients with end-stage renal disease, and EPO use before ESRD ranged from 27% (United States) to 65% (Sweden) [21].

At present, there is a "grey zone" also between the intervention threshold of Hb< 9 g/dl and an Hb level > 13 g/dl, at which CKD is associated with a higher risk of cardiovascular events. It seems to be clearly evident that ESA activate platelets directly and indirectly, and that pathologically extended bleeding time is normalized when an Hb level of 10 g/dl is reached; from the hemostaseological perspective, a threshold level for treatment of renal anemia with ESA is thus defined. According to the present state of knowledge, an Hb target range of 10-11 g/dl seems reasonable for renal anemia; this is also compatible with current recommendations by ESA producers and the Food and Drug Administration (FDA) [226]. This target range avoids the upper and lower risk levels for Hb, and probably ensures a pos-

itive ESA effect on quality of life; it is much more cost-efficient than the target range of 11-12 g/dl recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2007 [227]. ESA treatment for renal anemia should be aimed at reducing transfusion risk, with a treatment target in most patients of 10-12 g/dl; therapy should be individualized, rapid increases in Hb level should probably be avoided, and lowest appropriate ESA doses should be used. Temptation to increase ESA doses to very high levels in an attempt to overcome ESA hypo responsiveness should be resisted [219]. It seems that greater hemoglobin variability is independently associated with higher mortality [228]. Variability caused by laboratory assays, biological factors, and therapeutic response determines patient Hb level variability. Improving factors that can be manipulated (e.g., standardizing EPO and iron algorithms) and adjustment of the target Hb level range, specifically, by increasing the upper bound, likely will decrease the observed variability and further enhance the quality of anemia management [229, 230].

5. Conclusion

It is obvious that renal anemia in hemodialysis patients remain a serious problem. This was greater before EPO era, when blood transfusion was the only therapeutic approach. Insufficiency of iron and EPO are the most important causes of this anemia. Nowadays with the availability of new I.V. iron supplementation and ESAs this problem became more manageable. The high cost of the EPO treatment makes the iron therapy essential in order to maximize EPO administration result with the lower dose. The ideal hemoglobin target has to be established despite the numerous trials worldwide, and the treatment has to be individualized.

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Section 3

New Developments in Dialysis Focused on Methods and Instruments

Chapter 18

Analysis of the Dialysis Dose in Different Clinical Situations: A Simulation-Based Approach

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Additional information is available at the end of the chapter

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1. Introduction

End Stage Renal Disease (ESRD) is an important public health concern around the globe. It is associated with high morbidity and mortality being Hemodialysis (HD) the main applied therapy. [1]

A recent study (HEMO study) could not show any decrease in the morbidity and/or mortality associated with increases in the dose -expressed as equilibrated Kt/V (eqKt/V)- and/or the flow (comparing high versus low flux, where high flux is defined as a Kt/V of Beta 2 microglobulin (B2M) ≥ 20 ml/min) when utilizing the three-times-a-week (3-times/wk HD) schedule therapy. [2]

This led to development of several HD schedules proposals based on the variation of the session time duration (TD) as well as on its weekly frequency (Fr). However, more frequent HD schedules require new indexes to measure the delivered dose. In this context, the Equivalent Renal Clearence (EKR) [Casino y López] [3] and Standard Kt/V (stdKt/V) [Gotch] [4] indexes have been proposed to quantify the dialysis dose for different HD frequency schedules.

The EKR concept equalizes the time-averaged concentration (TAC) of Urea (U) for different therapies which is then normalized by U distribution Volume. Gotch has proposed that the weekly dialysis dose (WDD) is better expressed as standardized kt-V (stdKt/V) when dialysis is more frequent than 3-times/wk. Standard Kt/V combines treatment dose and frequency allowing comparison of intermittent (HD, High flux HD, Hemofiltration,

etc) and continuous (Continuous Ambulatory Peritoneal Dialysis) therapies; the formula is expressed as U generation rate (G) rate divided by the average peak concentration. [4]

EqKt/V is the true dialysis dose per session occurring when U rebound (R), which is related to compartments and flow disequilibrium produced during HD treatment, is completed 30-60 minutes after the end of the HD session.

The determination of eqKt/V requires the measurement or the "prediction" of the true Eq U because the value of sp (single pool)Kt/V - a dimensionless ratio which includes Clearence of dialyzer (K), duration of treatment (TD) and volume of total water of the patient (V) - is greater than the Kt/V achieved in the patient which is calculated using the immediate postHD blood U concentration.

In the last decade, several formulas were developed to predict eq Kt/V trying to avoid the extraction of an additional blood sample. The Daugirdas and Schneditz "rate formula" is the most popular and validated equation and it is based in the prediction of eqKt/V as a linear function of spKt/V and the rate of dialysis (K/V). [5]

An alternative and robust formula, based in the double pool analysis by Smye, [6] is the equation of Tattersall where he described a soluble time constant: the patient equilibration time (tp). [7]

The majority of these formulas of prediction have been validated in the 3-times/wk HD schedules.

New formulas to predict eq Kt/V have been recently published. Examples include the eqKt/V formula based on observations of the HEMO [8] study and two others developed by Leypoldt (based on blood sample analysis during hemofiltration and short and daily HD) [9].

The high accuracy of the extracellular U concentration evolution during and after (UR) an HD session by double pool U kinetic model has been verified in several studies. [10]

Access and cardio-pulmonary recirculation can both influence the UR, but the effect occurs in the first minutes after the end of HD and is considered to be mild. [10]

Several factors other than clearance of U might play a role in morbidity and mortality of hemodialyzed patients.

One of them, recently revised, is the role of the "denominator" to normalize the Kt. The results derived from the HEMO study showed that Kt/V failed to explain the paradoxical outcomes related to size (underweight versus obese patients) and gender. This factor was considered in the Frequent Hemodialysis Network (FHN) study which is currently underway. The investigators included the body surface area (BSA) as a potential tool for a better normalization of Kt and to allow more appropriate comparison among different HD populations. [11]

Since 1980 the idea of emulating reality in a computer environment by simulation rapidly spread among biomedical researchers, being accepted as one of the most powerful

tools both for understanding phenomenological aspects of a chosen physics or physiological complex and for predicting functional or operative conditions of technological systems. The main concept of this approach relies in numerically solving a mathematical model that governs a chosen physical system, whose the analytical solution is not known or potentially dangerous to reach for a specific application. In spite of many efforts spent in the past for formulating accurate and robust algorithms for solving mathematical models, the effectiveness of that approach heavily dependent on computational resources. This led to only recent widespread use of simulation strategy both scientific and medical problems [12].

A variable volume double-compartment (VVDC) kinetic model can reflect the behavior of different molecules and can be used as a mirror to analyze the profile in vivo by taking blood samples during the HD procedure. [13]

In this scenario, the computational simulation including all the variables which affect the dialysis procedure can be a safe and useful tool to mimic many treatment schemes to help improve our knowledge of the dialysis therapy. [14]

The aim of this study is to utilize a variable volume double-compartment (VVDC) kinetic model to simulate:

1. Several clinical situations that allow comparison between the true eqKt/V and all the developed predictors, including the effect of increasing the TD and Fr.
2. Changes in Kt/V, EKR and stdKt/V related to changes in TD and Fr.
3. Comparison between using V with BSA to normalize K.

2. Materials and methods

2.1. Simulation and analysis

A variable volume double-compartment (VVDC) kinetic model has been implemented based on the existing models of the U concentration behaviour. The model is described in Figure 1 and the equations are as follows:

$$\frac{d(V_e C_e)}{dt}(t) = G - K_c(C_e(t) - C_i(t)) - C_e(t)(K_e(t) + K_r + K_d) \quad (1)$$

$$\frac{d(V_i C_i)}{dt}(t) = K_c(C_e(t) - C_i(t)) \quad (2)$$

$$\frac{dV}{dt}(t) = \alpha(t) \quad (3)$$

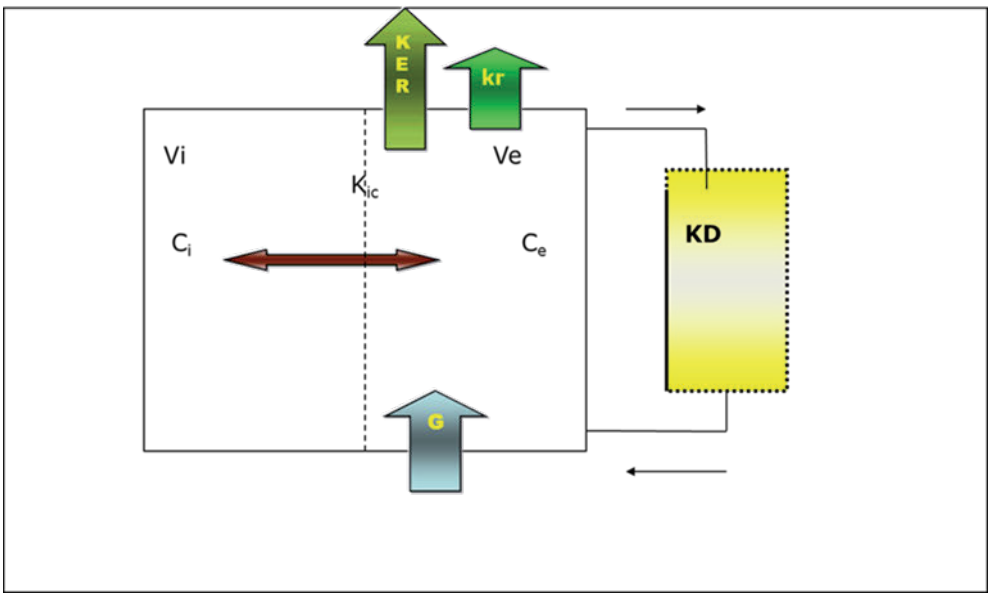

Figure 1. Scheme of Variable-Volume Double Compartment dialysis kinetic model

Whereas "V" is: solute distribution volume, "C": solute concentration, "K": clearance constant, "G": solute generation, "c": cellular, "e": extracellular, "i": intracellular, "r": renal, "d": dialyser, a: volume change velocity (this constant is positive between dialysis sessions and negative during them), "t": time. Equations 1, 2 and 3 make a dependent differential equation system that can be numerically solved. Through these simulations, it is possible to obtain the time profile of intra and extracellular volumes and concentrations of the studied solutes (figure 2).

By defining a behaviour determined for several time intervals on certain variables, such as α and Kd, it is possible to simulate different dialysis schedules, regarding session duration times (TD) and time between dialysis sessions or dialysis frequency (Fr).

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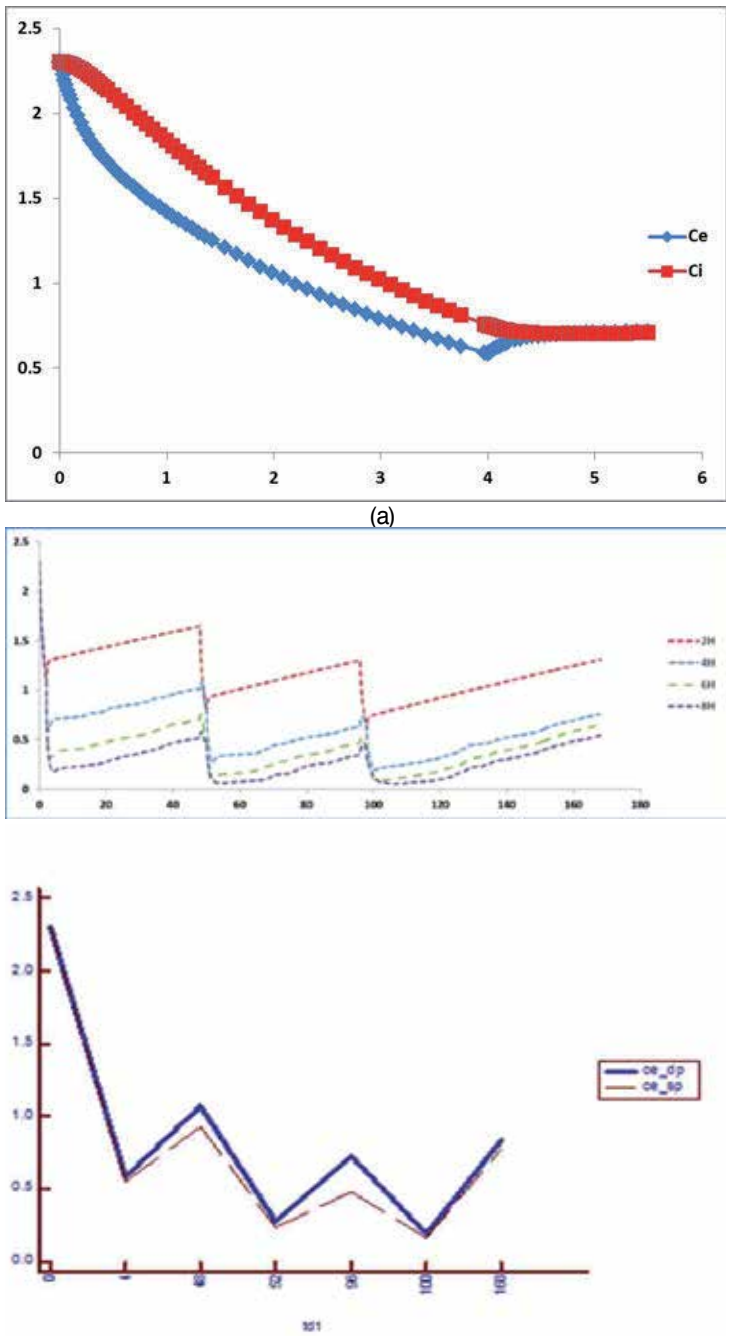

Figure 2. (a) Simulation of a profile during HD and the rebound of the solute immediately after the end. (b) Simulation of the weekly HD profile showing the effect of increasing the TD with fixed Kd and Kc. (c) Urea dinamycs simulated with double or single pool.

2.2. Simulated systems

2.2.1. Comparison between the true eq Kt/V and all the developed predictors

The simulations assumed that the subjects had a solute distribution volume of 580 ml/Kg and the intra and extracellular distribution relation is 2/3 and 1/3 of the total V. The extra-renal clearance constant (Ker) was considered invalid for the U.

Residual renal clearance (Kr) was 0. 1ml/min in all the cases.

Dialysis schedules with a duration between 2 and 8 hours at 2-hour-intervals of 2 hour were simulated and the weekly frequency of treatment were 3 and 7 days/wk.

The simulations resulted in a time-dependent evolution of the molecule concentration under study (U) in each of the compartments, that is, the intracellular (Ci) and extracellular (Ce) compartments.

We analysed 1005 determinations of U pre HD, U posHD and eqU (60 minutes after the end of the simulated session). This determinations were obtained in the midweek of the 4th and 10th week of simulation

These determinations were product of the manipulation of six (6) variables-Table 1-

Weight	Kc(ml/min)	Kd(ml/min)	$U_{onset(mg\%)}$	UF(ml/session)	UR%
60-120	400-1000	100-250	160 -240	500-4000	3.65-17.8

Table 1. Range of values of the different simulated variables.

U G was 6. 25mg/min in all the simulations.

2.2.2. Formulas

Simulated eqKt/V was compared with the previously described predictors with the next formulas :

$$Kt/V = Ln\left(\frac{U_{pos}}{U_{pre}}\right) \tag{4}$$

$$Kt/V = Ln\left(\frac{U_{eq}}{U_{pre}}\right) \tag{5}$$

$$Kt/V_{TATTERSALL} = Kt/V * \left[\frac{t}{t+35}\right] \tag{6}$$

$$Kt / V_{DAUGIRDAS} = Kt / V - 0.6 * \frac{Kt / V}{t} + 0.03 \quad (7)$$

$$Kt / V_{HEMO} = Kt / V - 0.39 * \frac{Kt / V}{t} \quad (8)$$

$$Kt / V_{LEYPOLDT1} = 0.924 * Kt / V - 0.395 * \frac{Kt / V}{t} + 0.056 \quad (9)$$

$$Kt / V_{LEYPOLDT2} = 0.915 * Kt / V - 0.485 * \frac{Kt / V}{t} + 0.106 \quad (10)$$

2.3. Changes in Kt/V, EKR and stdKt/V related to changes in TD and Fr

Typical 80-kg-patient with a residual renal clearance (Kr) of 0. 1ml/min and a weight gain a (interdialysis) and ultrafiltration (intradialysis) of 0. 65 ml/min was chosen to simulate the different therapeutic dialysis schedules.

The assumption was that this typical patient would have a solute distribution volume of 580 ml/Kg (46. 4 litres) and when the solute is U, the intra and extracellular distribution relation is 2/3 and 1/3 of the total V. The extrarenal clearance constant (Ker) was considered invalid for the U.

Dialysis schedules with a duration between 1 and 8 hours at intervals of 1 hour were simulated and the weekly frequency of treatment was changed from 3 to 7 days a week on each of them thus obtaining 28 different schemes.

The Fr applied to the simulations does not represent sessions uniformly distributed through the week; it was implemented according to the time tables used in the usual HD practice. For the 3-times/wk Fr, three sessions with an interval between the beginning of sessions of 48, 48 and 72 hours (that is, Monday, Wednesday and Friday) were performed. For the 4-times/wk sessions, the intervals are 24, 48, 24 and 72 hours. For the 5-and 6 -times/wk sessions, 4 and 5 intervals of 24 hours and the last one of 72 and 48 hours, respectively, are established. When the Fr is of 7-times/wk, the distribution is uniform.

The simulations resulted in a time-dependent evolution of the molecule concentration under study (Urea) in the intracellular (Ci) and extracellular (Ce) compartments.

Over the U time profiles, the real Time Average Concentration (TAC) is calculated. Since the main objective was to evaluate which of the proposed indexes more accurately showed the dose changes caused by the scheme changes, the behaviour of the weekly Kt/V, EKR (Casino), std Kt/V (Gotch) and the rebound percentage (% rebound), were compared according the following formulas:

$$\frac{Kt}{V} = \sum_{j=1}^{N} \ln\left(\frac{C_{ePre}}{C_{ePost}}\right)_j \tag{11}$$

$$TAC = \frac{1}{2N}\sum_{j=1}^{N}\left(C_{ePre} + C_{ePost}\right)_j \tag{12}$$

$$EKR = \frac{G}{TAC} \tag{13}$$

$$std\frac{Kt}{V} = \frac{G}{\frac{1}{N}\sum_{j=1}^{N}\left(C_{ePre}\right)_j} \tag{14}$$

$$\%R = \frac{100}{N}\sum_{j=1}^{N}\left(\frac{C_{eq} - C_{ePost}}{C_{eq}}\right)_j \tag{15}$$

2.4. Hemodialysis simulation tool: HD-SIM

The simulations of hemodyalisis kinetics were performed through the utilization of a software specially developed for hemodyalisis simulation: HD-SIM. [15] This software was developed on MATLAB (c) platform and consists of a calculation core and a graphical user interface (GUI).

HD-SIM calculation core utilizes MATLAB ® (version 6. 5) simulation package SIMULINK® to support the VVDC kinetics model. Given the set of required parameters through the GUI, solute compartmental concentrations (Ce and Ci) and volumes (Ve and Vi) are calculated as functions of time. Concentration-time profiles are used for the calculation of different hemodyalisis quantity-quality estimators such as: TAC, EKR, Kt/V, and stdKt/V. The calculation core solver is used with: ode113 algorithm (Adams – variable step) that is recommended by MathWorks for narrow tolerances, automatic integration step, maximum step of 1 (1 hr), duration of 1680 (10 weeks), absolute tolerance of 10^{-7} (10^{-7} mg/ml) and relative tolerance of 10^{-7}.

HD-SIM GUI provides a friendly set of windows that allows inserting patient and dialyzer specific data into the simulation system that is required to feed the VVDC model, defining sets of TDs and Frs to evaluate a wide range of treatment schedules, and managing the outcome of the simulations from visualizing estimator values and concentration profiles to file-saving selected results. (figures 3, 4 and 5)

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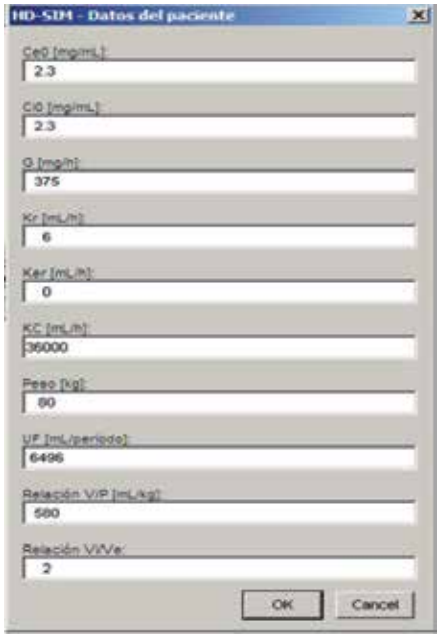

Figure 3. Patient and simulation data displayed by HD-SIM

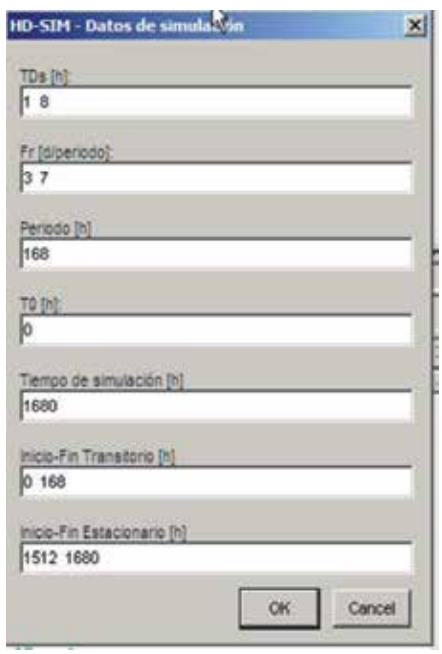

Figure 4. Patient and simulation data displayed by HD-SIM

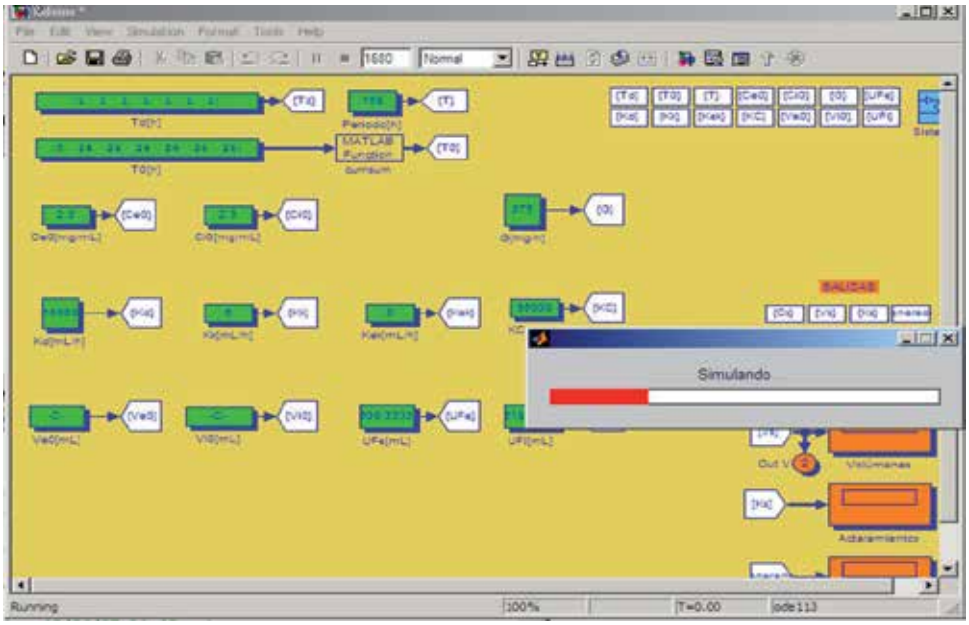

Figure 5. HDSIM running the simulations.

Table 2 shows the values at the the beginning of the simulation.

Solute	Ce onset (mg %)	G (mg/min)	Kc(ml/min)	Kd(ml/min)
Urea	230	6.25	600	250

Table 2. Values at the beginning of the simulation

3. Statistical analysis

All values are expressed as mean±standard deviation (sd) or median (range) as appropriate. Correlation coefficients were determined using the Pearson method. For analysis of agreement between methods (for example simulated (sim) eqKtV versus EqKtV predictors) we used Bland Altman analysis. To compare sim eqKtV with predictors we also used analysis of error: mean error (sim eqKtV-predictor) and % mean error ((sim eqKtV-predictor)/ sim eqKtV) x 100). We used MedCalc version 12. 3. 0(MedCalc Software,Mariakerke,Belgium) for the statistical analysis.

4. Results

4.1. Prediction of the eqKt/V

The eq KtV delivered in 1005 simulations was 0. 84±0. 47 with a median of 0. 78 and a range between 0. 10 and 2. 54, which represent the wide range of values commonly seen in current clinical practice. (Table 3)

	eqKt/V	Tattersall	Daugirdas	HEMO	Leypoldt 1	Leypoldt 2
Minimum	0.10	0.13	0.14	0.13	0.18	0.13
1st Quart	0.47	0.50	0.50	0.51	0.52	0.46
Mean	0.85	0.87	0.88	0.89	0.87	0.80
Median	0.78	0.80	0.82	0.82	0.81	0.75

Table 3. Statistical summary of Simulated and predicted eqKt/V values by different formulas. (1st Quart=first quartile)

4.2. Behaviour of predictors

All predictors showed a high Pearson correlation coefficient (≥ 0. 99) with sim eqKt/V and among themselves.

Daurgidas, Tattersall, HEMO and Leypoldt1 underestimated sim eqKt/V. Leypoldt2 was the only one to overestimate the sim eqKtV. (Tables 4 and 5)

	Daugirdas	Tattersall	HEMO	Leypoldt1	Leypoldt2
Mean	-0.0302	-0.0199	-0.0435	-0.0244	0.0428
SD	0.03680	0.03255	0.02959	0.05039	0.05670
Median	-0.0350	-0.0241	-0.0459	-0.0300	0.0304
Minimum	-0.101	-0.0836	-0.110	-0.110	-0.0454
Maximum	0.0783	0.0827	0.0721	0.170	0.259

Table 4. Mean Error (ME) between sim eqKt/V and predictors

	Daugirdas	Tattersall	HEMO	Leypoldt1	Leypoldt2
Mean	5.63	4.32	7.47	7.63	-3.18
SD	7.7	6.9	7.42	11.83	6.67
Median	4.65	3.23	5.89	4.60	-3.9
Minimum	-2.14	-2.26	-1.95	-1.14	-2.82
Maximum	5.37	3.54	4.08	8.55	3.43

Table 5. % Error (% ME) between sim eqKt/V and predictors

The lower error of prediction expressed as ME or % ME was obtained with the Tattersall and the Daurgidas formula. Leypoldt1 and 2 showed the worst predictive performance.

One interesting point was the effect of increase TD of Fr it was used in unconventional schedules (different from 3-times/wk). Error was higher in schemes shorter than 4 hours and the increasing of Fr did not affect the prediction (Figures 6 and 7)

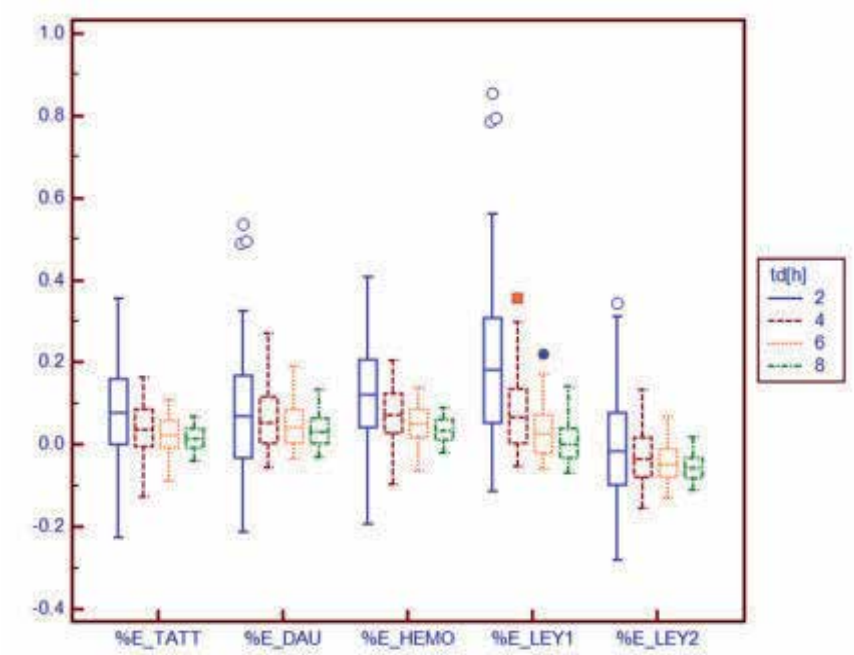

Figure 6. Effect of the TD and increased Fr in the % error prediction of eqKt/V

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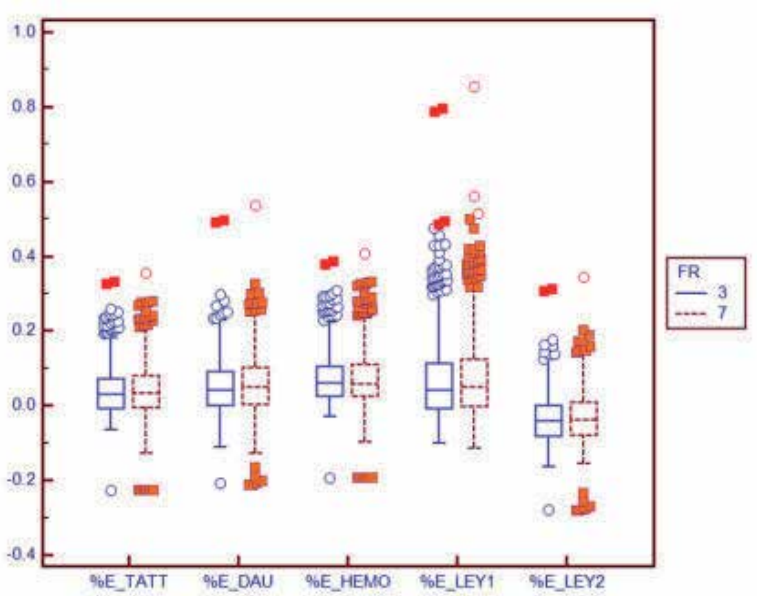

Figure 7. Effect of the TD and increased Fr in the % error prediction of eqKt/V

4.3. Bland-Altman analysis

A Bland-Altman analysis of agreement between gold standard (sim KtV) and eqKt/V predictors was performed. Tattersall and Daugirdas formulas showed the lower mean difference (±2sd): -0. 02 (+0. 04 -0. 08) and -0. 03 (+0. 04 -0. 1) respectively with a Gaussian distribution of error. Both Leypoldt formulas showed higher error with the increasing of the magnitude of eqKtV. HEMO study formula showed a higher mean difference than Tattersall and Daugirdas formulas with a lower 95% agreement interval (+0. 01-0. 1) (figure 8)

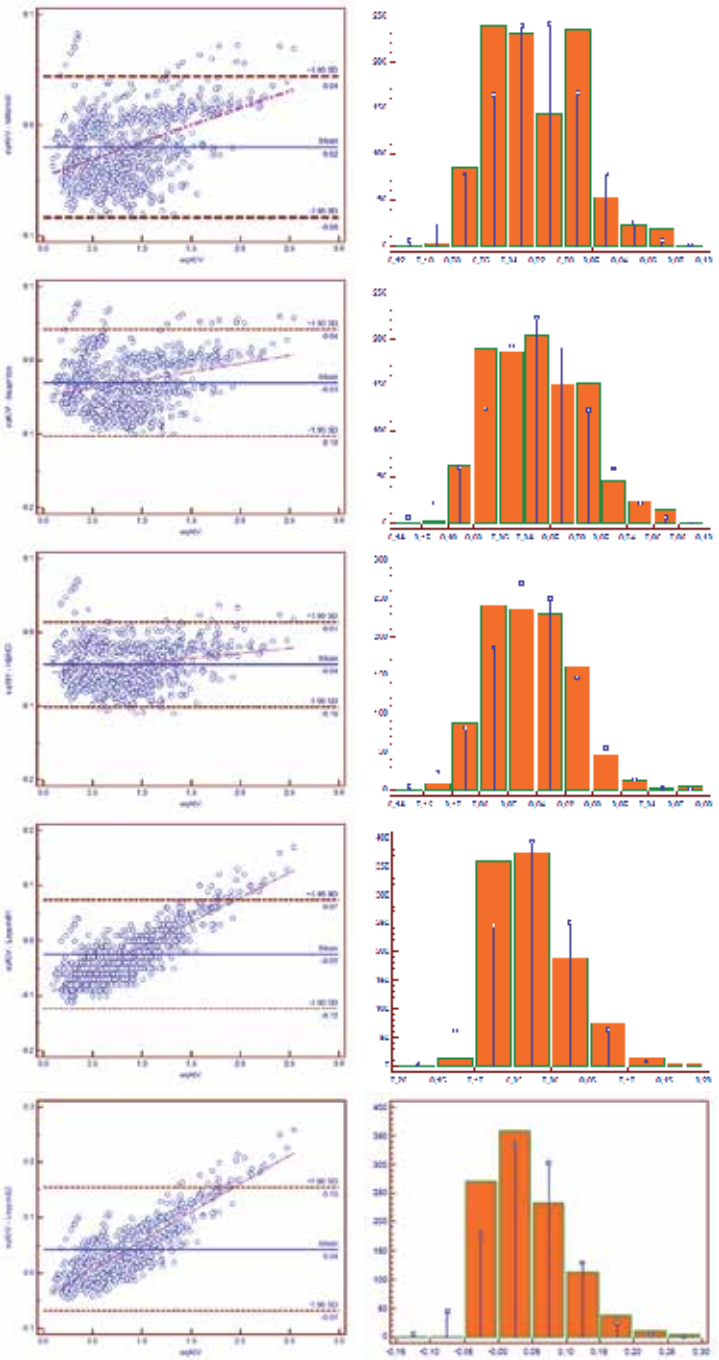

Figure 8. Left side: Bland Altman plot comparing simulated eq Kt/V and predicted eq Kt/V by different predictors formulaes. Right side: Histogram of Error between simulated eq Kt/V and predicted eq Kt/V by different predictors formulas.

4.4. Quantification of the Weekly Dialysis Dose (WDD)

The minimal dialysis dose recommended by the DOQI standards (Kt/V U/session = 1. 2) corresponded to EKR U =3. 17 ml/min and stdKt/V U = 2. 07 ml/min in a usual scheme of 3 days/4 hours (3d4hs) and the high dose equivalent similar to HEMO study (EqKt/V=1. 4) was 4. 28 ml/min and 2. 57 ml/min for stdKt/V in a schedule of 3 days 6 hours. Figure 9 shows the stdKt/V behaviour related to increase of TD and Fr as well as the equivalent values of minimal and high Kt/V.

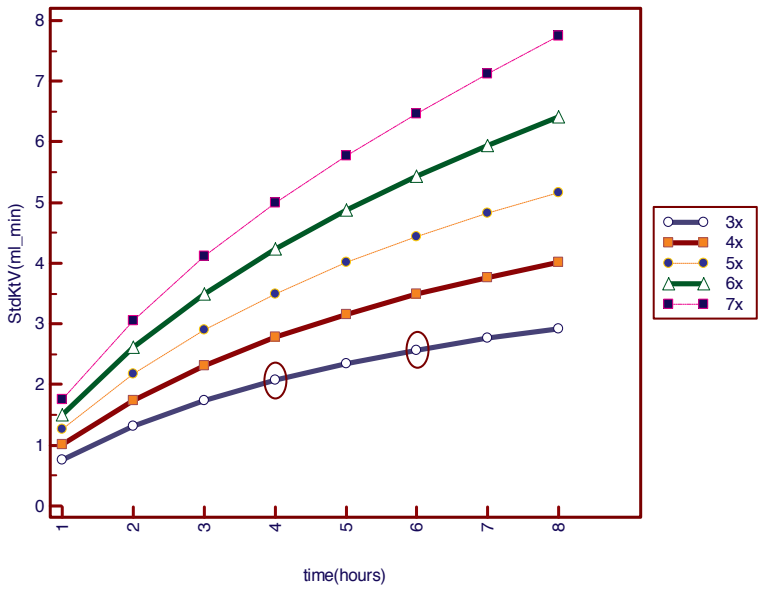

Figure 9. stdKt/V behaviour related to increase of TD and Fr as well as the equivalent values of minimal and high Kt/V.

Table 6 shows tipical values of EKR, stdKt/V, wk Kt/V (weekly Kt/V) and Kt/V by session according changes in TD y Fr in a typical 80-kg-patient.

Frequency	time[h]	EKR (ml/min)	stdKt/V(ml/min)	wk Kt/V(ml/min)	KTV/Session
3	4	3.17	2.07	3.55	1.18
3	8	5.11	2.92	5.82	1.94
4	4	4.23	2.78	4.61	1.15
7	2	4.06	3.05	4.78	0.68
7	4	7.45	5	7.52	1.07
7	8	12.69	7.75	10.54	1.51

Table 6. EKR, stdKt/V, wkKt/V and Kt/V by session according changes in TD and Fr in a typical 80-kg-patient. (Ce onset=230;KD=250 ml/min;Kc=600ml/min.

The weekly Kt/V, EKR and std Kt/V showed a high correlation to express increasing of TD and Fr (weekly Kt/v-std Kt/V r= 0. 987 EKR-stdKt/V r=0. 9937) showing the weekly Kt/V (5. 68±2. 46) and the EKR (5. 55±3. 02) values to be higher than std Kt/V (3. 56±1. 76)

The behaviour proved different when the three indexes were separately analysed. When they are compared to quantify 3-times/wk and weekly schedules, the ekr and std Kt/V have a similar behaviour, the EKR tending to overestimate the WDD as the TD increases. (Figure 11) When the difference EKR-std Kt/V is showed in a graph (Figure 10) a high correlation of it (R2=0. 99) is verified, with a logarithmic increase of the Kt/V/session and is lower with the increase of Fr in a fixed TD. The weekly Kt/V has a behaviour similar to that of the EKR in the 3-times/wk schedules but clearly fails in the daily schedules, especially in the TD schedules >4 hours.

When the Kt/V-session is analysed, the results match. The Kt/V/session increases as the TD increases when a certain number of sessions are fixed (Fr). When it is analysed for different Frs, the Kt/V/session only shows differences when duration is > 4 hours; however, if the Fr varies and the TD is fixed, instead we can observe that the Kt/V/session is not able to respond to the dose increases and tends to decrease as the WDD increases due to an increment of the Fr. (Figure 11)

The U rebound is complete one hour after the end of the HD session in all the simulations, decreasing as the TD increases.

Figure 11 showed the effect of TD and Fr on different predictors of the WDD (wkKt/V, EKR and stdKt/V) as well the changes Kt/V-session.

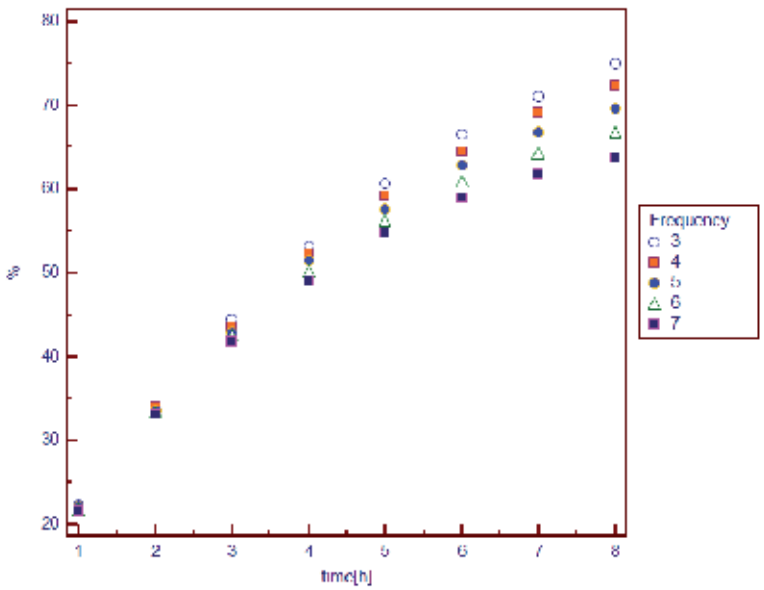

Figure 10. Difference (%) EKR-stdKtV related to Kt/V by session

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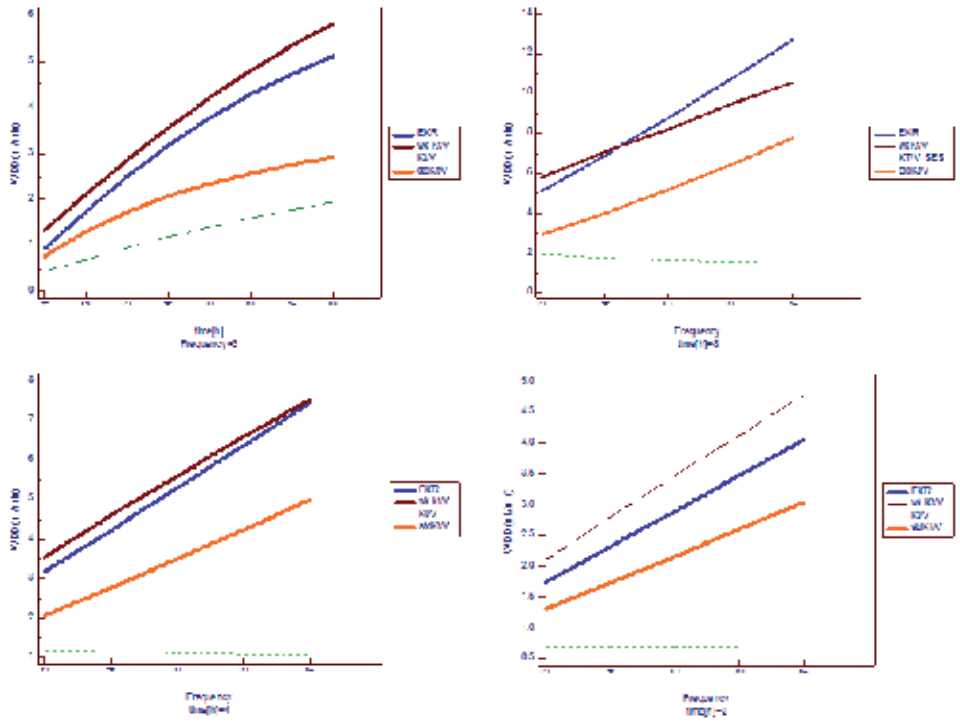

Figure 11. Effect of changes in increasing of TD and Fr on the behavior of WDD predictors (wkKt/V, stdKt/V, EKR) and Kt/V by session. (WDD=Weekly Dialysis Dose (ml/min)

4.5. Comparison of V with BSA to normalize Kt/V

In the last four decades dialysis dose expressed as KtV has been widely used due to its low complexity and ability to predict to be a strong predictor or mortality in HD population. However, recent studies showed paradoxical outcomes related to sex and higher mortality in patients with high Kt/V and low Volume, leading to the proposal of a normalized volume using and the correction by a Volumen normalized by Body Surface Area (BSA). has been proposed. [16]

We randomly simulated 1031 K*t with a range of between 14400 ml/min and 57600 ml/min and then Kt/V (using Watson formula for Volume) and Kt/V corrected by BSA (Dubois formula) were calculated and analysed

KtV values delivered by simulation showed a mean of 1. 01, a median of 0. 99, a range between 0. 29-2. 44 and a standard deviation of 0. 40 The results of the allometrical correction of Volume Watson formula by BSA were 0. 084*V 0. 86 (female) r=0. 98 and 0. 1229*V 0. 73 (male) r=0. 99. (Figure 12)

The results after V normalized by BSA clearly changed between men and women and the overestimation in patients with lower volumes was corrected (Table 7 and figures 13 and 14)

	Sex			
	f		m	
	Mean	SD	Mean	SD
Kt/V	1.158	0.4354	0.921	0.3415
Kt/Vcorr	1.862	0.6891	2.489	0.8909

Table 7. Kt/V and Kt/V corrected by BSA (Dubois) according to sex.

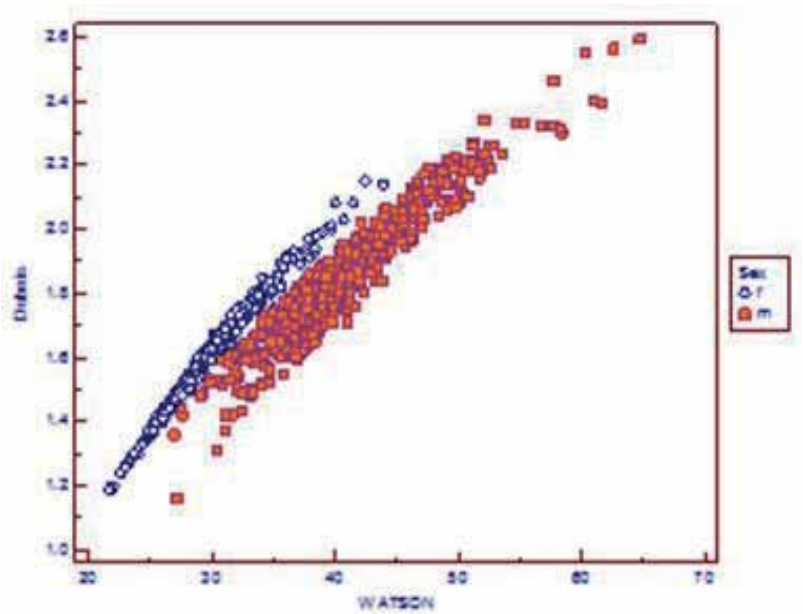

Figure 12. Allometric regression between Body Surface Area (Dubois) and Volume (Watson)

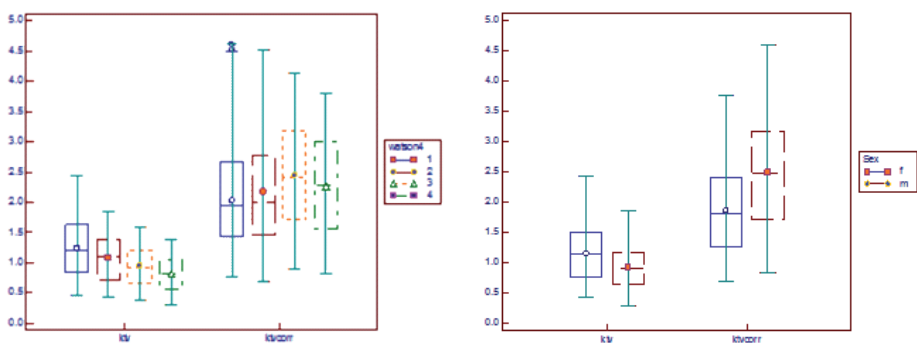

Figure 13. Effect of changes in Volume and Sex on BSA-normalized Kt/V and Watson Kt/V

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5. Discussion

In this work we propose the simulation with a VVDC kinetic model as a useful and safe tool to investigate, learn and find out the numerous aspects of the HD treatment related to dialysis dose. Single pool models used by Gotch [10] to developed the pharmaco- kinetic concept of Kt/V are simpler and also useful but it frequently leads to errors in showing the true behaviour of little known molecules or not yet validated treatments. VVDC kinetic model is used in current studies that analyze the influence of increasing TD and Fr in HD outcomes after the failure of HEMO study to demonstrate better results with high dose expressed as eqKtV. [2]

Exponencial decay curves defined by WWDC to fit dialysis dose by session are actually used in several medical devices based on ionic dialysance or urea sensors. [17] [18]

We used WWDC based curve fitting and neural networks to predict dialysis dose from samples provided by an on-line urea monitor. [17]

The main interpretation of the double compartment [19] represent intra and extracellular fluid spaces, with diffusion of molecules between the spaces characterised by a mass transfer coefficient, Kc. This interpretation is based on the observation that Kc correlated with patient size. This model had been deeply developed by Smye and it had been the basis of the Tattersall formula. However, Scheneditz et al suggests that the two compartment based in different regional tissue flows (high and low blood flow) may describe urea distribution, and transport during dialysis, more accurately. This theorical approach also permited the development of a formula for dialysis dose that accounts for molecular rebound but only is based only on measurements of urea made during HD procedure. This formula has proved higher clinical usefulness: the Daurgirdas formula.

In this study we confirmed the robustness of the two widespread eqKtV predictors developed under the two different ways: Tattersall [7] and Daugirdas formulas. They showed a high accuracy in the numerous simulated schedules. The lower error of Tattersall formula has been validated in clinical situations and could be explained in our study because it was developed under a theorical approach using a diffusion –based VVDC.

Formula emerged from the blood U samples analysis of 1131 patients in the HEMO study [8] showed as an interesting approach. It behaved with a higher error than Tattersall and Daurgirdas formulas but showing a very low bias in all the simulations.

Eq KtV was confirmed as the metric of dialysis session in the thrice a week schedule. Equivalent dose of stdKt/V for eqKt/V in schedules>3-times/wk may be easily calculated in a graphical fashion (Figure 9)

The main issue which justifies the fact that Kt/V U is considered the key of the adequacy of dialysis is that it is related to mortality. However, many studies have questioned the utility of Kt/V: mainly, scaling for the volume is a confounding factor since gender and body mass index directly affect morbidity and mortality in HD patients. [20]

In our study the influence of the denominator to achieve a real dose independent of sex and volume showed similar results with others studies.

VVDC proved particularly useful when we analysed the new proposed predictors of the WDD: EKR and standard Kt/V.

Std KtV was confirmed as the best project to explain the different schedules. EKR was showed closely related with Kt/V and sensitive to changes in TD, overestimating the dose in daily HD schedules. VVDC allowed to graph different weight, dialyzer and patient clearences, etc.

Other molecules such as B2M [21] and phosphorus related to mortality and different behaviour with urea have not been simulated in this work but VVDC have been successfully used for both. B2M is a molecule of high molecular weight, with typical lower levels in plasma and lower distribution Volume fully explained by VVDC when we know completely their characteristics. On the contrary, Phosphorus [22] shows a heterogeneous and complex behaviour that cannot be completely validated with a VVDC kinetic model.

In addition to U kinetics, clinicians must consider clinical indicators (in example extracellular volume control, blood pressure, anemia and cardiovascular status) and comorbidities (diabetes, ageing, undernutrition) when using frequent or prolonged dialysis no forgetting to provide the best possible clinical results and quality of life.

6. Conclusions

In our experience, a VVDC kinetic model proved to be showed as a useful and safe tool to analyse different HD schedules and novels techniques before the clinical validation. The use of graphical interfaces to extrapolate the numerical results enhanced the VVDC simulation. Clinical practice and simulation interact in a permanent feedback. Std KtV was confirmed as the best project to explain the different schedules. Tattersall and Daugirdas showed highly accurate in the numerous simulated schedules.

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Chapter 19

Adsorption in Extracorporeal Blood Purification: How to Enhance Solutes Removal Beyond Diffusion and Convection

Fabio Grandi, Piergiorgio Bolasco, Giuseppe Palladino, Luisa Sereni, Marialuisa Caiazzo, Mauro Atti and Paolo Maria Ghezzi

Additional information is available at the end of the chapter

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1. Introduction

Uremic syndrome is linked to a plethora of uremic toxins circulating in the body in ESRD patients. Their overall spectrum is partly or entirely unexplored despite the need to urgently define the specimens and the patho-physiology beyond their high blood levels to address new or more selective removal strategies.

It is generally accepted that convective hemodialysis is the best choice to remove large part of the molecular spectrum, even though it is not fully demonstrated its superiority in terms of clinical outcomes. Then, transport mechanisms can benefit from maximizing all the physico-chemical principles including diffusion for small solutes, convection for middle molecules and adsorption for large molecular size uremic toxins. The latter has not been fully adopted in hemodialysis and this transport mechanisms is limited to the intrinsic capability of dialysis membrane to adsorb macromolecules while transporting solutes by diffusion and/or convection. However, poorly has been explored about the use of sorbents to enhance the solute removal in hemodialysis.

The purpose of this chapter is to summarize the main contributions of so far published clinical and technical experiences.

The chapter will be structured as follow: first we introduced a summary of the basic principles of solutes transport and relative contribution of the different mechanisms to the overall

solutes removal; then, we described the extracorporeal techniques using adsorption as further transport mechanism; third we introduced the filtration adsorption architecture and we described the proteomic profile in extracorporeal adsorption hemodialysis; finally we reviewed the main clinical experiences with two techniques, the hemofiltration reinfusion (HFR) and coupled plasma-filtration adsorption (CPFA).

2. Some basic principle of solutes transport through a semipermeable membrane and relative contribution of the different mechanisms to the overall clearance

Main purposes of extracorporeal blood purification treatments are the elimination of toxins from the body and in the presence of renal failure (acute or chronic), the recover of the hydro-electrolytic and acid-base homeostasis. Beyond this direct aims, the extracorporeal treatments can also help, particularly in chronic diseases, to recover the anaemic, the nutritional status and to control the inflammatory body response. Extracorporeal blood purification treatments refer usually to three major techniques: hemodialysis (HD), hemofiltration (HF) and hemodiafiltration (HDF) which can be delivered as intermittent therapiesor continuous ones.

Mass transfer through a semipermeable membrane are governed by three major mechanisms: diffusion (described by Fick's law); convection (described by the Staverman law, solvent drag principle driven by the hydrostatic pressure drop); adsorption (which refers to the separation of a solute from a mixture by binding the specimen to a sorbent surface).

Usually, all the three mechanisms occur simultaneously through a semipermeable membrane but the relative contribution of each transport mechanism is given by the chemical-physical properties of the media respect to the specific solute (diffusivity, hydraulic permeability and solute affinity), and the driving forces (concentration gradient, hydrostatic pressure gradient). Then, depending on the specific membrane characteristics and operating conditions we can have only diffusive transport (HD) with negligible effect form convection and adsorption, only convection (HF, without any contribution from diffusion and negligible from adsorption), only adsorption (hemoperfusion - HP) or a combination of those.

In HD, a hydrosoluble solute movement through two phases is driven by its concentration gradient, but it is partially limited by the diffusive permeability, sieving coefficient and membrane cut-off in relation to its molecular weight and geometry. Then, the mass flow is usually high for low molecular weight, like urea and poor for middle-high molecular weight solutes, like β2-microglobulin.

In HF, a hydrosoluble solute movement is driven by the hydrostatic pressure gradient but it is limited by the hydraulic permeability of the membrane, the sieving coefficient and the membrane cut-off. The clearance and mass transfer are equal to ultrafiltration (*uf*) flow which is limited by the blood flow rate, hematocrit (Hct), total protein content. As a consequence middle-high molecular weight toxin are easier removed than in the only diffusive

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case, while small molecular weight toxins do not take so much benefit from the convective transport.

Adsorption, especially of proteins, always occur onto the inner surface of the membrane and inside the porous frame along the membrane wall. This phenomenon has two major implications during extracorporeal treatment: 1) it allows for mediating the hemocompatibility of the artificial surface and its thrombogenicity; 2) the adsorbed protein layer can significantly interfere with both diffusion and convection. Adsorption can be advocated as further removal mechanisms especially for low molecular weight protein, like β2-microglobulin, inflammatory mediators, like endotoxin fragment, IL-1 and IL-6, and in some extent also large molecular weight protein like immunoglobulin G [1].

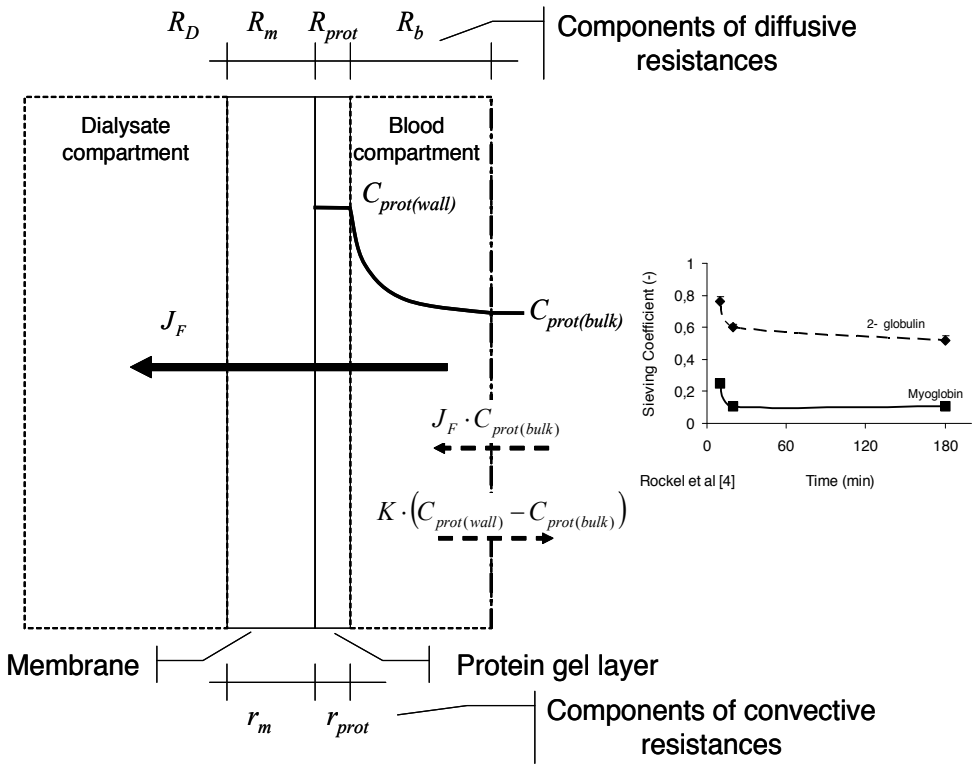

Figure 1. Major determinants of diffusive an convective transport behaviour through a semi permeable membrane. Legend of the figure: J_F=water flow rate, K=free diffusion coefficient, C protein concentration at wall or at the centre of the fiber.

In normal operating conditions it exists an interference among these three transport mechanisms. Indeed, convective solute removal can be heavily influenced by the membrane fouling or gelling and concentration polarization. Fouling refers to the formation of a protein layer onto the inner surface of the membrane which has been shown to significantly decrease the sieving coefficient of the membrane [2]. Concentration polarization indeed con-

sists of a second protein layer which is a function of theamount of protein delivered to the inner membrane surface by convective flow, and the amount of protein back diffusing from this high protein concentration boundary layer to the inner bulk phase of plasma at the center of the fiber (Figure 1). Again, the concentration polarization constitutes a barrier to solute movement toward the membrane surface decreasing both resistances to solute transport through the media and the overall sieving coefficient. In fact, the sieving membrane coefficient can be thought composed as: 1) intrinsic sieving coefficient (s_i=C_d/C_{wall}), (where C_d is the solute concentration in the dialysate and C_{wall} is the solute concentration at the membrane wall) which is inherent to the membrane characteristic and solute and 2) the observed sieving coefficient (S=C_d/C_{bulk}), (where C_{bulk} is the solute concentration at the center of fiber) which is also influenced by fouling and polarization [3].

In vitro data indicate that both hydraulic permeability and middle-high molecular weight solute sieving coefficient fall down during convection with high permeable membranes. Rockel et al [4] showed that middle-high molecular weight molecules decrease the sieving coefficient during the first minutes of dialysis with synthetic Polysulfone membranes. The extent of reduction was by 21% after 20 min and 32% after 180 min from the peak value of the sieving coefficient of 0.76 at 10 min for β2-microglobulin. Even more was the reduction of S for myoglobin which achieved -56% just after the firs 20 min of treatment.

Finally, fouling and concentration polarization also influences diffusion and convection by changing or introducing some further flow resistance components to the intrinsic characteristic membrane resistances (Figure 1).

Hemodiafiltration was initially proposed as a mixed technique that offered the advantages of two systems of transmembrane transport: diffusion and convection. This combination allowed better removal both middle molecules, particularly with respect to HD, and small uremic toxins when compared to HF [5, 6].

Although HDF is characterized by processes that can negatively interfere between diffusion and convection, leading to academic and clinical arguments over the choice between pre-, post- or pre/post dilution, overall the development of HDF offers, without doubt, an important positive evolution in dialytic strategy. Beyond the convection diffusion interference HDF is objectively associated with further two issues: a) quantity and quality of the reinfusion fluid; b) loss of important physiologic components in the *uf*. In fact, the choice of the Q_{uf} rate depends on several factors; first, from a practical point of view, the Q_{uf} must always be considered within the limits permitted by the blood flow (Q_b), Hct, total protein determining factors of fractional filtration. Elevated Q_{uf} improves the depurative efficiency of the treatment, but it also necessitates large quantities of reinfusion solution that must absolutely have a guarantee of safety for the patient. The utilization of *ready-to-use* reinfusion bags produced by the pharmaceutical industry are associated with notable problems including handling (repeated connections to the hematic lines, storage) and cost. This has led to interest in on-line production of reinfusion fluids that can guarantee sterility and allow elevated Q_{uf}, thus leading to economic and practical handling issues to give a good cost/benefit ratio. Furthermore, high Q_{uf} can often lead to severe depletion of substances such as vitamins, essential and branch chain amino acids (aa), as far as the albumin. Chronic renal failure patients

often have high nutritional losses during both convective and diffusive dialytic treatments that may be closely linked to other patient comorbidities or that may aggravate patient health and well being. HDF, in particular, is associated with remarkable losses of amino acids and it is not surprising that higher losses are found with higher hydraulic permeability membranes [7].

As far the interference between convection and diffusion is of concerned, *c*onvective clearance (and therefore mass transfer) of a diffusible solute in HDF can not be fully represented by the *uf* flow (Q_{uf}), in that the simultaneous process of both convection and diffusion diminish the solute's concentration.

The overall interferences can be simply accounted knowing the overall dialyzer clearance as a function of operating condition (Q_b,Q_{uf},) and overall mass transfer coefficient-area (*KoA*). Assuming the same approach described by Sargent and Gotch [8] the overall dialyzer clearance, K_T, is:

$$K_T = K_d\left(1-\frac{S\cdot Q_{uf}}{Q_b}\right)+S\cdot Q_{uf} \tag{1}$$

Where K_d, S, Q_{uf} and Q_b represent respectively the diffusive clearance, the sieving coefficient, the ultrafiltration rate and blood flow rate.

In turn, K_d, can be expressed as a function of the membrane characteristics, and operative condition of the dialyzer, as follow [9]:

$$Kd = Q_b\cdot\frac{e^{\left[\frac{KoA}{Qb}\cdot\left(1-Q_b/Q_b\right)\right]}}{e^{\left[\frac{KoA}{Q_b}\cdot\left(1-Q_b/Q_d\right)\right]}-\frac{Q_b}{Q_d}} \tag{2}$$

Where *KoA* is the overall mass transfer coefficient per surface area ($KoA=1/\sum_i R_i$) and Q_d the dialysate flow rate. The mass transfer coefficient is a function of the transmittance (inverse of the overall resistance *R*). From the equations above it can been simply accounted what is the K_T change for variations of *KoA* up to -50% and of Q_{uf} in the allowed range for a given Q_b (maximum 30%).

The overall clearance is plotted in Figure 2 as a function of Q_{uf} and *KoA* for two solutes like urea and vitamin B12 (molecular weight of 60 and 1355 Da, respectively), often used as markers to characterize the dialyzer performances. Values are shown as percentage respect to the nominal value of K_d. It is worth to note that K_T does not change linearly with Q_{uf} but it is proportional to its change with a slope <1. Moreover the change is much more marked for middle-high molecular weight solutes. In fact, in absence of *KoA* variations the urea K_T in-

creases up to +3% with Q_{uf}, while in presence of high *KoA* impairment when no convection is applied (Q_{uf}=0) the K_T decreases to -15%. The Vitamin B12 K_T increases linearly with Q_{uf} up to +16% in absence of *KoA* variations but decreases by -30% in case of *KoA* impairment in absence of convection. Nonetheless, when convection and fouling occur simultaneously, the positive contribution from convection itself, can be even knock down by *KoA* impairment and at higher Q_{uf} one should expect higher *KoA* changes especially for high molecular weight solutes. This observation is in line with the results by Rockel [4] who found that protein adsorption has a negligible impact on membrane characteristic of polysulphone membrane for low molecular weight solutes while it significantly alters the sieving coefficient of molecular weight substances above 11'000 Da.

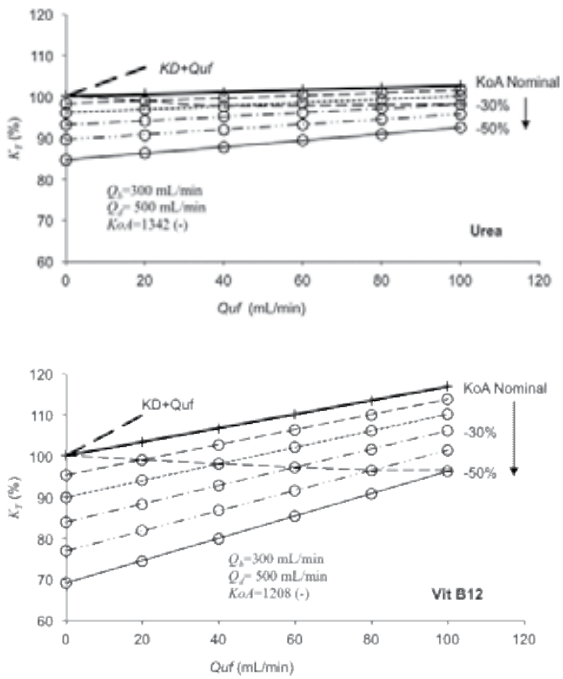

Figure 2. Relationship between K_T and changes of Q_{uf} and *KoA*.

Then according to these results, it is almost evident that less interference among the transport mechanisms should lead to better K_T. Maximum transport mechanisms can be achieved when they take place separately even though not all the interference like fouling and concentration polarization can be avoided at all but only minimized.

To solve this problem, Ghezzi et al [10] proposed a novel form of HDF that used a twin stage filter, in series, to separate diffusion from convection. The two stages permitted simultaneous convection and diffusion but also offered several benefits over traditional HDF combined in one filter unit. The first stage of the filter used a membrane with high hydraulic permeability for convective solute removal, while the second stage used a membrane with

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low hydraulic permeability for diffusive solute removal and to control the patient weight. Reinfusion of substitution fluids prepared on-line or in bags occurred between the two filter stages.This fluid was equal to the Q_{uf}, in order to maintain the effective Q_b. Therefore, this technique physically separates convection from diffusion, thus leading to two main results: a) the continuous availability of pure *uf* during the whole duration of the session; b) the absence of dialysate backfiltration. The method was called Paired Filtration Dialysis (PFD) [figure 3], and his efficiency and tolerance have been proven [11].

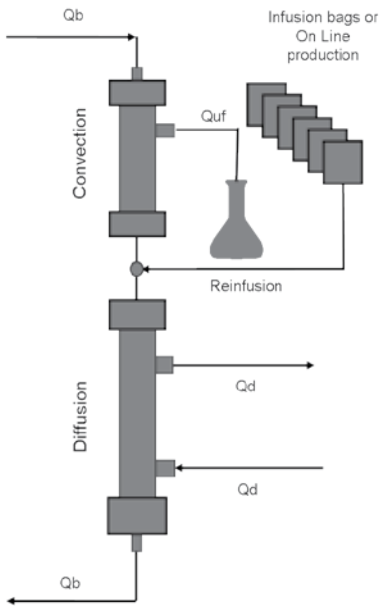

Figure 3. Paired Filtration Dialysis (PFD).

3. Extracorporeal techniques using adsorption

According to the "Consensus Conference on Biocompatibility," [12] adsorption is a method for removal of molecules from blood or plasma by molecules attachment to a surface incorporated in a device within an extracorporeal circuit. Sorbents are substances that, because of their physical and chemical characteristics, adsorb on their surface other elements in solution. In medicine, sorbents have been used to rapidly eliminate both industrial and pharmacological toxins, as well as some endogenous toxins such as bilirubin or porphyrines. They can be divided in two large categories: (1) those that have hydrophobic properties and therefore adsorb the molecules present in the solution in contact with the sorbent, and (2) those that eliminate solutes by chemical affinity [13]. Within the first category, hydrophobic sorbents, there are two subgroups: charcoal and non-ionic macroporous resin.

Charcoal is produced both from biological substances, such as coconut shells or peach pits and from non-biological substances, such as petroleum. The charcoal is activated by controlled oxidation in air (carbon dioxide) or steam. Adsorption into charcoal occurs through its pores, and therefore, its efficiency depends on the total number of pores and their radius. The charcoal may be coated or uncoated. Coating charcoal reduces some of its adverse effects, such as platelets entrapment, but it also reduces its efficiency, since the diffusion of the toxin from the blood to the charcoal is limited by the thickness of the polymer membrane, which covers it. The non-ionic macroporous resins are very similar to charcoal and are micro-sphere agglomerates, which adsorb the toxins they eliminate in their surface. Styrene-divinylbenzene polymers are generally used in clinical practice. The sorbents, which eliminate substances by chemical affinity, are fundamentally ion exchange resins, which exchange one ion for another of the same electrical charge. Some substances, which act by chemical links between the sorbent and the solute, are also considered "chemi-sorbents."

The use of sorbents in clinic can be divided in two big categories: hemoperfusion (HP) and plasma or *uf* perfusion.

Hemoperfusion is the passage of blood across material that adsorbs various solutes or substances [12]. In nephrology, sorbents were first used by Muirhead and Reid in 1948 [14] and later by Yatzidis in 1964 [15] in HP to eliminate uremic toxins. However, the adverse effects, principally platelets depletion, hemolysis, hemorrhage, and hypotension, outweighed the advantages. Although the majority of these adverse effects were solved thanks to the introduction of coated charcoal by Chang in 1966 [16, 17], the isolated use of HP for the treatment of uremia has been discontinued. At present, the use of HP is an accepted treatment for certain exogenous intoxication (pharmacological or suicidal).

After the abandonment of HP alone in the treatment of chronic renal failure, sorbents were used in combination and simultaneously with other dialysis methods. Gordon et al in 1969 [18] first described a HD technique in which the blood system, including the dialyser, was the usual one, but only six litres of dialysis fluid were used in the entire session, as the dialysate was regenerated by sorbents. The cartridge containing the sorbents consisted of four compartments: the first with urease, which transformed urea into ammonia; the second with zirconium phosphate, which eliminated ammonia, potassium, calcium, and magnesium; the third compartment, containing hydrated zirconium oxide, which eliminated phosphates; and the final compartment using charcoal, which eliminated a large number of both small and middle molecules. The system, called "Redy®," had the advantage of not needing running water nor any type of special installation and, therefore, could be quickly operated anywhere, for example, intensive care units and catastrophe sites, such as earthquakes. It also had various disadvantages, like unbalance of the sodium and acid-base equilibrium, but the most important was the release of aluminium to the dialysis fluid [19].

Another possibility of combining sorbents with HD was the inclusion of these substances in the dialyser membrane [20]. In this way, the patients blood was purified by diffusion as well as by adsorption on passing through the dialyser. The disadvantage to this method was its short efficiency period, as the sorbent became saturated in the first hour of dialysis and then stopped eliminating the uremic toxins. The Redy® sorbent cartridge was used by Shaldon et

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al [21] to regenerate the ultrafiltrate for reinfusion. This study was discontinued because of the appearance of osteomalacia in the patients [22].

4. Filtration adsorption architecture

The easy availability of isolated continuous *uf* during PFD led to the hypothesis that it could be "regenerated" and used as an endogenous reinfusion fluid. In 1992 [23] the first attempt to regenerate the *uf* was done with 130 mL of non-coated mineral carbon sorbent along the *uf* stream. The method was called Hemo Filtrate Reinfusion (HFR) and it is illustrated in Figure 4. HFR is a renal replacement therapy that utilizes convection, diffusion and adsorption. It uses a double stage filter that consists of a high permeability filter in the first convective stage and a low flux filter in the second diffusive stage.

The stages of the filter allow complete separation of convection from diffusion. The convective part of the first stage allows pure *uf* to flow through a sorbent resin cartridge. The potential of non-coated carbon sorbent to activate the contact phase [24,25], lead to switch the carbon cartridge to a hydrophobic styrenicdivinylbenzene resin (40mL). This has the potential advantage of a high affinity for several uremic toxins and middle molecules such as β2-microglobulin, homocystein, angiogenin, PTH, and several chemokines and cytokines [26, 27].

The resin structure allows molecules to flow through many pores and channels enlarging the sorbent surface area up to approximately 700 m^2/ gram. Despite its high affinity for many different uremic toxins, the resin has been proven not to [28] retain albumin and essential physiological molecules. Toxins are adsorbed to the resin beds and the purified *uf* is then reinfused between the first and second stage of the filter. The first convective/adsorption stage has no net fluid removal. The blood and reinfused regenerated *uf* then undergo traditional dialysis. The second stage works as conventional HD which also includes the patient net fluid loss.

Reasons to clear plasma water instead of whole blood are: a) a lower plasma water flow rate than the blood flow and consequently longer contact time with the resin and higher toxin adsorption; b) low sequestration of coagulative factors improving the hemocompatibility; c) absence of any depletion of inflammatory cells and platelets. The technique proved easy to use and offered high treatment tolerance, an optimal balance of bicarbonate (since it is not adsorbed and therefore it is reinfused) and was also associated with diminished inflammatory response often related to the exogenous reinfusion. Urea, creatinine, uric acid, Na^+, K^+, phosphates and bicarbonates are not adsorbed and remain unchanged after flowing through the cartridge. These can be managed during the second stage of the diffusive stage of the circuit. Thus the regenerated *uf* in the closed circuit is an endogenous reinfusion of patient plasmatic water. In particular, HFR has been associated with an aa loss similar to that observed with low flux HD, and surely much lower than other high flux HD or HDF on average as high as 33% [29]. The amino acids loss during HFR and low flux HD is approximately 10-11%.

The *uf* is much more than merely plasma water containing a few uremic toxins. Studies using proteomics and other chromatographic analyses have shown that *uf* contains between

over 18,000 proteins and peptides [30-32]. Richter et al [30] found that *uf*, analyzed by MALDI-TOF mass spectrometry, consisted of approximately: 95% masses that were smaller than 15 kDa; 55% of the masses were found to be fragments from plasma protein (fibrinogen, albumin, β2-microglobulin, cystatin); 7% were hormones, growth factors and cytokines; 33% consisted of complement, enzymes, enzyme-inhibitors and transport proteins. Weissinger et al. [32] also found a wide polypeptide's spectrum in a recent study that analyzed *uf* from uremic patients using either high or low flux hemodialyzer. In this study they found a higher number of polypetides in samples obtained from uremic patients with high flux dialyzers compared to low flux dialyzers (1394 polypeptides with high flux ones vs. 1046 with low flux dialyzers), as well as a significant differences when they used healthy donors *uf* by filtering plasma with a 5 kDa or 50 kDa cut-off membranes (590 polypeptides for the high cut off, 490 polypeptides for the low cut off).

Although the study focused on characterization of uremic toxins, there are certainly a lot of beneficial substances that are also lost during HDF with high convection. In conclusion, peculiar characteristic of HFR over classical HDF, is that the technique allows a better removal of high molecular weight toxins, and the reinfusion of vitamins, hormones and other physiologic compounds.

The cartridge adsorption was optimized progressively as investigated by different studies, to determine the maximal adsorption at different *uf* flow rates for different cartridge diameters and quantities of resin. The treatment is performed on the Formula Plus™ dialysis machine (Bellco, Mirandola, Italy) which is equipped with a dedicated algorithm which automatically determines the best *Quf* based initially on the maximal linear velocity (the flow rate that gives the best adsorption). The machine also determines the patient's Hct and transmembrane pressure to adjust the *Quf* based on these parameters.Thus the *Quf* is usually higher at the start of the treatment and then adjusts if necessary to reduce the flow rate based on changes in hemoconcentration [33]. For the handling point of view, this therapy does not add much more respect to an on-line hemodiafiltration, since it adds an external cartridge to be connected along the reinfusion pathway. The remaining extracorporeal circuit is fully preassembled and do not introduce any extra work for the nurses. On the contrary, the advantage of endogenous reinfusion relies in the reduction of extra costs and extra work associated to the analysis of the on-line substitution fluids and to the need of devices and preventive maintenance to guarantee the fluid purity. Finally, the complexity of intra-session management is located inside the dialysis machine being the Q_{uf} automatically adjusted according to the operative conditions in terms of pressures and flow. This tool, again, reduces the complexity of manual adjustment of ultrafiltration rate which must cope with the intra-session changing trans-membrane pressure developed in the hemodialyzer in conventional on-line hemodiafiltration. Very often, this aspect represents one of the major limitations to achieve high exchange volumes OL-HDF.

The HFR architecture has been next extended in terms of plasma water solutes selectivity and sorbent capacity. In fact, the use of more permeable membranes, in the convective chamber, with higher cut-off allows for high molecular weight solute to flow through the sorbent.

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In chronic dialyzed patients in order to reduce the effect of high molecular weight toxins retention, the micro-inflammation and the malnutrition status it is necessary remove molecule with high molecular weight over the albumin limit. For this purpose, the evolution of the HFR technique in SUPRA HFR (by the use of new super high cut-off membrane in the convective chamber: Synclear 0,2 with albumin sieving in water of 0.2), has allowed to achieve this purpose without loss of albumin. This is possible because the resin contained in the cartridge doesn't adsorb the albumin and therefore re-infuse that to the patient [28].

End stage renal disease patient is not the only one that could take advantage of the filtration and adsorption mechanism. Septic shock patients with or without Acute Kidney Injury (AKI) require the removal of high molecular weight inflammation mediators (like, IL-1β, IL-6, IL-8, IL-10, Macrophage Inflammatory Protein-α and β, TNF-α) which cannot be achieved with only ultrafiltrate flowing through the sorbent resin [34,35, 66, 67].

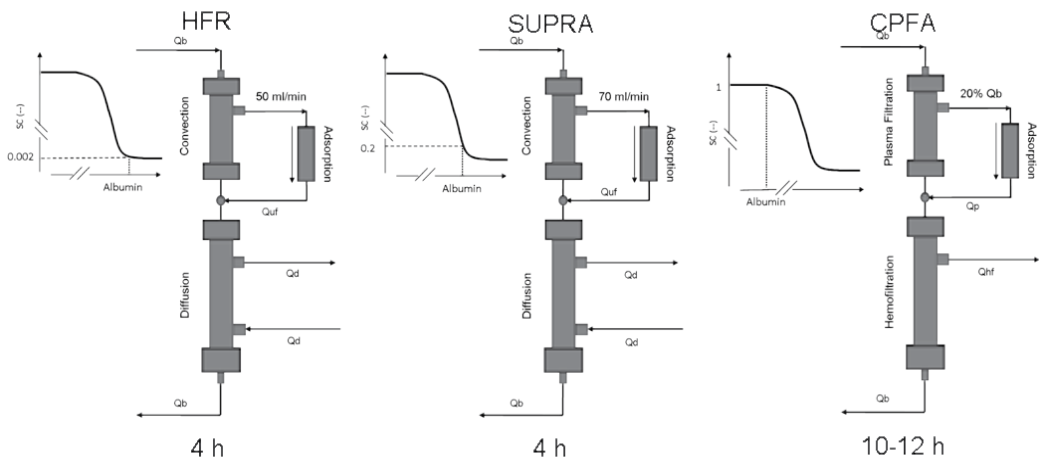

Figure 4. The Filtration Adsorption architecture, form left to right: standard HFR, super high-flux HFR (SUPRA) and CPFA. Figure shows also the albumin sieving coefficient o each convective chamber, the typical *uf* or plasma flow rate and the length of each session.

For this purpose a special technique, dedicate to this kind of patients, that couple plasma filtration with adsorption have been parallelly developed. The name of this technique is Coupled Plasma Filtration Adsorption (CPFA) [36].

The first stage is now a plasma filter (MICROPES 0.45 m^2 polyethersulfone which separates the corpuscular part of the blood from plasma) replacing the convective membrane. Obviously, the fluids treated are very different from those in HFR and then they required to develop a new cartridges with high sorbent properties and performances. Then, a nonselective hydrophobic styrene resin cartridge with macroporous structure 50'000 m^2/cartridge is used. Finally, a synthetic, high-permeability, 1.4 m^2 polyethersulfone hemofilter clears the reconstituted blood in a post-dilution mode to restore the hydro-electrolytic and acid-base bal-

ance and the removal of small molecular weight toxins. The outline of the development of this architecture is shown in Figure 4.

The post-dilution re-infusion rate can be set for up to a maximum of 4 liters/h. The blood flow is usually 150-180 ml/min while the plasma filtration rate is maintained at a fractional filtration of the blood flow (approximately 15-20%).

The treatment is performed for a 10 h period, after which haemofiltration in postdilution mode can continue according to the clinical conditions if needed for renal support.

5. Proteic profiles in extracorporeal filtration adsorption systems

The high-throughput technique Surface Enhanced Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (SELDI-ToFMS) is powerfully used to analyze the protein content of various biological samples [37]. In particular it helps to identifies the types of molecules that could cross the convective membranes and to quantify their relative adsorption onto the resin bed.

The extraction capability could be evaluated as regard to specific pro-inflammatory proteins such as Tumor Necrosis Factor-α (TNF–α), Interleukin 6 (IL-6), α-1-acid glycoprotein [AAG] and Albumin,.

Three different permeability membrane, Polyphenylene High Flux (pHF), polyphenylene Super High-Flux (pSHF) and Synclear 0.2 (Synclear 0.2), whose sieving coefficient are shown in Figure 5, have been investigated and analyzed for their permeability [38].

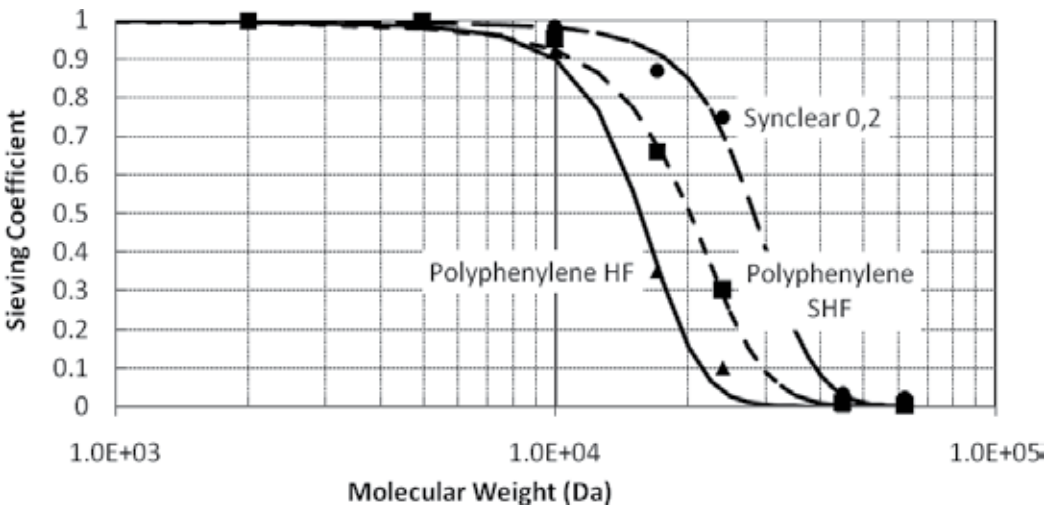

Figure 5. Sieving Coefficient calculated using *in vivo* data for the membrane Polyphenylene HF, Polyphenylene SHF, Synclear 02.

Through nephelometric quantification, (see Figure 6), it is clearly remarkable the high permeability of Synclear 0.2 membrane as shown by the different quantity of high molecular weight molecules which are present in the *uf*.

In particular, it is worth to note, that the membrane with higher pores dimension (Synclear 0,2) allows passage of a higher percentage of albumin with respect to the membrane with lowest pore size (pHF). Much more interesting is the extraction rate of a molecule as α-1-acid glycoprotein despite it has a molecular weight lower than albumin (41-43 kDa vs 66.5 kDa). The different behaviour of such a peptide can be explained by introducing the concept of Stokes radii of a protein, its glycosylation and its subproducts.

The Stokes radius or hydrodynamic radius, is the radius of a hard sphere that diffuses at the same rate as the molecule. This is subtly different to the effective radius of a hydrated molecule in solution. The behaviour of this sphere includes hydration and shape effects. Since most molecules are not perfectly spherical, the Stokes radius is smaller than the effective radius (or the rotational radius). A more extended molecule will have a larger Stokes radius compared to a more compact molecule of the same molecular weight. [39]. For an unglycosylated polypeptide, a value to +l g/mol can be obtained from sequence information or from mass spectrometry. A similar precision cannot be obtained for glycosylated proteins because of polydispersity deriving from the variability of a cell's glycosylation process. Many proteins -and glycoproteins- contain more than one non-covalently linked protein chain, particularly at higher concentrations, and important roles of hydrodynamic methods for mass analysis in protein chemistry are to give the molar mass of the "intact" or "quaternary" structure and to provide an idea of the strength of binding of these non-covalent entities through measurement of association constants [40].

Finally, Table 1 compares the percentage extraction of the different solutes according to molecular weight and the Stokes radius.

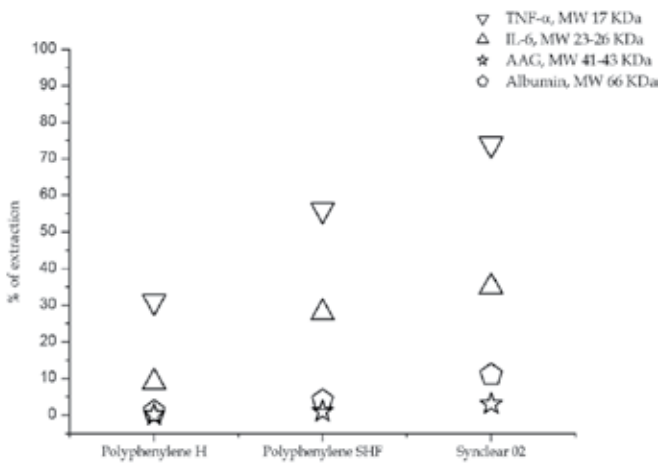

Figure 6. Extraction capability of three different membranes of four molecules.

	TNF-α	IL-6	Albumin	AAG
Molecular weight	monomer 17 KDa, trimer 51 KDa	23-26 KDa	41-41 KDa	66,5 KDa
Stokes radii	monomer 1.9 nm / trimer 2,3 nm	2 nm	3,5 nm	3,5 nm
Polyphenylene H	31%	9%	1%	0%
Polyphenylene SHF	56%	28%	4%	1%
Synclear 02	74%	35%	11%	3%

Table 1. Differences between molecular weight and Stokes radii of TNF-alpha, IL-6, AAG and Albumin. Stokes radii come from literature data: [41-44]. Extraction percentage of different molecules with different membranes.

6. Clinical experiences with HFR

Several studies have been published since the first introduction of filtration-adsorption therapies on the late 80's. Many of them showed that this technique is particularly suited for chronic patients at major risk of inflammation, malnutrition and with cardiovascular function impairment, such as diabetics, elderly, with high C-reactive protein (CRP) levels.

Table 2 shows the results observed in the main clinical trials comparing HFR against or standard HD or convective technique such as on-line HDF (OL-HDF). Most of the authors reported a significant reduction of pre-dialysis levels of β2-microglobulin, particularly marked when comparing the time pattern against standard HD. For instance Kim et al. found out a reduction of pre-dialysis plasma levels from 37.7 to 28.3 mg/L when patients were treated with HFR. Similar results were also observed from Bolasco et al (from 28.9±8.9 to 22.9±6.7 mg/L, p=0.008). Panichi et al did not find any significant reduction of the pre-dialysis β2-microglobulin over the time but the results were similar to those obtained with OL-HDF.

Pre-dialysis IL-6 significantly reduced over the time as shown by Panichi et al from 14.8±6.5 to 10.1±3.2 pg/mL and by Bolasco et al from 21.8±20.4 to 18.9±22.2 pg/mL. On the contrary Kim et al found out an increase of IL-6 even though the patients plasma levels were extremely low (1.69 to 2.48 pg/mL).

The results about CRP are in accordance to those on IL-6. In fact, CRP decreased by 30% to 50% over time respect to conventional HD. Similar results were obtained by Panichi in OL-HDF and the best results have been seen when patients presented high CRP plasma levels at the baseline.

It must be underlined that pre-dialysis albumin plasma levels did not changed significantly in all the studies reported (on average nearly 3.6 g/dL) even though Panichi reported a pre-

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albumin levels increase more pronounced in HFR than in OL-HDF (from 30.5±3.5 to 34.0±3.9 mg/dL in HFR vs 30.6±3.9 to 32.3±3.5 mg/dL in OL-HDF). This result can be partly explained by the use of a sterile apyrogen substitution fluid (which is true for OL-HDF and particularly for HFR where the substitution fluid is regenerated by patient *uf*) and by the lower removal of essential and branched chain aa typical of HFR. In fact, as already mentioned, in addition to a good removal of uremic toxins and reduction of inflammation of the molecules, the HFR is also characterized by a considerable saving of aa and vitamins. Hemodialysis high flux and OL-HDF are associated with a depletion nearly of 25-30% of the aa concentration from the beginning of the dialysis session, which quantifies in a loss of about 5-10 g/treatment [7, 50-52].

Ragazzoni et al. [53] have firstly shown that HFR is associated with a significant saving of total aa (essential and branched chain), in comparison with OL- HDF. In a pilot study, 11 patients in conventional HD were randomized to HFR or OL-HDF, and the overall aa removal measured as pre to post-dialysis plasma levels were from 3122±578 μmol/L to 2395± 493in HFR and from 3030±578 to 1852±302 in post-dialysis respectively.

Borrelli [48] confirmed these results by comparing the HFR with acetate free biofiltration (AFB). In particular, the 48 patients recruited (24 in HFR and 24 in AFB), were observed in a single session as regard the AA loss. The authors reported a depletion of plasma total aa levels from 3176±722 to 3044±687 μmol/L in HFR more pronounced than in AFB from 3399±621 to 2551±428 μmol/L ($p<0.01$).

Morosetti M. [58] conducted a pilot study of patients treated with HFR and on-line HDF, measuring plasma levels of vitamin C at the beginning, the end of treatment and in the uf in pre-and post-cartridge. The results have documented that, in HFR, levels of vitamin C in the ultrafiltrate are lower than those detected in plasma, a phenomenon due to the partial oxidation of vitamin during the convection (removal of other species anti-oxidants such as proteins), but at the same time has been shown that the vitamin C contained in the uf is not adsorbed by the HFR cartridge and therefore is re-infused to the patient. Furthermore, the authors have demonstrated that plasma levels of vitamin C, are higher in patients treated with HFR compared to those with on-line HDF

Calò et al. [55] recently studied the plasma levels of inflammation and oxidative stress markers, and the long-term changes in mononuclear cell protein expression of heme-oxygenase-1 (HO-1) in a prospective longitudinal study trial comparing HFR versus standard HD. Patients in HD were recruited and assessed at the baseline and then they were treated for one year in HFR. Change of oxidized low-density lipoprotein(OxLDL) was significantly lower after 12 months on HFR compared with baseline: 475.4±110.8 ng/mL (time zero) versus 393.1±101.9 ng/mL (12 months), $p < 0.04$. Moreover, during treatment with HFR the protein expression of HO-1 over time increased ($p< 0.00001$) and it approached the statistical significance versus time zero at six months (0.27±0.10 vs. 0.17± 0.11, $P = 0.0527$) and became significantly different from time zero at 9 (0.48 ±0.20, $p < 0.043$) and 12 months (0.59±0.32, $p < 0.004$). This result is accompanied by the lack of any change of inducible Nitric Oxide Synthase (iNOS) protein expression over time (1.02±0.39 and 1.06±0.42 from 0 to 12 months, respectively, p= ns).

Author	Patients	Study Design	Major Results on HFR	*p*
Panichi, 2006 [45]	Unselected n=25	Prospective randomized cross-over trial OL-HDF(4ms) – HFR (4ms) HFR(4ms) – OL-HDF(4ms)	β2-microglobulin no change in HFR while decreased by 7% in OL-HDF IL-6 reduction by 32% in HFR vs 21% in OL-HDF (significant vs baseline) CRP reduction by 30% in HFR vs 38% in OL-HDF(significant vs baseline) No change in albumin (3.7±0.3 g/dl) Prealbumin increase by 11.5 in HFR vs 5% in OL-HDF	ns <0.02 <0.05 ns ns
Bolasco, 2006 [46]	No severe cirrosis, no heart failure, no neoplasm or chronic inflammation n=44	Longitudinal HD (3ms) – HFR (6ms)	β2-microglobulin decrease by 21% CRP drecrease by 50% PTH no changes (on average 318 pg/mL) Phospates non change (on average 5 pg/mL)	0.022 0.02 ns ns
Kim, 2009 [47]	Unselected n=11	Longitudinal study BHD(12wks) – HFR(12wks)	72% reduction of plasma level of leptin 67% reduction of adiponectin No change of IL-6 72% reduction of plasma level of β2-microglobulin	0.014 0.001 ns 0.002
Borrelli, 2010 [48]	No severe cirrosis, heart failure, neoplasm chronic inflammation n=48	Observational matched case-control study HFR(1s) vs AFB(1s)	17% less post-dialysis level of total AA in AFB than HFR 20% less post-dialysis level of essential AA in AFB than HFR	0.0001 <0.0001
Bolasco, 2011 [49]	Patient with no chronic or acute recurrent inflammation n=38	Prospective randomized cross-over AF HFR(3ms) – HFR(3ms) - AF HFR(3ms)	25% reduction of pre-dialysis level of β2-microglobulin IL-6 reduction by 13% vs baseline HD CRP increase by 40% vs baseline HD 7% increase predialysis level Hgb 18% reduction of ESA consumption No change in cytokine preedialysis level No change in pre-dialysis serum albumin No change in vitamin supplementation	0.002 <0.04 ns <0.04 ns ns ns ns

Legend: AF=Acetate Free, AA=AminoAcids, AFB=Acetate Free Biofiltration, OL-HDF=On Line Hemodiafltration, ms=months, s=session, wks=weeks, ns=not significant, CRP=C-Reactive Protein.

Table 2. Summary of clinical trials HFR in the last six years comparing inflammatory parameters and nutritional makers

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Splendiani et al. [56] have shown that the styrenic resin HFR cartridge is able to adsorb significant amounts of homocysteine without simultaneous adsorption of vit. B12 and folate: this suggests an important mechanism for reducing cardiovascular risk. Cardiac troponin (cTnT) is a sensitive marker of cardiac hypertrophy and myocardial injury and correlates with left ventricular mass. There is evidence that the cTnT plasma concentration increases in chronic uremic patients in renal replacement therapies even without signs of heart disease [57, 58] and that cTnT is an independent predictor of cardiovascular events. De Filippi et al. [59] reported that cTnT can be elevated in 30% to 75% of uremic patients on hemodialysis, and that even small increases are associated with an increased likelihood of coronary heart disease. Lippi et al. [60] showed that variations of cTnT level after dialysis can be linked to blood hemoconcentration and membranes type. Sommerer at al. [61] reported the existence of a significant correlation between cTnT levels and non-native arteriovenous fistulae (implants and catheters), probably due to a state of chronic inflammation often associated with this type of vascular access.

Even though the recent scientific literature generally reports a diminished impact on inflammation and hyper-catabolism induced by extracorporeal dialysis [62] (maybe due to different types of membranes [63]), a further optimization of the various methods HDF must take into account also the buffer used in dialysis (Dialysis Solution DS) and reinfusion fluids. The use of large amounts of on line reinfusion fluid (pre-, post- or pre/post-dilution) exposes the patient to a risk of direct toxic effects or fluid hemo-compatibility with negative clinical consequences. It 's well known that accelerated atherosclerosis is the main risk factor for morbidity and mortality for dialyzed patients: in addition to traditional risk factors, some others play a key role, such as formation of non-enzymatic glycation products, hyper-homocysteinemia, alterations in calcium-phosphorus balance, hemo-incompatibility reactions. All this is due, not only to the dialysis membranes contact, but can be activated by components of the DS or substitution fluids.

Bolasco et al. [49] studied 25 patients in a cross-over longitudinal study. Patients were recruited and studied in a run-in period of three months in standard HD and they were subsequently treated with standard HFR and acetate free (AF) DS (Lympha ®), each period lasting three months. At the beginning and at the end of each period, blood samples were taken to analyse cTnT plasma levels while blood pressure and heart rate were recorded in all the sessions. The results showed a significant decrease in cTnT from standard HD, to HFR AF at the end of first period (from 1.32±0.35 to 1.12±0.31 ng/mL, $p < 0.05$), a subsequent rise in HFR with DS containing acetate (from 1.12±0.31 to 1.28±0.37 ng / mL, $p = < 0.05$) and a further decline (although not statistically significant) from 1.28±0.37 to 1.21±0.35 ng/mL in the last period of HFR AF. It was observed a significant systolic and diastolic pressure drop accompanied by a compensatory increase in heart rate during the sessions in standard HFR while arterial blood pressure did not significantly changed in HFR AF. No significant differences of acid-base recovery were observed in the two therapies.

Bolasco et al. [64] studied 16 patients, in a comparison of HFR with conventional HD, with regard erythropoiesis And erythropoiesis stimulating agents (ESAs) requirement. They demonstrated a statistically significant increase of Hb levels in HFR vs HD (from 11.22 to

11.66 g/dL, p <0.05), while for ESAs has been a simultaneous significant decrease from 29,188 to 16,750 IU/month (p = 0.01). The data showed that the HFR itself is able to determine an improvement of erythropoiesis.

Based on this study, the HFR seems therefore to be an HDF technique that can positively affect the level of Hb and the needs of ESAs. This favourable effect seems to be independent from the dialysis dose (Kt/V), the replacement fluid volume, and the presence or absence of acetate in the DS. This result could be attributed to a saving of useful substances such as aa and vitamins, and the lack of depletion of factors inhibiting erythropoiesis [60].

It must be pointed out that the reinfusion of the same closed-loop patient plasma water guarantees undoubtedly sterility and pyrogenicity that is not always assured in OL-HDF, then reducing the effects of micro-inflammation. In a study involving 166 patients, Axelsson et al. [65] have demonstrated, that there is a significant correlation between the indices of sensitivity to ESAs and levels of CRP and IL-6. Moreover, with a multivariate stepwise regression model they can concluded that ferritin (log), PTH, leptin (log), IL-6 (log)) are significantly associated with the ratio of ESAs/Hb.

The association between purity of dialysate solution and substitution fluid and ESA consumption or Hb levels in hemodialysis patients have shown that the ESA dose increases linearly as the plasma levels of IL-6. Patients in whom ultrapure dialysis fluid was used required less epoetin than those in whom standard dialysis fluid was used (64±22 vs 92±12 UI/Kg/week, p<0.05) [66].

Recently, Testa et al. [67] have published positive clinical results on the use of HFR for the removal of serum free light chains (Immunoglobulin Free Light Chains - FLCs). The FLCs are divided into two major classes κ and λ depending on the aa sequence in the constant portion of the polypeptide. Light chains k are usually monomers of the weight of 22 kD, those λ dimers of the weight of 44 kD. The production of light chains by plasma cells in the bone marrow is around 500 mg/day. They have a half-life of between two and six hours and are usually filtered and subsequently reabsorbed in the proximal tubule. It 'clear that the concentration of FLCs increases in two situations: increase in production (gammopathies) or reduced clearance, such as in renal failure. There is a direct correlation between serum creatinine and FLCs, and the increase of these units represents a reliable measurement of the progression of renal failure.

The highest rates of FLCs are typical of the uremic patients on hemodialysis, and this shows how the current methods of purification will not be able to offer an adequate clearance of these molecules, defined as true uremic toxins. By contrast, Hutchison et al. [68] have described an alternative strategy of HD intensive filters with membranes with high permeability (Poliariletersulfone with a cut-off of 45 kD), capable of removing significantly FLCs in excess, method, however, associated with an important loss of albumin of 20-40 g/session.

Testa et al. [67] have studied two different groups of patients treated with HFR: one with production of polyclonal light chains, the other with monoclonal antibodies; the results showed a significant reduction of FLCs in both groups (31% and 34% reduction rate of κ chains respectively in polyclonal and monoclonal FLCs group; 20% and 11% reduction rate

of λ chains again in polyclonal and monoclonal FLCs group). The analysis by *uf* at cartridge inlet and outlet confirmed the adsorptive capacity of FLCs.

In summary, it should be noted that the HFR can not be greater than the traditional HDF in the field of the elimination of toxic solutes, as the adsorption can not be more effective. The focal point is the best compromise between saving of essential elements and a satisfactory toxins removal in a wide spectrum.

7. Clinical experience with Couple Plasma-Filtration Adsorption (CPFA)

First animal experiments with CPFA were done to determine safety and efficacy, as well as whether CPFA could actually play a role in modulating the inflammatory response [69].

Table 3 reports the results obtained in the main clinical trials comparing CPFA with standard treatments. It can be seen that this therapy is in general able to ameliorate the hemodynamic response of septic shock patients highlighted by the general reduction or early interruption of vasopressors and amines in groups treated with CPFA. Moreover, the cytokines plasma levels seem to reduce faster in CPFA than standard treatments.

Ronco and co-workers studied haemodynamic parameters and the ability to restore leucocyte responsiveness in a cross-over trial of septic patients who underwent 10 h of CPFA followed by 10 h of continuous venovenoushaemodiafiltration (or vice versa)[70]. They also monitored leucocyte responsiveness to in vitro stimulation by endotoxin. At the beginning of the CPFA treatment the cells were not able to produce appropriate amounts of TNF-α, whereas production was restored at the end of treatment. Cell hyporesponsiveness to secondary bacterial challenges is part of an overall immunosuppressive effect seen in septic patients and is frequently associated with worse outcomes [74].

These authors observed a significant improvement in hemodynamics with the use of CPFA compared with hemodiafiltration. They also observed a significant increase in leukocyte responsiveness after CPFA treatment. For these experiments, they monitored spontaneous and endotoxin-stimulated leukocyte TNF- α production after 10 h of treatment. At the beginning of the treatment, there was a marked leukocyte hyporesponsiveness to endotoxin stimulation (immunosuppression). As the treatment progressed, the responsiveness increased. Further support for the role of CPFA in the restoration of immune responsiveness was observed by incubating pre and post resin plasma with monocytes obtained from healthy donors. The pre-resin plasma at the beginning of treatment had a strong immunosuppressive effect – unless the plasma had first been incubated with monoclonal antibodies to IL-10. In contrast, the post-resin plasma (at the beginning of treatment) produced higher quantities of TNF- α after endotoxin challenge, and nearly normal quantities after 10-hour treatment. One of the interesting observations of this study was the absence of significant changes in circulating plasma levels of IL-10 or TNF- α even though there was almost complete adsorption of these cytokines by the resin cartridge. This suggests that there may still be other factors that are adsorbed by the cartridge that play a role in immunosuppression.

For this reason, the results presented in this study may be particularly relevant as the end point of the study was restoration of immune responsiveness, rather than a net increase or decrease in specific inflammatory mediators.

Formica and colleagues conducted one of the first trials of CPFA to include septic patients with and without renal insufficiency all of them with a high APACHE II score (24.8 B 5.6) and multiorgan failure. Six of the 10 patients had normal renal function. The authors performed 10 consecutive sessions and observed a net decrease in vasopressor requirement, increased mean arterial pressure, improved pulmonary function and a reduction in C-reactive protein. The patients treated with CPFA had a 70% survival [71].

Another study by Mariano and colleagues [77] evaluated CPFA in burn and polytrauma patients with septic shock and acute renal failure. Patients were divided into either heparin or citrate anticoagulation based on whether they had a high bleeding risk. The citrate anticoagulation was well tolerated and gave comparable results to the group with heparin anticoagulation. The previous CPFA studies included septic patients with acute renal failure that required renal support.

Recently, Berlot et al. [78] showed in septic shock a case report in which CPFA was able to ameliorate the microcirculation during the session. Sublingual microvascular perfusion was assessed using the orthogonal polarisation spectral imaging technique at three different times: pre-CPFA, at two hours during the treatment and two hours after the end of the session. During CPFA, the number of perfused vessels increased compared with the pre-treatment period, but decreased again after its termination. The author concluded that the elimination of septic mediators during the procedure could account for the observed microvascular perfusion variations.

Further case histories pointed out the effectiveness of CPFA in several other diseases such liver failure [79], Weil's syndrome [80] acute respiratory distress syndrome (ARDS) [81].

Caroleo et al. studied a case of a 70-year-old woman who developed hypoxic hepatitis secondary to cardiogenic shock after cardiac surgery [79]. CPFA was used primarily as an extracorporeal supportive therapy for multiple organ failure (MOF). The authors reported a significant reduction of the plasmatic concentration of conjugated bilirubin, achieving a mean reduction rate (RR) of 53% during treatment. CPFA proved to be a valid tool for concomitant hemodynamic support and organ replacement therapy.

Moretti and coworkes reported a case of a 27-year-old man with Weil's syndrome accompanied with hypotension, anuria refractory to fluid therapy, ARDS, and hepatic involvement [80]. CPFA was started early after the onset of shock and five treatments were performed. Each session lasted for 10 h with 14 h interval. Weaning from vasopressors was achieved during the second course of CPFA, while weaning from ventilation was achieved after 6 days.

Lucisano et al reporteda case of a 43-year-old male who developed ARDS secondary to pneumonia and acute kidney injury, whose clinical conditions rapidly improved after early CPFA therapy [81]. CPFA was performed for 6–8 h (daily, for three consecutive days).

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Twenty-four hours after the first CPFA session CPAP was withdrawn. After 4 days, the oxygen saturation achieved 97% without ventilation. During the 3 days in which CPFA treatments were carried out, serum levels of pro-inflammatory cytokines, procalcitonin and CRP decreased progressively as well as APACHE II which achieved a score of 9 five days after the first CPFA session.

Author	Patients	Study Design	Major Results	*P*
Ronco 2000 [70]	Septic pts N=unknown	Prospective Randomized Controlled Trial CPFA – CVVH CVVH - CPFA	Improvement of hemodynamic response Reduction of norepinephrine dose	
Formica 2003 [71]	Septic shock pts N= 12	Prospective Longitudinal CPFA	Improvement of MAP Improvement of Cardiac Index Increase of SystVasc Res Index Improvement of PaO2/FiO2 No change extracvascular lung water intra-thoracic blood index Survival @ 28 days 90%, @90 days 70%	<0.001 <0.001 <0.001 <0.001 Ns Ns
Ronco 2002 [72]	Septic shock pts N= 10	Prospective pilot CPFA (10h) – CVVHDF (10h) CVVHDF (10h) – CPFA (10h)	Increase of MAP by 11.8 vs 5.5 mmHg Reduction of norepinephrine 0.08 vs 0.0049 ug/Kg/min	0.001 0.003
Lentini 2009	Septic shock, AKI N=8	Prospective Randomized Controlled Trial HVHF-CVVH-CPFA-CVVH CPFA-CVVH-HVHF-CVVH	No change MAP No change Norepinephrine No change Vasopressor No change PaO2/FiO2	0.29 0.18 0.22 0.08
Mao 2011 [74]	Septic shock, MOF N=7	Prospective Randomized Controlled Trial CPFA (10h) – HVHF (10h) HVHF (10h) – CPFA (10h)	Increase MAP 120.75±20 vs 115.3±18.5 mmHg paO2/FiO2 297.3±204 vs 265.45±173.7 reduction of Cytokines plasma levels	<0.05 <0.05
Hu D 2012 [75]	Septic patients or MODS N=14	Prospective Randomized Controlled Trial CPFA HVHF	TNFa (pg/mL): 178±58 →186.9±55.1 in HVHF; 229.8±44.2 → 151.8±29.4 in CPFA Intercellular adhesion molecule-1 (ng/mL): 708.1±98.3 to 675.6±44.4 in HVHF vs 798.1±134.1 to 347.6±181.5	<0.01 <0.01

Legend: CVVH=Continuous Venous-Venous Hemofiltration; HVHF=High Volume HemoFiltration; MAP=Mean Arterial Pressure; MODS= Mutli Organ Distress Syndrome.

Table 3. Summary of the main clinical CPFA trials.

8. Conclusions

Although extracorporeal treatments have shown several developments over the years in the attempt to achieve better results in terms of survival both in acute and chronic patients, nevertheless they still remain poorly selective and with many limitations linked to the loss of nobles substances.

Filtration-adsorption architectures seems to be viable forms of extracorporeal blood purification systems which can enhance the capability to remove molecules in a wide range of molecular weight spectrum with the advantage of retaining molecules essential to the organs and subject life.

HDF has bee proven to obtain better clinical results in chronic dialysis population, even though renal replacement therapies still suffer from drawbacks related to inflammation, oxidative stress, morbidity and cardiovascular associated diseases. Diabetes, hypertension and age, often translate into clinical frailty and poor quality of life, often closer to survival than to cope with the disease. All these factors are extremely important in the choice of the convective therapy to adopt. HFR seems to combine a high removal of uremic toxins thus lowering the micro-inflammation status which can bring to benefits especially in cardiac compromised.

Further developments of this architecture could come from the use of super high-flux membranes with cut-off values much higher than the albumin limit and/or from the discovery of new adsorbent resins even more selective to specific molecules responsible for particular diseases.

In the meanwhile, we can take advantages of the clinical results gathered so far which can address the HFR to malnourished and inflamed patients and CPFA to septic ones.

Further studies are advocated to understand the potential of such architectures on high-end points like survival of both acute and chronic population as well as quality of life.

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Chapter 20

Advances in Hemodialysis Techniques

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Additional information is available at the end of the chapter

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1. Introduction

Hemodialysis (HD) is a technique that is used to achieve the extracorporeal removal of waste products such as urea and creatinine and excess water from the blood when the kidneys are in a state of renal failure. HD is the most prevalent modality of renal replacement therapy for patients with kidney failure followed by kidney transplantation and peritoneal dialysis.

Hemodialysis treatment is provided for critically ill patients with acute kidney injury as inpatient therapy. More commonly, HD is routinely provided for stable patients with end-stage renal failure (ESRF) as an outpatient therapy conducted in a dialysis outpatient facility, either a purpose built room in a hospital or a dedicated stand-alone clinic. Less frequently HD is done at home, where it can be self-initiated and managed or done jointly with the assistance of a trained helper who is usually a family member.

The principle of HD is the same as other methods of dialysis; it involves diffusion of solutes across a semipermeable membrane. HD utilizes counter current flow, where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit. Counter-current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis. Fluid removal (ultrafiltration) is achieved by altering the hydrostatic pressure of the dialysate compartment, causing free water and some dissolved solutes to move across the membrane along a created pressure gradient. Urea, creatinine and other waste products, potassium, and phosphate diffuse into the dialysis solution. However, concentrations of sodium and chloride in the dialysate solution are similar to those of normal plasma to prevent loss. Sodium bicarbonate is added into dialysate in a higher concentration than plasma to correct blood acidity. A small amount of glucose may also be added to dialysate solution [1].

This chapter will focus on the recent advances in HD techniques, and illustrate and compare the different HD modalities that can achieve a better quality of life than the conventional HD treatment.

2. Background

Conventional HD remains the main modality of renal replacement therapy for patients with end-stage renal disease (ESRD) worldwide [1-5]. The technique of conventional HD is based on the physiologic principle of "*diffusion*", which means clearance or removal of high concentration of uremic toxins (in the blood) to the lower concentration solution (dialysate) through a semi-permeable membrane (the dialyzer or filter) [6]. Conventional HD is usually conducted over four hour duration three times per week for stable patients with ESRD. The dialyzer or filter used is usually of low-flux type, and the filtered molecules are water-soluble small-size (molecular weight< 500 Dalton) compounds.

Conventional HD treatment had over many years improved the survival rate of patients with ESRD [2] (figure 1a, 1b). However, this basic modality of dialysis is far from replacing the function of the normal kidneys. In fact, conventional HD prescription provides only about 10% of the clearance power of the natural kidneys [7]. Although it is capable of removing excess water and small size uremic toxins, yet conventional HD is not capable of removing middle and large size (>500 Dalton) and protein-bound toxic molecules [8]. These middle- and large-size molecules, which cannot be cleared and could be harmful, include β_2-microglobulin (β_2-M), which is strongly associated with carpal tunnel syndrome and dialysis-related amyloidosis [9], and pro-inflammatory cytokines and severe vasoactive molecules such as p-cresol and uridine adenosine tetraphosphate (table 1). The accumulation and retention of all types and sizes of uremic compounds (and excess water), which have concentration-dependent toxicity, leads to increased morbidity and mortality. Furthermore, the unphysiologic pattern of conventional intermittent HD (three times per week) with rapid change in fluid volume and electrolytes and uremic solutes serum concentrations results in permanent disequilibrium of internal milieu and inter and intra-dialysis complications [10].

Conventional HD has been associated with frequent intradialysis complications (hypotension, sickness and cramps) and post-dialysis complaints of headache, fatigue and inability to concentrate and function, which may impair significantly the quality of life, result in poor compliance, inconsistency in achieving HD prescription and inadequacy of HD sessions. Inadequate HD is mainly due to poor compliance and non-adherence to HD regimens (e.g. fluid restriction, regular attendance of dialysis sessions and adherence to four hours session) and the clearance limitations of the conventional HD technique. It has been shown that skipping at least one dialysis session is associated with a 25%-30% increase in the risk of death [4]. Moreover, even patients attending regular HD sessions are at increased risk of death, heart attacks and hospital admissions (for myocardial infarction, congestive heart failure, dysrhythmia and stroke) on the day after the two-day interval between HD treatments each week than at other times [11]. Inade-

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quate HD delivery also has cost implications as a consequence of increased hospitalization rate; days stay at hospital and inpatient expenditures [12].

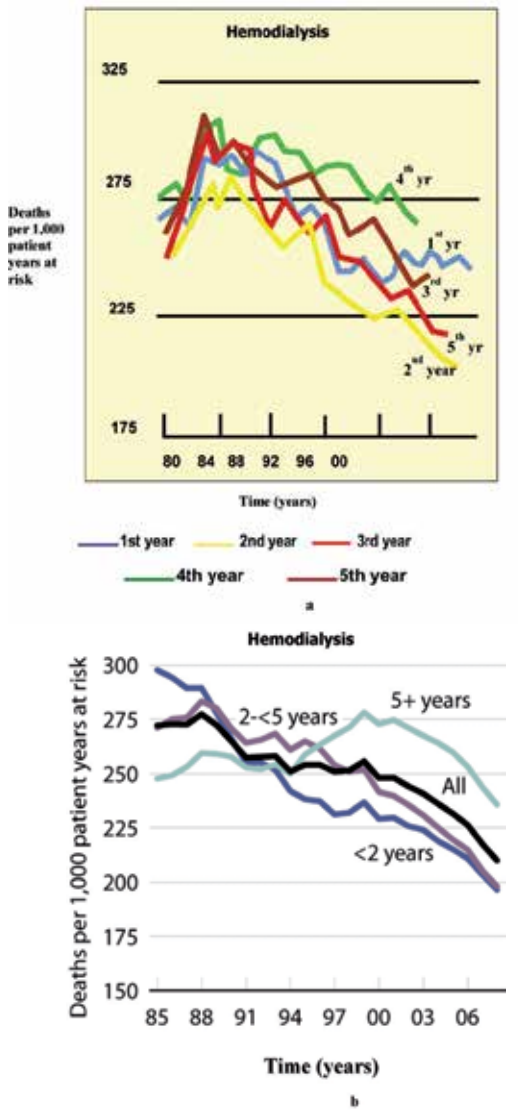

Figure 1. a: The undeniable clinical progress in hemodialysis reflected by the significant drop in mortality rates in incident ESRD patients from 1980-2010. *U.S. Renal Data System, the data supplied by the United States Renal Data System (USRDS): 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.* **b:** The undeniable clinical progress in hemodialysis reflected by the significant drop in mortality rates in incident ESRD patients from 1980-2010. *U.S. Renal Data System, the data supplied by the United States Renal Data System (USRDS): 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010*.

Small Water Soluble Molecules (MW <500 Daltons)	Middle Molecules (MW >500 Daltons)	Protein-Bound Molecules (MW >500 Daltons)*
Sodium (23)	Adrenomedullin (6032) (potent hypotensive peptide)	Hippuric acid (insulin resistance and glucose intolerance)
Phosphorus (31)	AGE*	Homocystein (atherogenecity and thrombogenecity)
Potassium (35)	AOP*	Indoxyl sulfate (pro-inflammatory effect & endothelial dysfunction)
Urea (60)	Vitamin B12 (1355)	- *p*-cresylsulfate – *p*-cresol (endothelial and pro-inflammatory)
Creatinine (113)	Endothelin (4238) (strong vasoconstrictor)	Polyamines (inhibit erythroid colony growth in a dose-dependent way)
Uric acid (168)	PTH (9225)	
Glucose (180)	β_2-M (11800)	
	Leptin (16000)	
	Cytokines (15000-30000)	
	Immunoglobulin LC (28000 – 56000 Da)	
	Uridine adenosine tetraphosphate (very strong vasoconstrictive)	

Table 1. Examples of types and sizes of different uremic toxic molecules.

Patients managed with conventional HD are potentially exposed to hemodynamic instability, excessive intradialytic weight gain, anemia, mineral and bone metabolism disorder, inadequate nutrition, infection and sexual and psychosocial problems. The increased risks of fatal and non-fatal cardiovascular complications, which are the main cause of death in HD patients, continue to be much higher than in the general population. It has been reported that only 32% to 33% of patients on conventional HD survive to the fifth year of treatment [13]. In fact, the mortality rate in conventional HD ranges between 14-26% in Europe [14, 15] and 24% in USA [1, 2]. Actually, conventional HD does support life but has failed to restore the patient to full functional normality and longevity.

Quality management of dialysis patients is best achieved by implementation of "pre-dialysis care" [16], and care improvement at "post dialysis" stage [17]. Post-dialysis care should ensure strict control of infection [18, 19] and predominance of arterio-venous fistula (avoidance of indwelling catheters for vascular access) [20]. Furthermore, dialysis care should include (1) adequate control of body fluids (achievement of euvolemic status), where strict volume control has been shown to reduce both morbidity and mortality and dialysis ade-

quacy outcomes [21, 22], (2) mitigation of left ventricular hypertrophy and fibrosis, and (3) efficient removal of all types and different sizes of retained uremic toxic solutes that would result in inflammation and exacerbation of cardiovascular damage [20]. Actually, improvement in quality HD care should achieve optimum HD rather than adequate HD.

The aim of HD technique has, and will always be, to simulate or reproduce the physiologic process of glomerular ultrafiltration. Conventional HD, which is performed over 4 hour duration and conducted three times per week, does not fulfill this criterion [1]. The major deficiencies of this technique are limited solute clearance and volume control, which have been associated with poor quality of life [23] and unacceptable high rates of morbidity and mortality [2, 14, 15, 24, 25].

Over the past four decades it has been suggested that the accumulation of various 'uremic toxins', and in particular middle-size and protein-bound molecules, contribute to this increased mortality. These toxins include urea, phosphorus, parathyroid hormone (PTH), β_2-microglobulin, homocysteine, leptin and a variety of esoteric molecules such as advanced glycation end products, asymmetric dimethylarginine and advanced oxidation protein products [8, 26, 27]. Furthermore, the persistence of increased interdialytic weight gains and the limited ability of conventional HD to maintain adequate homeostasis, without frequent episodes of hypotension and increased risk for cardiovascular and all-cause mortality [28], results in failure of many HD patients to achieve adequate volume control and remain permanently volume overloaded [21]. This has been associated with increased prevalence of hypertension, left ventricular hypertrophy and increased cardiovascular mortality, as a major cause of death, among patients treated with conventional HD [21, 29].

Observational studies [30-35] and randomized controlled trials [36, 37] of improving the efficiency of hemodialysis, by increasing frequency and duration of HD treatment, demonstrated better clearance efficiency of uremic toxins and volume control, and improved quality of life. However, the recent innovations in HD technologies paved the way for better quality HD. These include higher specifications of HD machines, creation and improvement in dialysis membranes with different transport (clearance) capabilities of middle, large and even protein-bound molecules by using all the available membrane separation phenomena: diffusion, convection and adsorption, and quality improvement in the technology of water treatment plants, with almost nil presence of bacteria growth and endotoxin concentration. Based on different observational studies and randomized clinical trials and new innovations, this chapter illustrates the possible and available options of different advances in HD techniques, their influence on improving the adequacy of HD, the patient's quality of life and the reduction in morbidity and mortality rates.

3. Adequacy of hemodialysis

The adequacy of HD is usually assessed and measured by Kt/V [38]. This represents the product of clearance (K) per time multiplied by the duration (t) and adjusted for body size by dividing this clearance by the distribution volume (V). Kt/V reflects the clearance of urea,

as a surrogate marker for the clearance of small, but not middle or large-sized, uremic toxins. The single-pool Kt/V overestimates the delivered dose of dialysis, because it fails to account for blood urea rebound after dialysis. A more accurate measure of the dialysis dose, the equilibrated Kt/V, corrects for urea rebound and is usually 0.15 to 0.20 lower than the single-pool Kt/V. Ideally, single-pool Kt/V should not be below 1.4, as lower values have been associated with increased morbidity and costs [12], and reduction in survival rate [39-41]. The efficacy of HD, where low flux dialyzers are usually used, is limited by its inability to clear from circulation the middle or large-size or protein-bound toxic molecules. Increasing the dose of dialysis or using high-flux dialyzer membrane can help in ensuring optimal values of Kt/V. However, the hemodialyis (HEMO) Study, which was a randomized clinical trial, did not alter survival or morbidity by increasing the dose of dialysis or using a high-flux dialyzer membrane [42].

Adequacy and efficiency of HD can be increased by avoiding intradialytic hypotension episodes and frequent interruption of the 4 hours HD session. This can be achieved, in part, by controlling intradialytic weight gain (<4%) by fluid intake and sodium restriction and lowering dialysate sodium concentration [43], and avoiding rapid ultrafiltration (not to exceed 10 ml/Kg/hr), where exceeding this limit has been associated with increased risk for cardiovascular and all-cause mortality [28, 29]. The adequacy and efficiency of HD can also be improved by increasing the blood [44-47] and dialysate [48, 49] flow rates and the dialyzer size and surface area [50, 51]. However, recent improvements in dialyzers technology, such as hollow fiber undulations, spacer yarns and changes in fiber packing density [52], have led to improvement in dialysate flow distribution through the dialysate compartment (with improved urea clearance) and reduced the need of increasing dialysate flow rate from 600 ml/min to 800 ml/min; an achievement with important economic impact allowing a significant reduction (25%) in water consumption [53].

4. Efficient hemodialysis

The efficiency of HD is largely dependent on arterial blood flow rate from a well-preserved and functioning vascular access [44-47]. The vascular access is the life-line for end-stage renal disease patients on regular hemodialysis. There are three major types of vascular access: arterio-venous fistula (AVF), arterio-venous graft (AVG) and central venous catheter (CVC). The type of vascular access is associated with patient outcome. Despite the recent improvement and advanced technology of catheters, temporary and permanent catheters have been associated with increased incidence of luminal thrombosis, central venous stenosis, inadequate blood flow rate, inadequate dialysis, increased risk of infection, increased risk of hospitalization, increased risk of death and high cost [54-61]. AVG has also been associated with bleeding, infection and graft failure. The KDIGO guidelines published in 2001 [62] defined the ideal vascular access as that which (a) delivers a flow rate adequate for the dialysis prescription, (b) has a long use-life, and (c) has a low rate of complications (infection, stenosis, thrombosis, aneurysm and limb ischemia). Although none of the major types of vascular access fulfills all of these criteria, the native AVF is the closest to this definition [62].

The "Fistula First Breakthrough Initiative" [63] was established in 2003, where a goal set to have 40% AVF use in prevalent US hemodialysis patients. This goal was achieved in 2005. The bar was subsequently raised to 66% AVF use, a level which was comparable to that achieved in several European countries [64]. The current USA prevalent AVF use rate by network is about 60% but incident AVF use rate by network is still below 20% [65]. DOPPS 4 of 2010 Study showed Australia, New Zealand and some European countries (France, Italy and Germany) have achieved more than 70% AVF use compared with Japan who achieved more than 90% [65].

5. Compatible hemodialysis

Dialyzer membranes used to be made primarily of cellulose (derived from cotton linter). The surface of such membranes was not very biocompatible, because exposed hydroxyl groups would activate complement in the blood passing by the membrane. More recently, membranes have been made from synthetic materials, using polymers such as polyarylethersulfone, polyamide, polyvinylpyrrolidone, polycarbonate, and polyacrylonitrile [66]. These synthetic membranes activate complement to a lesser degree than unsubstituted cellulose membranes. Synthetic membranes can be made in either low- or high-flux configuration, but most are high-flux. Nanotechnology is being used in some of the most recent high-flux membranes to create a uniform pore size. These recent innovations in the technology of dialysis membranes have resulted in improvement of their biocompatibility and anti-thrombotic effect, as well as in their hydraulic and perm selective properties [67].

The contact and interaction of blood with artificial surfaces within the extracorporeal circuit (dialyzer, needles, catheters, tubing, and the arterial and venous bubble traps) induces profound activation of plasmatic coagulation [68]. Further risk factors for clotting of the extracorporeal circuit include slow/turbulent blood flow, excessive ultrafiltration (due to hemoconcentration), high hematocrit, and blood transfusions into the extracorporeal circuit [69]. This non-physiological environment leads to activation of platelets, leukocytes, and the coagulation cascade, resulting in fouling of the membrane and ultimately in clotting of fibers and the whole hemodialyzer. As hemodialysis requires access to the circulatory system and the passage of blood in the blood lines and the dialyzer, anticoagulation is vital to maintain the in- and outflow of blood through the extracorporeal circuit and dialyzer without clotting. There have been different anticoagulants used to prevent thrombosis in the blood circuit. These include unfractionated heparin, low molecular-weight heparin, natural and synthetic heparinoids, direct thrombin inhibitors, prostanoids, saline flushes and citrate infusion or citrate based dialysate [70]. Heparin has been the most commonly used anticoagulant as it is generally well tolerated, easily administered, low cost, short biological half-life, and can be quickly reversed with protamine sulfate [69]. However, long-term use of heparin can expose hemodialysis patients to thrombocytopenia, hypertriglyceridemia, osteoporosis, hypersensitivity, alopecia, metabolic disturbances, and hypotension [70]. Furthermore, there are some patients at high risk of bleeding, where heparin cannot be used. The recent improvement and innovation in dialysis membranes have yielded high-flux membranes graft-

ed with unfractionated heparin that can be used to avoid or reduce the exposure to systemic heparin [71].

6. High-flux hemodialysis

The creation of larger pore size semipermeable membranes in compact cartridges (high-flux dialyzers), with variable sizes of these pores, enhanced their ability to remove small solutes and 'middle molecules' [66]. High-flux dialyzers allow the passage and removal of retained solutes of higher molecular weight than do low-flux membranes. Dialyzers are considered as high-flux type if their ultrafiltration coefficient (KUF) exceeds 15 ml/h/mmHg and their ability to clear β_2-M exceeds 20 ml/min (low-flux dialyzer clears KUF <15 ml/h/mmHg and β_2-M < 10 ml/min) [50]. However, the fluids (dialysate and water) used with these high-flux dialyzers should be sterile non-pyrogenic and endotoxin free in order to avoid reverse filtration of endotoxins and blood contamination [72]. Microbiological contamination of water is a serious health concern for patients on dialysis. Therefore, it is essential to regularly monitor both bacteria and endotoxin levels in the water used for dialysis especially with high-flux dialyzers and for patients treated with online hemofiltration or hemodiafiltration.

Conventional and high efficiency HD techniques, using low-flux dialyzers, are incapable of removing larger sized uremic toxins and/or protein-bound toxic molecules of > 500 Dalton (table 1). This would result in their accumulation in circulation where they can exert concentration-dependent toxicity, particularly on endothelium and cardiovascular system. Examples of these molecules include uridine adenosine tetraphosphate and endothelin [27], which exert vasoconstrictive effect, indoxyl sulfate and p-cresylsulfate – p-cresol, which has pro-inflammatory effect and cause endothelial dysfunction together with the pro-inflammatory cytokines, and has been associated with increased cardiovascular mortality [73]. Other retained molecules which are known to cause harmful effects include β_2-M, immunoglobulin light chains, parathyroid hormone, advanced glycation end products [74] and advanced oxidation products [27, 75, 76].

Beta 2-microglobulin, which is considered a surrogate marker of middle molecules, is strongly associated with carpal tunnel syndrome and dialysis-related amyloidosis [77]. Different studies have documented the efficiency of high-flux dialyzers in removing β_2-M from the circulation of patients on dialysis, which has been associated with clinical and radiological improvement of carpal tunnel syndrome and dialysis-related amyloidosis [78]. In addition, high-flux HD has been shown to be superior to peritoneal dialysis in clearing β_2-M and the protein-bound middle molecule p-cresol [71]. Furthermore, observational studies have documented the improvement of survival rates of patients on high-flux-dialyzers when compared with those on low-flux dialyzers [9, 79-82]. These findings have been confirmed by two large randomized clinical trials: the HEMO study and the MPO study. In the entire cohort in the HEMO Study the high-flux arm had no significant effect on the all-cause mortality rate or any of the four arm secondary outcomes. However, the high-flux HD provided significantly less cardiac and cerebrovascular mortality rates after 3.7 years HD than low-

flux HD [42, 83, 84]. The Membrane Permeability Outcome (MPO) study, which was conducted in Europe, showed higher survival rate in high-flux HD patients with low serum albumin (≤ 4 g/dl) and diabetic patients [85]. Following these two major studies, the European Best Practice Guidelines have recommended the use of high-flux dialyzers in patients at high risk (serum albumin < 4 g/dl) and even in low-risk patients [86]. Ever since, high-flux dialysis has surpassed low-flux use worldwide [87].

7. Super high-flux hemodialysis

New 'super high-flux' membranes for hemodialysis have been developed with a high cut-off pore size allowing efficient removal of middle and large size uremic toxin molecules that cannot be removed by conventional dialysis membranes. The recent availability of a new generation of hemodialysis membranes with molecular weight cut-offs closer to that of the native kidney (65000 Dalton) has led to great benefits in several different clinical settings. These membranes have shown efficient removal of myoglobin in patients with rhabdomyolysis [88], efficient and direct removal of free light chains and other plasma components [89], and greater clearance of inflammatory cytokines than conventional high-flux membranes [90]. They also have a positive impact on restoration of immune cell function, attenuation of hemodynamic instability and decrease in plasma interleukin-6 levels in septic patients with acute kidney injury [91]. However, albumin loss may be a disadvantage of these membranes, though albumin losses can be replaced by infusion of human albumin solution [90].

8. Adsorption hemodialysis

Despite the efficiency of removing middle-size uremic toxin molecules by high-flux HD, yet this technique is still incapable of removing larger-size and, more importantly, the protein-bound uremic toxins. Protein-bound uremic toxins are, in fact, small in size but become larger molecular weight compounds (50,000 – 200,000 Dalton) once are bound to different types of proteins depending on their binding affinity. Protein-bound uremic toxins have been potentially involved in important uremia co-morbidities such as itching and altered immune response caused by the retained and deposited free molecules (κ-type and λ-type) of the immunoglobulin light chain in internal organs [92-95].

Removing protein-bound uremic toxins from the blood by means of diffusion and convection is virtually impracticable. The technology of dialysis membranes have yielded thicker type of membranes (more than conventional 1 micron thickness) that have a great affinity to stick larger size molecules to their surfaces, hence known as adsorptive membranes [96]. Adsorption can occur at the outer surface of the membrane when molecules cannot pass through the pores of the membrane and/or within the inner membrane matrix when the molecules can permeate the membrane [97]. Synthetic membrane micro porous zeolite silica lite (MFI) has been shown to be quite effective in adsorbing high levels of the protein-bound

solute P-cresol [98], which is not eliminated efficiently by conventional HD. Furthermore, the synthetic thick polymethylmethacrylate (PMMA) membranes (30 micron thickness), which have good solute permeability and a high degree of biocompatibility, do have high adsorptive capacity reaching up to 160,000 Dalton [99].

Recent studies have shown a variety of efficient clinical implications for adsorption HD. The use of PMMA membranes has been shown to ameliorate the severity and frequency of pruritis [95] in HD patients due to adsorption of a 160,000 Dalton molecular weight molecule with stimulatory effect on mast cells [100]. PMMA membranes also efficiently adsorb β_2-M (representative of middle molecules), where they have been shown to improve carpal tunnel syndrome or total joint pain score in HD patients [99]. In addition, patients dialyzed with PMMA membrane have lower need for erythropoietin due to the elimination of an inhibitor of erythropoesis retrieved in the dialysate [101]. Furthermore, the free molecules (κ-type and λ-type) of the immunoglobulin light chain (Bence Jones protein), which accumulate at high levels in the blood of HD patients [102] may lead to various protein deposits in the internal organs and act as inhibitors of leukocyte and immune function in dialysis patients. These molecules, which usually exist as dimmers (56,000 Dalton) and not removed by high-flux HD, are significantly removed by HD with PMMA membrane [103] in patients with primary amyloidosis [104] and in patients on HD resulting in reduction in pain and frequency in analgesic treatment [105]. In addition, PMMA (BK-F) membranes have been shown to be quite effective in removing soluble CD40 from circulation of patients on HD. Soluble CD40, which mostly coexists as dimeric and even higher oligomerized forms of 50,000 and 150,000 Dalton, respectively [106], acts as natural antagonist of the CD40/CD40L contact [92, 106, 107] and have been associated with a lack of response to hepatitis B vaccination. The efficient removal of these molecules by PMMA membranes have been associated with improved response to hepatitis B immunization [94].

Finally, adsorption techniques have been used successfully, in conjunction with plasma filtration and hemofiltration, in clearing efficiently pro-inflammatory mediators in experimental animals [108] and in humans with acute kidney injury and sepsis [109]. This is known as "coupled plasma filtration adsorption" (CPFA) technique, where the treatment consists of the separation of plasma from the whole blood, using a plasma filter with high cutoff membrane of 800,000 Dalton, coupled with adsorption of the inflammatory mediators and cytokines from plasma, using a cartridge contains hydrophobic resins, followed by hemofiltration using a hemofilter.

9. Frequent hemodialysis

A significant improvement in efficiency of HD can be achieved by increasing the duration and frequency of dialysis sessions [110]. Different studies have confirmed that dialysis duration of less than 4 hours was associated with increased mortality rate by up to 42% [24, 25, 29]. By contrast, increasing the duration of dialysis, independent of blood or dialysate flow rates, to 8 hours has been associated with significant improvement in clear-

ance of urea, creatinine, phosphorus, uric acid and even β_2-M, but not much of protein-bound toxic molecules [29, 111, 112].

Another approach to improve the efficiency of HD is by increasing the frequency of HD sessions. This can be achieved by avoiding the two days weekend gap and implementation of in-center every other day dialysis [11, 113]. A recent study of analyzing records of 32,000 people receiving dialysis three times a week from 2005 through 2008 found a 22% greater risk of death on the day after a long break, compared with other days. In particular, stroke and heart-related hospitalizations more than doubled on the days after the long break [11]. The efficiency of HD can also be improved by short daily dialysis [30, 34, 36, 111, 114], long slow nocturnal dialysis [32, 33] or home daily or nocturnal HD [35, 51], instead of three HD sessions per week.

Home, and in particular nocturnal, HD is probably the most convenient and efficient modality of HD. It can be performed on daily basis or at night at most suitable times, where the patient on nocturnal HD dialyzes for about twice the time (approximately eight hours per session) of conventional in-center HD sessions. This ensures a better chance that the patient will not be under-dialyzed; therefore, more toxins and fluids may be removed. Because this process occurs more slowly, there is less of a chance of cramping and hypotension episodes during dialysis [35]. Unlike conventional HD, patients on nocturnal HD do not report the "washed out" feeling after longer dialysis (no need to take a nap after treatment). Different studies have repeatedly confirmed the strong positive impact of nocturnal or more frequent dialysis on ultrafiltration rate (much better control of fluid excess), clearance of uremic toxins and adequacy of dialysis [36]. The better ultrafiltration rate has been associated with better control of blood pressure [33, 36, 37], where the majority of dialysis patients discontinued antihypertensive medications after 6-12 months of daily/nocturnal dialysis [30, 115]. Increasing dialysis frequency, and in particular nocturnal HD, has also been linked to significant improvement in renal anemia [31, 116] and reduction in erythropoietin dosage and iron supplements [115], significant reduction in left ventricular mass index [33, 36, 117], improvement in mineral metabolism and significant reduction in phosphorus binders [33, 36, 37, 114], improvement in nutritional status [30, 118], enhanced quality of life [33, 36, 119] and increased cumulative survival rate [34]. Moreover, patients on nocturnal HD have a similar survival rate as that in deceased kidney transplant recipients [120].

Despite its great benefits (Table 2), the implementation of daily/nocturnal HD has not gained much attraction among patients, treating physicians and decision makers. Kjellstrand et al [34] contributed the slow and difficult introduction of daily dialysis to multiple factors including logistic problems, conservatism by physicians and nurses, patient worries and worries about expenses by governments and administrators, which is expected to be a major obstacle. However, the clinical and quality of life improvement brought by daily/nocturnal HD has been associated with dose reduction in different pharmaceutical medications (antihypertensive medications, phosphorus binders and erythropoetin dosage and iron supplements), extended use of dialyzers and tubing and decreased waste production and transportation upon implementation of home HD, and significant reduction in hospitalization and morbidity (and mortality) rates, all of which may result in reduction in manage-

ment costs and total annual expenses [32, 119]. A recent economic assessment model for in-center, conventional home and more frequent home HD has shown that home-based conventional and more frequent HD are similar in cost to in-center HD in the first year but can be less costly than in-center HD from the second year onward [121]. The higher cost for more frequent home HD in first year is mainly due to higher consumables usage due to dialysis frequency. Frequent home HD (and conventional home HD), however, have been associated with much lower hospitalization costs than for in-center HD treated patients in first and subsequent years.

1	Improved uremic toxins and fluid removal
2	Less cramping and no "washout" feeling
3	Less hypotension episodes, better blood pressure control, less antihypertensive drugs
4	Improvement in anemia, reduction in EPO dose and iron supplements
5	Reduction in left ventricular mass index
6	Improvement in mineral metabolism and reduction in phosphorus binders
7	Improvement in nutritional status
8	Enhanced quality of life
9	Reduction in hospitalization rates and costs
10	Increased cumulative survival rate

Table 2. Benefits of Frequent (Daily/Nocturnal) Hemodialysis

10. Hemofiltration and hemodiafiltration

Attempts to increase the intensity or "dose" of HD with higher blood and dialysate flow rates, larger and adsorptive membranes and longer and more frequent dialysis sessions have improved the adequacy of HD, but failed to bring about the desired improvement in outcome [36, 37, 42, 83-85]. Recent innovations in the HD techniques have resulted in advancements in specifications of HD machines, HD medical devices, sterile ultrapure solutions and high quality water treatment plants [122]. These advancements have largely contributed to the ability to reconsider the implementation of the other physiologic principle of "convection" [123, 124]. This means that larger size uremic toxins can be dragged and removed from blood by filtering large volume of fluid pushed under high hydrostatic pressure through a larger pore size membrane (high cut-off membrane/high-flux dialyzer). This technique is known as "hemofiltration". Fluid balance is maintained by infusion of replacement solutions, which can be administered before the filter (pre-dilution) or after the filter (post-dilution). These solutions are infused directly into blood in order to replace the large volume of filtered fluids (convection volume). The replacement solutions, which also referred to as substitution fluid, are mixed with the blood and should, therefore, be sterile non-

pyrogenic and endotoxin free buffered solutions with a composition similar to plasma water. Combination of the two physiologic principles of diffusion (hemodialysis) and convection (hemofiltration) in the management of patients with ESRD is known as "hemodiafiltration" [6]; a technique that has been described and implemented in 1974 [123] and a treatment modality that simulate to a large extent the natural function of a normal kidney.

11. Online hemodiafiltration

The implementation of hemofiltration (HF) or hemodialfiltration (HDF) as a renal replacement therapy in patients with ESRD requires the supply of large quantities of replacement solutions. These solutions are usually industrially prepared in autoclaved expensive plastic bags, which have been used in earlier studies, in order to fulfill the requirement of sterile non-pyrogenic and endotoxin free buffered solutions [125]. However, the need of large quantities of these bags makes the implementation of this technique rather costly and impractical. The recent advancement and improvement in the performance of water treatment plants that are capable of producing ultrapure water (almost nil bacterial growth and endotoxin free) have greatly contributed to the success of this technique [15, 126]. Such quality of water, which is available continuously and in unlimited amounts at the dialysis machine during each treatment, has been used directly from the water treatment plant to form the dialysate and the replacing solutions for the HDF [125], and hence this technique is known as "online hemodiafiltration" [127].

Online HDF offers the most physiologic clearance profile for a broad range of small, medium-sized and large toxic molecules (table 1). Like conventional HD, online HDF session is usually performed three times per week as an outpatient treatment that usually lasts for four hours. Prescription of effective online HDF should ensure higher blood and dialysate flow rates, ultrafiltration not less than 20% depending on the mode of HDF (it differs between post and pre-dilution HDF), and substitution/replacement fluids 5-25 liters/session. Earlier studies defined replacement fluids of 5–14.9 liters/session as low-efficiency HDF, and replacement fluids of 15–24.9 or more liters/session as high-efficiency HDF [15, 112]. However, the data from recent randomized controlled studies: CONTRAST [128, 129] and Turkish [130] studies suggested a convection volume higher than 15 liters in the post-dilution mode should be targeted in order to achieve successful HDF.

The implementation of both physiologic principles of diffusion and convection has enabled HDF, and in particular online HDF, over that of HD (low- and high-flux) in achieving better adequacy of dialysis and better clearance of small and middle-size uremic toxins [131]. In clinical practice, HDF (low- and high-efficiency) has been shown to be more effective than HD (low-flux and high-flux) in achieving significantly higher values of Kt/V (averages of 1.37 and 1.44 versus 1.35 and 1.33, respectively) [15].

Hyperphosphatemia, which has been associated with vascular calcification and considered as an independent predictor of mortality in dialysis patients [132], has been well controlled with efficient removal of phosphorus by online HDF [113, 129, 133] with marked reduction

in phosphate binders [113]. Furthermore, the reduction ratio of β_2-M per session has been shown to be 20–30% higher with online HDF than with high-flux HD (72.7 versus 49.7%) [134]. Likewise, online high-efficiency HDF achieves higher serum free light chain removal than high-flux HD in multiple myeloma patients [135]. In addition, HDF is highly efficient in clearing other larger solutes such as myoglobin (16000 Dalton), retinol-binding protein (25000 Dalton) and the protein-bound p-cresol than high-flux HD [131, 136]. It has also been shown that online HDF efficiently reduces the circulating levels of advanced glycation-end products [74, 137]. The efficient removal of different types and sizes of uremic toxins by online HDF [138] has been associated with reduction of skin pigmentation [139], promotion of catch-up growth in children on chronic dialysis [140] and nutritional status improvement [141]. More recently, Maduell et al [113] have demonstrated a remarkable improvement in nutritional status with adequate social and occupational rehabilitation.

Online HDF is empowered with biocompatible high-cut-off membranes, ultrapure water and efficiency of removal of pro-inflammatory stimuli including oxidative stress molecules, advanced glycation end-products, homocysteine [142], p-cresol and pro-inflammatory cytokines, all of which would ensure abolishing virtually the possibility of stimulation of an inflammatory process in dialysis patients [124]. This effect of online HDF, at least in part, has been shown to improve the patients' responsiveness to erythropoetin and reduce the requirement of erythropoietin stimulating agents [143].

Hemodiafiltration, and in particular online HDF, had attracted much attention in recent years as a promising optimum modality of HD [144]. In addition to its efficient improvement in dialysis adequacy and clearing small and large-size uremic toxins [145], HDF significantly reduced inter-dialysis symptoms including less fatigue and cramps together with effective correction of intradialytic haemodynamic instability and blood pressure control [146, 147], especially for elderly, heart-compromised or patients prone to hypotension. A recent study by Maduell et al [113], where high volume (high efficiency) online HDF combined with more frequent (every-other-day nocturnal 7-8 hours) dialysis sessions, showed marked improvement in hypertension control with a substantial reduction in drug requirements and regression of left ventricular hypertrophy; an independent cardiovascular risk factor which has been associated with mortality in dialysis patients [148, 149].

Finally, observational studies have shown the benefit of online HDF in decreasing the mortality rate in patients on dialysis [150, 151]. Canaud et al [15] reported a significant 35% lower mortality risk with high-efficiency HDF compared to low-flux HD. Jirka et al [151] also observed a 35.3% reduction rate in mortality risk in online HDF-treated patients after adjustment for age, co-morbidities, and time on dialysis. More recently, in a randomized clinical trial the subgroup of HDF patients treated with a substitution volume over 17.4 liter per session (n=195), cardiovascular and overall survival were better than both the HDF subgroup with substitution volume ≤17.4 liter per session (n=196) (p=0.03) and the HD group (p=0.002). Primary outcome was similar in these 3 groups (85.2%, 83.8% and 81.2%, respectively, p=0.26). In adjusted Cox-regression analysis, HDF with substitution volume over 17.4 L was associated with a 46% risk reduction for overall mortality [RR=0.54 (95% CI 0.31-0.93),

p=0.02] and a 71% risk reduction for cardiovascular mortality [RR=0.29 (95% CI 0.12-0.65), p=0.003] compared to HD [130].

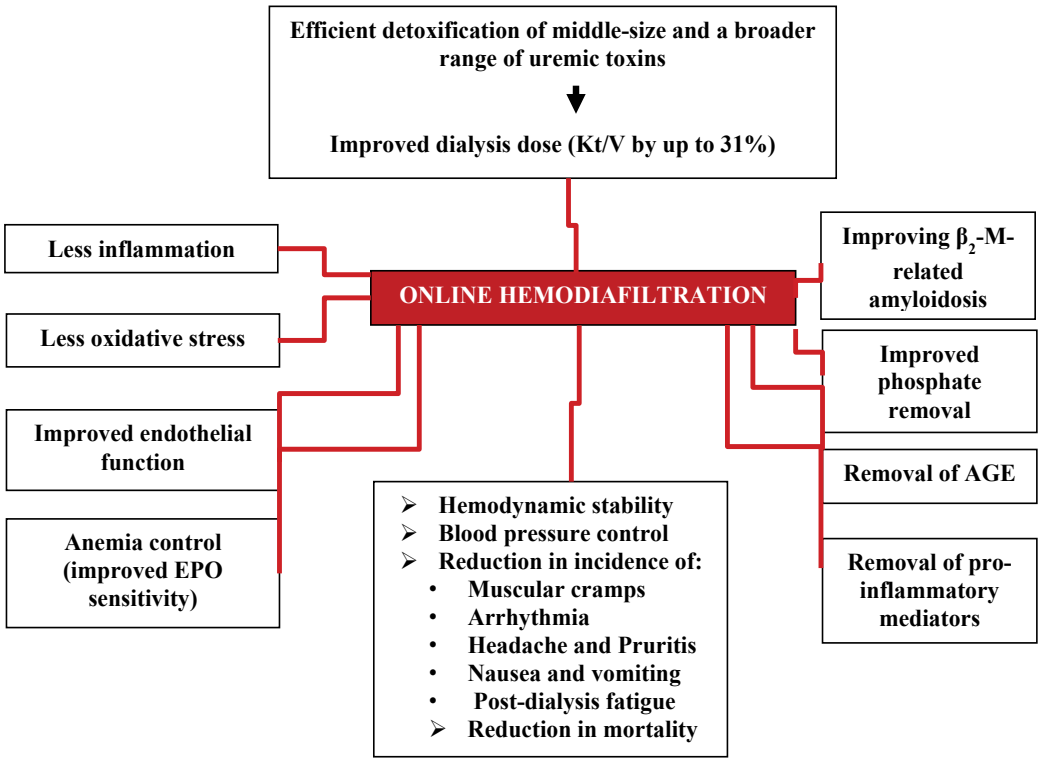

Figure 2. Benefits of online hemodiafiltration EPO: Erythropoetin, β_2-M: Beta 2-microglobulin, AGE: Advanced glycation end-product

The performance, success and benefits of online HDF (figure 2), however, depends on availability of special requirements. These include (1) experienced nephrologists and nursing staff, (2) high quality water treatment plant that can provide ultrapure water (bacterial growth < 0.1 colony factor unit/ml and endotoxin level < 0.03 endotoxin unit/ml) with frequent assessment of water quality [152-154], (3) dialysis machine specially designed and approved for online fluid preparation, (4) high-flux dialyzers and (5) good functioning vascular access with adequate blood flow. These essential requirements for ensuring successful online HDF therapy may incur extra costs and may limit its widespread implementation. However, training of medical and nursing staff is achievable, high flux dialyzers have already be recommended and in use in conventional HD with lower cost, different quality online HD machines are becoming cheaper and more affordable, and investing in quality ultrapure water treatment plant should not be a major barrier toward implementation of this premium modality of HD. In fact, investing in these requirements would not only improve the quality of life of dialysis patients but reduce the rates of morbidity and mortality. Fur-

thermore, additional savings can be achieved by (1) reduction in the costs associated with hospitalization due to high morbidity rate of conventional HD [12, 155], (2) less requirements of phosphate binders due to better clearance of phosphorus [114], (3) better control of hypertension with less use of antihypertensive drugs [114], (4) less doses required of erythropoietin stimulating agents (ESA) and iron supplements, due to improved sensitivity to ESA as a result of abolishing or reducing the inflammatory response [125], and (5) improved hemodynamic stability, with no or less frequent hypotension episodes [114, 147], and consequently less consumption of normal saline and human serum albumin.

12. Continuous hemodialysis

Continuous renal replacement therapy (CRRT) is defined as "any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for or aimed at being applied for 24hrs/day" [156]. CRRT modalities include slow continuous ultrafiltration (SCUF), continuous HD, continuous hemofiltration (HF), and continuous hemodiafiltration (HDF) [157]. SCUF technique is based on passing the blood through the dialyzer without dialysate or replacement fluids, and is basically used to remove excess body fluids as in patients with congestive heart failure and pulmonary edema [158]. The technique of continuous HD is similar in principle to that of intermittent/conventional HD except that it is continuously applied for a longer period of time and at slower blood (100-200 ml/minute) and dialysate (40-70 ml/minute) flow rates. The techniques of hemofiltration (HF), which is based on the physiological principle of convection (dialysate is not used but replacement fluids) and hemodiafiltration (HDF), which based on the physiological principles of diffusion and convection (both dialysate and replacement fluids are used), are the same as those described earlier in this chapter, but are applied in continuous format and over a long period of time [159]. These techniques/modalities of CRRT are usually applied and used for critically ill patients with septic acute kidney injury and/or multi-organ failure in intensive care units. Other indications include cardiopulmonary bypass, fulminant hepatic failure, rhabdomyolysis, respiratory distress syndrome, severe burns, cerebral oedema, and tumor lysis syndrome [160]. The dialysis dose effect in these treatment modalities is assessed by adequacy and efficiency of fluid balance (and replacement/effluent fluids volume in HF/HDF), electrolyte balance, acid-base balance, and removal of small and middle-size uremic toxins [161]. Although expensive, these modalities provide smooth dialysis without fluctuation, hemodynamic/cardiovascular stability, improved fluid balance, removal of inflammatory mediators, allow supportive measures (nutrition), steady biochemical correction, and possibly improve survival rate [162, 163]. The disadvantages of these techniques include necessity for continuous anticoagulation, hypothermia, severe depletion of electrolytes (particularly potassium and phosphorus), where care is not taken, immobilization of the patient, possible side effects from lactate-containing replacement fluid or dialysate, 24 hour staffing (well trained and dedicated staff) and increased cost [160].

13. Slow low-efficiency hemodialysis

This slow low-efficiency dialysis (SLED) technique combines both intermittent and continuous modalities of HD [164]. It is based on providing intermittent/conventional HD but with low blood and dialysate flow rates (100-200 ml/minute) and for longer period of time usually 8-12 hours per session usually for 5 or 6 days per week [165]. SLED technique provides a gentle reduction of small solutes clearances over prolonged periods with an efficacy comparable to that of conventional intermittent HD and continuous hemofiltration [166, 167]. It has been considered an ideal technique of HD for critically ill patients with multi-organ failure and acute kidney injury in intensive care unit (ICU). SLED technique has several advantages which include easy-to-perform treatment, flexible timing of treatment (nocturnal SLED has the benefits of unrestricted physician access to the patient during the day and minimizing the interference of renal replacement therapy with other ICU activities), reduced costs [164], and hemodynamic/cardiovascular stability [168].

In conclusion, conventional or standard HD remains a valuable and basic life-supporting treatment for ESRD patients. This modality had over many years improved the survival rate of patients with end-stage renal disease. However, standard or conventional HD prescription is far from being optimal in replacing the function of normal kidneys. Its unphysiologic clearance pattern and inability to remove all types and sizes of uremic toxins results in inter and intra-dialysis complications and an unacceptable high rate of cardiovascular morbidity and mortality. The efficiency of HD can be improved by increasing blood and dialysate flow rates, the dialyzer size and surface area, and by increasing the duration and frequency of dialysis sessions. Home HD, where short daily or long slow nocturnal HD sessions can conveniently be performed, provides an excellent choice for quality of life improvement and reduction in morbidity and mortality. SLED technique is an ideal modality for critically ill patients in ICU with multiple organ failure and acute kidney injury. The recent innovations in the specifications of HD machines, HD medical devices and the improvement in dialysis membranes characteristics including the high-flux dialyzers, and water treatment technology paved the way for achieving quality HD. These advancements have resulted in efficient implementation of adsorption, diffusion and/or convection principles using adsorption HD, hemofiltration, hemodiafiltration and online hemodiafiltration modalities aiming at achieving optimum HD. High-flux dialyzer provides significantly less cardiac and cerebrovascular mortality rates, and has been associated with higher survival rate in dialysis patients with low serum albumin and diabetic patients. Therefore, since there have been no better results with low-flux dialyzers, high-flux dialysis should not be limited to high risk dialysis patients. Online HDF is an ideal HD technique with much less morbidity and mortality rates. In fact, online HDF is considered currently as the premium modality of HD that ensures optimum dialysis. Therefore, these HD modalities, and particularly online HDF, should be considered more seriously, if financial and human resources are available and/or affordable, to replace conventional HD should we aim at improving the quality of life and reducing the morbidity and mortality rates among HD patients, which are still unacceptably high, and reducing the costs associated with conventional HD.

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Chapter 21

Implementation and Management of Strategies to Set and to Achieve Clinical Targets

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1. Introduction

Today health care and care provider organizations are facing new challenges. They must continually improve their services to provide the highest quality at the lowest cost. Pressures to increase the quality and lower the costs are coming from accreditation and certification boards, public health authorities and the media that publish comparisons and rank facilities by performance. In addition, new demands on health care systems require action accountability with hard outcome data based on morbidity and mortality. Quality control, quality assurance and continuous quality improvement (CQI) processes derived from the manufacturing and industrial world have been progressively applied with success to medicine and in particular to the treatment of end stage renal disease.

[1,2]. It is generally accepted that quality control describes the process for reviewing and checking that targets according to whether a defined set of criteria has been achieved, while quality assurance is the process in which systematic monitoring, collecting and evaluating the performance of a facility or a care network are assessed to ensure that standards of care are met [3]. CQI describes the action that takes place after analyzing outcomes with the intent of improving the results and reducing variation from the target. In this respect, renal replacement therapy by dialysis represents a particular field of application where quality control and quality assurance processes have been shown to be very efficient tools for optimizing treatment adequacy and improving patient outcomes.

Over the last ten years, it has been well documented that survival and outcomes of stage 5 chronic kidney disease patients on dialysis are depending on age, comorbid status at the start of treatment, but also on quality care and practice patterns [4,5,6]. Renal replacement therapy by dialysis is a clear paradigm where results are quite closely tied to quality assurance and CQI processes. Dialysis adequacy is a multi-target concept developed to face complexity of uraemia disorders and to provide physicians with an easy tool based on a 'checklist' to address the patients' vital metabolic needs. Dialysis prescription and adjunctive medical treatment are intended to provide over time (from years to decades) an adequate and regular correction of metabolic disorders to each patient, to prevent side-effects and 'un-physiology' of intermittent dialysis and to preserve quality of life at an affordable cost. Treatment adequacy is then closely tied to the quality assurance process that links prescription and treatment delivery [7]. On one hand, prescription of the haemodialysis treatment relies mainly on the patient's metabolic needs, cardiovascular and general tolerance of sessions, dietary compliance, residual renal function [8] and local health care and economic offer. It is not our intent to revisit here the principle of prescribing dialysis but just to remind that it relies on five primary elements: dialysis modality (haemodialysis, haemodiafiltration, ect), dialyzer type, total weekly treatment duration (number of sessions per week and duration of session), blood flow and 'dry weight' achievement. Additional components need to be considered as secondary part of the prescription being part of the prescription such as dialysate flow, substitution flow in convective therapies, dialysate electrolytic composition, antithrombotic drugs, specific medications (iron, erythropoiesis-stimulating agents, vitamins ect) [9]. On the other hand, adequate delivery of haemodialysis relies on the continuous achievement of pre-specified targets using quality control markers intended to monitor major metabolic disorders of the uraemic syndrome. The markers clearly identified and recommended by international best practice guidelines (formerly the European Best Practice Guidelines, EBPG, now the European Renal Best Practice, ERBP, KDOKI at http://www.european-renal-best-practice.org/, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, NKF KDOQI, Kidney Disease: Improving Global Outcomes, KDIGO) are summarized in clinical performance measures (CPM) covering 10 main domains: 1.[7]; 1. Lack of clinical uraemic symptoms; 2. Fluid volume control; 3. Blood pressure control; 4. Adequate dialysis dose delivery (small and middle molecules); 5. Acidosis correction; 6. HyperkalemiaHyperkalemia control; 7. Divalent ion metabolism (phosphatemia, calcaemia and magnesaemia); 8. Iron repletion and anaemia correction; 9. Prevention of malnutrition; 10. Prevention of inflammation and oxidative stress. As shown by the international Dialysis Outcome Practice Patterns (DOPPS) study, clinical practices should be now considered as a major component of quality of care having a direct impact on dialysis patient outcomes. By linking country and unit, specific practices to patient outcomes, the DOPPS study introduced a new dimension in the control of the overall quality of care of haemodialysis patients. Among the main findings of DOPPS it must be stressed that less use of central venous catheter [10,11], longer duration of dialysis with reduced ultrafiltration rate [12], adequate dialysis schedule [13], higher dialysis dose delivered [14], better control of fluid overload and blood pressure control [15], prevention of metabolic bone disease [16,17], better control of anaemia with lower erythropoiesis-stimulating agent dose require-

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ment [18,19], enhanced convective dose [20] are all beneficial to patient outcomes. In addition, DOPPS has also shown that overall clinical practices at the facility level were essential for improving patient outcomes [21]. In other words, dialysis facilities achieving optimal targets for a core of selected quality control items in the majority of patients were extending life expectancy to each patient individually [21]). In this new perspective, it is then necessary to implement complementary items of quality control probing the degree of compliance of dialysis facilities with best clinical practices [22,23]. A quality control tool in this case may be simply expressed as the percentage of patients within the predefined target range per unit. Combining clinical performance measures and percentage of patients complying with targeted objectives, a new key performance indicators (KPI) may be elaborated for a group of patients treated either within a dialysis unit and/or within a network. In addition to directly addressing clinical practices and patient outcomes, DOPPS has been used as a platform for economic and policy analyses [24]. Fresenius Medical Care as the world's largest integrated provider of products and services for individuals undergoing dialysis because of chronic kidney failure was historically involved in the development of continuous quality improvement processes of dialysis care. We take this opportunity to present additional results collected within the Fresenius Medical Care network system (EuCliD, European Clinical Database). In this article, we discuss some practical ways of implementing the CQI process based on real time collection of clinical performance measures and KPI. Using selected indicators we explore the beneficial effects over time of achieving targeted criteria of good medical practice in terms of patient outcome and cost saving effect. In developed countries, health care costs are currently progressively increasing and in case of U.S. exceeds 17% of the Gross Domestic Product (GDP). Other countries spend less of their GDP on health care but demonstrate the same increasing trend.

Today, national health care systems worldwide are expected to deliver more and better services to a greater number of patients, while dealing with ever more reduced economical resources on the one hand and increased costs on the other hand. Major challenges posed to healthcare systems include global ageing and increase in so-called civilization diseases, growing budget deficits and slowing economic growth, worldwide health care workers shortage and commodity shortage. The need to provide innovative and high-quality, innovative products and treatments should able to contribute to improving outcomes and to be in balance with new perspectives addressing the health care change. Innovation has to contribute to solving the challenge of the economic pressure, though innovation will need standardization according to the rules of good clinical practice and proved by evidence-based medicine. Perverted incentives may also contribute to rising costs as well as reimbursement as providers are reimbursed for performed procedures rather than achieved ones. Moreover, a common weakness of health care systems is linked to the low level of responsibility for the costs generated by the patients at the time they require the medical service. The costs for renal replacement therapy is exceedingly high and are consuming a significant proportion of health care budgets. The global prevalence of kidney failure continues to rise, and treatment is costly; thus, the burden of illness is growing and the resources allocated to treatment are increasing. According to the U.S. Renal Data System (USRDS) Annual Report 2011, total Medicare costs in 2009 rose 8%, to $491 billion; costs for ESRD rose

3%, to $29 billion, accounting for 6% of the total Medicare budget. ESRD data for 2009, however, do not include Part D (costs of drugs), which amounted to $2 billion in 2008 (Best Dialysis Centres at [25]. In European health care systems, the costs of treatment for the growing population of chronically ill patients (including those requiring renal replacement therapy) are considered an emerging public health problem. Indeed, renal failure persists as a chronic worldwide epidemic with an exponential growth trend on a global scale. Over the last decade, the prevalence of ESRD in Europe grew by an annual average rate of 5%. By the end of 2011, the number of ESRD patients in Europe was estimated to be 657,000 and, of these, approximately 433,000 (around 66%) received dialysis treatment [26]. Currently, many healthcare systems in Europe try to address the growing budget pressures by savings. Savings alone can provide relief to the challenged financial situation only to a very limited extent. Providers and payors turn to simplistic actions such as across-the-board cuts in expensive services, staff compensation, and head count. Imposing arbitrary spending limits on discrete components of care, or on specific line-item expense categories, achieves only marginal savings that often lead to higher total systems costs and poorer outcomes. The inability to properly measure cost and compare cost with outcomes is at the root of the incentive problem in health care and has severely retarded the shift to more effective reimbursement approaches. Moreover, poor measurement of cost and outcomes also means that effective and efficient providers go unrewarded preventing them from making systemic and sustainable cost reductions. A broad consensus exists regarding targets for best medical practice in renal care [27]. Concepts regarding how to achieve these targets in the most efficient way, however, vary significantly. The variety of solutions, reflected by different national models of renal care as well as ongoing reforms and recent reform proposals, suggest that the search for an optimum is still ongoing.

Achieving the right balance between high-quality service for chronically ill patients and its cost is now one major challenge for the health care industry. It is crucial to recognize the benefit of collecting and analyzing large amounts of data, comparing treatment modalities and opting for the highest quality. The wide use of evidence-based medicine and the implementation of national and international guidelines for optimal care play a very important role in this process of improvement of care, drawing a clear line of effective treatment. A recent study by the DOPPs emphasizes how quality of treatment may diverge among centers [28]. In the present context of an ever-growing number of patients requiring treatment in a system of scarce available resources, the optimization of care protocols in terms of "improved care for less money" has become a very complicated challenge. Standardized guidelines coupled with innovative models for process improvement have made it possible to accomplish this otherwise herculean task.

Fresenius Medical Care, has included QPI in an elaborate system called Balanced Scorecard, aimed at evaluating and comparing clinics, countries and regions, providing the stakeholders with an important tool allowing an insight into what is the actual level of care provided in the clinics, besides from the usual financial data [29]. Fresenius Medical Care's approach to 'optimal care' is being applied in more than 3,000 dialysis clinics in North America, Europe, Latin America, Asia-Pacific and Africa. NephroCare, the service provider for Fresenius

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Medical Care in Europe, coordinates the clinics in Europe, Middle East, Africa and Latin America, that use state-of-the-art dialysis products, renal pharmaceuticals and therapies (all of which are constantly being improved), as well as care from qualified, motivated clinic personnel who regularly participate in training programs. In every country of its European network, NephroCare adapts its care model to reflect the national health care architecture and to further develop concepts within the predefined regulatory frame [29]. To impact the quality and efficacy of a health care service, patient and cost related information must be captured, updated, and shared with all stakeholders in a timely and effective manner to not only ensure universal access to quality data, but also to extend essential information to key clinical decision makers [30]. The Balanced Scorecard tool has allowed NephroCare to promote the collaboration between public institutions and the private provider in more than 20 European countries, giving in the hands of the public a way to control the quality outcomes achieved in the clinics [31,29]. This has been an important achievement for quality in the European healthcare context where dialysis is still mainly provided by public hospitals. It has to be noted that all this would not be possible without the implementation of the electronic medical record EMR). Like in the rest of the health care context, the use of a specialized software to keep track of the patients' medical history has made it possible for the nephrologist to have immediate access to an enormous amount of patient information. In the last few years, a large number of software platforms have been proposed and some of them offer personalized versions, which could be customised to the needs of the nephrologist (The DoctorsPartner Nephrology EMR, by DoctorPartner LLC ectectect).

2. The Electronic Medical Record (EMR): Benefits of the worldwide web, quick and simple data collection and analysis, statistics as a tool to predict outcomes

Paper-based records are still by far the most common method of recording patient information for most hospitals and practices in the world. A critical aspect of paper-based records is legibility. Handwritten paper medical records can be associated with poor legibility, which can contribute to medical errors [32]. Pre-printed forms, the standardization of abbreviations, and standards for penmanship were encouraged to improve reliability of paper medical records. The majority of physicians still find it easier to handle paper-based records and consider entry of data into an EMR tedious. However, paper-based data require a significant amount of storage space and to retrieve information is quite difficult and time-consuming [2]. This is particularly true in the case of person-centred records, which are impractical to maintain if not electronic. For this reason, retrospective analysis based on large historical case series and programs based on data, as Continuous Quality Improvement, are only recently becoming popular with the deployment of EMR. Because of these many "after entry" benefits, governments, insurance companies and large medical institutions are heavily promoting the adoption of EMR. The benefits can be especially high considering the different uses of the same information, i.e. for monitoring a patient, CQI requirements, for reporting purposes or for billing a service. A critical aspect of EMR is the codification of information.

In human communication, free text is the natural approach used not only for oral communication but also for written medical records. Free text offers the option to maximize the benefit of a given language to describe situations well, but it may be difficult to maintain the same content once translated into another language. Additionally, it cannot be used for statistical purposes. Codification is somehow universal, and a code is a kind of ideogramme readable by people of different languages. To get more out of an EMR, information has to be codified as much as possible, allowing an easier use. In general electronic records help with the standardization of forms, terminology and abbreviations, and data input. However, the increased portability and accessibility of electronic medical records may also increase the risk of unauthorized access and theft by as acknowledged by increased security requirements. The ability to exchange records between different EMR systems ("interoperability") facilitates the co-ordination of health care delivery in non-affiliated health care practices. Nowadays it is very common to see primary physicians working with computerized systems in their practice. However, very often they use systems which could be described as minimally functional since they include only orders for prescriptions, orders for tests, viewing laboratory or imaging results, and clinical notes. A more sophisticated use, including further analytical elaboration of the data as required by the CQI approach, is normally not part of the routine. To ensure the quality of care delivered to patients treated in its dialysis units, Fresenius Medical Care continuously monitors its dialysis services. The overall quality management system of the company, which is based on CQI, provides the necessary framework. CQI programs, incorporating the implementation of clinical practice guidelines and CPM by dialysis providers, demand the development of computerized monitoring systems in order to collect and supply information on the dialysis treatment. Therefore, Fresenius Medical Care developed a specific clinical database as a tool to monitor critical aspects of dialysis care and improve the quality of care.. This central database is called EuCliD, the acronym for European Clinical Database as the database was first developed in Europe. EuCliD collects the most-important medical information on the treatment of dialysis patients. The data provide a basis for clinical trials and help improve the treatment of dialysis patients by comparing the different treatments. The description of the first version of the database has already been published [33]. Right from the outset, EuCliD was structured to follow a logical information flow. During the last years the software has been updated and a new project based on an enlarged scope has been initiated. EuCliD 5 now includes daily treatments performed throughout European, Latin American and African Countries. The new project was aimed not only at supporting quality assurance, but also to facilitate the day-to-day work of the clinical staff. As a result, EuCliD 5, is a multilingual and fully codified software using, as much as possible, international standard coding tables (ICD10, WHO: International Statistical Classification of Diseases and Related Health Problems 1992; ISCED, UNESCO, 1997;ISCO-88, International Standard Classification of Occupations 1988 etc.). EuCliD 5 collects and handles sensitive medical patient data, and ensures the confidentiality of these data [34]. EuCliD 5 has been approved by the respective national or regional authorities prior to data entry and the initiation of data transfer. Of course, the transfer of private patient data out of the dialysis center is not permitted. The availability of EuCliD 5 data, as well as the increasing interoperability of data present in other systems has allowed

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the practical implementation in a clinical environment of tools like the Balanced Scorecard, a tool developed in the scientific domain of complex system management. Key characteristic of Balanced Scorecard is the aim of maximizing concurrent interests of different stakeholders in a balanced form, concentrating on KPIs able to describe variables whose improvement can improve the overall system behavior [29,30]. Each KPI is not a reported value only, but much more the headline of a project or program to improve performance in a strategic relevant, target oriented way. KPIs are dynamic and when they approach saturation need to be substituted by new ones in a continuous development process of quality improvement and know-how and operational excellence Related to the use of a Balanced Scorecard, there are certain *caveat* to consider: since the Balanced Scorecard is nothing else than a model of stege 5 chronic kidney disease management, Wrong or inadequate model design and definition and wrong or inadequate implementation (or execution) can lead to erroneous conclusions. In this sense the right selection of KPI and the appropriateness of the derived actions are of crucial importance as well as the validation of data and their causal relationships with outcomes. It is fundamental to understand how to manage and not just measure performance and this will not happen without regular review sessions at all levels

3. Self-organizing maps for continuous quality improvement

In order to derive improvements from the clinical data Self-Organizing Maps (SOMs), an innovative approach recently introduced by Fresenius Medical Care, could complement standard statistical methods used to extrapolate information. A brief description of SOMs follows: As an example, let us consider a dataset containing the values of four variables (Weight, Height, Body Mass Index – BMI –, and Fat) for 251 patients, for which we built a SOM with 84 neurons (Fig. 1). In this case, each neuron is characterized by a vector of four elements, one for each variable: each neuron can be seen as an "average patient", whose height is the average height of all patients associated with that neuron, and the same goes for the other three variables. Neurons that are close in the SOM represent patients that are similar from the point of view of the considered variables. Once the SOM has been configured, different effective views of the distribution of the data can be obtained. In particular, one can focus on a specific variable of the input data by color-coding each neuron of the SOM based on the value of that variable. This kind of plot is called component plane of the SOM (see, for instance, Fig. 1). By comparing different planes (i.e., different variables) it is possible to identify relations existing among the variables. Notice that each given neuron (depicted in Fig. 1 as a hexagon) always represents the same subset of data, over all the different component planes. For example, in Fig. 1 it can be noticed that the same units in the top left of the four component planes represent patients with large weight, medium to small height, large BMI, and large percentage of fat. The units in the bottom right of the graph represent patients with small weight, medium to small height, small BMI, and small percentage of fat. It should be noted that, although the SOM algorithm is not aware of how the BMI is computed, the relation between height and weight that determines the BMI clearly emerges

from the component planes. This example shows how the SOM can be effectively used to extract the relations among the variables of interest.

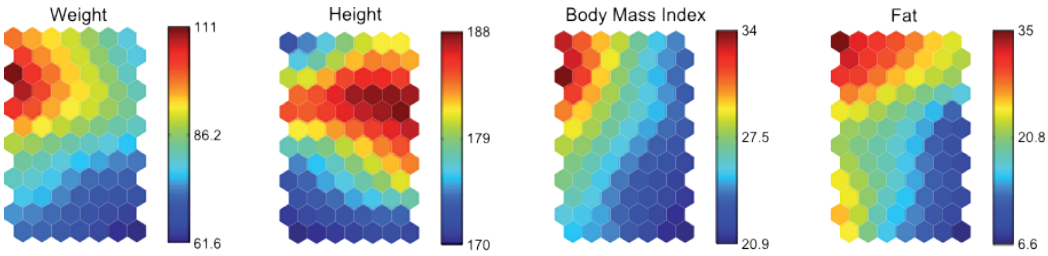

Figure 1. Example of SOMs of different variables (Weight, Height, Body Mass Index – BMI –, and Fat) for 251 patients.

To ensure the implementation of CQI policies, extensive data collection from the care units, and their reassembly into meaningful performance indexes need to be put in place. Such processes generate massive amounts of data, which carry information that is not always easily extracted by means of standard statistical approaches. On the other hand, the wealth of the available data allows the application of machine learning approaches, which are able to find structure in complex datasets, even in the absence of an a priori hypothesis about what should be looked for. In other words, the data-driven approach of such techniques *lets the data speak for themselves*, allowing interesting, possibly unanticipated information to emerge. In turn, such information can be used by the management to discover areas of excellence, or clinics where a margin for improvement exists, as well as strategies for achieving such improvement. In the context of the Balanced Scorecard, the available data are organized as vectors of KPI scores, one per clinic-month. Given these data, it is of particular interest to extract the relations existing among different KPIs for particular groups of clinics, in order to identify clusters that share a similar performance pattern, as characterized by correlated scores on specific KPIs.

For this reason, we have recently introduced the use of SOMs to analyze BSC data [34]. SOMs have already been validated as reliable tools in health care, for instance for population studies [35](Basara H, Yuan M, 2008) and for organization [36] or economic evaluations [37]. A Self-Organizing Map is a machine learning paradigm mainly used for clustering and visualization of data in high dimensional spaces (ie, data with a large number of variables) [38]. The SOM model is composed of units, often referred to as *neurons*, organized in a low dimensional reticular structure (generally in bi-dimensional or tri-dimensional space), which act as prototypes of the input data in such lower-dimensional space. The SOM learns in an *unsupervised* way to assign each input data point to the neuron that is most similar to it, by means of a training procedure that aims at preserving the topological characteristics of the input space – that is, similar input vectors are mapped to close regions in the SOM. Once the SOM has been configured, different effective views of the distribution of the data can be obtained. In particular, one can focus on a specific dimension of the input vectors (in our case, one specific KPI) by colour-coding each neuron of the SOM based on the value that the

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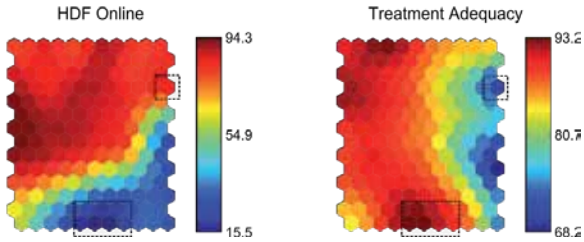

Figure 2. Two component planes (relative to the HDF online KPI and to the Treatment Adequacy KPI, respectively) of an SOM trained on BSC data from Portuguese clinics of the NC network. The dashed rectangles superimposed on the planes indicate regions of the SOM where interesting groups of clinics can be found (see discussion in the text). SOM training and visualization were performed in MATLAB using the SOM toolbox [39]. The SOM is shown as a collection of neurons (hexagons) placed in a two-dimensional grid, where the focus is on the relative, rather than the absolute, position of each neuron: that is, the main information content lies in the neighborhood relationships among neurons, as adjacent neurons contain similar KPI records. We can therefore compute the average score for a given KPI in each neuron: this is represented by a color code (colorbar shown on the right) in the component plane relative to that KPI

prototype takes on that particular dimension. This kind of plot is called *component plane* of the SOM (Fig. 2).

Many interesting insights can be achieved when running an SOM-based analysis on BSC data. For instance, Fig. 2 shows two component planes obtained from an SOM trained on the BSC data of Portuguese clinics (33 clinics, monitored for 28 months, from January 2008 to March 2010). By comparing different planes (*i.e,* different KPIs), it is possible to identify groups of data (in our case, clinic-month KPI vectors) that share a similar pattern of performance (as they are located in the same region of the map) and characterize such patterns in terms of specific KPI relations. Thus, for instance in Fig. 2, all KPI vectors that are assigned to the upper left corner of the SOM share a similar structure, which is characterized, among other things, by a high score both on the HDF Online and the Treatment Adequacy KPIs (positive correlation). From these planes one can notice that, while these two KPIs are positively correlated for most clinics in the dataset, there are also cases where treatment adequacy is low (see marked unit on the right side of the map), and cases where a good treatment adequacy is achieved (bottom part of the map). These groups of clinics thus show an interesting performance pattern that might prompt further investigations, and possibly corrective measures. To this end, one can easily trace back the clinics falling into these regions of the map to retrieve all relevant information about them. Similarly, in Fig. 3, two different component planes from the same SOM as above are shown: as expected, the patient growth and new patient inflow KPIs are, in general, directly correlated. However, it is also possible to identify groups of clinics that show a moderately high new patient Iinflow while maintaining a low patient growth score (upper left corner).

This observation can allow to quickly identifying those clinics where, presumably, there is a relevant outflow of patients and, therefore, there might be the need for corrective measures. As a final example, consider Fig. 4 where two component planes of a different SOM, trained on data from Turkey (46 clinics monitored during the same period as those in Portugal), are shown.

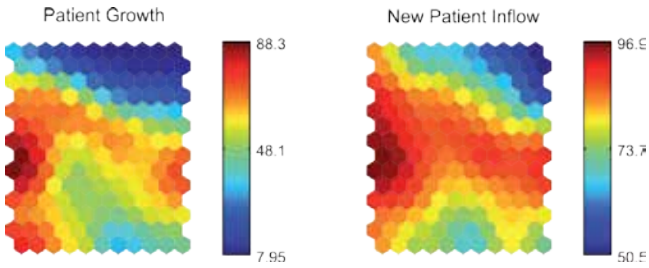

Figure 3. Two component planes from the SOM for the Portuguese clinics of the NC network. The shown planes refer to the Patient Growth and New Patient Inflow KPIs, respectively.

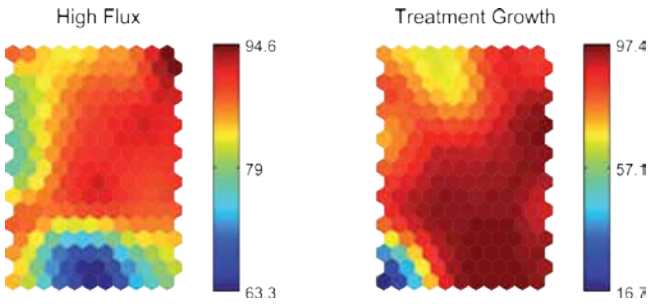

Figure 4. The High Flux and Treatment Growth component planes of an SOM trained on data from Turkish clinics of the NC network.

Here, it can be noticed, in particular, that an interesting group of clinics exists (bottom part of the map) where high Treatment growth is observed but the use of High Flux dialysis is low. This means that patients may be referred to this group of clinics for reasons different than quality of treatment (*i.e.* proximity) as expressed by this KPI. These were just a few examples of benefits from an SOM-based analysis on performance data; other results are extensively described [35]. Together, these results show how SOMs have the potential to unveil significant relationships among KPIs and to identify groups of clinics with different performance patterns, which in turn may require different corrective actions. Thus, SOMs offer valuable hints on the potential areas of intervention in the context for CQI. Information about correlated features emerges directly from the data, without the need for the management to specify a working hypothesis in advance; in this way, also relationships that were not previously advanced can be unveiled, which underlines the greater power of the SOM approach with respect to more traditional statistical analyses. Moreover, it should be remarked that another attractive feature of SOMs is that they can be visualized in an intuitive way so as to immediately convey the correlation structure of the data: this is an extra value of the approach that makes it particularly suited for prompt communication at the management level. This innovative approach to intelligent analysis of clinical data could be a contributing factor to more effective guidance of disease management.

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4. Conclusions

Every care process and particularly chronic care has to be centered on patients; therapeutic performance should therefore be measured on outcomes and not on inputs and/or procedures. This holistic approach of organizational models shall encompass all therapeutic aspects. Full availability of data and transparency are fundamental to make this patient orientation possible and long term sustainable for all involved stakeholders. Furthermore data will allow the extensive use of tools like the Balanced Scorecard and CQI. Tools of the domain of Computational Intelligence will help to develop unconsidered working hypothesis that could open to physicians new horizons of clinical research and improve understanding of functional processes in an "in vivo" environment at affordable costs. Collecting comparable and meaningful data requires the adoption of therapeutic protocols and the extensive use of guidelines. This will not lead to mere standardization and flattening of clinical activity but to a conscious personalization of clinical path. In complex models, with multiple correlated variables, consistent implementation of standards is fundamental to isolate the therapeutic change doctors want to initiate. In an environment of limited resources. their correct utilization could reduce the number of therapeutic errors with consequent reduction of waste of chances for the patient, doctor time, pharmaceutical and biomedical therapies. This would be reached through induction of error-free behaviours, increase of doctor time dedicated to real relevant things (*e.g.* using proven algorithms instead of calculating every time therapetic effort) and a patient orientation focused on relevant issues. A strong distinction has to be made between formal and substantial adoption and application of guidelines: it is not about formally adopting a given guideline, it is much more about their correct and consistent implementation and maintenance along the years. In this sense, it has to be highlighted role and relevance of training and continuous education. Finally, the complex nature of systems like the ones dealing with chronic illness care has to be considered. Complex systems tend to adapt to changes and to adsorb variations; the focus on execution and the application of guidelines tend to decrease and/or reduce their marginal benefit. To achieve the step from performance measurement to performance management, it is necessary to understand the real nature of KPIs as projects, with a start, an execution and an end according to a certain plan and with given resources. And to be ready to exchange new *vs*. old KPIs as soon as the project target has been achieved (e.g. when the KPI tends to saturation).

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All the authors are full-time employees of Fresenius Medical Care.

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Chapter 22

Push/Pull Based Renal Replacement Treatments

Kyungsoo Lee

Additional information is available at the end of the chapter

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1. Introduction

The incidence of kidney disease is rapidly increasing worldwide [1], accompanied by widespread research and development resulting in remarkable improvements in the technologies used for treatment in end-stage renal disease (ESRD) patients. Polymeric membranes are better at preventing the transfer of pyrogenic substances into the blood stream and membrane biocompatibilities are much improved [2]. The sharp molecular cut-offs of these membranes also prevents further loss of albumin during high-dose convective treatment [3]. These membrane technology advancements have been accompanied by the evolution of varied choices for renal replacement treatment. Particularly, better outcomes achieved by convective treatment have encouraged the use of synthetic membranes with high water permeability and sieving characteristics in clinical setups worldwide [4, 5].

Maintenance hemodialysis (HD) nevertheless remains a standard protocol for treating ESRD patients, despite the development of renal replacement modalities. This process is a result of two physical phenomena that facilitate mass transfer in purifying blood. Diffusion caused by a concentration gradient between blood and dialysate contributes to the removal of uremic solutes, particularly small-sized, water-soluble molecules. Excess water and mid-sized molecules are removed primarily by convective mass transfer, resulting from the transmembrane pressure gradient [6]. Plasma water flow through a membrane leads to the simultaneous movement of a solute through the membranes. Thus, volume-controlled high-flux HD adequately clears mid-size solutes without sterile fluid infusion because forward filtration exceeding the desired volume removal is compensated for by backfiltration [7], and this modality can provide a simpler form of dialysis treatment than other treatment methods. However, although the convective dose delivered during high-flux HD has been shown to

reduce mortality in patients at risk [8], overall patient survival remains comparable to that of low-flux HD [9]. This is presumably caused by the limited amount of internal filtration involved due to limitations imposed by fluid dynamics and the geometric nature of the hemodialyzer.

In contrast, hemodiafiltration (HDF) is characterized by a large filtration volume that far exceeds the desired volume removal. Given that, the dehydration must be corrected in real time by infusing exogenous sterile replacement fluid. HDF has been reported to deliver better dialysis outcomes than high-flux HD, because of the improved middle-to-large size molecular removal, better control of EPO and inflammation [10-13], resulting in less patient mortality [14, 15]. However, HDF use is limited globally because the requirement of exogenous fluid infusion raises concerns about water quality, safety and cost. This has led to modifications of HDF strategies to increase convective mass transfer without the need for exogenous replacement fluid infusion. This is achieved by spontaneous fluid reinfusion at a rate that matches convection. Backfiltration and regenerated ultrafiltrate can be the methods of spontaneous fluid restoration.

Push/pull strategies have also been examined to increase total filtration volumes without the exogenous replacement fluid infusion. The push/pull technique uses the entire membrane as the forward filtration domain for a period of time. However, backfiltration must accompany the forward filtration to compensate for the fluid depletion that occurred due to the forward filtration, and as a result, making it necessary to switch the membranes to a backfiltration domain. In other words, push/pull systems rely on alternate repetitions of forward and backward filtration during dialysis treatment and the repetitive filtration contributes to the increased total filtration volume.

In this chapter, the trials of push/pull-based renal supportive treatments are reviewed in terms of their technical description, hemodialytic efficacy and applicability for clinical use. In addition, the fluid management accuracy of the push/pull dialysis method will be discussed in depth.

2. Backfiltration and push/pull operation

Precise volume control is a crucial pre-requisite in renal replacement therapy. With kidney malfunction, the accumulation of uremic toxins and surplus water is a consistent fact in ESRD patients, and appropriate, timely renal supportive treatment must be conducted to avoid deadly uremic conditions. It has been recently reported that dialysis outcomes are considerably improved with enhanced convective mass transfer during hemodialysis, and techniques to maximize the convective volume exchange have been extensively explored. As the volume depletion exceeds the prescribed amount, it must be promptly compensat-

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ed. A straightforward way is to infuse sterile fluid after calculating the desired fluid level. However, the external infusion of sterile dialysate raises concerns like high standard water quality and treatment-related cost. Reverse movement of dialysate within a hemodialyzer has been tried as an alternative approach.

Backfiltration is the phenomenon that dialysate moves into the blood stream across membranes, in the area where dialysate pressures are higher than hydraulic blood and osmotic pressures. A pressure drop is inevitable as fluid flows through a cylindrical tube, and blood and dialysate pressures decrease along the dialyzers. In a normal countercurrent dialysis setup, because blood and dialysate flow in opposite directions, these pressure drops occur with opposing gradients, and in some regions hydraulic blood and dialysate pressures overlap. Thus, the sum of hydraulic and osmotic pressures, termed transmembrane pressure (TMP), is positive in the proximal region of a hollow fiber dialyzer, and plasma moves to the dialysate compartment across the membranes (forward filtration). However, fluid movement occurs in the opposite direction in the distal region because TMP becomes negative, and backfiltration occurs. This backfiltration compensates for fluid loss in the proximal region (Figure 1) [16].

While backfiltration method could provide fluid restoration easily, the amount of forward filtration in the normal countercurrent dialysis setup is limited, because (1) a small area of the membranes is used for the filtration inside the hemodialyzer and (2) the increase of pressure gradients through the hemodialyzer is limited in a particular hemodialyzer geometry and flow conditions. These limitations have led to investigations for techniques to increase the blood-to-dialysate pressure gradients. As fluid pressure drop through a cylindrical tube is proportional to the tube length, but is inversely proportional to the 4th power of tube diameter, hemodialyzers with reduced fiber diameters or elongated hemodialyzers have been developed [17-19]. In addition, a unique design for the hemodialyzer was also introduced [20-22] in which forward and backward filtration regions are separated longitudinally, instead of horizontally, giving the independent control of blood or dialysate pressures in each region.

Additionally, push and pull actions were devised for an infusion-free HDF technique. Differently from other methods, forward filtration and backfiltration repeat in the push/pull technique. During a given period of time, the entire membrane is used as the forward filtration domain, as in the HDF method, by regulating blood pressure higher than dialysate. Thus, the filtration rates necessarily exceed prescribed rates. Immediately after the forward filtration, the pressure gradients through the hemodialyzer are reversed, the fluid movement is switched to the opposite direction. This opposite fluid movement compensates for the excessive fluid loss during the previous filtration phase. The alternate repetition of forward filtration and backfiltration constitutes a cycle of fluid movement and the difference of the forward and backward filtration rates, i.e., net-filtration rates, is regulated at the desirable level.

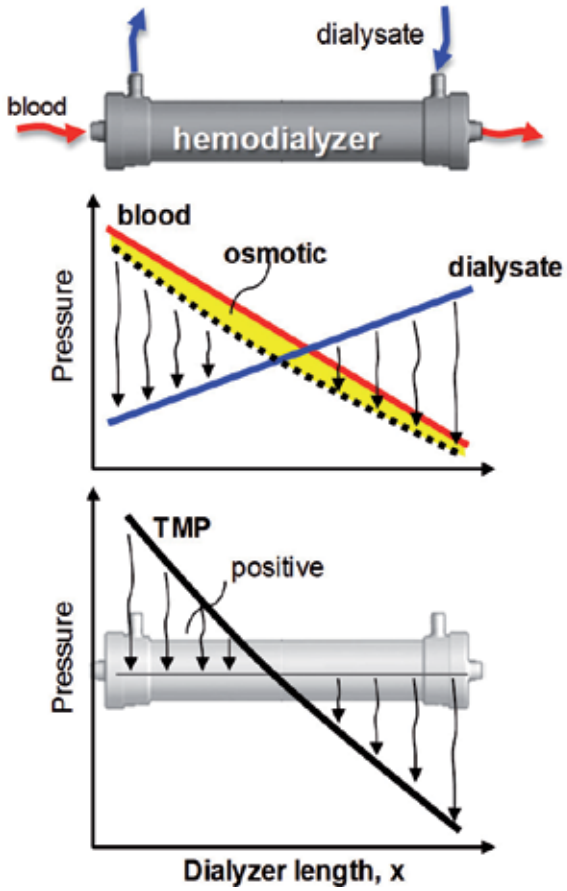

Figure 1. Transmembrane Pressure Gradient along Dialyzer Length.

3. Push/pull hemodiafiltration

The concept for repetitive use of forward and backward filtration during conventional dialysis treatments was first introduced in Japan in the early 1980's, in an effort to simplify the infusion-free HDF technique, using a serial arrangement of two hemodiafilters [23-25]. However, that system requires a means of repeating backfiltration [26]. Thus, a redundant dialysate bag is integrated downstream of the hemodialyzer and connected to the dialysate stream by a bidirectional peristaltic pump [27]. The push/pull action accomplished by this bi-directional pump alternates the evacuation and replenishment of the bag. During normal operation, dialysate flow rates upstream and downstream of the hemodialyzer are maintained in balance and the desired volume removal is achieved by a separate ultrafiltration pump. Therefore, when the bidirectional push/pull pump pulls a portion of dialysate into the bag (e.g., 70 ml/min for 3 minutes), hydrostatic pressures through the dialysate compartment decrease, because the dialysate compartment is closed and has a fixed volume, and

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water flux occurs from blood to the dialysate compartment (ultrafiltration) at the same rate as dialysate removal from the dialysate compartment. Soon after the ultrafiltration completes, the pump reverses and pushes the dialysate in the bag into the dialysate stream, causing a volume overload in the dialysate compartment. The surplus dialysate in the closed dialysate compartment is then moved to the blood compartment (backfiltration). Another bag and an additional bidirectional peristaltic pump is also integrated into the venous chamber, and conducts the pulling and pushing of blood, although in this case, the actions of the blood-side pump are 180^{O} out of phase with those of the dialysate side pump to keep blood flow returning to the patient constant.

When pure dialysate is pushed into the blood stream, solute concentrations in blood are immediately equilibrated and decreased by dilution. Soon after, the blood-to-dialysate pressure gradient reverses from negative to positive, and plasma fluid in blood is forced to move into the dialysate compartment, which removes various molecules from the plasma. This repetitive ultrafiltration contributes to convective mass transfer and increases the removal of small-sized (urea) or mid-sized (beta-2-microglobulin) molecules compared to hemofiltration (HF) or hemodialysis method, respectively [28]. On the other hand, repetitive backfiltration during push/pull HDF prevents volume depletion. In addition, the repetitive backflushing of dialysate also helps prevent membrane bindings of various blood components [26].

However, the disposable bags and separate bidirectional peristaltic pumps make this unit notably complicated. To overcome these shortcomings, a double-chamber cylinder pump was devised. The double cylinder pump includes two independent chambers and a reciprocal piston, and each chamber is connected to either dialysate or the blood stream [29], as seen in Figure 2. When the piston squeezes the chamber on the dialysate side, the dialysate compartment, which has a fixed volume, is pressurized and backfiltration begins. At this time, the chamber on the blood side expands and blood in the venous chamber starts flowing in the direction of the cylinder pump. Since the blood volume that returns to the blood-side chamber of the pump is equal to the backfiltration volume, blood flow returning to patients remains constant. The piston then moves in the opposite direction and squeezes the blood-side chamber, the dialysate compartment begins to expand, and the dialysate compartment is depressurized, leading to ultrafiltration. However, despite the large amount of ultrafiltration, blood flow in the venous line is maintained, because the ultrafiltrate removed in the hemodialyzer is replenished in the venous chamber.

The reciprocating movement of the piston is regulated by pressure differences between the two chambers of the cylinder pump (i.e., Pb-Pd). The rotation torque of the driving motor attached to the piston can be adjusted in accord with TMP (i.e., torque = TMPxSxLxsinθ). Voltage applied to the motor is adjustable, allowing the TMP to be set at 400 mmHg during forward filtration, but at -400 mmHg during the backward filtration phase. Pressure-controlled push/pull HDF can maintain transmembrane pressures at the maximum permissible level throughout treatment [30]. In addition, contrary to the original push/pull HDF, in which one cycle of filtration and backfiltration takes approximate 4~5 minutes, the pressure controlled push/pull HDF unit can repeat one cycle in1.5~1.7 seconds.

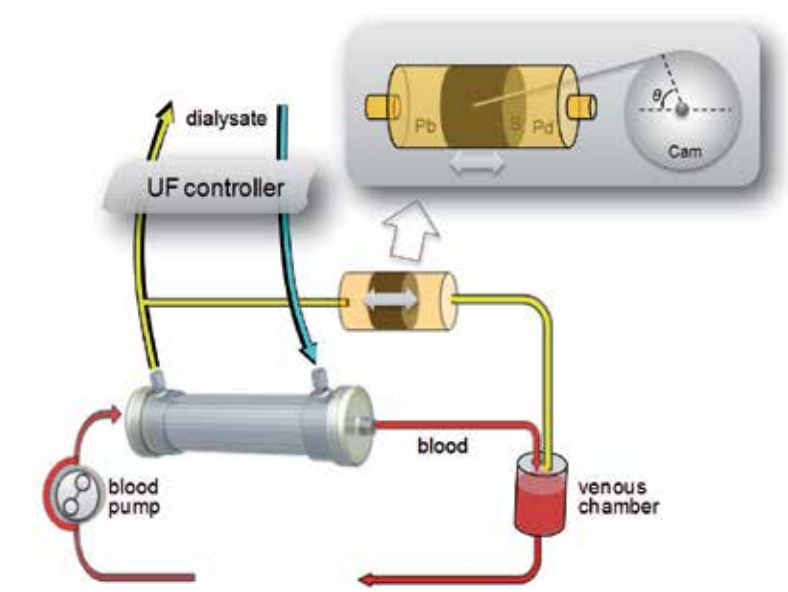

Figure 2. Push/Pull HDF and Double-Chamber Cylinder Pump

This optimized use of transmembrane pressure and more frequent alternations of forward and backward filtration in the revised push/pull HDF unit are obviously accompanied with a markedly larger total filtration volumes and higher solutes clearances [30]. The push/pull HDF unit tends to relieve symptoms like arthralgia (joint pain), irritability, pruritus, and insomnia more rapidly than conventional HD mode [27, 31, 32]. Furthermore, the optimal maintenance of membrane permeabilities by prompt backfiltration has the added benefit of considerably inhibiting albumin loss while increasing convection and diffusion [33]. Some albumin loss is unavoidable when using membranes with high water permeabilities and sieving characteristics [34]. Since convective therapy is based on larger amounts of fluid exchange and solvent drag during fluid exchange occurs randomly, albumin permeation becomes more worrisome during convective treatments [3]. In addition, filtration-induced elevated albumin concentration at the inner membrane wall also aggravates the albumin loss [35]. Protein concentration polarization develops quickly after sudden TMP development and the hydraulic permeabilities of the membrane decrease rapidly in about 2 seconds. However, during push/pull HDF, backward flushing of dialysate takes place within the time frame required for the protein layer to fully develop (i.e., 1.5~1.7 seconds), and thus, it can effectively wash out the inner lumen and inhibit excessive albumin leakage [33]. This dialysate backflushing eventually allows membrane hydraulic capabilities to be better maintained throughout the treatment.

In summary, push/pull HDF was developed in an effort to perform infusion-free, simultaneous HD and HF by using a single hemodialyzer. Thus, it alternates between ultrafiltration and backfiltration instead of dividing ultrafiltration and backfiltration regions. Pressure-controlled push/pull HDF can maintain TMPs at maximal levels and the total filtration vol-

umes achieved are far greater than that of any other treatment modality. In addition to the filtration quantity, repetitive cycles in a shorter time than the time required for a protein layer to be established ensure superior membrane use throughout treatment, further inhibiting albumin loss. Push/pull HDF is assumed to be close to pre-dilution mode HDF because the repetitive dilution exceeds blood flow rates [36]. Even though post-dilution HDF is more efficient in terms of solute removal, the substantial amount of total filtration and the optimal use of membrane offered by the push/pull HDF technique probably translate to outstanding hemodialytic outcomes. Therefore, a prolonged prospective study on push/pull HDF may be worthwhile to determine the benefits of this modality versus other forms of convective renal replacement.

4. Pulse push/pull hemodialysis

Flow patterns have been an obvious research avenue for treatments requiring extracorporeal blood circulation. Blood pulsation has been accepted, although with controversy, as beneficial during cardiopulmonary bypass, because it achieves greater perfusion to peripheral vessels and end-organs [37, 38]. Blood pulsation in a pediatric CRRT animal model delivers adequate performance over a 2-hour period in terms of ultrafiltration rates and cross-filter blood pressure drops [39, 40]. It was further found that the pulsatile flow tends to enhance ultrafiltration rates versus non-pulsatile flow [41, 42], attributable to increased rheological power of pulsatile flow. However, little evidence is available clinically or experimentally that explains the efficacy of pulsatile flow on dialysis outcomes. Pulse push/pull HD (PPPHD) is a convection-enhanced dialysis treatment, using pulsatile devices for blood and dialysate to achieve the cyclic repetition of forward and backward filtration. During an early trial, a T-PLS pump (Twin Pulse Life Supporter, AnC Bio Inc., Seoul, Korea) was used as the pulsatile pump [43]. The T-PLS consists of blood and dialysate sacs, a reciprocating actuator and a motor-cam assembly [44], with the actuator between the blood and dialysate sacs (Figure 3). When the actuator squeezes the blood sac, blood can move forward due to one-way check valves. At the same time, the dialysate sac expands and is filled with fresh dialysate. In the same manner, dialysate also moves forward when the sac is squeezed and the blood sac is filled with blood. These reciprocating movements create pulsatile flow. By setting their phase difference at 180^{O} degrees, the pushing phases of blood and dialysate pumps alternate, and TMPs cycle between positive and negative, driving consecutive periods of ultrafiltration and backfiltration.

The hemodialytic efficiencies of PPPHD have been demonstrated, and studies show that PPPHD substantially improves uremic marker molecules clearance, particularly for mid-sized molecules (Table 1) [43]. Increased filtration volumes in the PPPHD unit may also be due to reduced membrane fouling. In an *in vivo* setup on PPPHD, one cycle of ultrafiltration and backfiltration took 3 seconds at a pulse frequency of 20 bpm [45]. When ultrafiltration and backfiltration times were defined as the durations of positive and negative TMPs, respectively, ultrafiltration and backfiltration times for the PPPHD unit were approximately 1.7 and 1.3 seconds, respectively. Since protein concentration polarization on the blood-side

membrane develops during forward filtration and is reduced by backfiltration, membrane convective capacity could be better maintained during PPPHD than during CHD, showing smaller reductions in post-dialysis hydraulic permeabilities [45].

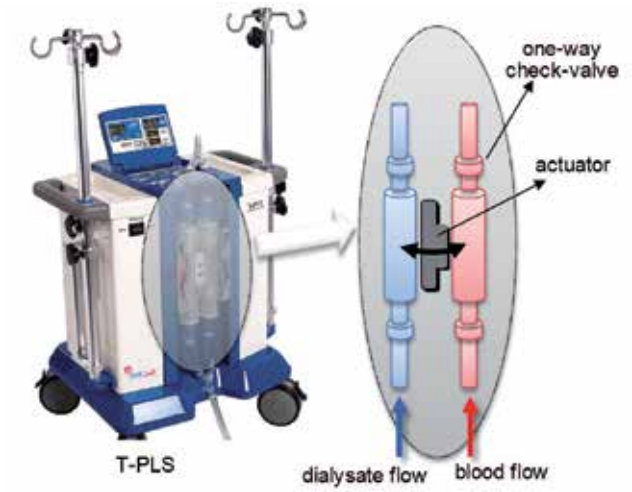

Figure 3. T-PLS pump for the original PPPHD

Group	BPM	QB	QD	Clearance (ml/min)			
				BUN	Creatinine	Vitamin b12	Inulin
CHD	-	236±3.6	420±3	161.1±4.3	127.2±3.9	37.5±6.3	25.3±5.1
PPPHD	40	234±3.1	419±3	166.2±3.8	136.9±4.2	55.7±5.0	37.8±3.9
% Increase		-	-	3.2	7.6	48	49
P-value		NS	NS	0.053	<0.05	<0.001	<0.001

Table 1. Solutes Clearances. (CHD, conventional high-flux HD; PPPHD, pulse push/pull HD; BPM, beats per minute; QB, blood flowrate; QD, dialysate flowrate; BUN, blood urea nitrogen; NS, not significant) (Reproduction was permitted by a publisher)

5. Modified pulse push/pull hemodialysis

Pulsatile circulation of blood and dialysate offers a simple and efficient strategy for the repetitive cycle of filtration and backfiltration. However, blood pulsation during extracorporeal renal replacement treatment is potentially problematic. Specifically, instant suction generated by a pulse pump through a narrow catheter may cause blood damage, vessel narrowing, or vessel collapse. In addition, instantaneous negative pressures generated up-

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stream of a pulsatile blood pump not only introduce the possibility of circuit aeration, but could lead to a failure to maintain predetermined blood flow rates [46, 47].

Hence, PPPHD unit was revised, and while many facets of the original PPPHD were retained, including the alternating water flux across the membrane, blood pulsation was excluded. This was achieved by employing dual pulsation in the dialysate stream, that is, pulsatile devices in the dialysate stream upstream (a dialysate pump) and downstream (an effluent pump) of the dialyzer [48]. Backfiltration occurs when the sum of the cross-membrane pressures is negative, but ultrafiltration when the sum is positive. The hydraulic pressures of blood and dialysate were both manipulated in the original PPPHD, but since blood pulsation was eliminated, dialysate pressure alone regulates TMP in the revised unit. Therefore, the following two assumptions were made; (1) dialysate compartment pressures must be far higher than blood-side pressures when pure dialysate is forced into the dialyzer, and (2) dialysate pressures drop to lower than blood pressures during effluent pump expansion. Given these assumptions, the dialysate and effluent pumps are replaced with a dual pulse pump [49].

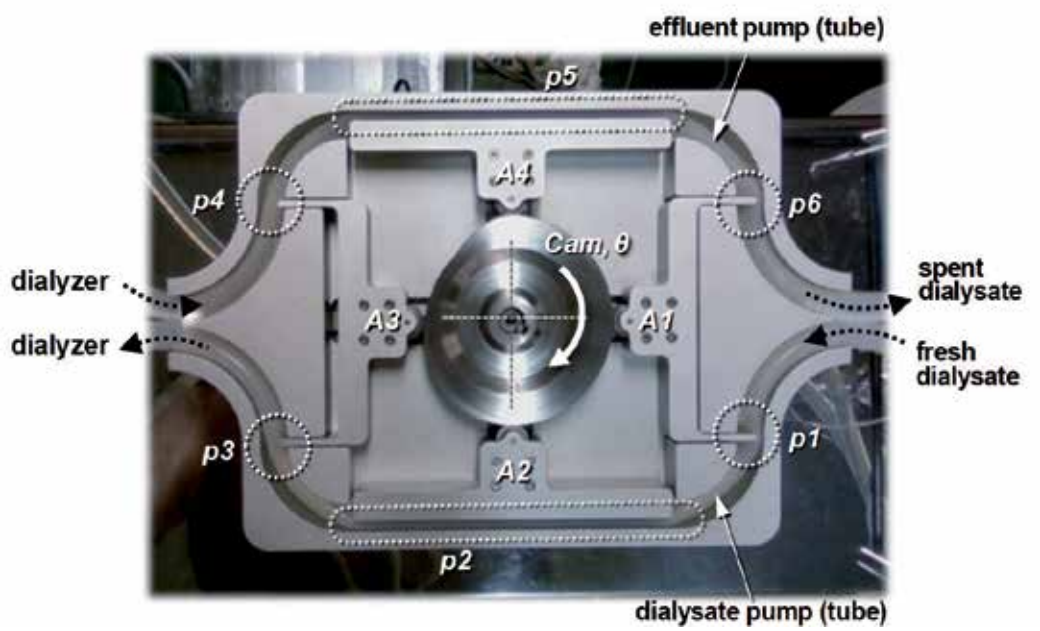

Figure 4. Dual Pulse Pump (DPP). DPP is composed of a base plate, a unidirectional electric motor, a cam, and four actuators. It contains two separate silicone tubes. Pulsatile flow is generated by squeezing each dialysate and effluent tubing segments. (A1~A4, actuators 1 to 4; p1~p6, silicone tubing segments at positions 1 to 6, respectively) (Reproduction was permitted by a publisher)

The dual pulse pump (DPP) is a pulsatile device that was developed to eliminate the one-way valves that are generally required for pulsatile devices to prevent retrograde flow. Instead, time-delayed tube openings and closings constitutes a cycle of pulse generation (Figure 4). In other

words, two separate silicone tubes in the DPP are periodically opened or closed. Pulse generation with DPP can be described in terms of four phases as determined by cam rotation, which translates motor rotation to actuator linear displacement. As the cam rotates, the four actuators periodically push on the tubing segments at the positions shown in Figure 4. Actuator 1 pushes on the tubing segments at positions 1 and 6 (p1 and p6) simultaneously, and actuator 3 squeezes the tubing segments at positions 3 and 4. Actuators 2 and 4 squeeze tubing segments at p 2 and p5, respectively, and cause the dialysate in the tube to move in the required direction. For pulse generation by the dialysate pump, as the cam rotates from θ=0° to 90°, the p2 tubing segment opens and p1 closes, and these processes overlap such that pure dialysate fills p2 tubing. While p2 expands, p3 remains closed, acting as an upstream valve to prevent retrograde dialysate. These tube openings and closings are depicted diagrammatically in Figure 5. During the first phase, with p3 closed, p2 tube openness increases whereas p1 tube openness decreases. During the 2nd phase (θ=90°~180°), with p1 closed, p2 begins to be squeezed and simultaneously p3 begins to open, and pure dialysate is driven into the hemodialyzer. Closure of p1 fulfills the same function as atrioventricular valve closure during left ventricular systole, which prevents retrograde flow. Likewise, during the 3rd phase (θ=180°~270°), p3 is closed, while p1 and p2 remain closed and in the final phase (θ=270°~360°), p1 is open, and p2 and p3 remain closed in preparedness for the next filling phase. These time-delayed tube openings and closures constitute one cycle of pulse generation. In the same manner, effluent pulsations were also generated through the effluent tube, although in this case, the actions of actuators 1 and 3 were reversed, and the pulsatile flow pattern was 180^{O} out of phase with that in the dialysate tube.

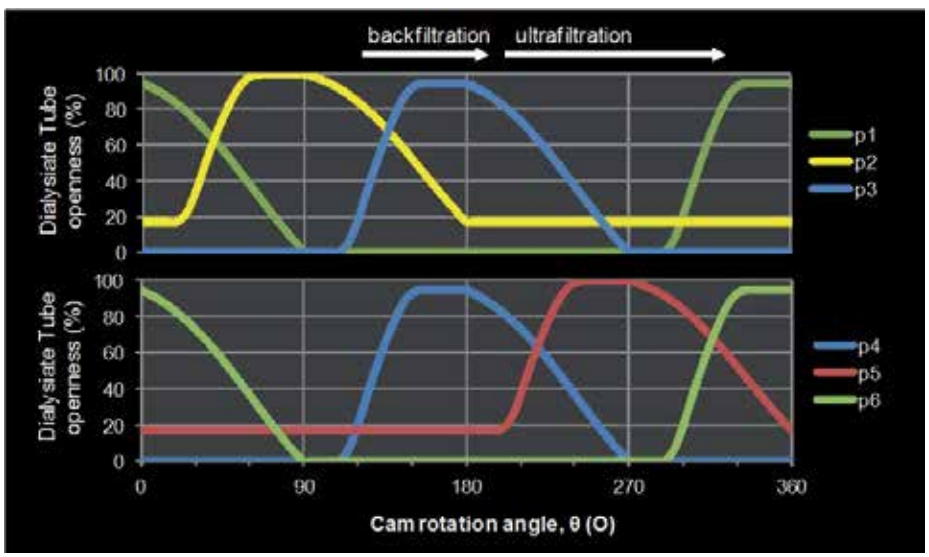

Figure 5. Changes in DPP Tube Openness at p1~p3 for Dialysate Pump (top) and at p4~p6 for Effluent Pump (bottom). Tube openness is defined as the ratio of compressed to original tube cross-sectional area. Tube openness at p1 (p6) and p3 (p4) during cycles ranged between 94% and 0%, corresponding to fully opened and completely closed, respectively. The p2 and p5 had an openness that ranged from 99% to 17%. (p1~p6, tubing segments at positions 1 to 6, respectively, as shown in Figure 4) (Reproduction was permitted by a publisher)

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Theoretically, forward and backward filtration rates during one cycle of PPPHD are identical to effluent and dialysate flow rates, respectively. The moment when pure dialysate is driven to the dialyzer (i.e., during p2 squeezing), the effluent dialysate path is closed at p6. At the same time, p1 is also closed, and thus, the pure dialysate pushed into dialyzer moves into the blood stream (backfiltration), because the whole dialysate compartment is fixed and closed. Immediately after the backfiltration is completed, the effluent tubing (p5) begins to expand (i.e., p5 expansion during the 3rd phase), and since the dialysate and effluent pathways are still closed at p1 and p6, respectively, dialysate pressures in the hemodialyzer drop steeply and ultrafiltration takes place at a rate determined by effluent stroke volume.

During experiments using the revised PPPHD, the animals remained stable without any procedurally related complications. Molecular removals were satisfactory while total protein levels, albumin concentrations, and glucose levels were preserved uniformly throughout sessions (Table 2) [50]. As stated before, the DPP is additionally characterized by a lack of valves, which makes the pulsatile device simple and inexpensive, and thus, any medical-grade silicone tubes can be used as dialysate and effluent sacs. With the exception of small tubing sections at p1, p3, p4, and p5, most of the tubing is operated non-occlusively, reducing the chances of tubing rupture and spallation [51, 52].

					PPPHD					
(h)	aPTT	PT	WBC	Hct	TP	ALB	Glu	Ca2+	Na+	K+
0	16±14	6.0±2.6	10.5±6.1	28.5±4.6	5.3±0.4	3.1±0.1	119±7	12.4±0.8	136±5.7	5.7±0.6
1	48±48	3.9±2.1	6.9±2.6	27.8±4.0	5.3±0.4	-	-	-	-	-
2	166±149	4.8±1.9	8.0±3.1	28.0±3.6	5.6±0.7	3.1±0.2	111±4	11.5±0.8	134±4.2	5.1±0.6
3	317±220	4.4±1.3	8.7±2.8	28.5±2.9	5.6±0.7	-	-	-	-	-
4	205±69	3.8±0.7	9.2±2.7	27.3±3.5	5.3±0.4	3.1±0.2	126±44	10.8±0.5	132±3.1	4.3±0.5
	CHD									
(h)	aPTT	PT	WBC	Hct	TP	ALB	Glu	Ca2+	Na+	K+
0	16±6	3.2±1.1	9.3±4.1	30.3±6.8	5.7±0.4	3.2±0.3	124±10	11.7±0.4	138±4.9	5.9±0.2
1	170±93	3.8±0.6	6.9±4.4	27.3±5.5	5.7±0.1	-	-	-	-	-
2	232±125	4.5±0.5	7.8±4.8	28.3±6.1	5.6±0.2	3.2±0.3	111±8	11.3±0.3	136±5.5	4.2±2.4
3	154±50	4.3±2.3	7.5±4.2	28.0±5.6	5.5±0.3	-	-	-	-	-
4	248±150	6.0±1.6	9.1±4.7	26.3±5.1	5.2±0.3	3.1±0.3	108±10	10.7±0.2	137±5.2	4.9±0.7

Table 2. Physiologic Parameters and Electrolytes Balance during PPPHD and CHD. (aPTT, activated partial thromboplastin time in sec; PT, prothrombin time in sec; WBC, white blood cell in $10^3/\mu l$; Hct, hematocrit %; TP, total protein in g/dl; ALB, albumin in g/dl; Glu, glucose in mg/dl) (Reproduction was permitted by a publisher)

6. Pulse push/pull hemodialysis with dual piston pump

Pulse push/pull HD is conceptually similar to the push/pull HDF method. Both modalities were devised to increase total filtration level by alternating forward and backward filtration. However, the underlying design of PPPHD significantly differs from push/pull HDF. The supplementary component required to switch from ultrafiltration to backfiltration phases or vice versa used in push/pull HDF is not needed for PPPHD because the alternating bimodal pulsation in the dialysate stream creates the cyclic repetition. In addition, the dual pulsatile device in the PPPHD unit serves as a flow equalizer.

Maintaining pre-determined flow rates and precise volume control are pre-requisites of extracorporeal renal replacement treatments for ESRD patients, particularly when using membranes with high-water permeability. Accordingly, the dual pulsatile pump integrated into the dialysate stream has been remarkably improved to achieve substantially more accurate fluid balancing, and the dual pulsation system acting on the PPPHD dialysate compartment was replaced with a dual piston pump. Figure 6 is a schematic diagram for the PPPHD system as combined with the dual piston pump. This modification allows pulse generation and push/pull actions to be achieved, not only by the novel design of the piston pump, but also by the unique control of piston movements offered. As the dialysate piston compresses the cylinder, pure dialysate is forced into the dialyzer, but at this time, the effluent stream is functionally closed at the effluent piston pump, thereby increasing dialysate compartment pressures rapidly and backfiltration occurs (a→b in Figure 7).The effluent piston then begins to expand and dialysate moves into the effluent cylinder, while the dialysate supply line remains closed at the dialysate pump. Because of effluent suction, dialysate compartment pressures fall sharply and water flux from blood lumen to dialysate occurs (b→c). During the final step (c→a), pure dialysate fills the dialysate cylinder, and simultaneously used dialysate is drained.

In an *in vitro* test of PPPHD with the dual piston pump, in which bovine blood was circulated, the phenomena of push (backfiltration) and pull (ultrafiltration) were well sustained throughout, and their levels perfectly balanced those of stroke volumes of the dialysate and effluent pumps. In addition, dialysate and effluent piston pumps served as a means of controlling isovolumetic dialysate flow rates upstream and downstream of the dialyzer. Results showed the balancing error between dialysate and effluent piston pumps was less than 0.09% of total dialysate volume. During the 4-hour session, total dialysate volume supplied to the dialyzer is 95.8L, and 95.7L of the used dialysate was collected during the same period. Furthermore, TMPs clearly cycled positive and negative due to huge fluctuations in hydraulic dialysate pressures (Figure 8). Despite the use of a peristaltic roller pump for blood, the blood pressures acquired during PPPHD showed an obvious fluctuation which was perfectly synchronized with dialysate pressure pulsation. Generally, peristaltic roller pumps create small fluctuations in flow and pressure because of the way they squeeze tubing. However, the blood pressure fluctuations acquired during PPPHD were much larger than that observed with peristaltic roller pumps during conventional HD, providing clear evidence of dialysate flux to the blood stream. Hydrostatic dialysate pressures were approxi-

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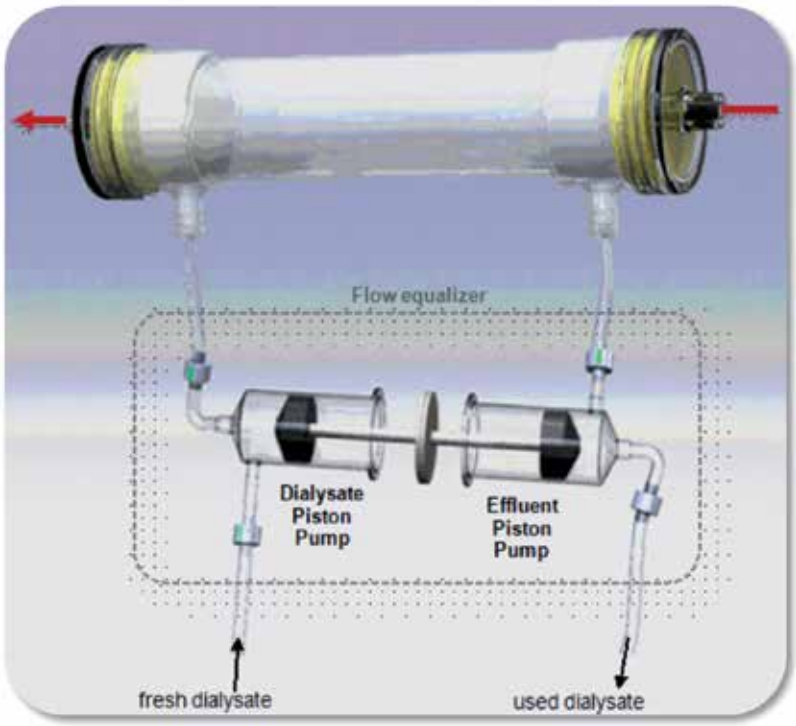

Figure 6. Circuit Diagram for PPPHD with Dual Piston Pump.

mately 620~660 mmHg during the backfiltration phase and -480~-520 mmHg during the ultrafiltration phase, which correspond to the positive and negative TMPs of 400~420 mmHg and -460~-506 mmHg, respectively.

In addition, the optimal use of transmembrane pressures and enhanced convective mass transfer translates into a significant increase of molecular removal. Even though no significant difference was observed with respect to clearances of low molecular weight substances, the inulin clearances were increased significantly for the PPPHD versus the conventional high-flux HD (CHD) mode. In addition, there is a clear tendency that the proportionate increase (%increase) of solutes clearances between the PPPHD and CHD was increased as the molecular weights increase.

PPPHD with the dual piston pump is also versatile and can be easily converted to conventional high-flux HD mode. Time-controlled piston operations perform the push and pull operations, but when the two piston movements are synchronized alternately (that is, dialysate piston compression and effluent piston expansion or dialysate piston expansion and effluent piston compression occur simultaneously), dialysate passes through the hemodialyzer without significant volume exchange. In this situation, the two piston pumps serve as a flow equalizer only and dialysis is largely achieved by diffusive mass transfer.

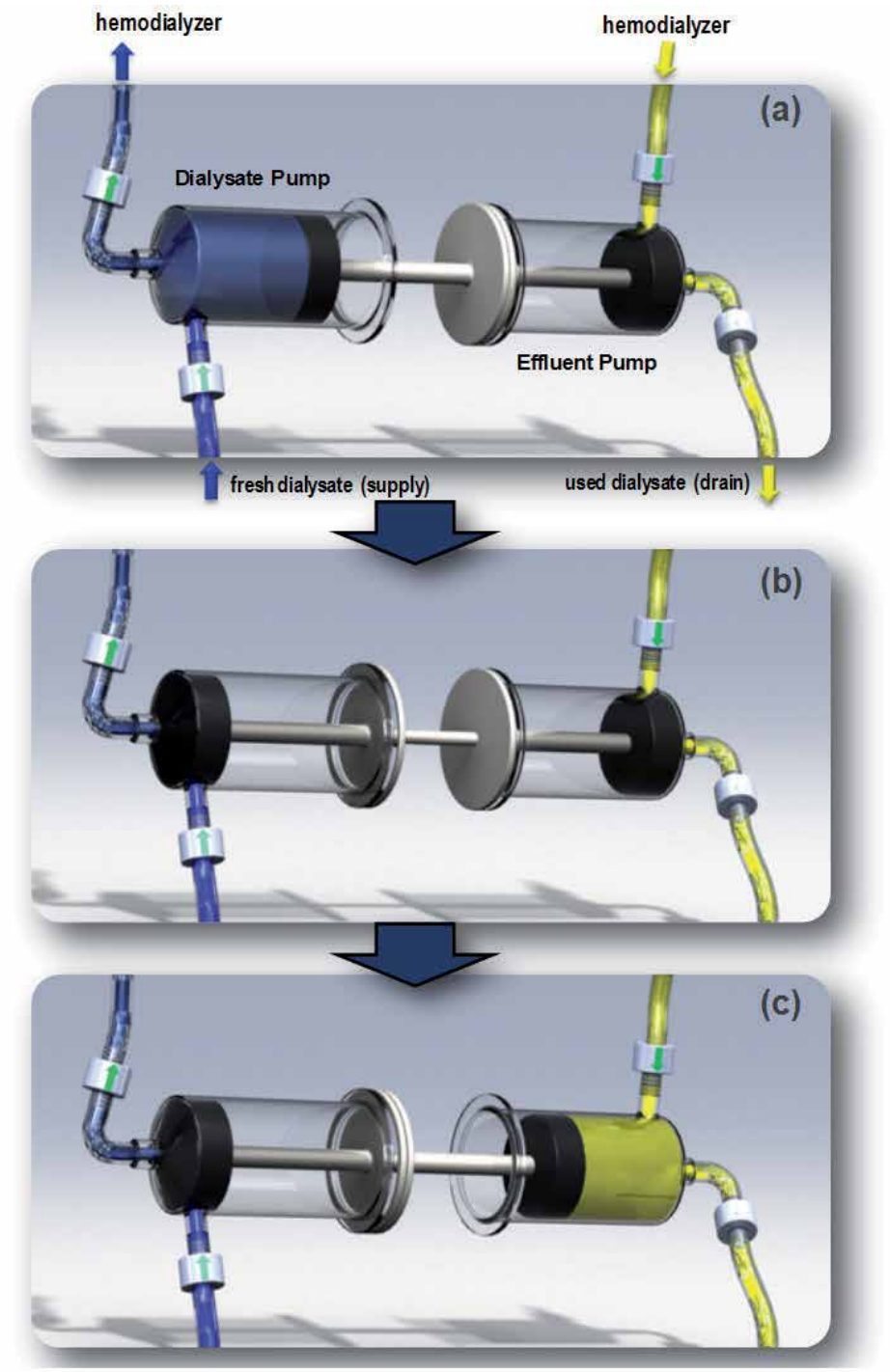

Figure 7. Three Phases for Push/Pull Generation for the PPPHD with Dual Piston Pump.

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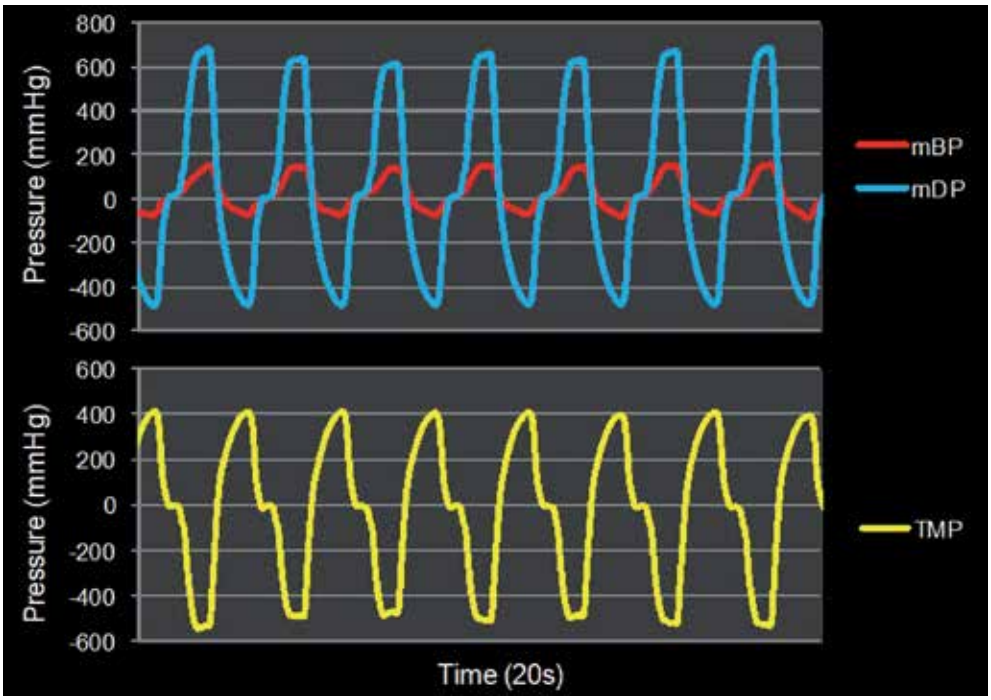

Figure 8. Pressure Profiles during PPPHD treatment (mBP, mean blood pressure; mDP, mean dialysate pressure; TMP, transmembrane pressure defined by mBP-mDP)

7. Conclusion

Much evidence shows that HDF delivers better dialysis outcomes than high-flux HD, and these benefits have been attributed to the higher convective doses permitted during HDF. In addition, advances in water treatment allow ultrapure replacement fluid to be prepared in real time, which further inhibits the inflammation risk in the ESRD patients [53]. In this chapter, the author reviews HDF techniques that are based on the push/pull operation. Push/pull based HDF techniques were derived by considering the time-split phase separation, which is based on the notion that the repetitive ultrafiltration contributes to the increase in the total filtration volume and convective mass transfer. While the push/pull HDF requires the use of a separate device so that dialysate pressures are regulated instantaneously, the pulse push/pull method employs the pulsatile circulation of dialysate and effluent to effect the repetitive procedures. In addition, the devised dual piston pump in the most advanced PPPHD unit not only offers unmatched fluid balancing accuracy, but also the maximal permissible level of convective volume exchange, and the entire dialysis system for PPPHD could be substantially simplified. Based on these features of the devised PPPHD, the author believes that the PPPHD system should be further improved by being equipped with features that simplify overall dialysis treatment and enable dialysis to be performed in free-standing clinics. A dialysis unit equipped with these features may also provide treat-

ment alternatives beyond the current thrice weekly 4-hour practice, and perhaps allow even daily home dialysis for ESRD patients.

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Chapter 23

Select Ion and Preparation of Patients for Dialysis

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Additional information is available at the end of the chapter

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1. Introduction

The prevalence of chronic kidney disease (CKD) is increasing [1]. This rise is probably attributable to the progressively aging population and to the increased prevalence of comorbid conditions namely obesity, diabetes, and hypertension. According to the data from the National Health and Nutrition Examination Surveys, the prevalence of CKD in participants 70 years old and older is 46.8% compared to 6.7% in those between 40–59 years of age [1]. Many patients with CKD are unlikely to exhibit sufficient progressive decline in renal function to require renal replacement therapy (RRT), in fact according to the findings present in literature only a small percentage of CKD patients ultimately require RRT [2-5]. In part, this low rate is explained by the increased risk of death from cardiovascular causes before progression to end-stage renal disease (ESRD) can occur [6]. In part, it is secondary to the earlier referral than in the past to nephrologists with improvement of nondialytic maximum conservative management (MCM) focused on quality of life and patient comfort (i.e. maximizing renoprotective therapies, additional dietary interventions) [7,8]. In 2008, more than 110,000 Americans were started on maintenance RRT, a life-saving therapy for patients with ESRD [6]. Ideally, when patients begin RRT they should meet the following conditions: firstly, they should not require hospitalization for the management of untreated acute or chronic complications of uraemia; secondly, they should have a thorough understanding of the different treatment options; and thirdly, they should have a functioning, permanent access for the RRT of their choice [9].

Unfortunately still a sizable proportion of patients in the USA are not adequately prepared for starting RRT. In 2008, 44% of patients received no predialysis nephrology care and only 25% had received ongoing care by a nephrologist for more than 12 months prior to initiating dialysis [6]. Despite the critical importance of lifestyle management fewer than 10% of pa-

tients receive dietary counselling prior to starting RRT [6]. Furthermore, many patients newly diagnosed with ESRD are not offered alternatives to RRT (such as home dialysis or preemptive transplantation), even in the absence of medical contraindications [10,11]. More than 80% of patients in the USA initiate RRT with a central venous catheter (CVC), a type of access associated with significantly higher rates of infectious complications and of long-term non-infectious complications compared with a permanent vascular access [6, 12-14]. Inadequate preparation for RRT in the USA can only partially be accounted for delayed referral to nephrologists; as a considerable number of patients who have received more than 1 year of specialist care prior to initiating RRT are also inadequately prepared for this treatment [6]. In 2006, the annualized mortality in the first 3 months of starting RRT for patients in the USA was approximately 45%, which was in part due to inadequate preparation and education [15]. The available data on RRT preparation practices outside the USA are limited but seem highlight the same challenge, the need of a better selection and preparation to RRT [16]. Analyses from the Dialysis Outcomes and Practice Patterns Study (DOPPS) and findings from studies conducted in the 1980s and 1990s indicate a high rate of delayed referrals to a nephrologist in Europe, and contemporary data from Canada also demonstrate a high incidence of suboptimal RRT initiation [1,16-19].

Although dialysis prolongs the lives of many individuals with ESRD, the burden of RRT might not justify the potential benefits of treatment in certain patients, such as the elderly [20]. However, as illustrated by the North Thames Dialysis Study and by one Canadian study, judgment on the appropriateness for RRT should not depend solely upon chronological age but should instead be based on a composite assessment of the health and functional status of the individual [21,22]. Results from other studies suggest that there are subgroups of patients who have a low likelihood of benefiting from RRT [23-25]. For example, initiating RRT does not reverse the progressive decline in functional status; instead this decline seemingly accelerates after RRT initiation [23]. For selected individuals with advanced CKD, nondialytic MCM might, therefore, be superior to initiating RRT [24] this suggestion highlights the importance of considering the appropriateness of RRT for individuals with CKD early in the disease course. Assessment of disease management requires shared decision-making between patients, their family members, and the treating physicians [25]. Most of the data on the principles of management and outcomes of patients with advanced CKD who elect to have MCM are derived from the United Kingdom [24,26,27]. In most of the published studies to date, the life expectancy of patients with advanced CKD who choose MCM is shorter than that of patients with matching characteristics who choose RRT; the median life expectancy of patients with ESRD who forgo RRT has been reported to range from 14 months to 23 months [24,26,27]. However, the primary goal of care in patients who opt for MCM should be focused on symptom management to enhance quality of life and ensure patient comfort [9].

2. How is the choice made between hemodialysis and peritoneal dialysis?

Global comparisons show interesting differences between countries in the proportion of patients with ESRD treated by peritoneal dialysis and hemodialysis. The wide discrepancy between countries such as UK [45% of patients treated by peritoneal dialysis), and its

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neighbour France, where only 10% are so treated, indicates strong non-medical influences on the choice of dialysis modality [28].

Economic reasons: the reimbursement to the physicians and the dialysis facilities for the cost of providing treatment varies widely around the world. There are also large differences between the levels of payment for hemodialysis and peritoneal dialysis in many countries. For example in French the facility is not reimbursed for peritoneal dialysis and the physicians receive no fee. Conversely in countries such as Hong Kong, where dialysis is only available in the private sector, more patients are treated by peritoneal dialysis than by hemodialysis, as the former is less expensive. If the physician has a financial interest in the hemodialysis facility, this may directly influence the decision on which modality of treatment to recommend.

Physician preference: there is a strong preference for hemodialysis among some influential nephrologists on both sides of the Atlantic. This is supported by data from USRDS [29]. In a large US-based survey reported in 1997, only 25% of patients remembered having peritoneal dialysis discussed with them. In contrast 68% of patients on peritoneal dialysis had had discussions on hemodialysis. Interestingly, a much greater proportion of patients on hemodialysis felt that the choice had been made by the medical team rather than by either themselves or by joint decision [29].

Geography and sociocultural influences: home dialysis, peritoneal dialysis or hemodialysis, is a much more attractive proposition if the alternative is a long journey to the dialysis facility. For example in New Zealand, in 1990 only 58% of dialysis patients lived in cities with dialysis facilities. As a result, 50% of patients received peritoneal dialysis and 32% home dialysis. In countries, such as Japan, most patients prefer to receive their medical care in a hospital setting [27]. They feel that is not appropriate for treatment to be done in the home and are often reluctant to take responsibility for delivering their own care, as a result only 6% of Japanese dialysis patients are on continuous ambulatory peritoneal dialysis.

3. Medical indications for peritoneal dialysis and hemodialysis

The majority of patients with ESRD are suitable for treatment with either peritoneal dialysis or hemodialysis. There are no completely reliable data comparing mortality or morbidity for these treatments and it is difficult to envisage an ethically acceptable trial where patients are allocated randomly to different dialysis modalities [30,31].

3.1. Contraindications to dialysis modalities

3.1.1. Peritoneal dialysis

There are few situations where there is a consensus that peritoneal dialysis is contraindicated. The consensus panel of the NKKF-DOQI has agreed the following relative contraindications to peritoneal dialysis [32]:

- Fresh intra-abdominal foreign body (e.g. aortic graft, ventriculo-peritoneal shunt): patients with prosthetic aortic grafts have been successfully treated with peritoneal dialysis. Hemodialysis is usually used initially for up to 16 weeks to allow the graft to be covered with epithelium and so avoid the risk of graft infection via peritoneal dialysate. However this risk must be balanced against that of bacterial seeding from the patient's hemodialysis access.
- Body size limitations and intolerance of intra-abdominal fluid volume: body size can be a problem at both ends of spectrum. The effect of increased intra-abdominal pressure can be particularly marked in patients with chronic respiratory disease, with low back pain and with large polycystic kidneys. In general, it is hard to predict a patient's tolerance of intra-abdominal fluid and so these limitations usually appear after a patient has started peritoneal dialysis.
- Bowel disease and other sources of infection: the presence of ischemic bowel disease, inflammatory bowel disease or diverticulitis is likely to increase the incidence of peritonitis due to organisms passing through the bowel wall into the peritoneum. Abdominal wall infection may lead to peritonitis via the exit site and catheter tunnel.
- Severe malnutrition or morbid obesity: patients should ideally commence peritoneal dialysis in an adequate nutritional state. Severe malnutrition may lead to poor wound healing and to leakage from the catheter tunnel. In addition peritoneal protein losses during dialysis may exacerbate hypoalbuminenia. At the other end of the spectrum it may prove difficult to satisfactorily place a catheter through the abdominal wall in patients with morbid obesity. Thereafter absorption of glucose from the dialysate may contribute to further weight gain.

3.1.2. Hemodialysis

Contraindications to hemodialysis are few. Access to the circulation can usually be obtained even in patients with extensive vascular disease or previous surgery. An aversion to needle puncture of the arteriovenous (A-V) fistula is common in the early stages but can usually be overcome by careful use of local anaesthetic and nursing encouragement. Some patients with severe cardiac disease may not tolerate the shifts in volume and electrolytes that occur during hemodialysis treatment. However, there are no objective measurements that will reliably identify such patients. Severe coagulopathy may make management of anticoagulation for the extracorporeal circuit difficult.

4. Vascular access for hemodialysis: Surgical considerations

The maintenance of adequate, durable vascular access for hemodialysis is essential for the wellbeing of the patient with ERSD. The provision of hemodialysis requires repetitive vascular access that can achieve a blood flow in excess of 350 mL/min. If vascular access cannot be achieved for even short period of time the patient will die from uraemia. Hemodialysis is

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employed in chronic maintenance hemodialysis, acute renal failure and elimination of poisons from the body. For the provision of chronic maintenance hemodialysis the requirements for vascular access are very different from those for acute hemodialysis.

5. Vascular access for acute hemodialysis

5.1. Dual-lumen cuffed catheters

The vascular access requirements for acute hemodialysis are best served by the use of dual lumen, non-cuffed, temporary catheters. These catheters are made of a variety of materials including polyurethane or polytetrafluoroethylene. These materials have the useful property that a room temperature they are rigid, which facilitates their insertion, but when in place, they achieve body temperature and become much more flexible. Dialysis catheters are most commonly placed in the femoral, subclavian or jugular vein. Each of these sites has advantages and disadvantages depending on specific clinical circumstances. The femoral vein is in most patients the easiest site to insert a catheter and is associated with the lowest risk of life threatening complications. The major disadvantages of using the femoral vein are that the patient must remain recumbent while the catheter is in place and the high rate of infection if the catheter is left in place for more than 72 hours. It is preferable to use femoral catheters of 24 cm length as the recirculation in these catheters has been shown to be considerably lower than in the shorter 15 cm catheters. For patients who require longer periods of renal replacement (>72 hours and <3 weeks), a dialysis catheter placed in the jugular vein is preferable. The acute complications associated with both jugular and subclavian line insertion are similar. However subclavian line insertions are associated with the longer-term complication of subclavian vein stenosis, thus compromising the use of ipsilateral limb for long term vascular access. Catheters placed under aseptic conditions in either the jugular or subclavian vein may be left in place for up to 3 weeks. Complications associated with subclavian or jugular catheters include pneumothorax and arterial or great vein puncture with associated mediastinal, pleural or pericardial haemorrhage. The risk of great vein perforation is probably greatest in patients who have previously had multiple line insertions and have developed subclavian vein stenosis. Patients with a previously documented subclavian vein stenosis should never have a temporary catheter inserted on that side. It is imperative that a chest X ray is taken prior to the initiation of hemodialysis after either jugular or subclavian lines are inserted. This is to exclude the development of either a pneumothorax or hemothorax and to confirm that the catheter is in a position compatible with the desired vessel. If there is any doubt that the tip of the catheter is within a great vein, a small amount of contrast should be injected into the catheter under fluoroscopic control.

Although a far inferior choice for vascular access than a primary artero-venous (A-V) fistula or polytetrafluoroethylene (PTFE) graft, dual-lumen cuffed catheters have assumed an important role in the provision of vascular access for ESRD patients. Whenever possible some form of vascular access other than a cuffed catheter should be sought for a patient who has a

prognosis of more than 6 months. In our opinion the cuffed catheter is best used as a bridge between failed access and the establishment of permanent access.

6. Permanent vascular access

There is no doubt that a pre-emptively placed forearm primary A-V fistula is the most effective form of long-term vascular access for the uremic patient. It is important for physicians caring for patients with renal insufficiency to begin making plans for the provision of renal replacement therapy at an early stage and this usually begin when creatinine clearance is < 25 mL/min or serum creatinine> 4 mg/dL. Pre-emptive planning for the provision of vascular access is certainly cost-effective; it avoids emergency placement of femoral or subclavian catheters and also reduces hospital admissions for infection and temporary access failure.

7. Types of permanent vascular access

7.1. Primary fistula

In 1962 Cimino and Brescia described the technique of anastomosing the radial artery to the adjacent veins [33]. This technique allowed repeated puncturing of veins for dialysis access. The most frequent problem associated with A-V fistula is a failure to mature, as manifested by early thrombosis or inadequate blood flow rates. For patients in whom it is not possible to create a primary radio cephalic A-V fistula, an upper arm brachiocephalic fistula is a second best alternative and preferable to the use of a polytetrafluoroethylene (PTFE) graft. An upper arm brachiocephalic fistula takes few weeks to mature. Up to 80% of primary A-V fistulae will be functioning 3 years after creation.

7.2. PTFE grafts

PTFE was introduced in 1976 as a material for vascular bypass grafts. Since that time this material has become the mainstay for vascular access in dialysis when autologous A-V fistula is either technically impossible or has failed to mature. Using PTFE as a conduit, a fistula is created between an upper limb artery and vein.

More than 80% of the vascular procedures performed in the US [34]. Recent studies have demonstrated that the use of PTFE grafts is actually increasing rather than decreasing. These discrepancies between the US and other parts of the world have been attributed to the increased age of the dialysis population in the US and the increased proportion of ESRD patients with diabetes and with poor quality vessels that provide inadequate vascular access, as well as to the surgical practices that have evolved. More than 40% of patients who present ESRD in the US have not had vascular access created prior to the initiation of hemodialysis. Studies looking at the survival of PTFE grafts have noted cumulative patency rates for PTFE grafts of between 63-90% at 1 year and 50-77% at 2 years; fewer than 50% survive beyond

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the third year. Newly inserted PTFE grafts should not be needled for at least 14 days because adhesions of the subcutaneous tunnel and graft has not yet occurred; potential bleeding into the graft tunnel and hematoma thereof may ruin the access site.

Prior to the creation of a new vascular access route, it is important to evaluate the patient for possible central vein stenosis. Clinical clues that should raise suspicion include oedema in the extremities, collateral vein development, differential size of the extremities, and current or previous placement of a cardiac pacemaker. If any of these findings are present the patient should undergo venography or duplex ultrasound. If venous stenosis is identified, it is preferable to plan access for the contralateral side if possible, although we have had occasional success in performing angioplasty on proximal veins and then proceeding with A-V fistula or PTFE graft insertion.

8. The importance of preparation for dialysis

Every patient would make an informed choice between peritoneal and hemodialysis after a period of counselling and preparation, unfortunately RRT is frequently started in less than ideal circumstances. Reports from both Europe and US clearly document the excess of morbidity and mortality associated with patients presenting late in ESRD and requiring RRT as an emergency procedure [14,15]. In fact patients starting RRT as an emergency usually receive hemodialysis and require a temporary CVC. Compared with non-emergency patients, their length of hospital stay is significantly greater and during this time there is a higher incidence of major complications and death. Data from USRD report [1997] showed that 25% of hemodialysis and 16% of peritoneal dialysis patients stated that a nephrologist first saw them less than one month before starting RRT; many of these patients would not have sought any medical attention prior to their presentation but it is clearly important that GPs promptly refer these patients for a specialist opinion.

Predialysis care by the nephrologist is focused on preventing or treating complications of CKD, preserving residual renal function, ensuring that the patient has sufficient understanding of his condition to chose between different RRT, and then arranging for appropriate access to be created in time before dialysis is required. In addition to the nephrologist giving advice, further benefits may be gained if patients are offered a multidisciplinary educational program.

Although few clinical trials have been conducted, there is enough evidence of clear benefits of CKD education [35-41]. Early patient education is highly effective when focused on health promotion, shared decision-making and discussion of treatment options [36]. In one randomized, controlled trial on patient education, a one-on-one educational session followed by phone calls every 3 weeks significantly extended the time to requiring dialysis [38]. *Post hoc* analyses from this clinical trial, as well as findings from other observational studies, demonstrate a variety of additional benefits from patient education, including the following: reduced patient anxiety; reduced number of hospitalizations; reduced numbers of emergency room and physician visits; increased likelihood that the patient will remain em-

ployed in work and be more adherent to therapy; and reduced mortality [37,39,40]. Furthermore, results from several studies have demonstrated a substantially reduced need for CVCs following patient education [40,41]. Consequently, it is important to maximize these benefits by engaging patients in CKD education prior to planning dialysis access placement. Patient education involves messengers, messages, receivers and a process. Before patient education can begin, the physician must initiate the discussion of what is often called breaking the bad news [42,43]. Patients do not want insensitive truth telling but prefer for the truth to be told with support to assist them in decision-making [44]. It is estimated that it takes an average of five encounters before individuals actually understand the message; therefore, patient education on CKD should be iterative [45]. The initial message should be delivered in a private room that is free of interruptions, and preferably when the patient has a supportive friend or relative with them [45]. Components of successful CKD education programs have also included individualized and ongoing education throughout the course of the disease, tours of dialysis facilities, meeting patients who are undergoing treatment with different dialysis modalities, use of videos and written materials, and behaviour changing protocols with small group problem-solving activities [37,46,47]. These and other strategies can be incorporated into any CKD education program. The educator needs to possess skills in patient communication and to understand the nature of the patient's barriers to receiving the information.

Presenting treatment options to the patient is a major undertaking for the educator, and offering decision support is an important goal of successful CKD education. There is a large variability in the uptake of home dialysis options (peritoneal dialysis or hemodialysis) between centres, regions, and different countries [6]. Data from the USA indicate that the low uptake of peritoneal dialysis in the country does not reflect patient choice but is instead more often a reflection of the choice not being offered to patients by healthcare providers [10,11]. Results from recent studies indicate that the 5-year and 10-year survival rates of patients treated with in centre hemodialysis are equivalent to survival rates with peritoneal dialysis [48]. Accordingly, for the vast majority of patients with CKD, decisions about dialysis modality should be based on what fits best with their lifestyle a decision that patients and their families must make for themselves [49]. Widespread, comprehensive CKD education will also empower patients to assume responsibility for their dialysis care, thereby increasing the uptake of home dialysis options. Expansion of home dialysis therapy is likely to be safe as the equivalency of outcomes of home peritoneal dialysis with in centre hemodialysis are maintained even when much larger proportions of patients are treated with the former therapy [48]. This therapy is also potentially more cost-effective given the lower societal costs for providing peritoneal dialysis, compared with in centre hemodialysis, in many countries[50].

The discussion about treatment options should begin with open questions and can be followed by introducing the two choices available to patients, dialysis or MCM. If the patient's preference is for dialysis, the choice of home dialysis versus in centre dialysis should be discussed next. Notably, fear and/or lack of knowledge of home dialysis has been shown to dissuade many patients from selecting this option [51]. One of the goals of patient education

should be to offer patient support and help overcome such fear. Regular contact between the educator and the patient over the weeks to months after starting education is important in the process of decision-making. However, it is should be noted that the patient's choice of dialysis modality is simply the treatment with which they begin RRT, as many patients will actually transition between different therapies (for example, changing dialysis modalities, or from dialysis to transplantation and possibly back to dialysis again).

9. When RRT should be started?

In the 1990s, expert groups recommended that initiation of dialysis be considered when renal function declines to a predetermined level (mean of urea and creatinine clearance of ≤10.5 ml/min/1.73 m2] [52]. Over the past years, however, the mean estimated Glomerular Filtration Rate (eGFR) of patients starting dialysis in the USA has progressively increased [6,53]. Notwithstanding this change over time, there is no relationship between the duration of pre- dialysis nephrology care and eGFR at the time of starting dialysis [54]. Furthermore, patients who start dialysis with a high eGFR are as likely as patients with a lower eGFR to use CVCs as the first dialysis access [54]. These observations suggest that nephrologists might be recommending patients for dialysis for the same general reasons, irrespective of eGFR. For example, individuals with low levels of serum creatinine (and a high eGFR) might need to start dialysis if they are likely to have poor tolerance for the consequences of renal function decline. Findings from several observational studies demonstrate that patients who start dialysis with a high eGFR are substantially more likely to have characteristics associated with an increased mortality (such as older age, male sex, white ethnicity, diabetes mellitus and other cardiovascular comorbidities). Concerns about the rising trend of starting RRT in patients with a high eGFR have been raised, particularly since many studies now show a direct association between a high eGFR at the time of RRT initiation and subsequent risk of death [54-64]. This risk persists even after statistical adjustment for potential confounders and also when analyses are restricted to the healthiest subgroup; however, there is always the issue of residual confounding in observational studies [57,58]. Furthermore, with decreasing renal function, muscle mass becomes a more important determinant of serum creatinine level than is eGFR [65]. It follows then that the association between high eGFR and an increased risk of death might, in part, be a reflection of the effect of cachexia (muscle loss causing lower levels of serum creatinine at any given level of eGFR) on mortality [56]. Given the limitations of observational studies, it is fortuitous that the importance of renal function at RRT initiation has been tested in a randomized controlled clinical trial. In the IDEAL study, there was no difference in terms of survival between patients randomly assigned to begin dialysis early (at a creatinine clearance of 10–14 ml/min) or late (at a creatinine clearance of 5–7 ml/min) [66]. It is important to note that three-quarters of patients randomly assigned to starting dialysis late actually needed to begin treatment earlier, primarily owing to the development of uremic symptoms [66]. These data suggest that initiation of dialysis simply when renal function approaches a predetermined threshold, as measured by eGFR, is not appropriate. Indeed, it seems that dialysis can be safely delayed in otherwise

asymptomatic individuals with advanced CKD. This is particularly important in patients in whom a permanent dialysis access is not ready for use, and deferring dialysis might mitigate the need for CVCs. However, findings from the IDEAL study also indicate that it might not be universally possible to defer initiation of dialysis until patients reach an eGFR<7 ml/min/1.73 m2 as many patients with advanced CKD can develop uremic symptoms at high levels of renal function [66]. In addition to the indications for emergent dialysis (hyperkalaemia, volume overload, pericarditis and encephalopathy), dialysis therapy has been shown to be effective in ameliorating uremic anorexia and is associated with improvement in measures of protein energy wasting [67]. Hence, it is important to observe patients with advanced CKD for the early development of symptoms and/or uremic complications and begin dialysis at an appropriate time such that it precludes the development of complications that might require hospitalization or emergency intervention.

10. Conclusions

It is extremely important to ensure that the resources dedicated to ESRD treatment are used to best effect. If the greatest benefit is to be gained from RRT, the importance of selection and preparation of patients reaching ESRD must be recognised and addressed. Educating these individuals about CKD might, nevertheless, facilitate their participation in selection of RRT modality and might also result in an earlier transition to a permanent RRT. Several studies show that those measures lead to a reduction of the proportion of patients who start RRT as an emergency procedure (higher incidence of major complications and death) [14,15] and to an increasing number of patients that actively participate in developing their care plan and who start dialysis with a permanent access [68,69].

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Chapter 24

Reduction of Heparin and Oxidative Potential by Means of Citrasate® in High-Flux Dialysis (HFD) and Online Hemodiafiltration (olHDF) in Pre and Postdilution

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Additional information is available at the end of the chapter

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1. Introduction

Citrasate® is a new innovative dialysis acid concentrate, in which 3 mmol/l of acetic acid have been replaced by 0.8 mmol/l of citric acid along with 0.3 mmol/l of acetate.

Using citrate-containing dialysate, a reduction of the heparin dose by up to 55% was described in the literature (Kossmann et al., 2006, 2009). At the same time, the efficacy of dialysis was found to be increased. A local anticoagulation inside the dialyzer was supposed to be the reason, caused by a strong decrease of free calcium ions. A diminished thrombus formation inside the dialyzer should allow a higher mass transport across the membrane. The reduction of acetate concentration in the dialysate was found to increase the hemodynamic stability of hypertensive patients (Gabutti et al., 2009). So far, the question has not been investigated whether the reduction of acetate diminishes the inflammatory potential of acetate in such a way that the activation of thrombocytes and leucocytes as well as the release of cytokines will be reduced. Until now, a reduction of beta-2-microglobulin (beta-2-m) was observed, which could be attributed to an improved permeability of the membrane (Kossmann et al., 2009). The possible reduction of heparin by means of Citrasate® during chronic hemodialysis could lead to an economical benefit. The clinical benefit for patients would consist of the reduction of described side effects of acetate and heparin. Because of the small number of publications, it makes sense to verify the previous results and to check if the observed reduction of beta-2-m could be caused also by a reduction of oxidative potential in case of Citrasate® application.

Therefore the following questions should be answered:

- Is it possible to reduce the dosage of heparin by means of Citrasate® for chronic dialysis treatments remaining the efficacy of treatment (Kt/V), and without increasing clotting events in dialyzer and extracorporeal circuit?
- Which impact of Citrasate® can be found on the reduction of inflammatory and oxidative potential measured by the following parameters: plasma concentration of beta-2-m, hsCRP, prealbumin and myeloperoxidase (MPO)? Recently, MPO was described as a suitable marker for oxidative stress during acute dialysis treatment (Maruyama et al., 2004).
- Which influence can be observed on the plasma level of phosphate and ionized calcium as a result of application of Citrasate®?

In addition to the High-flux Dialysis study (HFD), it should be investigated if Citrasate® concentrate can be used also for on-line hemodiafiltration (olHDF). Because the infusate for olHDF will be prepared directly from the dialysate, the use of Citrasate® dialysate means the infusion of a considerable amount of citrate directly into the blood. Using olHDF in predilution mode, the substitution fluid will be infused into the blood stream before the dialyzer, meaning citrate will be included in the mass transfer processes of the dialyzer. During olHDF in postdilution mode, the citrate- containing fluid is infused into the peripheral blood behind the dialyzer. Since the effects of Citrasate® on free calcium ion concentration and coagulation system cannot predicted precisely, Citrasate® should be applied at first in the predilution mode of olHDF, and only later in the postdilution mode.

During the Citrasate® application in olHDF, the focus should be directed to the following questions:

- Is it possible to maintain a reduced heparin dose?
- Can the influence of Citrasate® on coagulation processes inside the dialyzer increase the efficacy of dialysis?
- Is it possible to reduce MPO activation?
- Will the plasma concentrations of calcium and phosphate stay in the physiologically optimal range?

2. Materials and methods

2.1. Time schedule

The HFD part of the investigation was conducted with the following time schedule:

Weeks 1-2: Measurement of parameters specified below, with standard dialysate and heparin dosage (baseline).

Weeks 3-6: Change to Citrasate® without any change in other treatment conditions.

Weeks 7-10: Dialysis with Citrasate® and 50% reduction of heparin bolus.

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Weeks 11-14: Dialysis with Citrasate® and 50% reduction of bolus and maintenance amount of heparin resulting in 50% total reduction of heparin.

Afterwards, the investigation was continued with olHDF:

Week 1: Measurement of parameters mentioned below during HFD with Citrasate® (Ca^{2+}:1.5 mmol/l) using the reduced 50% heparin dose (bolus – 50% and maintenance dose -50 %).

Weeks 2-3: Change to olHDF predilution (substitution rate: 150 ml/min) with Citrasate® (Ca^{2+}: 1.5 mmol/l).

Weeks 4-5: olHDF predilution as described above, but with standard concentrate (Ca^{2+}:1.25 mmol/l).

Weeks 6-7: Change to olHDF postdilution (substitution rate: 60 ml/min) with Citrasate® (Ca^{2+}: 1.5 mmol/l).

Weeks 8-9: olHDF postdilution as described above, but with standard concentrate (Ca^{2+}:1.25 mmol/l).

2.2. Materials

The following types of standard concentrate were used, differing only in the K^+-concentration (3.0 or 4.0 mmol/l, respectively): Concentrations of final mixed dialysate:

Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	Acetate	HCO_3^-	Glucose
mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l
138	3.0/4.0	1.25	0.75	110.0	2.00	33	1.0

Table 1.

The following types were used for treatments with Citrasate®:

Type	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	Acetate	Citrate	HCO_3^-	G lucose
MTN	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l
413	135.3	3.0	1.25/1.50	0.50	107.0	0.30	0.80	32.60	1.0
415	135.3	4.0	1.25/1.50	0.50	111.0	0.30	0.80	32.60	1.0

Table 2.

The treatments were performed with dialysis machines of type FMC 5008 (autoflow deactivated for olHDF treatments).

The following FMC-high-flux dialyzers were used for hemodialysis: FX60, FX80 and FX100. The blood flow was equal to Q_B= 300 ml/min. Unfractionated heparin brand "Heparin sodium 5000 ratiopharm" was applied for anticoagulation.

2.3. Patients and heparin dosages

Ten patients were selected from the running dialysis program fulfilling sufficient inclusion and exclusion criteria. All specific data of patients and used heparin dosages are included in the table "patient's data" (see table 1).

No.	Sex	Age	Time h	Dialyzer	Body mass/kg	Hep.bolus IU	Hep./h IU	Total hep./IU	Hep.bolus theor.*)	Hep.rate theor.*	Total hep. theor*/IU
1	f	68	4.0	FX60	50.0	4000	1000	**7500**	1340	1750	**7465**
2	f	79	4.0	FX80	58.0	2000	250	**2875**	1420	1750	**7545**
3	m	78	4.0	FX60	8.,0	3000	750	**5625**	1430	1750	**7555**
4	f	65	4.0	FX60	61.5	2000	500	**3750**	1455	1750	**7580**
5	f	75	5.0	FX100	76.5	2500	500	**4750**	1605	1750	**9480**
6	m	68	4.5	FX60	82.0	3000	750	**6000**	1660	1750	**8660**
7	f	87	4.0	FX60	65.5	2500	625	**4688**	1195	1750	**7320**
8	m	76	5.0	FX80	75.0	2500	500	**4750**	1290	1750	**9165**
9	f	57	5.0	FX60	68.5	2500	500	**4750**	1225	1750	**9100**
10	m	87	4.0	FX60	62.5	2500	625	**4688**	1465	1750	**7590**

Table 3. Enrolled patients and administered heparin dosages, compared with theoretically proposed dosages (Ouseph/Ward formula)

The heparin dosages before study start were optimized by regarding bleeding time and clotting behavior. The theoretical heparin doses were calculated by means of the Ouseph/Ward-formula (Ouseph et al., 2000):

$$\text{Heparin-Bolus}\,(\text{IU}) = 1600 + 10^{*}(\text{BW} - 76) - 300^{*}\text{Fd} - 100^{*}\text{Fs} \tag{1}$$

Infusion Rate (IU/h) = 1750

BW: body mass (kg), Fd =1 diabetic, Fd = 0 non diabetic, Fs = 1 smoker, Fs = 0 non smoker.

The applied heparin doses during the baseline treatments were lower than theoretically proposed.

Two patients had to be excluded from the study after 7 weeks because of hospitalization. Another patient dropped out during the olHDF postdilution phase.

2.4. Measured parameters

Based on the HFD results, during the olHDF investigations some changes regarding the measured parameters were used:

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No measurements of blood cell counts, albumin, hsCRP, but addition of iPTH measurements. Beta-2-microglobulin (beta-2-m) was measured before and after treatment, because the reduction rate of beta-2-m can be used as a measure for the efficacy of medium-sized molecule clearance. Instead of ACT, the activated prothrombin time (aPTT) was measured because of its higher reliability.

Parameter	Period of measurement
Ionized Calcium	before and after each treatment
Total Calcium	before and after each treatment – 1x per week
Bicarbonate	before and after each treatment
pH	before and after each treatment
Na^+	before and after each treatment
K^+	before and after each treatment
Thrombocyte count	1x per week , before, after 15 min and after treatment
Leucocyte count	1x per week , before, after 15 min and after treatment
Phosphate	before and after each treatment – 1x per week
ACT	1x per week , before, after 15 min and after treatment
Kt/V	once per month
beta-2-microglobulin pre-dialysis	once per month
Albumin pre-dialysis	once per month
hsCRP pre-dialysis	once per month
Weekly EPO [TN: please define] dose	each week
Weekly iron dose	each week
Myeloperoxidase (MPO)	2x during each period of study before, after 15 min and after treatment [TN: isn't that rather 3x than 2x?]

Table 4. Parameters to be measured

2.5. Analysis of data and statistical methods

The analysis of data was performed by means of Microsoft-Excel-Software.WinStat for Excel and SigmaStat were used for descriptive statistics. All parameters are shown as mean values and with standard error of the mean (SEM).

Differences between measured values during different treatment modes were evaluated by t-test for paired samples. The Mann-Whitney test (U-test) was used in case normal distribution was lacking. A p-value < 0.05 was considered statistically significant. Since the investigation had to be discontinued for 2 patients, their measured values were not included in the analysis.

Because of the change on hematocrit values during treatment, the measured plasma values (Ca^{2+}, phosphate, MPO) had to be corrected according to the following formula (van Beaumont, 1972):

$$C_{corr} = c_* \left(Hcto/Hctn\right)*\left(1\text{-}Hctn\right)/\left(1\text{-}Hcto\right) \quad (2)$$

Hcto = hematocrit before treatment

Hctn = hematocrit during sampling time n

Measured values related to total blood volume (thrombocyte and leucocyte count) were corrected to reflect the change in hematocrit value:

$$c_{corr} = c_* \left(Hcto/Hctn\right) \quad (3)$$

According to the manufacturer's information (Radiometer), the ionometer values (pH, Ca^{2+}, Na^+ und K^+) do not have to be corrected because ion activities are measured (Christiansen, 1991).

If Hct-values were not available (olHDF treatments), post-treatment concentrations (Total-Ca, phosphate, beta-2-m, MPO) were corrected using the plasma volume reduction by ultrafiltration by means of the Bergström-formula:

$$c_{corr} = c_* (1/(1+\Delta BW/0.2BW_{post}) \quad (4)$$

ΔBW: change of body mass, BW_{post} : body mass after treatment

3. Results and discussion

3.1. High-Flux Dialysis (HFD)

3.1.1. Efficacy of dialysis in dependence on the heparin dose

When performing hemodialysis with Citrasate®, it is assumed that the citrate causes a local anticoagulation inside the dialyzer because of chelation of ionized calcium. This process should be reflected by measurements of coagulation parameters like the "activated clotting time (ACT)". In fig. 1, the mean values of ACT measurements are shown before dialysis but after heparin bolus, after 15 min and after the end of treatment during the different periods of study (baseline: HD with standard concentrate, 50 % heparin reduction in the bolus, 50 % reduction of total heparin dose). Obviously, the influence of citrate-containing concentrate is not strong enough to achieve significant ACT changes in comparison to standard dialysate. After reduction of heparin in the bolus and in the maintenance dose, however, the changes in ACT are significant.

The possibility to reduce the heparin dose by using Citrasate® without incurring clotting events was in agreement with results of other authors (Kossmann et al., 2006: -55 %; Ahmad et al., 2006: -30 %, Sands et al., 2012: -33 %). An improvement of efficacy, especially concerning the value of

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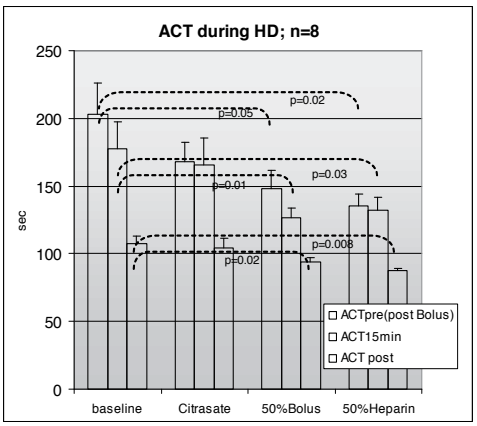

Figure 1. Activated clotting time pre dialysis, after 15 min and post dialysis during the different study phases: baseline (standard concentrate), Citrasate® instead of standard concentrate (treatment conditions unchanged), Citrasate® with reduction of the heparin bolus by 50 %, Citrasate® with total heparin dose reduced by 50 %.

Kt/V and elimination of beta-2-m, was detected as well (Kossmann et al., 2009, Sands et al., 2012). These results could not be confirmed in our investigations. Fig. 2 illustrates the values of spKt/V and eqKt/V (calculated using the Daugirdas formula) for the different study periods. The change from standard concentrate to Citrasate® has shown constant efficacy of dialysis, whereas the reduction of heparin dosage resulted in a non-significant decrease of Kt/V. This result was in agreement with data of Ahmad et al. (2006) while the investigations of Kossmann et al. (2009) and Ahmad et al. (2000) resulted in a significant increase of Kt/V using Citrasate® even after the reduction of heparin. These investigations, however, were performed with reuse of dialyzers. The increase of Kt/V was found to be dependent on the number of reuses. The smaller the number of reuses the smaller the increase of Kt/V. Exact data, however, were not given.

Also, the values of beta-2-m do not indicate an improvement of treatment efficacy due to use of Citrasate® (see fig. 3), in contrast to the results of Kossmann et al. (2009).

With regard to the HCO_3^- concentrations before and after dialysis, it was found that both values were somewhat lower (4…5%) if Citrasate® was applied. This is due to the slightly smaller HCO_3^- concentration in the Citrasate® concentrate (32.6 mmol/l instead of 33.0 mmol/l for standard concentrate).

Changes in the electrolytes Na^+ and K^+ before and after treatment could not be observed during the different periods of investigation.

3.1.2. The influence of Citrasate® on inflammatory and oxidative potential

The typical temporary drop in leucocyte count after start of dialysis treatments was found to be associated with the activation of complement factors C3a and C5a (Craddock et al., 1977). A decrease of iCa inside the dialyzer should be followed by a smaller complement activation and smaller leucocyte drop because of the importance of ionized calcium (iCa) in the cascade of complement activation. This effect, however, was not observed under the conditions of pure

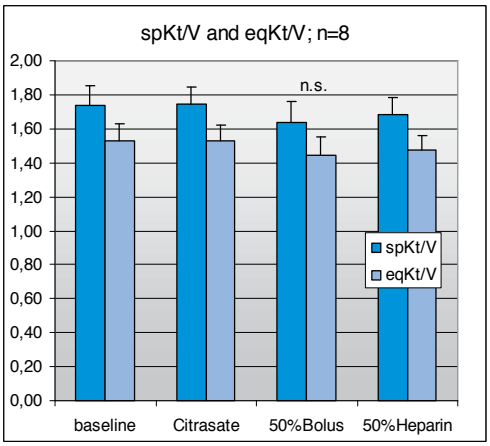

Figure 2. Single pool and equilibrated Kt/V during the different study phases.

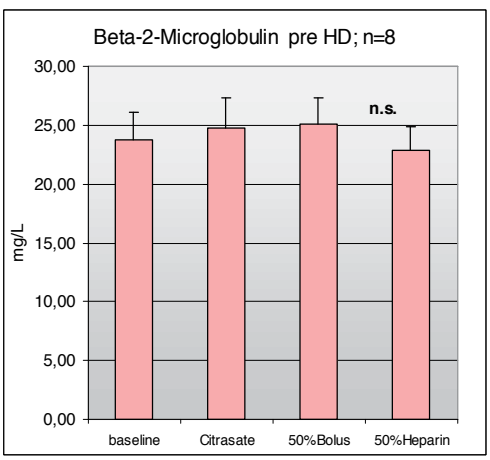

Figure 3. Pre dialysis beta-2-microglobulin during the different study phases.

citrate anticoagulation (Opatrný et al., 2007). A significant reduction of complement activation can be expected if the iCa concentration decreases to < 0.2 mmol/l (Hartmann et al., 2006). According to Opatrný, the iCa concentration of 0.4 mmol/l, which is usually found during citrate anticoagulation, does not guarantee a decrease of thrombogenicity and complement activation. Therefore, a distinct influence on the decrease in leucocytes cannot be expected during dialysis with Citrasate®. Nevertheless, according to Polakovic et al. (2010), a significant decrease of leucocyte count was observed during application of Citrasate®. In our investigations a similar trend was visible, which was not significant, however. After decrease of heparin dosage this trend disappears (fig. 4):

The likewise measured levels of albumin and hsCRP were stable during all study phases. However, with regard to myeloperoxidase (MPO), a significant influence was found.

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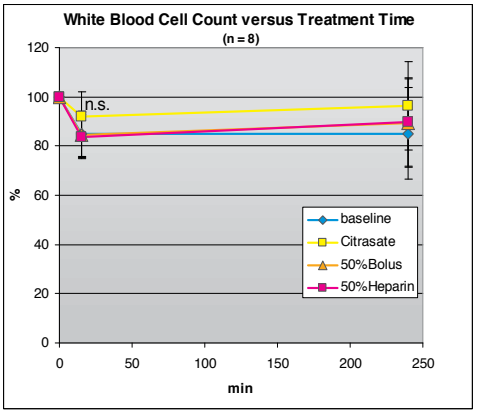

Figure 4. Leucocyte drop during HFD treatments in different study phases

MPO is considered an important parameter of biocompatibility and mortality during dialysis treatment (Borawski et al., 2006, Hörl, 2008, Gritters et al., 2006). MPO is part of the family of heparin-binding proteins. Additionally, MPO is contained in granulocytes, monocytes, macrophages and is also located along the vessel walls (e.g. Hörl, 2008). MPO is considered to be a marker of degranulation of neutrophils and, therefore, also as a parameter of biocompatibility of dialysis and oxidative stress (Borawski et al., 2006). During hemodialysis, the value of MPO increases by more than 100% (Gritters et al., 2006). MPO release can be inhibited by regional citrate anticoagulation, which suggests a strong influence of heparin on the degranulation of neutrophils. According to a review of Hörl (2008), MPO induces vascular complications by a variety of mechanisms:

- Inhibition of NO-dependent vasorelaxation.
- Production of endogenous NO-inhibitors.
- Oxidation of LDL with consecutive increased absorption in local macrophages.
- Production of reactive species.

The plasma levels of MPO are associated with atherosclerotic vascular complications as well as with the mortality of hemodialysis patients and the general population (Hörl, 2008).

The measured values of MPO show a strong increase 15 min after start of treatment (fig.5). After the change from standard dialysate to Citrasate®, no significant changes can be observed, but a tendency can be seen towards lower values after 15 min. The reduction of heparin dosage, however, causes a significantly smaller increase of MPO values as well as a tendency towards lower values before and after dialysis.

3.1.3. The influence of Citrasate® on the plasma levels of calcium and phosphate

The complex formation between Ca-ions and citrate causes a decrease of ionized calcium (iCa) in the plasma. After the metabolization of citrate, one part of iCa returns into the blood plasma.

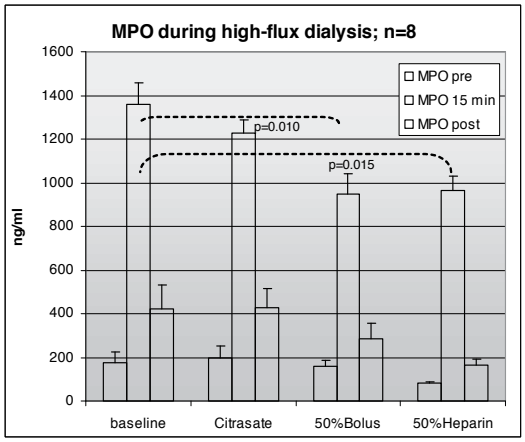

Figure 5. Myeloperoxidase during different study phases of HFD

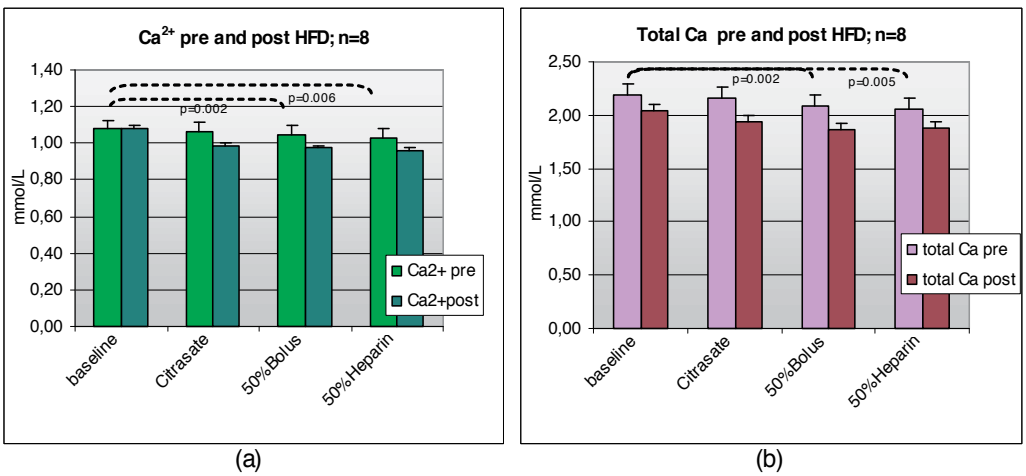

Figure 6. a, b. iCa and total calcium before and after dialysis during the different study phases of HFD

The other part of calcium-citrate-complex will be removed by means of dialysis. Therefore, a decrease of iCa can be observed during dialysis treatment, as shown in fig.6a.

The mean decrease of iCa amounts to 7 % for all treatments with Citrasate®, as can be seen in fig. 6a. The decrease of total calcium is shown in fig.6b. A decrease of total calcium can be observed also during treatments with standard concentrate, but it is more pronounced for treatments with Citrasate® (baseline: - 7%; Citrasate®: -9…-11 %).

The drop of iCa was also observed in the same magnitude from other users of Citrasate® (Sands et al., 2012), at least if the concentration of calcium was 1.25 mmol/l. With a calcium concentration of 1.5 mmol/l in Citrasate®, the iCa drop was smaller (e.g. Leimbach et al., 2011, Polacovic et al, 2010).

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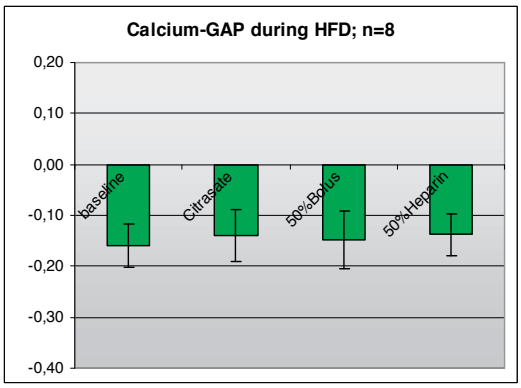

Figure 7. Calcium GAP during different study phases of high-flux dialysis

Compared with values of standard dialysis (baseline), the statistically significant decrease of pre-dialysis total Ca (see fig. 6b) results in values below the standard values (2.2…2.65 mmol/l). Because of a possible hypocalcemia, it is recommended to perform treatments with Citrasate® with a calcium concentration of 1.5 mmol/l in the dialysate (see also Polacovic et al., 2010).

The danger of an accumulation of citrate during the dialysis treatment does not exist under the given conditions. The accumulation of citrate can be expressed by the Ca-GAP:

$$\text{Ca-GAP} = \left(\text{totalCa post} - \text{totalCa pre}\right) - \left(\text{iCa post} - \text{iCa pre}\right) \quad \text{(Gabutti et al., 2009)} \tag{5}$$

If the metabolization of citrate is quick, the Ca-GAP becomes < 0.2 (Gabutti et al., 2009). As fig. 7 shows, this condition was fulfilled in case of dialysis with Citrasate®:

Regarding the likewise measured phosphate, it can be stated that the phosphate elimination was effective with approx. 70% and did not differ between the different periods of the study.

3.2. Online hemodiafiltration in pre- and postdilution mode

3.2.1. olHDF in predilution mode

3.2.1.1. Objectives

In addition to the study with high-flux dialysis (HFD), it should be investigated if Citrasate® concentrate can be used also for on-line hemodiafiltration (olHDF). Since the infusate for olHDF will be prepared directly from the dialysate, the use of Citrasate® dialysate means the infusion of a considerable amount of citrate directly into the blood. Using olHDF in predilution mode, the substitution fluid will be infused into the blood before the dialyzer, which means citrate will be included in the mass transfer processes of the dialyzer. During olHDF in postdilution mode, the infusion of citrate containing fluid takes place behind the dialyzer into the peripheral blood of patients. Since the effects of Citrasate® on free calcium ion concentration

and coagulation system cannot be precisely predicted, Citrasate® was applied at first in the predilution mode of olHDF.

During the Citrasate® application in olHDF predilution, the focus was directed to the following questions:

- Is it possible to maintain the 50% reduced heparin dose?
- Can the influence of Citrasate® on the coagulation processes inside the dialyzer increase the efficacy of dialysis?
- Is it possible to reduce the MPO activation as well, as found in high-flux hemodialysis?
- Will the plasma concentrations of calcium and phosphate stay within the physiologically optimal range?

Time schedule, materials, methods, patients and parameters were as described in section 2.

3.2.1.2. Results and discussion

The olHDF study was started with reduced doses of heparin (-50 % for bolus and -50% for maintenance dose) determined in the previous HFD study. This was possible without any problems for the baseline treatments (week 1 with HD and Citrasate®). After transition to olHDF in predilution with Citrasate® and a dialyzer FX100 with a larger surface area, it was necessary to increase the heparin dose for some patients. For one patient, the baseline dose had to be restored. For all other patients, the heparin dose remained –20…-50 % lower even if the predilution HDF was performed with acetate-containing standard concentrate.

Figures 8 and 9 show the results regarding the impact of olHDF in predilution on treatment efficacy. For small molecular substances such as urea or creatinine, an increase of efficacy cannot be expected after transition from HFD to olHDF especially for the predilution mode (Ahrenholz et al., 1997). Therefore, the determination of dialysis dose (spKt/V or eqKt/V) in fig. 8a shows no significant changes between the different treatment modes of study.

For medium-sized molecules such as beta-2-microglobulin, the treatment with olHDF is more effective than with HFD because of the larger part of convective transport. Accordingly, the reduction rate of beta-2-m increases from 66.6% to 70.5% after changing from HFD to olHDF. However, because of the large spread of HFD values, this change does not become significant. After changing from HFD with Citrasate® to olHDF with standard concentrate, a significant decrease of the beta-2-m reduction rate by 2% was observed ($p=0.03$) despite the small sample size. From this result, it can be presumed that the Citrasate® dialysate and -infusate perhaps reduces thrombus formation inside the hollow fibers of the dialyzer.

The time course of the myeloperoxidase (MPO) concentration during treatments with Citrasate® corresponds to the one of the HFD study baseline period (see fig. 5). Compared with this result, figure 10 shows an increase of the 15 min value during predilution olHDF with Citrasate® and, once more, during predilution olHDF with standard concentrate, which was not statistically significant. The stepwise increase in the heparin dose seems to be the reason for this observation (see fig. 11). A correlation between activation of MPO and heparin

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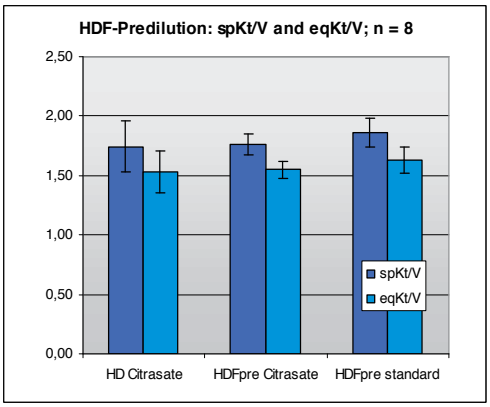

Figure 8. Single-pool and equilibrated Kt/V for treatments with HFD with Citrasate® and predilution olHDF treatments with Citrasate® and standard concentrate

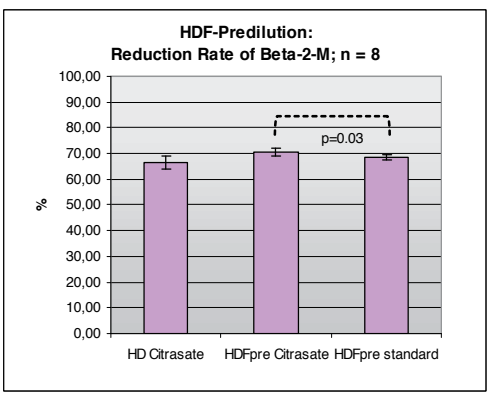

Figure 9. Reduction rate of beta-2-m for HFD treatments with Citrasate® and predilution olHDF treatments with Citrasate® and standard concentrate

concentration in blood was found also in some other investigations addressing extracorporeal blood purification (Hörl, 2008, Gritters et al., 2006, Daphna et al., 1998).

As a result of the HFD study with 1.25 mmol/l calcium in the citrate-containing dialysate, the calcium concentration had to be raised to 1.50 mmol/l (concentrate MTN 413/415). As shown in fig.12, the calcium concentrations reach a mean level of 1.09 mmol/l after treatment. The same observations could be made in case of predilution olHDF with standard dialysate (Ca^{2+}: 1.25 mmol/l). Patients usually treated with standard concentrate with 1.25 mmol/l Ca^{2+} should obtain 1.50 mmol/l Ca^{2+} after changing to Citrasate®. This increase becomes necessary to compensate for the iCa-losses resulting from calcium-citrate complex formation.

As shown in fig. 13, the total calcium concentration stays constant at 1.50 mmol/l-Ca^{2+}-Citrasate® during HFD and predilution olHDF, whereas the values after treatment with standard concentrate (Ca^{2+}: 1,25 mmol/l) are reduced by about 9%. This phenomenon can be

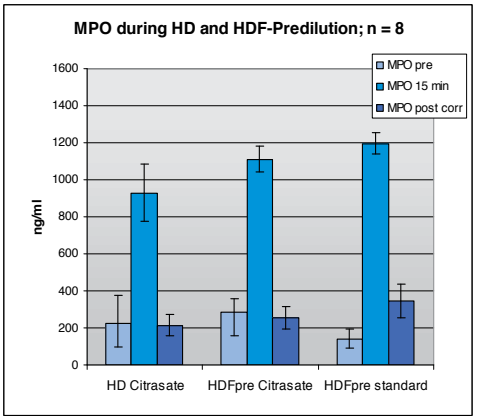

Figure 10. Myeloperoxidase concentrations pre-treatment, after 15 min and post-treatment for HFD and olHDF with Citrasate® and olHDF with standard concentrate

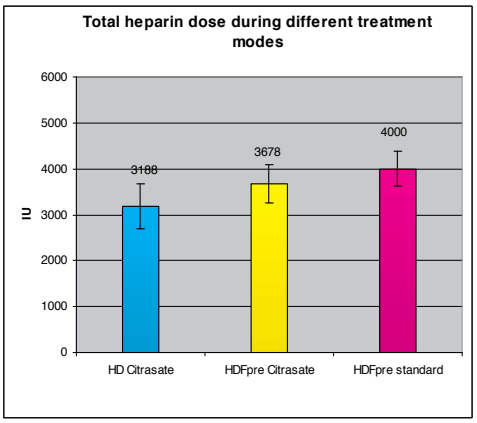

Figure 11. Total heparin dose for HFD and olHDF with Citrasate® and olHDF with standard concentrate

explained by the release of free calcium ions from the calcium-citrate complex due to citrate metabolism inside the bloodstream.

The balance between changes of total Ca and iCa during treatments can be expressed as Ca-GAP (see equation 5). The value of Ca-GAP should be less than +0.2. Fig. 14 shows that on average, this condition was fulfilled.

3.2.2. olHDF in postdilution mode

3.2.2.1. Objectives

Following previous studies on the suitability of Citrasate® concentrate for high-flux hemodialysis (HFD) and online hemodiafiltration in pre-dilution mode (olHDF-pre), it should now

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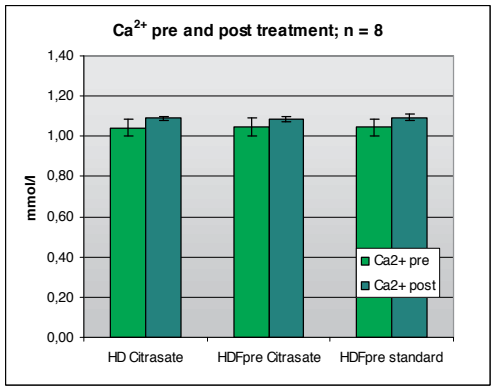

Figure 12. iCa concentrations pre and post treatment for different treatment modes with and without Citrasate®

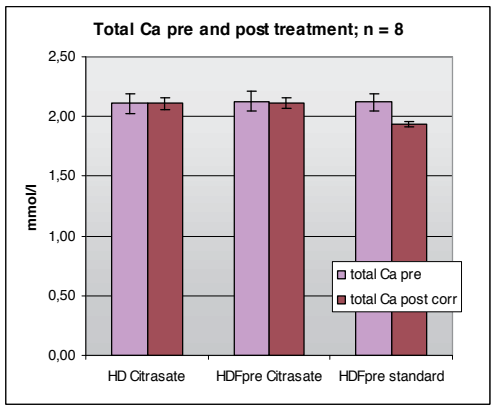

Figure 13. Total Ca concentrations pre and post treatment for different treatment modes with and without Citrasate®

be investigated whether the use of citrate-containing dialysate can cause problems during olHDF in postdilution mode (olHDF-post).

In contrast to olHDF-pre, the infusion of citrate-containing solution with olHDF-post occurs *behind* the dialyzer, i.e. directly into the peripheral blood of the patient, so that the physiological effects are more difficult to assess.

As with olHDF-pre, the main focus of Citrasate® application for olHDF-post should be whether:

- The reduced dose of heparin can be maintained,
- The influence on coagulation processes in the dialyzer leads to improved effectiveness,
- The MPO activation can be reduced in the same way as was possible with HFD,
- The plasma concentrations of calcium and phosphate can remain within the physiologically optimal range.

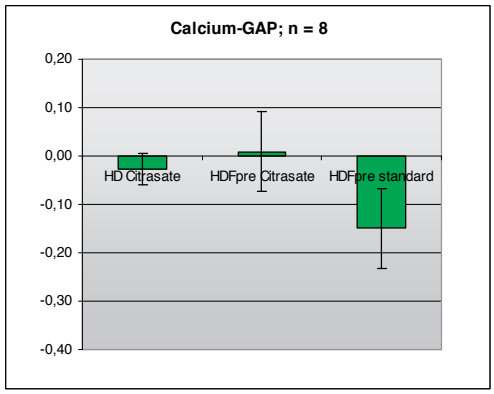

Figure 14. Ca-GAP for different treatment modes with and without Citrasate®

Time schedule, materials, methods, patients and parameters were as described in section 2. One patient dropped out after the olHDF-pre study (n = 7 during the olHDF-post investigations).

3.2.2.2. Results and discussion

The investigation was continued with the heparin dosages from the prior olHDF-pre study (the baseline dose was reached again in one patient, whereas with the remaining patients, the dose even for olHDF employing standard concentrate was 20... 50% lower; see section 3.1.1.2).

The comparison of the activated prothrombin time (aPTT) between olHDF-post with Citrasate® and olHDF-post with standard concentrate showed that Citrasate® had no influence on systemic coagulation.

While with olHDF employing predilution, there was no significant difference regarding the removal of low molecular weight substances such as urea compared to HFD, olHDF employing post-dilution was more effective than HFD. However, a difference in effectiveness between the olHDF post-treatment with Citrasate® and standard concentrate could not be found (see Fig. 15). Regarding the removal of beta-2-microglobulin, an improvement in effectiveness compared to HFD could be seen, but a difference between the olHDF-post with Citrasate® and standard concentrate, as was seen in the predilution treatments, could not be determined here (see Fig. 16).

MPO is one of the most important predictors for compatibility and mortality for dialysis treatments. In the previous HFD study, there were significant differences between the individual study phases. Therefore, MPO was measured again at different time points (before treatment, after 15 min of treatment, and after treatment). As with the olHDF in predilution, there was no significant difference in MPO activation for treatments with Citrasate® or standard concentrate. The MPO values after treatment start tended to be somewhat larger for olHDF-post treatments (probably not significant due to the small number of cases). This is most likely due to the much greater ultrafiltration and therefore, also to the greater dilution of blood with infusion solution employing olHDF-pre (150 ml/min versus 60 ml/min).

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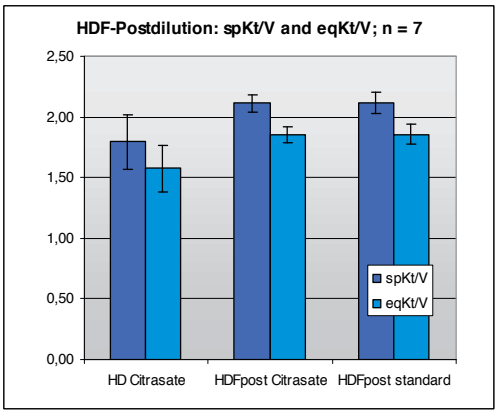

Figure 15. Single-pool and equilibrated Kt/V for treat-ments with HFD with Citrasate® and olHDF-post treatments with Citrasate® and standard concentrate

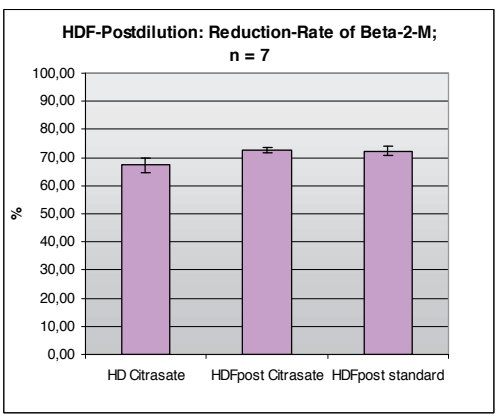

Figure 16. Reduction rate of beta-2-m for HFD treatments with Citrasate® and olHDF-post treatments with Citrasate® and standard concentrate

Since the heparin dose was constant for all olHDF treatments, an effect of heparin concentration on MPO activation as the one seen in the previous olHDF-pre study could not be observed (comparison MPO during olHDF-pre and –post: see fig. 17a, b.).

As a result of the HFD study with 1.25 mmol/l Ca^{2+} in the dialysate, the Ca^{2+} concentration was raised to 1.50 mmol/l (concentrate MTN 413/415). As shown in Fig 18a, b., the Ca^{2+} concentrations of the individual patients level out to values of about 1.10 mmol/l after treatment, just as in the case of olHDF treatments with normal dialysate (Ca^{2+} : 1.25 mmol/l). Losses of ionized calcium by chelation were adequately compensated by choosing a higher dialysate Ca^{2+} for olHDF both in pre- or post-dilution.

The balance between the changes in total calcium and the iCa during treatment can be expressed by the Ca GAP (see equation 5, sections 3.1.3 and 3.1.1.2):

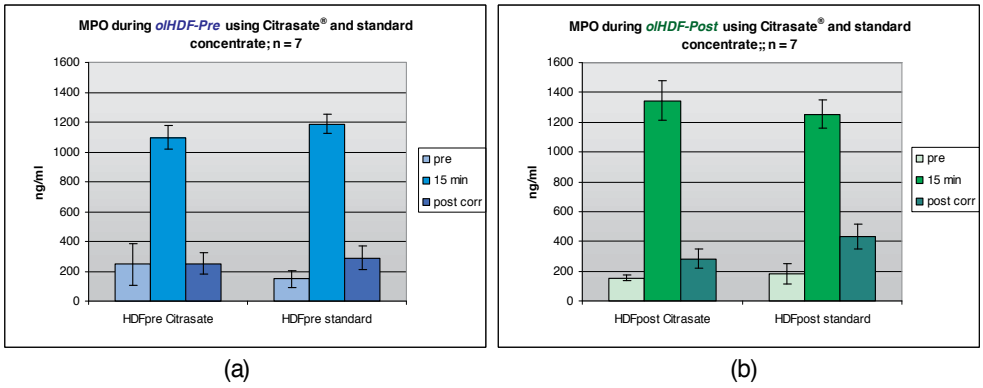

Figure 17. a, b. Comparison of the MPO values during olHDF with pre- and postdilution (same patient group, constant heparin dose)

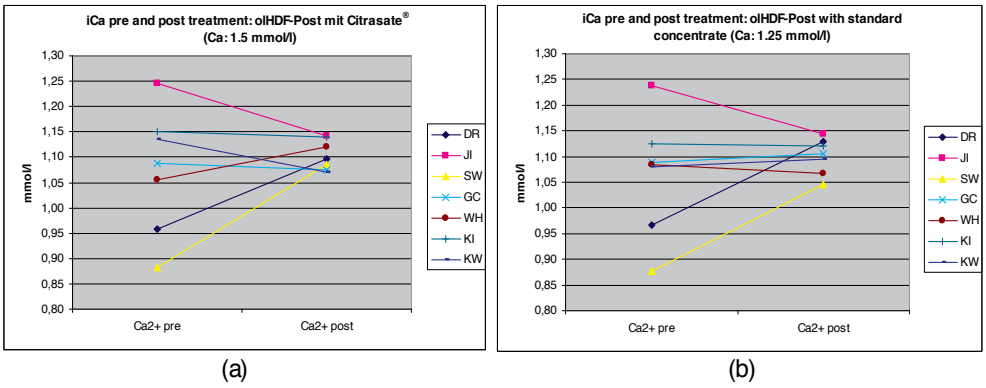

Figure 18. a, b. Comparison of the individual plasma Ca^{2+} concentrations during olHDF-post with Citrasate® (1.5 mmol/l Ca^{2+}) and standard concentrate (1.25 mmol/l Ca^{2+})

Figure 19 shows that with olHDF-post, there is no positive balance for total calcium. Accordingly, no surplus amount of bound Ca remains in the bloodstream, which would indicate an incomplete metabolism of the calcium citrate. According to studies by Bauer et al. (2005), this is also not to be expected. In that study, citrate kinetics during citrate anticoagulation were investigated both in patients with normal renal function and those on hemodialysis. It was found that citrate is also metabolized adequately with renal failure, as well as with mild hepatic dysfunction. Only in patients with severe liver failure is citrate anticoagulation not indicated. If one considers that with citrate anticoagulation the citrate infusion rate is about 0.3 mmol/kg/h, while with olHDF in post dilution with Citrasate® dialysate it is only about 0.04 mmol /kg /h, then problems arising from incomplete citrate metabolism are not to be expected (example: olHDF-post: 0.8 mmol/l citrate, infusion rate 3.6 l/h, 70 kg patient).

The calcium-phosphate balance is determined largely by parathyroid hormone. Disruptions of the balance due to non-physiological treatment conditions would therefore be reflected in

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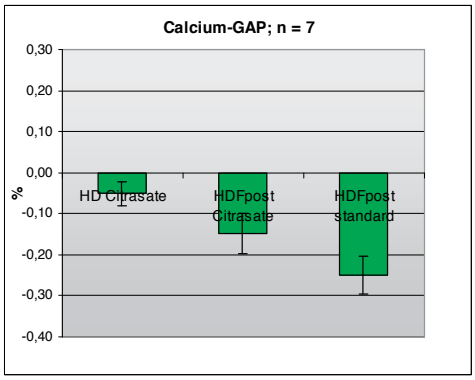

Figure 19. Calcium GAP for the different study phases HFD, olHDF-post with Citrasate® and standard concentrate

the concentrations of Ca^{2+}, phosphate and PTH. As shown in Figures 20 and 21, however, no significant differences between olHDF-post treatments with Citrasate® and standard concentrate were observed.

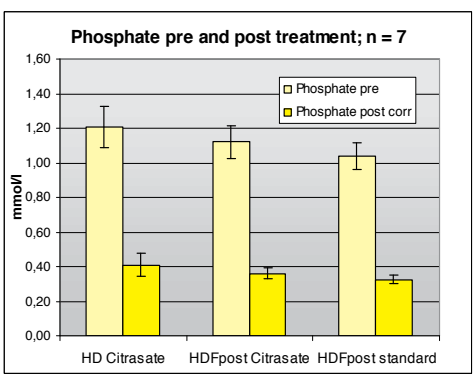

Figure 20. Plasma phosphate concentrations pre and post treatment for different treatment modes: HFD with Citrasate®, olHDF-postdilution with Citrasate® and standard concentrate

Regarding other measured parameters such as bicarbonate (HCO_3^-), Na^+, K^+, there were no significant differences in the individual study phases. The mean ESA (Aranesp®) and iron intake (Ferrlecit) remained constant during all study phases.

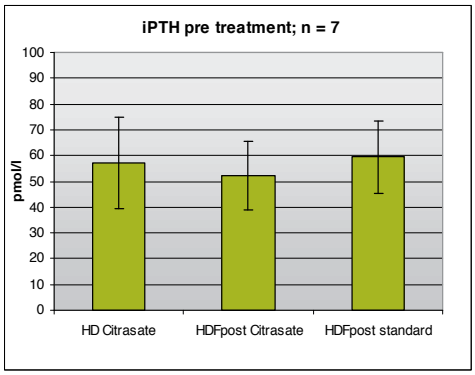

Figure 21. iPTH pre treatment for different treatment modes: HFD with Citrasate® and standard concentrate Citrasate®, olHDF-postdilution with

4. Summary

4.1. High-flux dialysis (HFD)

Using Citrasate® for HFD treatments, the results can be summarized as follows:

- A reduction of total heparin dose by 50% was possible (50% bolus and 50% maintenance amount) without increase of clotting events in the dialyzer or extracorporeal circuit and without change of treatment efficacy (Kt/V).
- An influence of Citrasate® on sensitive inflammation parameters such as beta-2-microglobulin, hsCRP and serum albumin was not detected. MPO has reacted sensitively as marker for granulocyte degranulation and oxidative stress on the reduction of heparin dosage.
- The plasma level of phosphate was not influenced by the application of Citrasate®.
- A reduction of ionized calcium and total calcium was observed during application of Citrasate®. The reduction of total calcium was found to be partially below the normal range. Therefore, it has to be recommended to use 1.50 mmol/l Ca^{2+} instead of 1.25 mmol/l Ca^{2+}, which is common for standard dialysate. The Ca-GAP was found to be sufficient small, therefore a quick metabolization of citrate can be assumed.

In conclusion, the study has demonstrated that Citrasate® can be applied for high-flux dialysis, saving heparin and increasing the biocompatibility of treatment by reduction of oxidative stress.

4.2. Online hemodiafiltration with predilution (olHDF-pre)

The results can be summarized as follows:

- Several patients could be treated in this investigation with the 50% reduced total heparin dose, just as during the previous HFD study. This reduced total heparin dose, however,

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could not be maintained for all patients under the conditions of larger surface areas for dialyzers (FX100) during olHDF predilution.

- The beta-2-microglobulin elimination was slightly, but significantly, increased in comparison to standard concentrate. For urea, however, the efficacy could not be improved by olHDF predilution as expected.
- The activation of myeloperoxidase (MPO) corresponded to the values of the previous HFD study with Citrasate®. An increase in mean heparin dosage was connected with an increase in MPO concentration.
- The course of ionized Ca during HD and olHDF predilution with Citrasate® corresponds to the one of standard dialysate with 1.25 mmol/l Ca^{2+} after raising dialysate calcium from 1.25 to 1.50 mmol/l.
- The mean plasma concentrations of phosphate and iPTH remained at the same level during all periods of study. The small size of Ca-GAP means that disturbance of Ca-phosphate balance did not occur because of the high infusion rate of citrate-containing infusion fluid and because of the sufficiently quick metabolism of citrate.

In conclusion, the study has demonstrated that Citrasate® can be applied also for online Hemodiafiltration (olHDF) with predilution mode. As found during high-flux dialysis as well, Citrasate® saves heparin and increases the biocompatibility of treatment by reduction of oxidative stress.

4.3. Online hemodiafiltration with postdilution (olHDF-post)

In summary, it can be stated that:

- The doses of heparin from the previous olHDF-pre study could be maintained also with olHDF-post. The baseline dose at the beginning of all three studies had to be re-administered in one case; with the remaining 6 patients, a 20…50% reduced total heparin dose could be administered. However, this was also possible with the olHDF post-treatment using standard concentrate.
- As expected, the treatment effectiveness was improved both in terms of the Kt/V values and the beta-2-m removal rate compared to HFD. However, no differences between the olHDF-post treatments with either Citrasate® or standard concentrate could be identified.
- Regarding the activation of myeloperoxidase (MPO), there were no significant differences between treatments with Citrasate® and standard concentrate. Compared to the treatments with olHDF-pre, with postdilution olHDF the MPO values tended to be somewhat larger, which is presumably due to the higher dilution of the blood with HDF-pre.
- After increasing the dialysate calcium from 1.25 to 1.50 mmol/l compared to the first study (HFD), the course of the ionized Ca during Citrasate® HFD and olHDF-post with Citrasate® corresponded to the one of olHDF-post with normal dialysate and 1.25 mmol/l Ca^{2+}.
- The mean plasma concentrations of phosphate and iPTH were at about the same level in all study phases. As with the significant shortfall of the Ca-GAP at 0.2, this means that

disruptions of the Ca-phosphate balance by the high infusion rate of citrate containing substitute infusions did not occur and that there was a sufficiently rapid metabolism of citrate.

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Section 4

Vascular Access

Chapter 25

The Controversial Vascular Access for Hemodialysis – Own Experience

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M. Maruszyński

Additional information is available at the end of the chapter

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1. Introduction

Over the last ten years the number of patients requiring dialysis has been growing at a rate of nearly 10% per year. This trend, noted in both the United States and Europe [1], is likely to continue during the years to follow. Since 1966 the preferred vascular access for hemodialysis (HD) has been the arteriovenous fistula (AVF) [2]. However, despite the experience amassed over the years, vascular access dysfunction still remains the main reason for hospitalization of patients undergoing dialysis [3]. Because of this creation of an access in the lower limb or a complex bypass surgery using artificial material may be necessary in some patients. This chapter describes some of the complex surgical procedures likely to be alternatively implemented in cases of a problematic vascular access [4].

2. Surgical interventions

2.1. The contra lateral internal jugular vein bypass

In patients with an impatent brachial fistula caused by the ipsilateral central vein occlusion or stenosis the contralateral jugular vein (IJV) bypass can be used [5]. The patient is anesthetized in the decubitus position with the head turned toward the thrombosed fistula. An incision is made in the neck along the anterior side of the sternocleidomastoid muscle. Than the IJV is dissected. Next, an incision is made high in the arm to dissect and declot the fistula by using a Fogarty's catheter. A subcutaneous tunnel running on the anterior aspect of the chest is created and the polytetrafluoroethylene (PTFE) graft is passed through accompanied

by the intravenous injection of heparin. The distal anastomosis is made with the 5-0 end-to-side polypropylene running suture with the declotted part of the fistula by using the incision made for the Fogarty's catheter introduction. The proximal anastomosis to IJV is created using the same suture. Technically, vascular surgeons are familiar with the procedure, but this particular intervention has not been commonly used.

2.2. The femorofemoral crossover bypass

The patient is anesthetized in a supine position. The femoral artery and vein are dissected on both sides through small incisions in the groins. A subcutaneous tunnel is created on the anterior aspect of the lower part of the abdominal wall bellow the umbilicus. Heparin is injected intravenously and the graft is passed through the tunnel. The connection of the graft with the arterial part of the fistula is made by the end-to-side anastomosis with the common femoral artery using the 5-0 polypropylene running suture. Next, a connection is made by the end-to-side anastomosis with the common femoral vein using the same suture [6]. This procedure is dedicated to a group of patients in whom several AVFs created in the upper arms have eventually failed [7]. Potential infectious complications should by considered prior to the surgical intervention. One of the underestimated, but very important factors to be taken into account, especially when a patient is a young woman, is the cosmetic result of the operation.

2.3. The necklace bypass

A generally anesthetized patient is placed in the decubitus position with the elevated shoulders. Surgical approach to the subclavian vessels is gained by the one-cm incisions below each clavicle. The pectoralis major is dissected, the fascia opened and the pectoralis minor dissected and split. Than the axillary artery and vein are dissected. Next, a subcutaneous tunnel is created running in front of the superior 1/3 of the sternum. The graft is passed through the curved tunnel. Heparin injection is a common procedure. The venous anastomosis is made using the 5-0 polypropylene running suture. The arterial anastomosis is obtained with the same way. Finally, to control the hemostasis the graft is flushed with blood [7,8].

2.4. The axillary loop

For creation of the axillary loop the same technique as above is used including the surgical approach, prosthesis, and sutures, but the graft tunnel is longer extending from the axillary artery to the axillary vein. However, elongation of the graft increases the risk of infection, clotting, stenosis, and occlusion [7,8,9].

2.5. The saphenous vein transposition

We used this technique as described by Gradman and Pierre-Paul [10,11] in one patient with the bilateral obstruction of the brachiocephalic veins. The patient was neither diabetic nor obese. Mobilization of the saphenous vein (SV) provides an exceptionally long arm of the

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fistula. Creation of the U-shaped tunnel and the anastomosis between SV and the ipsilateral common femoral artery is needed. Unfortunately, as the fistula is placed in a very fragile skin area each punction is painful and the risk of infection is high. Theoretically, however, the SV transposition gives a very good vascular access for HD with all its pros and cons in a selected group of patients.

2.6. The axillary artery to the popliteal vein bypass

This bypass, used as the arteriovenous fistula, was first described in 2004 by Calder et al [12]. The authors performed this technique in five patients who were either obese or diabetic and presented symptoms of the superior vena cava obstruction. In addition, these patients could not undergo peritoneal dialysis because of a previous failure of the technique, obesity, or a previous major abdominal surgery. Being aware of the disadvantages such as the risk of infection, occlusion, stenosis etc. associated with a long graft created for other vascular indications as well as the unsatisfactory long-term patency of the graft in e.g. atherosclerotic patients we do not recommend this type of fistula to be performed in such patients.

2.7. The femoral artery to the right atrium bypass

In this type of the fistula the cardiopulmonary bypass is not necessary. The patient is anesthetized in a decubitus position and the median sternotomy is performed. Then, the pericardium is incised and the heart and the great trunks are dissected. Next, the right Scarpa is incised and the femoral artery with its branches are dissected. A subcutaneous tunnel is created along the lateral aspect of the abdomen and the chest wall. Just before the second intercostal space an incision is made laterally on the chest. The graft is passed through the incision to the chest and anastomosed to the atrium. The distal anastomosis is created end-to-side with the superficial femoral artery. A patient qualified to this procedure should not be eligible for peritoneal dialysis or transplantation [7]. Since this procedure is most challenging for both the patient and the surgeon indications for it should be strictly limited to a carefully selected group of patients. Indeed, we support the opinion expressed by some other authors who call this kind of access “exotic”. However, in spite of all the shortcomings there are conditions in which application of this technique can be the only effective renal replacement therapy.

3. Summary

In certain clinical situations a surgeon faces the problem of the AVF creation in patients who have undergone several surgical interventions and, in addition, are in their 70’s or 80’s. Moreover, there are no simple and clear protocols for selecting the type of the vascular access in hemodialysis. There are, however, some practical clues. For example, in patients with no possibility to create AVF in the upper limb a saphenous vein loop to the femoral artery is recommended. Also, transposition to the popliteal artery or a loop graft to the femoral artery can be performed. As indicated above, long saphenous vein fistulas are associated with

the low patency rate [7,11] requiring several additional interventions [7]. Because of the manipulation in the Scarpa's triangle each femoral graft is associated with the risk of infection and poor and prolonged wound healing. Hence, most surgeons advocate that this procedure be used in patients with the central venous stenosis or occlusion who are not candidates for peritoneal dialysis and are neither obese nor diabetic. For the latter patients most authors recommend the axillopopliteal bypass. The main benefit of this AVF is avoidance of the involvement of the femoral triangle [7,12].

Most vascular surgeons refrain from creating long bypasses, but those who specialize in AVF approve of them since the long fistula arm allows avoiding the sharp angulation of the graft [13]. Moreover, long bypasses offer a larger area for cannulation. In turn, as described by Chemla et al. [7], the left femoral artery to the right atrium bypass functioned successfully for only three months. For the same group of patients Karp et al. [14] preferred to use the renal vein as the outflow because of the ostensibly decreased morbidity associated with this intervention. However, several revisions were needed in the patient treated by these authors. The indications to create this kind of AVF should be regarded as the last-chance measure in a patient who cannot be switched to peritoneal dialysis or undergo transplantation [7].

The axilloaxillary bypass has been described previously, but long term results have not been satisfactory although good results and patent grafts were obtained in individual cases [7,12]. This AVF is recommended for patients with the unilateral subclavian artery or vein occlusion. The necklace bypass seems to be a reasonable solution for patients at risk of the steal syndrome [9]. The femorofemoral bypass can be an option for patients who care for cosmetic problems because in this case the cicatrix is minimal and hidden behind the panty line [7,12].

The problems in functioning of AVF after complete thrombosis of the ipsilateral subclavian vein and IJV may be solved by using a jump graft from the fistula to the contralateral IJV [7,15]. This way HD can be continued without the need for the temporary catheter insertion and the fistula can be immediately cannulated [7].

Noticeably, each difficult and complex patient with the history of several surgical interventions in all the limbs should be carefully and individually analyzed. Only a vascular surgeon experienced in AVF can perform the most difficult operations aimed at creating rare fistulas. Another important thing is to minimize the operating risk which is aggravated when the central vessels are used for the AVF creation. Some of the proposed AVF are challenging and most of us will never have the opportunity or the need to make them. As shown by the last ten years endovascular procedures proved to be the powerful tools that have significantly changed our vascular access strategy. Currently, most of the vascular departments are equipped with angiographs allowing to perform angioplasty of a stenosis or a local thrombolysis of the clotted fistulas. Percutaneous angioplasty can be supplemented by implantation of a stent [16].

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Chapter 26

Vascular Access With or Without Synthetic GOR-TEX

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Additional information is available at the end of the chapter

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1. Introduction

Ownership of dialysis facilities has shifted over the past decade. Where nonprofit organizations once managed these facilities, large companies now have control. Shareholders of these companies are primarily interested in the profitability of their investments rather than the well-being of the patients being treated. Market forces rather than scientific inquiry now drive much of the research related to end-stage renal disease (ESRD). These developments have created ethical dilemmas for physicians. This editorial describes some of these ethical challenges and asserts that the doctor–patient relationship and its ethical imperatives are more important than company profit and loss statements.

2. Dialysis

2.1. History

Gaining proper access to the human circulatory system is required to transport blood from the patient to the artificial kidney and back again during hemodialysis. In 1943, Dr. Willem J. Kolff first encountered the problem of vascular access for hemodialysis [1]. After 34 days of puncturing readily accessible blood vessels, he failed to enter the bloodstream. As a consequence, his patient died. The chronic hemodialysis era began almost 20 years later, when Quinton and Scribner introduced the first external arteriovenous shunt constructed of Teflon, which allowed repeated access to the vascular system [2].

In 1966 a major breakthrough in vascular access surgery was achieved with the introduction of the first endogenous fistula by Brescia and Cimino [3, 4]. They created a side-to-side anastomosis between the radial artery and cephalic vein, which ensured functional vascular access. Later, brachiocephalic and transposed brachiobasilic fistulae were constructed,

followed by the emergence of various prosthetic grafts as an alternative to native fistula. Polytetrafluoroethylene is now the most frequently used graft material. Nevertheless, vascular access-related complications are still often responsible for patient hospitalization, morbidity, and even mortality [5, 6]. Facility preference and variations in approach to vascular access practice still seem to be major determinants of vascular access success or failure [7].

2.2. Costs

Therapy for ESRD patients is expensive and therefore impracticable in some countries. Even some of the more affluent countries do not provide readily accessible free treatment to all renal failure patients; in 2002, 58% of hemodialysis providers in the United Kingdom had no vacant staffed slots for new patients [8]. In the United States, discussion has been ongoing as to whether the Medicare system, which provides public funding for patients with renal failure, should be modified as post-World War 2 'baby boomers' reach old age [9, 10].

Patients should be allowed time off from their jobs for dialysis treatment and extra time off when complications arise. Paid leave for medical treatment requires cooperation from government and employers. [Remark 3]

This chapter sets out our view of the minimum standards required to provide sufficient care for patients with ESRD. These standards may require modification in response to local circumstances or new research data, but we hope that they will help doctors in all countries to argue for sufficient resources for their patients with ESRD.

[Remark 3] Timing

One ethical issue to be discussed involves the timing of dialysis initiation. Traditional indicators for starting dialysis included the presence of signs and symptoms of uremia in combination with pertinent results of biochemical analyses of serum and plasma [13]. However, several observational cohort and case–control studies have suggested that early initiation of dialysis may improve patients' survival, quality of life, and capacity for employment while decreasing complications [14, 15]. Although such studies were potentially limited by biases related to lead time, patient selection, and referral time, the clinical practice guidelines that were in use in the late 1990s [16] recommended the commencement of dialysis when the directly measured or calculated (estimated) glomerular filtration rate was higher than the values previously targeted for the initiation of dialysis. However, more recent observational data have suggested that starting dialysis early may in fact be harmful [17, 18]. We assert that if early dialysis benefits patients, it should be used, and, by contrast, if it causes harm, it should not be used, in accordance with the principle of nonmaleficence. [Remark 1]

3. Ethical issues

3.1. Fair selection

Ideally all patients who can benefit from dialysis should be offered it free of charge. However, many countries cannot afford the substantial cost of treating all patients with renal fail-

ure by dialysis and transplantation [19]. The problem for poorer countries is exacerbated by their higher incidence of renal failure. The aim of patient selection for dialysis should be to use scarce resources to provide maximum benefit. This implies that patients should be selected who are likely to enjoy a good quality of life as a result of treatment. Selection should not be influenced by race, color, creed, caste, or political affiliation. Age per se should not be a selection criterion. Since comorbidities are more likely in elderly patients, the majority of patients selected for dialysis is likely to be younger. However, many elderly patients may also enjoy a good quality of life [20].

If the only way of obtaining regular dialysis is by payment into a private medical insurance system, patients able and willing to pay the costs should be allowed to do so. No 'waiting list' for dialysis should be maintained, nor should any patient be assigned to a therapy known to be inappropriate to meet his or her needs.

3.2. Patient choice

Patient preference plays a part in the selection of the dialysis modality, but this is often overridden by other factors, including availability of hemodialysis stations, difficulty with vascular access placement or preservation, and failure of peritoneal dialysis techniques. In addition, a certain proportion of patients presents late as 'uremic emergencies'. Patients must be informed of the advantages and drawbacks of the various available types of dialysis, the prognosis with and without dialysis treatment, and its effect on quality of life so that they can make informed choices on the basis of current information [21, 22]. Treatment decisions should be consistent with the goals of regaining or maintaining active employment and maximizing rehabilitation of patients into society.

[Remark 3]Privacy and patient rights

The processes of diagnosis, consultation, surgery for vascular access, and dialysis treatment should be conducted in ways that protect patient privacy. They should know the identity of the physicians, nurses, and others involved in their care. They are entitled to (i) refuse a recommended type of treatment and be informed of the medical consequences of this action; (ii) consent or decline to participate in research studies after being fully informed of their purpose [22]; (iii) be treated with respect, dignity, courtesy, compassion, and cultural sensitivity; (iv) have any treatment, possible complications, and self-care requirements explained in an understandable manner, with sufficient time to ask questions and receive answers; (v) be allowed to obtain a second opinion for a given treatment and ask for consultation with another physician; (vi) designate relatives or friends to be kept informed of their medical condition; (vii) be informed about names, dosages, indications, and adverse reactions of all prescribed medications [21]; and (viii) be fully informed about the results of laboratory analyses and any tests they undergo. Gardner et al. demonstrated that a well-developed single-item measure can be appropriate in avoiding common methods variance, which is often a problem with psychological measures that require respondent self-reports of attitudes, beliefs, perceptions, and the like [23]. [Remark 4] Notwithstanding this limitation, we suggest that patients' beliefs about their illness and treatment are important for their sense of (global) autonomy and self-esteem. Correlations have been identified between appropriate medi-

cal management, time on dialysis, and positive self-perception of health with better problem-solving ability and higher autonomy, but lower sociotropic personality styles. [Remark 5]

3.3. Loss of autonomy

A few studies have been published on the number of patients who decided to withdraw from dialysis once treatment was initiated [11, 12]. [Remark 3] Loss of autonomy was one of the most important reasons for patients to decline dialysis treatment. Patients who chose not to start dialysis were reluctant to give up their freedom and become dependent on medical treatment. They would rather live for a shorter time with more freedom, than live longer with the limitations of a comprehensive treatment such as dialysis. "You are going to die anyway … and making a trip to the hospital 3 times per week, already being tired and exhausted, and while basically handing your life to others, is such a great deal of effort, I can't do that!" [Remark 6]

3.4. Quality of life

One of the most important factors in the choice of treatment in patients with ESRD is quality of life. For many patients, the challenges of living with chronic kidney disease may not prevent them from appreciating the small things in life. Several studies have demonstrated that participation in an exercise program either before or during dialysis can improve quality of life. [Remark 7]

ESRD and its treatments may have a negative impact on quality of life. Nephrologists, like all physicians, must offer their patients all reasonable treatment options. When dialysis is (or is not) a reasonable option is an important ethical issue. The justification for dialysis, like any life-sustaining treatment, is that it prolongs life for a patient who either wishes to live longer or, if cognitively impaired, would (in the opinion of others) be likely to benefit from extension of life.

Case Against Dialysis [Remark 8]

The following section focuses on patients with advanced dementia or severe and irreversible brain injury who were no longer capable of enjoying life, and hence gained no benefit from dialysis. Guidelines are presented for withholding and withdrawing dialysis and suggestions are offered to help nephrologists avoid causing harm when the patient's family demands that dialysis be performed [24]. [Remark 9]

3.5. Dialysis refusal

The Medical Code of Ethics states that patients have the right to refuse medical treatment, and that physicians must accept and respect these decisions. Physicians must guarantee that patients die with dignity while not prolonging or shortening their lives. [Remark 3] Many patients have reported enjoying life and have expressed a desire to live for as long as possible, but not at any price. In one study, however, many patients chose not to start dialysis.

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Most patients who declined dialysis had made the decision before they received information on the treatment and would not have even considered the possibility. These patients indicated that they would have considered treatment when they were younger, in better health, or in severe pain [25].

[Remark 3]In another study, patients decided to discontinue dialysis because of an unacceptable quality of life, depression, and a chronic failure to thrive. Health professionals must support end-of-life decision-making using an ethical decision framework [26].

3.6. Age-associated decrease in vitality

Some patients decline dialysis due to an age-associated decrease in vitality. Most patients who declined dialysis reported that they had good lives. However, the discrepancy between their former active lives and their present lives was large. They were incapable of doing many things. Patients noted that they had already had to give up so much in life, and that adding dialysis treatment would be too much. Patients who refused dialysis seemed to be able to face the finiteness of life. They all spoke about the good life they had lived. The serious disruption of life caused by dialysis was unacceptable to them.

A few patients indicated that their overall ability to plan and organize significantly deteriorated with age. As a result, making doctor appointments and arranging to get there in time required too much energy. For most patients, the decision not to pursue dialysis treatment was not well-considered, but in their perception, it was the only option. For those patients with relatively good health, dialysis seemed like a natural decision. Earlier studies showed a worse quality of life in elderly dialysis patients with a higher number of comorbidities and no better survival rates than in patients not undergoing treatment [27–29]. The extent to which elderly patients with poor health status may benefit from this treatment is therefore questionable.

For most patients who declined dialysis, the anticipated loss of autonomy in combination with their age-associated decrease in vitality fueled their refusal. Many patients declined dialysis due to a preference to live from day to day without stress related to illness and treatment. In this study, patients who declined dialysis treatment were mostly men. [Remark 10]

Previous research on the impact of gender on the initiation of dialysis was not available. However, patient withdrawal after treatment initiation has been demonstrated as more common among women than men [30].

4. Other issues

4.1. Social support

Lack of social support is a significant predictor of mortality, even when a large number of medical variables are controlled.Remark7 Findings of several studies are consistent with the view that social support is an important factor in general health outcome and adjustment to

chronic and acute illness [31]. Therefore, health care personnel should provide information with honesty to help patients to predict their quality of life and death. Support for the patient and family during the end-of-life period should be multidisciplinary, with clear and timely communication between all members of the team [26]. Understanding the importance of social support at the start of dialysis treatment and its association with survival and well-being may have important clinical benefits for patients with ESRD. Clinical practice can then be geared toward the promotion or improvement of patients' support networks. Social support affects health through behavioral, physiological, and psychological mechanisms [32]. Provision of social support can be emotional or tangible. It may involve sharing information or giving advice. The characteristics of ESRD and its treatments are functionally debilitating, affecting social relationships and activities of daily living [33]. Diverse expectations regarding social support between patients and their families and friends may exist. While patients may hope to minimize lifestyle changes despite the restrictions of dialysis, people in their support network may be unaware or unsure of how to cope with the patients' treatment and dietary needs [34]. Feeling socially isolated can induce stress and anxiety, which in turn can produce physiological changes, such as a compromised immune system [28]. If prolonged, these changes could lead to higher morbidity and mortality [35]. Depression has also been associated with lower levels of perceived social support in HD patients [36].

The fact that patients on dialysis require different types of social support has important clinical implications. Clinical care providers may tailor intervention programs to improve social support based on patients' needs, making recommendations to appropriate programs like self-help groups [37] or psychoeducational programs [35–38] designed to promote self-efficacy in coping with dialysis. ESRD patients undergoing dialysis require different types of social support depending on their social environment and severity of the illness. Future studies may provide a longitudinal assessment with several points of data collection, charting possible changes in social support needs since the start of dialysis and their association with survival.

4.2. Transport and facilities

For the majority of patients, one-way travel time to receive dialysis should be less than 30 minutes. Ideally, dialysis units and their satellites should be distributed throughout the country. If the nearest unit is far from a patient's home, transportation costs should be fully reimbursed [19]. The dialysis unit should be designed for comfort while waiting as well as during treatment. Communication regarding appointments and medical advice should be readily available.

Approximately half of ESRD patients in developed countries have their own transportation, while the other half are dependent on ambulance or hospital transportation services [20]. Transport should aim to make the dialysis day as short as possible. Each dialysis unit should have nurses trained in renal care, cardiac or respiratory emergencies, and hemodialysis procedures. Each dialysis station can treat up to four ESRD patients per day, but time must be allowed for cleaning and disinfecting the dialysis room and machines.

Hemodialysis satellites facilities need good road communications and parking facilities. Each dialysis station should have a dialysis machine that measures and controls ultrafiltration, a weighing bed or armchair for the patient, an abundant oxygen supply, and adequate lighting. Testing for viral hepatitis should be performed every 3 months in all patients. HBsAg-positive patients should ideally be dialyzed in a separate dialysis area with dedicated hemodialysis machines, but in practice a dedicated side room and equipment are often used. Patients with hepatitis C virus and HIV carriers can be treated in regular dialysis units, but should be dialyzed with designated hemodialysis machines [22].

4.3. Dose

A strong correlation has been demonstrated between hemodialysis dose and patient mortality and morbidity [39]. Hemodialysis adequacy and delivered hemodialysis dose should therefore be assessed regularly, at least once a month, in both adults and children. A stable single-pool Kt/V>1.2 should be provided for at least 90% of patients. More frequent measurements are necessary when the prescribed hemodialysis dose is not regularly delivered [39].

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Chapter 27

A Holistic Approach to Vascular Access in Hemodialysis

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Dean Williams

Additional information is available at the end of the chapter

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1. Introduction

Vascular access for haemodialysis (HD) and other forms of renal replacement therapy where access to blood is required (such as haemofiltration) is a broad area that encompasses a variety of specialties including nephrology, intensive care, interventional radiology and surgery. Within the acute setting, vascular access via catheter placement can be performed in an emergency. However, longer-term access in the form of an arteriovenous fistula (AVF) or graft requires considerable pre-procedural planning and often involves multidisciplinary input throughout the patient's "dialysis lifetime". In this chapter, we aim to discuss the common types of access and provide a holistic approach from a UK perspective, whilst also focussing on some practical aspects that have been noted from our personal experience and evidence-base.

1.1. Identification of patients who require vascular access

In the setting of acute kidney injury (AKI), a vascular catheter is the commonest access route for HD. There has to be a clear indication for insertion and this may include satisfying stage 3 of the Acute Kidney Injury Network classification, life-threatening hyperkaemia refractory to medical therapy, acidosis, uraemia and fluid overload resistant to diuretic therapy [1]. Nonetheless, there may be other specific indications considered on a "case-by-case" basis. Such instances include anticipation of non-recovery from AKI or those with chronic kidney disease (CKD) who receive debulking chemotherapy for haematological malignancies and may not cope with rapid rises in urate and potassium from cell lysis [2].

In CKD, it is generally recommended that plans to establish any form of dialysis access should be discussed with the patient between stages 4 to 5 (estimated glomerular filtration rate of 30 ml.min.1.73m$^{2\text{-}1}$ or less) and an informed decision documented [3]. In HD,

this often involves surgery for an autogenous AVF or graft. Vascular catheters are not recommended as a first-line approach given their complications. Timely preparation will ensure the smoothest transition towards renal replacement therapy. Patients who referred late for consideration have poorer outcomes compared to those who have been established with nephrology services for longer: they are consistently shown to have increased mortality, reduced treatment choices, access to transplantation, increased morbidity and hospitalisation [4].

One fundamental difference between vascular access types is blood flow and this will determine dialysis adequacy (defined as a Kt/V of ≥1.2) [5]. Sometimes, flows are not as optimal in catheters compared to AVFs or grafts. Regardless, the need for vascular catheters in patients with end-stage renal disease is becoming increasingly commonplace in 4/5 patients who suddenly deteriorate, when AVF or graft is not possible or maturation has failed [6]. Their convenience of insertion and immediate painless use makes them popular with patients. Temporary vascular catheters (VC) are generally used for no more than two weeks (shorter duration for femoral vein catheters), whereas tunnelled cuffed vascular catheters (TCVC) are indicated for short to long-term venous access. If maintained correctly, such devices can last for a few years. Although traditionally inserted by an interventional radiologist, in many UK centres a nephrologist will now perform the majority of procedures as a day case. A more recent development within the UK has been the creation of specialist nurse-led services dedicated to this area [7].

Establishing vascular access will remain the key rate-limiting component for HD. The vascular access nurse plays a crucial role in prioritising patients and contributes to a multidisciplinary approach involving specialist nurses, surgeons, radiologists and nephrologists. Deciding on when to start dialysis once access is created in CKD is an area of intense debate but has to be determined on an individual basis. Factors may include rapidity of estimated glomerular filtration rate (eGFR) decline, symptoms of uraemia, failure to thrive or poor quality of life. However, the recent Initiating Dialysis Early and Late (IDEAL) trial definitively demonstrated that elective earlier initiation of dialysis (based on eGFR 10-14 ml.min. $1.73m^{2-1}$ vs. 5-7 ml.min.$1.73m^{2-1}$) was not associated with improved clinical outcomes or quality of life [8].

2. Types of vascular access

2.1. Arteriovenous fistulae and grafts

2.1.1. Requirements

Preferably, patients should receive counselling on the requirements of HD before referring for *any* access procedure. It is useful for them to visit a dialysis unit to experience how treatment is administered and gain familiarity with environment. This may help to adjust patients to a potentially lifelong routine.

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A vascular surgeon at our centre performs AVF and graft surgery. In the UK, both renal transplant and vascular surgeons provide this service based upon local arrangements. On considering referral for access surgery, the renal physicians and vascular access nurse assess both the patient and the upper limb vessels for ease of AVF formation. This is an invaluable adjunct to the process, as priming both the patient and surgeon regarding potential difficulties provides for a more effective service.

Once referred, a vascular assessment of the patient is performed with particular focus on both upper limbs. Clearly, the successful creation of AVF or graft is dependent upon optimising its location, arterial inflow and venous outflow. In particular, the veins in both upper limbs should be examined for size, location, and patency whilst simultaneously checking for the character of radial, ulna and brachial pulses and vessels. The non-dominant limb is usually used for access surgery. Where there is a suspicion of arterial disease, we perform upper limb brachial and radial systolic blood pressure and qualitative Doppler waveform analysis at the same clinic visit.

Although clinical assessment of the patient is key to the formation of an AVF, ultrasound duplex scanning can be valuable to assess vessels and quantify flow rates. Surgeons may use duplex scanning routinely or selectively prior to surgery. Patients with diabetes frequently represent a greater challenge due to a higher incidence of arterial calcification particularly more distally at the forearm and wrist: studies demonstrate they are more likely to need a proximal AVF with their inherent risk of the steal syndrome (see below) [9].

We have seen an increasing trend in more elderly and frail patients being referred for access surgery. The increased incidence of co-morbidities including cardiac disease, loss of tissue quality and atherosclerosis in the elderly means that they represent a greater challenge both in terms of creating a fistula and avoiding associated complications [10]. If a reduction of inflow is identified in the limb being considered for surgery, then magnetic resonance arteriography (MRA) is requested to detail arterial disease. MR or venograms can be performed if there is suspicion of venous disease particularly in patients with a history of multiple central vascular catheter use: subclavian catheters being well-recognised to predispose to central vein stenosis [11]. Patients with central vein stenoses and occlusions present a significant obstacle, but can be managed by interventions such as venoplasty and stenting, and carefully selecting the site of venous anastomosis.

Informed consent for access surgery should include detail not only on the reasons for surgery and explanation of the procedure, but also information on the immediate and longer term complications that may occur. This should be based on the individual surgeons practice and observations [12]. The type and frequency of complications that we include in discussion, comprises of failure to achieve a usable fistula, haemorrhage, ischaemia, damage to surrounding structures including nerves and wound complications. Over 90% of our access surgery is performed as a day-case under local anaesthesia.

Given the burden of cardiovascular disease, it is common to find patients on antiplatelet and anticoagulant medication. Aspirin is not stopped prior to surgery. Clopidogrel and antiplatelet combinations are modified based on an assessment of risk [13]. Typically, we ask pa-

tients to omit clopidogrel for five days prior to surgery. Warfarin is omitted typically four days before surgery to achieve an International Normalised Ratio (INR) of 1.5 or less, although there is no definitive evidence for this practice [14]. Regarding the provision of regional anaesthesia for access surgery, an INR of 1.3 or less is required. If warfarin cannot be stopped for an interval of several days (e.g. in patients with prosthetic heart valves), then we typically admit patients for intravenous heparin infusion that is stopped approximately two hours prior to theatre and recommenced two hours following surgery. The platelet count should be 50,000.μl^{-1} or greater but guidance on the possible qualitative defects in platelet function due to uraemia in stage 5 CKD is not well defined [15-16].

AVF formation should ideally be timed so that patients who are deemed likely to need access have a mature fistula when dialysis is required. Clearly, access surgery should be performed as soon as is possible. However, this should not preclude optimisation of patients in terms of co-morbidities and the investigation and treatment of arterial or venous disease that will improve the likelihood of a successful outcome. Hastily performed access surgery in a sub-optimised patient is more likely result in the loss of a potentially precious AVF. Of course, it is possible that a patient will require dialysis during the period of investigation, interventions or fistula maturation and a vascular catheter with their inherent risks becomes vital.

2.1.2. Autogenous arterio-venous fistula and details of procedure

This is the gold standard and should be considered in *all* patients who required vascular access [17]. It is recommended to create a fistula in the non-dominant upper limb before approaching other sites, particularly for those considering home dialysis. The lower limb should be considered only when the upper limb options are exhausted given the higher risk of infection [18]. The commonest type of autogenic AVF is radio-cephalic where the cephalic vein is anastomosed to the radial artery at the wrist. Although initially described as a side-to-side anastomosis, many surgeons perform end-to-side procedures, ligating the vein and attaching the proximal vein to an arteriotomy.

Typically, in our practice, a patient will give signed consent and have the limb marked on the day of surgery. The vein, artery and line of incision are marked approximately in parallel, with the incision mark placed closer to the artery than vein. The procedure is performed in theatre under aseptic conditions; venous cannulation is performed on the dorsum the non-surgical hand and a single bolus of a broad-spectrum antibiotic is administered, e.g. co-amoxiclav 1.2g. Unfractionated heparin is also given via the cannula just prior to application of arterial clamps. Monitoring of pulse and oxygen saturation is continuous. No sedation is used.

The limb is placed on an arm board and prepared with a topical antiseptic e.g. iodine-based. We place the unprepared hand in a clear aseptic plastic bag. Local anaesthetic, typically in the form of 1% lidocaine, is infiltrated into the marked area. The vein is identified first, as its status will influence the rest of the procedure. Once sufficient length is judged to be exposed and dissected free of surrounding tissues, the vein is marked along its length with a surgical marker pen to avoid rotation. The vein is then ligated and cut. The proximal end is initially

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flushed to check run-off, then gently occluded to assess calibre as venospasm is routinely encountered during local anaesthesia.

Once the vein is assessed as viable, the artery is then exposed sufficiently to allow an arteriotomy and placement of two paediatric non-crushing arterial clamps. The vein is cut to adjust for length and end circumference to avoid excessive tension and anastomotic disparity. Once clamped, an arteriotomy is made, typically of four to six millimetres and the end-to-side anastomosis performed using a double ended 6-0 or 7-0 polypropylene suture (Figure 1). We routinely flush all vessels just prior to completion of the anastomosis to flush out any clot that may have formed. Closure is then performed in layers with absorbable sutures. Occasionally, non-absorbable sutures are used to close the skin when the cutaneous tissue is thin and unsuited to subcuticular closure.

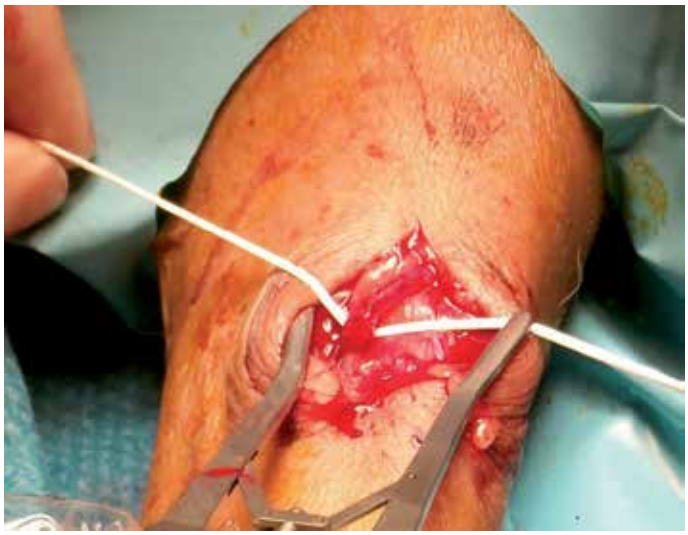

Figure 1. Completion of anastomosis in a radio-cephalic fistula.

The degree of urgency and co-morbidities are factors to consider when deciding on the location of an AVF [19]. For patients vulnerable to factors such as reduced arterial inflow due to cardiac failure, a proximal AVF may be preferable as it is more likely to develop quickly and be resilient to changes in the patient's cardiovascular status. Although more proximal AVF are likely to achieve better primary outcomes, we strive to perform distal procedures - frequently performing snuff-box AVF, distal to the wrist in the anatomical snuff box [20]. Distal AVF surgery can be more technically demanding because the vessels are of smaller calibre requiring finer sutures and instruments. Despite this, the great advantage of a distal AVF apart from ease of use for the patient and staff, is that failure will most commonly only cause local venous thrombosis and not limit venous return for any subsequent, more proximal AVFs. This approach allows for better utilisation of veins with potential for a greater

number of AVF in each limb. Thus, if a snuff-box or wrist AVF fails, then a more proximal radiocephalic or antecubital fossa AVF can be created.

An antecubital fossa AVF involves anastomosing the median cephalic vein (or local variation of this), to the brachial artery. Other approaches include distal ulnar-basilic, radio-basilic or brachio-basilic transposition, performed as a single or two separate procedures. The basilic transposition involves a basilic or median cubital vein anastomosis to the brachial artery, but requires transposition of the vein from its normal deep lying medial location to an anterior and superficial position to enable access for puncture. If the upper limbs are not suitable or fistula maturation has failed, then the lower limbs can be used. For example, a long saphenous vein proximal thigh loop or mid/distal superficial femoral or popliteal artery anastomosis. Other more unusual approaches to AVF formation have been described for patients with particular challenges for access surgeons [21].

Autogenous AVFs exhibit a long-term patency rate superior to prosthetic grafts and vascular catheters [22]. Their relative cost is reduced with thrombosis and septic complications tending to be low. However, there are also disadvantages including the prior requirement of healthy veins that have not experienced inflammation and trauma leading to fibrosis and stenoses, the commonest cause of which is repeated cannulation [23]. This is particularly relevant to the cephalic vein in the forearm, the most precious of veins for AVF formation. Vein cannulation is a common occurrence and the importance of the cephalic vein is often forgotten by clinicians in the patient approaching end-stage kidney disease. Another important drawback when comparing AVF to grafts is a maturation time of typically four to six weeks. Grafts can be used far more quickly.

2.1.3. Prosthetic graft fistula

Prosthetic grafts are derived from several materials including polytetrafluoroethylene (ePTFE) and polyurethane. Despite their relative lack of vascular compliance, ePTFE grafts have an inherent stability as their hydrophobic properties make them less likely for blood to adhere [24]. Perforations created by dialysis needles tend not to close but are instead occluded by the development of a pseudointimal lining and platelet deposition. This is opposed to polyurethane grafts, which do possess self-sealing properties. Biological grafts of bovine origin (mesenteric vein, ureter and carotid artery) are available, but seldom used in the UK. Although more expensive than prosthetic grafts, biological grafts are less prone to infection.

Our unit uses grafts only occasionally when upper limb veins are not viable. We have a small stock of ePTFE grafts readily available usually as standard wall six millimetre diameter, with external reenforcement for loop grafts to prevent kinking. Unlike AVF, grafts require subcutaneous tunnelling. The most common procedures employing grafts are the forearm loop graft with anastamoses to the brachial artery and basilic/cephalic veins and brachio-basilic bridge graft with a venous anastamosis placed proximally towards the axilla. Grafts, in common with AVF, require good inflow and outflow. Their advantage over AVF is that needling can be performed much earlier (e.g. within two weeks) and cosmetically, they may be more acceptable to patients. Where urgent dialysis is required, synthetic grafts are available that can be used within 24 or 48 hours. Grafts can also be used for more unusu-

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al bridge procedures, such as the necklace axillo-axillary graft and bridge grafts extending from more central vessels in the upper and lower limbs.

2.1.4. Post-procedure follow-up

In our practice, we routinely cover wound dressings with an additional layer of soft bandage typically from the hand to mid-forearm. This acts as a deterrent to hospital staff inadvertently grasping the surgical site in the immediate post-operative period. Following return to the ward, the patient is typically observed for two hours to monitor for bleeding and any acute neurovascular compromise that requires urgent revision surgery (see below). An audible bruit and often a mild thrill should be detectable following successful surgery. The vein in an autogenous AVF should become more prominent as maturation occurs. The patient should be educated about managing the surgical wound and reminded about the avoidance of cannulation and blood pressure recording in the fistula limb. In the early post-operative period, it is imperative that maturation is assessed on a weekly basis – usually by the surgeon or the vascular access specialist nurse.

During maturation the vein proximal to the anastomosis dilates rapidly over a three-week period and then at a slower rate subsequently. Although during this period, forearm exercises are advocated by the Kidney Foundation Disease Outcomes Quality Initiative, the evidence so far for this is patchy with little randomized-controlled trial data. Our unit recently conducted a pilot randomized-controlled trial of the effects of progressive handgrip training on autogenous AVFs. There was a small but sustained effect upon the change of venous diameter and accelerated arterial remodelling in the exercise group in the first four weeks of study [25]. These findings, although taken from a small sample size, suggest larger studies should be undertaken to clarify the significance of this intervention [26]. ePTFE grafts on the contrary do not change in size. Another, not uncommon cause of poor maturation in our population is vein branching causing flow reduction in the main draining vein. This may be related to stenoses secondary to cannula trauma. Prompt ligation of branches usually remedies this, occasionally combined with surgical or percutaneous management of associated stenoses.

Significant flow changes occur at the fistula anastomosis with normal laminar arterial blood flow becoming turbulent as blood flows abruptly from a high pressure/low volume vessel into a low pressure/high volume system with changes in wall sheer stresses. This is associated with variable degrees of intimal hyperplasia and venous stenosis. Vein ischaemia following sometimes extensive dissection, is also likely to influence wall fibrosis and stenosis. Our experience also suggests that the presence of vein valves in close proximity to the anastamosis is also associated with hyperplasia. Timely intervention using percutaneous angioplasty or surgical revision to improve vessel calibre can preserve fistula development [27]. Grafts can be affected by neointimal hyperplasia causing a gradual narrowing, particularly at the venous anastomosis and can lead to significant pre-and post-stenotic stasis and thrombosis. Flow monitoring has been advocated to detect these changes earlier, but the evidence is mixed and good trial data is desperately needed.

2.1.5. Long-term complications

The greatest risk universal to all fistulae and grafts is thrombosis. This may occur as an early or late complication. Interventions for complete occlusion of AVF are very time dependent, as unless it is immediate (typically within 24 hours of the event), the resulting phlebitis induces thrombosis and precludes a successful outcome [28]. Grafts are not subject to inflammation, although the adjacent vein will be susceptible. Thrombosed grafts can undergo thrombectomy or thrombolysis several days following occlusion.

There is limited evidence for use of antiplatetlet agents or warfarin to maintain fistula patency [29,30]. Further, any benefits may be offset by an increased risk of bleeding episodes. Fish oil has also been tried, but large trials are still awaited [31]. Nonetheless, in our experience, such measures should be considered in patients who have required multiple fistulae or when further attempts at any form of vascular access will be extremely challenging. In our unit, reducing flow rates are initially imaged using duplex scanning. The management of vein or anastomotic stenoses is influenced by whether the patient is dialysis dependent. Our preference is for surgical correction, most commonly more proximal re-implantation, over fistulogram and fistuloplasty in patients not requiring dialysis because of the nephrotoxic profile of the majority of contrast agents. Anecdotally and possibly related to a more elderly population, we are encountering more 'blow-outs' of autogenous veins, occasionally causing large haematoma formation and subsequent stenosis. Thinner, more fragile veins may be a contributing factor.

Infection is a dreaded complication, particularly when using grafts and is associated with false aneurysm formation. Local signs of inflammation such as warmth, erythema, oedema and tenderness should raise a high index of suspicion. Cultures should be taken to target antimicrobial therapy, although *Staphylococcal*-targeted antimicrobials are commonly used. Excision of the entire graft with arterial repair is not uncommon. Infection is not exclusive to grafts: following the advent of the buttonhole needling technique for autogenous AVFs there have been outbreaks of infection leading to *staphylococcus aureus* septicaemia [32]. Autogenous vein infection should be treated with conventional antibiotics and if possible alternative dialysis access sought on a temporary basis. Patient and staff education is an essential part of management and involves meticulous and repeated assessment of correct needling technique without the introduction of healing scabs into circulation.

Neurovascular compromise to a limb following access surgery may present as the steal syndrome and is characterised by classic signs of acute or worsening chronic ischaemia [33]. It can present hyperacutely with complete anaesthesiae of the hand, pain, loss of motor function or culminate in a more chronic form as severe ulceration and gangrene (Grade IV steal syndrome). Acutely, this represents a surgical emergency and necessitates immediate management to improve perfusion including revision surgery such as the distal revascularisation and interval ligation (Dril) procedure or reversal of the fistula to prevent permanent injury [34].

After a long period of AVF maturation, high output cardiac failure can occasionally develop. Given the burden of cardiovascular disease in the dialysis population this should not be

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forgotten as a potential cause of worsening congestive cardiac failure. This develops due to left to right shunting of large volumes of blood via the fistula. The resulting increase in preload leads to higher cardiac output, and over time, the rise in overall cardiac workload leads to a progressive cardiomyopathy [35]. Access flow monitoring can demonstrate massive blood flows over the fistula (e.g. 2 litres.min^{-1}) and echocardiography reveals variable ejection fractions. Treatment with conventional therapies (e.g. angiotensin blockage, beta-antagonists, diuretics and fluid restriction) can improve the condition, but often banding or ligation of the AVF is needed which may create a dilemma over future vascular access.

Cosmetically, fistulae can be unappealing to some given the possible progression to aneurysmal dilation and venous collaterals from venous hypertension. The latter can be exacerbated by central vein stenosis from multiple catheter usage. Central vein angioplasty with possible stenting may be attempted to settle this but such intervention should be avoided if dialysis is adequate. Advances in buttonhole needling techniques have seen a reduction in the frequency of aneurysmal dilation. [36]. Occasionally, aneurysms and pseudoaneurysms (in grafts) need to be surgically removed as they carry a high risk of bleeding and infection.

2.2. Vascular catheters

2.2.1. Requirements

Similar to AVF creation, anatomical planning is crucial to ensure a successful outcome and reduction in complications. Deciding upon the site of catheter insertion depends upon several factors. Generally, haemodialysis catheters are inserted into either one of the internal jugular veins. Commonly the right side is approached given: 1) larger lumen than its counterpart and 2) its direct path into the superior vena cava and right atrium. The course of the left internal jugular vein is less straightforward as it makes a turn at the junction with the left brachiocephalic vein and a second turn at the superior vena cava. If a left-sided approach is being contemplated, it is recommended to perform this under fluoroscopic guidance so any tortuosity is safely traversed.

Although anatomical landmarks continue be used to guide insertion, current NICE guidance in the UK recommends the use of ultrasound scanning (USS) pre- and/or intra-procedure [37]. This enables the operator to accurately determine site of entry, trajectory, proximity of the artery relative to the vein and assess vessel calibre. Compressibility of the vein is a defining feature distinguishing it from the neighbouring artery (usually in a slightly posterior-medial position with an internal jugular approach; Figure 2). This may however be reduced if thrombus is present. Arterial pulsation detected on USS can also act as a discriminating feature, but caution is advised in the face of a critically ill patient who is hypotensive. From our personal experience, an entry point of approximately two centimetres above the clavicle is satisfactory. A higher approach may be less comfortable as the external portion of the catheter may protrude into the neck and restrict movement. Moreover, a lower approach facilitates conversion of a VC to a TCVC if desired at a later stage.

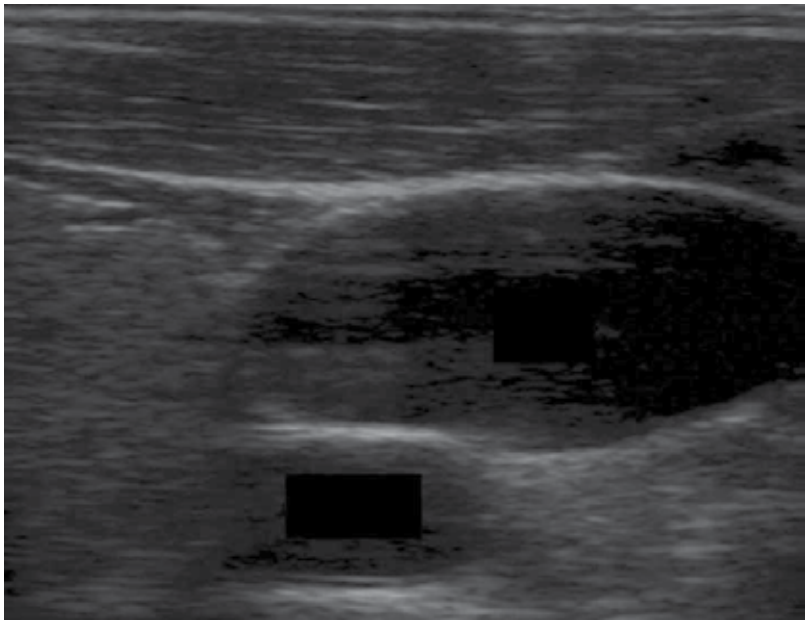

Figure 2. Transverse ultrasound image of internal jugular vein with the common carotid artery in a posterio-medial position.

Occasionally, alternative sites are sometimes sought, as patients may not be able to lie supine for a prolonged period due to dyspnoea or cervical osteoarthritis. In addition, it is common for dialysis patients to have multiple catheters inserted during their lifetime and this can result in thrombosis and stenosis making future insertions difficult: attenuated internal jugular veins with multiple collaterals is suggestive of a central occlusion [11]. Therefore, subclavian and femoral veins can also be considered. However, the latter is thought to be undesirable given the increased risk of infection despite evidence for the contrary [38]. Subclavian insertions are not recommended given their propensity to subsequent stenosis or thrombosis by inducing endothelial damage and may compromise future AVF formation. Thus, the remaining discussion will focus on the internal jugular approach as it is the most widely used.

Written informed consent is advisable. The entire procedure should be explained in detail and complications outlined. In the emergency setting, where the patient lacks capacity to give consent, this may not be required and the procedure can be performed under the auspices of Common Law in the UK. Common complications include arterial puncture, bleeding and risk of infection. In our experience, pneumothorax is overstated and is rarely seen in internal jugular insertions. However, in a subclavian approach, there is a higher risk of pneumothorax and pleural injury given proximity of the lung apex.

Those with active septicaemia should not have a TCVC inserted where possible, but should be postponed until negative blood cultures are obtained. Patients should also have a satisfactory coagulation system and similar precautions should be taken as outlined in the previous section.

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2.2.2. Details of insertion procedure

For *any* insertion, an aseptic technique is essential and can be achieved readily in a pre-designated area for catheter placement (Figure 3). Ideally, an assistant should be present who can provide material to the operator and reassure the patient. The operator should don sterile mask, gown, gloves and a lead-protective apron if fluoroscopy is being utilised. Moreover, a sterile drape should be placed over the patient with a window exposed over the proposed site of catheter entry (Figure 4). Electrocardiogram monitoring can be useful to detect any ventricular arrhythmias encountered during the procedure.

The patient should be placed in the supine position with the neck turned opposite the site of entry. If possible, the chin should also be slightly elevated. We have found that elderly patients find this particularly uncomfortable. Pillows placed under the head and tilting the head-end of the bed to a Trendelenberg position may resolve such difficulties (vertical head tilt of -15 or -30°). The latter manoeuvre assists in venous filling and thus aids in identification and venepuncture. Otherwise, an alternative entry site should be sought.

Figure 3. The operator needs to ensure asepsis at all times throughout the procedure.

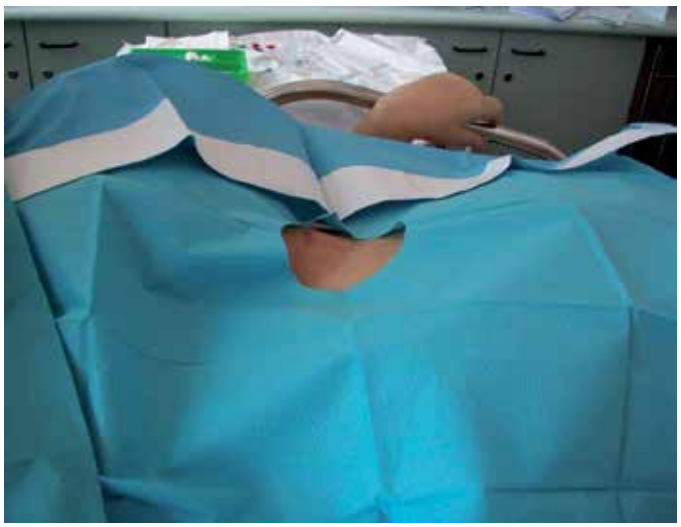

Figure 4. Fenestrated drapes are readily available that can be placed over the procedure site. Care must be taken to minimise patient discomfort, as this will inevitably cover their face.

Once landmarks have been identified and the exposed areas have been cleaned (iodine or chlorhexidine 2%), adequate anaesthesia should be applied with 1% lidocaine through a 25-gauge needle or equivalent. This should be applied generously - initially with a skin wheal or bleb at the entry point and then subcutaneously with USS guidance down to the superior wall of the vein (Figure 5). Visual guidance and intermittent negative suction will reduce the risk of inadvertent intravenous or intraarterial injection. However, if this does occur, the needle should be gently withdrawn until blood is no longer aspirated. From our experience, this is a satisfactory approach and sedation is rarely required. Maintaining visual contact and reassurance during the procedure can avoid the need for sedatives. However, if high levels of anxiety are anticipated, pre-medication with a short-acting benzodiazepine may suffice.

Following this step, a wider-bore 21-gauge needle is attached to a small syringe (five or ten millilitres). The needle should be wide enough to accept a straightened J-curve microwire through its lumen. Ideally, the USS image should incorporate a transverse view with the internal jugular vein centred. The operator should limit the amount of pressure applied on the skin as too much may obliterate a satisfactory image and result in transection of the vein. Aiming for a similar trajectory as during anaesthetic infiltration, the needle is inserted through the skin adjacent to the centre of the USS probe whilst applying negative suction. Entry into the vessel is indicated by free aspiration of blood (Figure 6).

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Figure 5. The operator should use real-time USS guidance for both anaesthetic infiltration and cannulation of the internal jugular vein. The needle in both cases should be placed adjacent to the probe.

Figure 6. Entry into the internal jugular vein will be indicated by free aspiration of blood. If blood fills the syringe in a pulsatile fashion then arterial puncture should be suspected.

Some authorities advocate visualisation of the needle tip in the lumen of the vessel. However this is not always possible, and in our collective opinion aspiration of blood is a more reassuring sign of vessel entry. Carotid artery puncture will result in pulsatile filling of the syringe and the access attempt should be abandoned temporarily and gentle pressure applied over the puncture site for five to ten minutes. A resulting haematoma may compress the vein and reduce visibility.

When aspiration is achieved, the operator should carefully keep the needle in position whilst removing the syringe from the bevel. At this point, the microwire should be introduced through the bevel and passed through freely to enter the vessel (Figure 7). Occasionally, the guidewire may enter into the right ventricle and irritation may result in short bursts of ventricular tachycardia. Simply withdrawing the wire slowly into the right atrium can resolve this. If resistance is encountered then gently withdrawing around one centimetre and twisting the guidewire before reintroducing may help, as the wire may be deflected superiorly within the vein. Otherwise, the syringe should be reapplied and checked to see if blood is freely aspirating. If not, the needle should be completely withdrawn and puncture reattempted. The wire should not be pulled through the needle, as there is a theoretical risk that the sharp bevelled needle can sheer off the tip of the microwire – particularly if a kink had developed [39]. Kinked wires may restrict passage of the catheter and should therefore be replaced with a fresh wire. If despite clearly entering the vessel and obtaining good aspiration flow, guidewire passage fails, then possibilities include stenosis or a collapsing vessel. Such circumstances may be remedied by asking the patient to perform a Valsalva manoeuvre to aid venous filling or using a thinner guidewire coupled with real-time fluoroscopic screening [40].

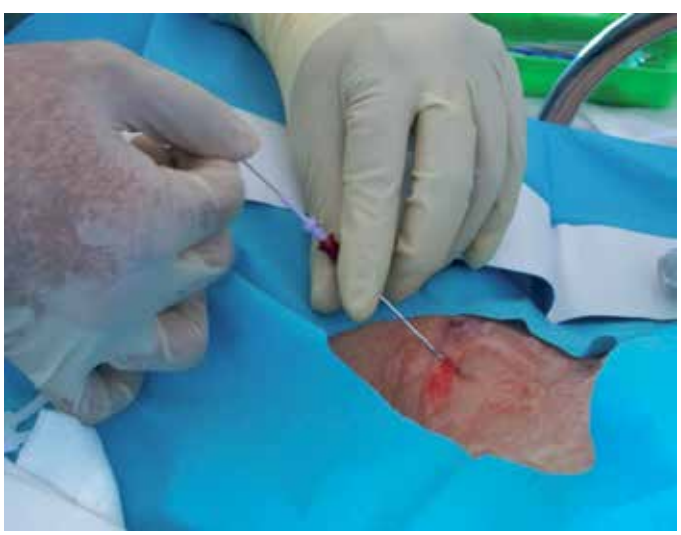

Figure 7. The microwire usually has to be straightened at the J-tip to permit smooth entry through the wide-bore needle.

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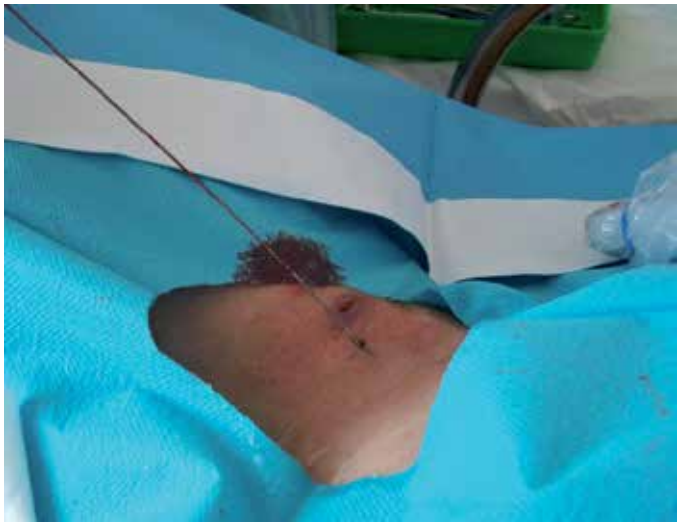

Figure 8. Once in place the needle should be removed over the wire whilst ensuring the wire is stabilised.

If a guidewire has been successfully introduced, the wide-bore needle should be removed over the wire (Figure 8). At this point, fluoroscopy should be used to image the path of the wire, which should lie in the right atrium. A 0.5-1 centimetre horizontal incision is made over the superior end of the wire's exit point and widened with mosquito forceps (Figure 9). Care should be taken that there are no skin tags and the wire freely moves across the incision. A smaller incision can lead to considerable resistance when introducing dilators or a catheter and may result in the guidewire kinking.

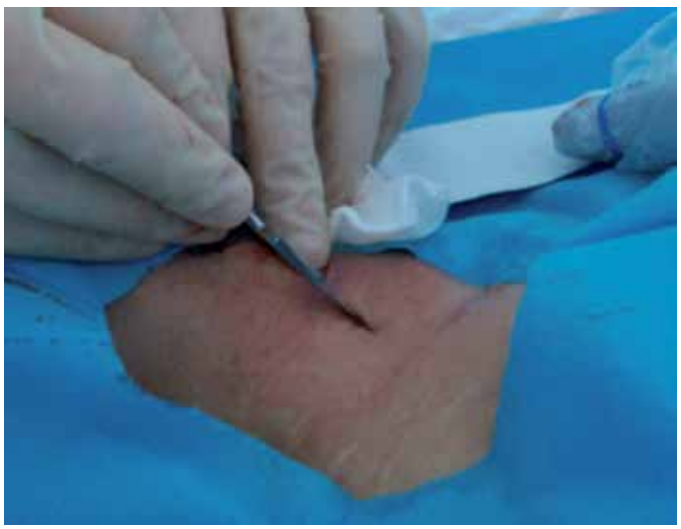

Figure 9. The scalpel blade should be inserted over the superior aspect of the guidewire.

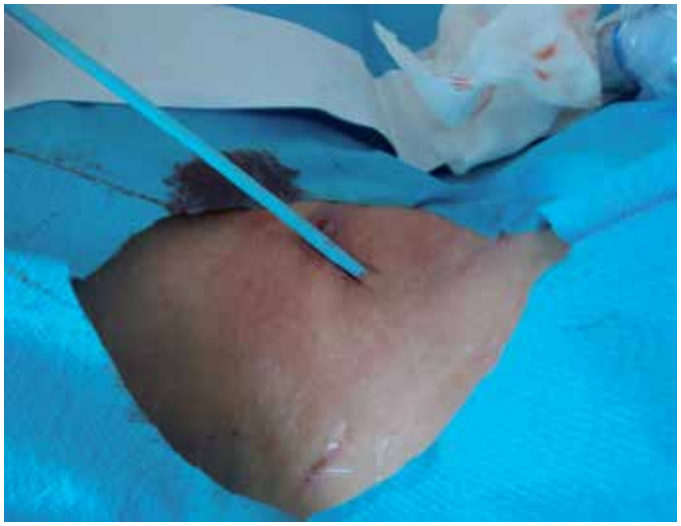

Figure 10. A stiff flexible dilator is placed over the wire to puncture the vein and form a tunnel that will permit smooth passage of the catheter. Knowing how far the dilator needs to be pushed in can be estimated from the distance of the internal jugular vein to the skin using ultrasound.

A stiff dilator is then inserted over the guidewire (Figure 10). There are two aspects to take note at this point: firstly, it is advisable to forewarn the conscious patient that dilator insertion will cause pressure discomfort; secondly, the dilator should be inserted in a firm but smooth motion from the distal (tip) end so as to avoid guidewire kink. Advancing the dilator several centimetres is only required: pushing further may theoretically result in vessel damage – particularly in a left internal jugular approach owing to its tortuosity. Following removal of the dilator heavy bleeding may occur, so pressure over the exit site must be applied.

The catheter should then be placed over the guidewire until its tip is seen protruding from one of the catheter hubs. The remaining length of catheter can then be inserted to its hilt with simultaneous withdrawal of the wire (Figure 11). Free aspiration should be attempted from each hub to ensure smooth flow in and out. If there is resistance, it may indicate that suction of the distal tip against the atrial wall. The catheter should be flushed with saline through each port and a heparin lock solution applied. This may take the form of 5000 iu of heparin diluted 1:5 or a preformed solution with anticoagulant and antimicrobial properties (e.g. Taurolock™). There is evidence that filling the hubs after dialysis with antibiotic solution prevents the formation of a biofilm inside the catheter lumen: biofilms can form within 24 hours after placement and create an opportune environment for bacterial colonisation [41]. The final stages of the procedure should include applying sutures to the entry site and to secure the line (Figure 12). The neck should be cleaned thoroughly and dried before applying adhesive dressing. Sutures should remain in-situ for the duration of catheter use, but be inspected regularly for evidence of infection or suture abscess.

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Figure 11. Once the catheter has been fully inserted to its hilt, flow should be immediately checked and be smooth with little effort required. Any resistance may complicate subsequent dialysis. Testing should be followed with liberal saline flushes.

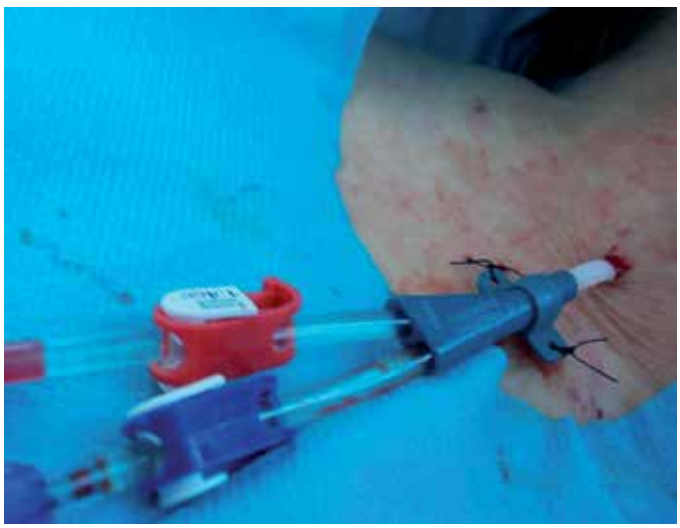

Figure 12. Two sutures should be applied at the butterfly wing as shown to anchor the catheter and avoid displacement.

2.2.3. Tunnelled catheter insertion

Most TCVCs are derived from polyurethane or silicone. This provides good elasticity and enough rigidity to permit high flow rates required during renal replacement therapy. Numerous designs are available but no one specific design shows significant superiority over another [42]. It is useful to have a non-sterile TCVC to assess the length required and location of the intended exit site prior to the actual procedure. Clearly, owing to the tortuous course of the left internal jugular vein, a longer catheter is usually required. Body habitus is also another factor to consider with smaller individuals probably requiring shorter catheter lengths. Additionally, predicting whether the tip will suck against the atrial wall after placement is important as this can influence flow rates.

Essentially, most of the above applies to insertion of TCVCs, though several additional steps during the procedure should be noted. Firstly, once the guidewire has been inserted into the internal jugular vein, the horizontal incision made superior to the wire should be followed by generous widening with a mosquito forceps - prising apart subcutaneous tissue bridges (Figure 13). This is thought to reduce the risk of intractable kinking at the turning point of the catheter.

Secondly, a subcutaneous tunnel has to be created for the entry point for this is usually on the chest wall, and this is best achieved by using a lumbar puncture needle to inject anaesthetic up to the entry point of the internal jugular vein. The catheter is then tunnelled through with gentle pressure using a pliable metal introducer (attached to the catheter tip) out through the entry point incision, adjacent to the guidewire. The tunneller is then disconnected from the catheter. Sometimes, it is preferable to perform a two-stage tunnelling process to form a smooth curved entry into the internal jugular vein, which may reduce chances of kink formation and thus sluggish flow. If a kink is encountered following the procedure, occasionally a gentle pull of the catheter from the proximal (hub) end may resolve this. Once tunnelled, the polyester (Dacron) cuff should lie subcutaneously within the formed tract. Over time, a fibrotic reaction between the cuff and the subcutaneous tissue occurs and thus provides effective stabilisation and a mechanical barrier to infection. If a cuff does not adhere sufficiently, the catheter may become displaced and "fall out". In such cases, no attempt should be made to reintroduce any exposed catheter back into the tract but it should be removed and replaced when convenient.

Finally, TCVC kits usually include several dilators of differing diameter. All should be used to create a satisfactory puncture within internal jugular vein to facilitate insertion. Of note, the catheter tip is inserted into the vein by means of a "pull-apart" introducer/dilator. This is inserted last in a similar fashion to a dilator device, but has a central lumen capable of accommodating the dialysis catheter through into the vein once its central stiff portion has been removed. Sutures (2-0 Prolene) should be applied to the entry point to the internal jugular and proximally at the butterfly wing. The latter sutures can be typically removed after ten days.

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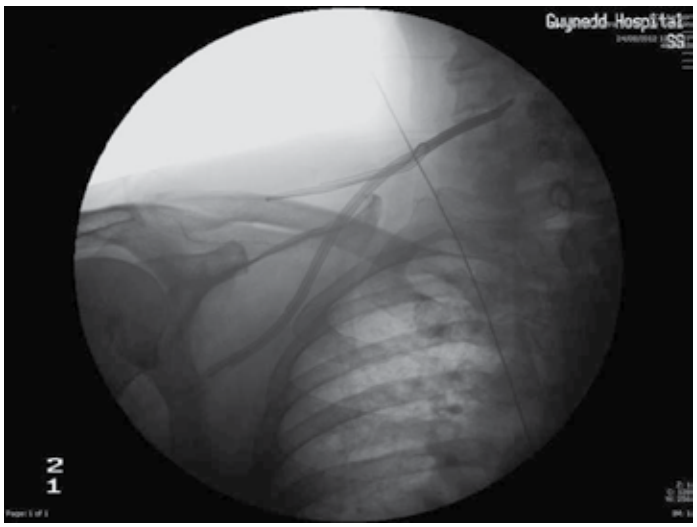

Figure 13. Successful insertion of guidewire into right internal jugular vein. Tunnelled catheter can be seen adjacent, ready for final placement.

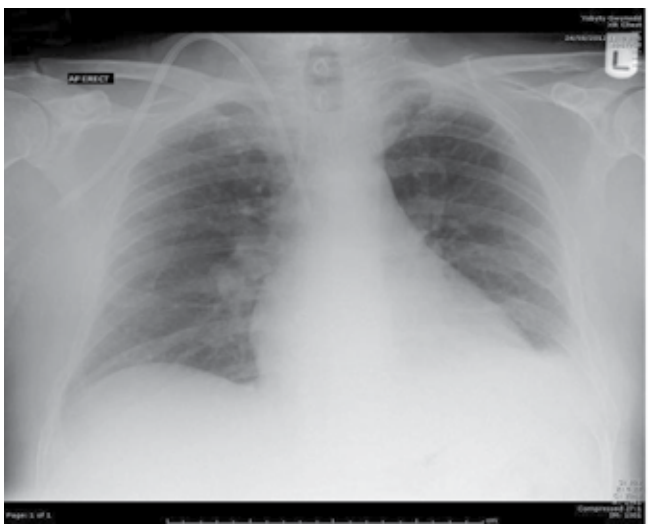

Figure 14. Post-procedure chest radiograph with the tip of the tunnelled catheter within the right atrium.

2.2.4. Post-procedure

A post-procedure chest radiograph is essential to assess the position of the catheter tip and check for any complications (e.g. pneumothorax or inadvertent insertion into azygous vein). Position of the catheter tip is a point of contention: most operators believe the ideal location is the junction of the superior vena cava and right atrium (Figure 14). If the tip is lower it

may induce ectopic beats and possibly occlude if it is opposed against the vessel / atrial wall. If the tip is not in satisfactory position, gentle catheter withdrawal and re-imaging may be attempted. Pneumothorax should be treated by conventional means.

2.2.5. Complications

Bleeding is common early complication that usually responds to firm compression over the exit site for up to 30 minutes. This can be followed by application of a pressure dressing and/or haemostatic wound dressing [43]. If these measures fail, then a purse-string suture can be performed. This should be left for a period of no more than 24 hours. However, in the rare event of persistent bleeding, thrombin can be injected into the tunnel or the catheter should be removed altogether [44]. Additionally, if there has been considerable bleeding during the procedure it is common practice to administer a single dose of vancomycin (1g IV) post-procedure to reduce the possibility of bacteraemia. Although this is widely practised, the evidence-base for this is currently lacking [45].

After each dialysis session, both hubs should be locked with an anticoagulant and/or antimicrobial solution. Various types are available and there is some evidence that citrate-based solution may offer distinct advantages to heparin [46]. If poor access flow occurs, then trial with an infusion of a thrombotic agent (e.g. tissue plasminogen activator 1mg.ml^{-1} or urokinase 5000 IU.ml^{-1}) may be helpful in removing thrombosis within the lumens. Recurrent blockages may respond to low dose warfarin to maintain patency (aiming for an INR of 1.4 – 1.9), but again the evidence for this is very limited at best [47]. Occasionally, poor flow may also result from catheter kink and repositioning the patient during dialysis can be tried. When all these measures fail, catheter removal and replacement is indicated.

Infection is a widely recognised problem with indwelling dialysis catheters – especially long-term tunnelled lines. The prosthetic nature of the catheter promotes formation of biofilms within the lumen and can result in exit site infections or bacteraemia [40]. *Staphyloccoci*, *corynebacterium* and *enterobacter* are common culprits and dialysis units should have protocols in place to treat such infections. In our unit, exit site infection is swabbed for microscopy, culture and sensitivity. If fever is present, peripheral and catheter blood cultures must be taken. Methicillin-resistant *staphylococcus aureus* (MRSA) remains a serious problem in UK dialysis unit [48]. Pending results, appropriate empirical *staphylococcal* antibiotic in the form of vancomycin should be administered as this will cover MRSA and methicillin-sensitive (MSSA) strains. If MRSA is confirmed then intravenous vancomycin should be continued for a minimum of two weeks for exit site infections. Gram-negative cover can also be considered, but this depends upon local microbiological epidemiology. Given that vancomycin is renally excreted, dosing schedules should be based on trough levels every four to seven days, aiming for a therapeutic concentration between 10 to 15 mg.l^{-1}. For MSSA, an oral course of flucloxacillin should suffice for a local exit site infection.

If infection is more severe (e.g. the presence bacteraemia, systemic features of illness or tunnel track infection), lengthy intravenous treatment is recommended. Patients should also be thoroughly examined and appropriately investigated for evidence of bacterial seeding e.g. endocarditis and septic arthritis. Management of other organisms should be discussed with

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microbiology services. If despite these measures there is a lack of response and the catheter cannot be salvaged, the removal is the most effective form of treatment [49]. Nonetheless, this often is a last resort option, especially in patients whom achieving any form of vascular access is historically very difficult. There is no benefit in attempting to salvage temporary devices and these should be removed and replaced if required.

Following insertion of all catheter devices, patient education is of paramount importance to ensure longevity and to reduce infection. Keeping the catheter dry is important and ensuring aseptic technique whenever handled – particularly in patients who perform home dialysis. There is limited evidence that *staphylococcal* screening and decolonisation may reduce the incidence of catheter-associated infection, but large trials are lacking to assess the cost-effectiveness of this approach [50]. In general, in-house quality assurance programs should be implemented to ensure best clinical practice with lowest infection rates possible and will require a multidisciplinary approach.

2.3. The role of the vascular access nurse

In 2004, the Department of Health in England and Wales launched The National Service Framework for Renal Services. In this document one of recommendations as a marker of good practice is that all patients with established renal failure receive '*timely preparation for renal replacement therapy*' as well as '*timely and appropriate surgery*' for permanent vascular access which is '*monitored and maintained to achieve it maximum longevity'* [51]. Later, when reviewing the provision of vascular access services and the volume of the workload, a joint report with the Renal Association UK recommended that units providing vascular access for patients appoint a dedicated vascular access co-ordinator to ensure smooth progression throughout the patient pathway [52]. Today, an extensive network of vascular access nurse specialists exist working within UK renal units to improve service delivery with an particular emphasis on minimizing the use of dialysis catheters.

2.3.1. Identification of patients

One of the broad roles of the vascular access nurse is to work closely with other members of the renal team to identify the most suitable type of renal replacement therapy for patients, whilst taking into account the patient's wishes and preferences. Current best practice is that 65% of patients starting HD do so with a fully functioning AVF and that planning should take place when the patient has reached CKD Stage 4 or an eGFR of 30 ml.min.1.73m$^{2\text{-}1}$ or less [53,54]. Through liaising closely with the patient, family and renal team during the early stages of planning allows one to identify potential problems that may contribute to creating access and permit timely, appropriate referral to the surgical and radiological teams. It is suggested that vascular access is created six months prior to the anticipated start of HD or even earlier [55-57]. This period accounts for planning, creation and maturation of the access and any further procedures that may be necessary to ensure functionality [58]. Overall, this strategy enables the delivery of an individualized plan of care.

2.3.2. Information provision

The vascular access nurse can be a valuable source of information and advice. The importance of preserving veins for dialysis access cannot be emphasized enough (Figure 15). As discussed above, patients with CKD undergo frequent blood sampling that damages veins rendering them unsuitable for access creation, and a plan to preserve vessels should be made early on [59,60]. Moreover, following fistula creation, patients and caregivers should be constantly reminded of vascular preservation for future access and inappropriate use of a fistula (Figure 16).

Figure 15. Custom armbands can help warn patients and healthcare staff about vascular preservation for access creation and therefore avoiding venepuncture.

Figure 16. Sadly, this is still a common site where even after fistula creation, vascular access for dialysis is abused. Education of staff is of paramount importance to prevent this potentially catastrophic occurrence.

Patients with CKD often attend multiple hospital clinics and careful planning of appointments by the vascular access nurse to coincide with each other may reduce the number of visits to hospital. One-stop access clinics, whereby the patient is reviewed by the vascular nurse and surgeon, receives Doppler scans of both arms as well an pre-operative assessment, have been shown to greatly reduce the number of hospital appointments [61]. Following AVF creation, studies indicate that there is developmental change from two to four weeks, and that skilled physical assessment can accurately predict its maturity for cannulation [62]. Early follow-up and assessment of the patient by the access nurse is critical to ensure that prompt action and re-referral to the surgeon can be taken should the fistula fail for the initiation of dialysis.

2.3.3. Assessment pre- and post-access creation

By becoming familiar with the patient in the early stages of assessment enables the access nurse to manage the referral process efficiently and to prioritise the surgical waiting list according to the rate of decline in eGFR and patient symptoms. This helps expedite surgery, investigations and revisions according to clinical need, as well as providing a 'familiar face' and a point of contact for the patient.

2.3.4. Access monitoring

Another essential but labour-intensive role of the access nurse is monitoring, surveillance and co-ordination access salvaging procedures within the entire HD population. The use of advanced surveillance techniques are recommended by the Renal Association in addition to systematic observation of access [53]. Although it is accepted that monitoring and surveillance of vascular access is an integral part of HD patient care, evidence in the form of randomized controlled studies is lacking as to the most effective method of access surveillance [59]. Nonetheless, it is accepted that measuring access flow is an accurate predictor of AVF or graft dysfunction and all surveillance methods are directly or indirectly linked to this [53,57]. Many units now use flow-based methods of measuring access flow (QA) and recirculation (such as the Transonic™ ultrasound flow dilution system), that has the advantage of being performed during HD and thus limits patient inconvenience. Access flows of < 400 $ml.min^{-1}$ or < 600 $ml.min^{-1}$ in grafts can indicate stenosis and therefore a high risk of thrombosis. This also can limit blood pump flows (QB) and lead to recirculation – both impacting upon kT/v.

It is important note that access flow readings only represent one aspect of monitoring and that a compete clinical picture is established in conjunction with other information, including: physical examination of the fistula, the presence of cannulation problems, dialysis clearance and the patient's general physical condition. Further investigation is often necessary - initially in the form of USS and then contrast-based fistulograms to establish the presence of a lesion affecting the flow (e.g. stenosis or aberrant tributaries). Indeed, the access nurse has a pivotal role in coordinating these investigations and arranging interventional radiology or surgery if necessary [61].

The success of monitoring and surveillance depends on a team approach with good communication between all members of the renal team and the dialysis nurses who manipulate access on a daily basis [59]. Depending on patient numbers and workload of individual units, the access nurse can be directly responsible or can coordinate with designated dialysis "link" nurses to conduct surveillance. Finally, the patient should be encouraged to familiarize themselves with their vascular access and alert staff to any unexpected changes.

2.3.5. Education

Regular education of staff and patients on access-related issues is essential for preservation, as poor needling techniques can cause damage to fistulas, stenosis and subsequent risk of failure. Written protocols for cannulation of fistulas, handling central venous catheters and physical examination of the fistula prior to cannulation should exist and be managed by the access nurse with clinical competency assessments performed periodically to ensure standards are maintained. The access nurse can also assist with cannulation care planning, difficult cannulations and advising on the most suitable technique for individual patients. For example, it is important to ensure that the fistula is not 'area needled', which can result weakening of the vessel wall and subsequent aneurysm formation [63]. Although the buttonhole technique is currently the favoured cannulation technique preferred by staff and patients, the risk of infection is higher than the more traditional site rotation method [64,65]. Patients should be therefore risk profiled before using buttonholes, and if selected, educated to minimize the risk of sepsis. Notwithstanding, the buttonhole technique does contribute to preservation of the fistula for patients with a limited needling area and is aesthetically more pleasing when body image is an important consideration (Figures 17 and 18). It has also proven to be an integral part of care for our patients on daily home dialysis.

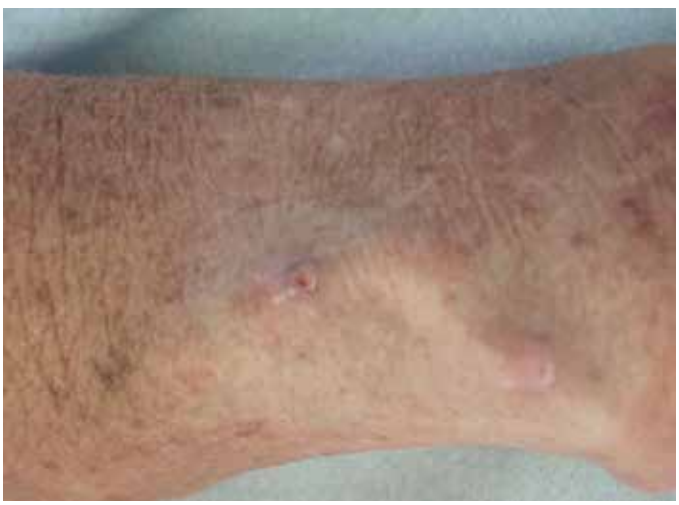

Figure 17. Buttonholes in a 78 year old female patient.

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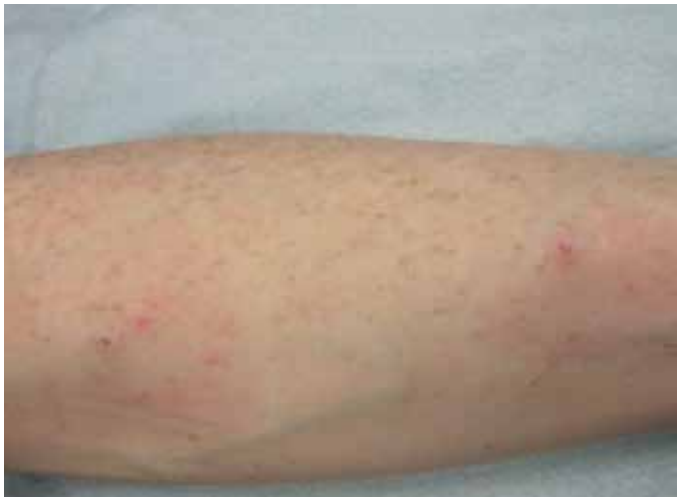

Figure 18. Buttonhole sites after 6 months in 21 year old, needle phobic male patient. Both patients had major issues regarding body image prior to fistula creation.

2.3.6. Vascular catheter care

While it is accepted that vascular catheters should not be actively encouraged as first-line HD access, often the vascular access nurse plays a pivotal role in catheter care. Many of the above principles apply to central venous catheters usage. The main issues concerning the access nurse involve minimizing infections and promptly treating poorly functioning catheters - a relatively common event for HD patients [53]. Regular assessment of catheters can detect failing flow and ensure that prompt action is taken to avoid further dysfunction or complete failure. Similar to AVFs and grafts, protocols should be in place for catheter maintenance and dysfunction as well as for rapid treatment of sepsis - suspected or proven. Increasingly, there has also been development of a more "hands-on" approach encompassing catheter insertion and removal. Within the UK, this has been extended in some units to involve vascular access nurses independently inserting catheters after undergoing a comprehensive training programme, and has the distinct advantage of reducing waiting times and burden on clinical staff [7,66].

2.3.7. Audit and research

Monitoring of access outcomes and documentation allows for future planning and clinical audit. This and research are essential to evaluate outcomes and provide up-to-date, evidence-based care. In an area of dialysis care that is continually evolving, the access nurse needs to be flexible with the role according to the ever-changing needs of the patient and the requirements of the service.

The target of 85% prevalent HD patients dialysing with an autogenous AVF has been a challenge to achieve by many renal units in the UK as indicated by data collected by the national Renal Registry [53,67]. There is now increasing evidence that appointing a vascular access nurse reduces catheter use in favour of autogenous AVFs [68]. In our unit, AVF prevalence has risen from 60% to 82% since appointment in 2009, and statistical analysis of our outcomes indicate that a regular programme of monitoring and surveillance has helped to achieve this and improving dialysis adequacy above the Renal Association standard. This is not only due to the increase in fistula prevalence, but an improvement in the quality and survival of existing fistulae through emphasis on prompt referral for investigation and intervention for poorly functioning ones.

3. Concluding remarks

Vascular access in haemodialysis is crucial step to maintain quality of life once native renal function ceases. The acute setting differs markedly from chronic disease where the patient will encounter numerous specialties and procedures on multiple occasions. The procedures involved are complex and require detailed planning to ensure good outcomes and reduce short- and long-term complications. A multidisciplinary approach is commonplace and roles within the context of vascular access are constantly evolving to optimise care. Implementation of a vascular access nurse ensures that the patient's journey into haemodialysis is a timely one and follow-up care is likewise.

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Chapter 28

Vascular Access for Hemodialysis - How to Maintain in Clinical Practice

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Additional information is available at the end of the chapter

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1. Introduction

Establishing and maintaining hemodialysis access is a cornerstone of long term renal replacement therapy. As hemodialysis techniques have improved sufficiently to allow the survival of patients as long as dialysis access can be maintained so it is justified to say that vascular access is an access to life [1].

2. Historical background

Since 1944 when WJ Kolff designed the first practical dialysis machine, the search for vascular access for hemodialysis began and still continued until nowadays. At first, it was necessary to do repeated cutdowns on an artery and vein for each dialysis, following which the vessels were ligated, so dialysis was therefore limited to the treatment of acute renal failure [2].

Chronic access to the circulation became a reality in 1960 when Scribner, Dillard, and Quinton introduced the Teflon-Silastic arteriovenous (AV) shunt. The Scribner shunt rarely could be used for more than 3 months because of: interference of the external appliance with normal activity, infection, thrombosis, and bleeding [3]. These disadvantages were overcome by introduction of the subcutaneous AV fistula by Brescia, Cimino, Appel and Hurwich in 1966 which is a fistula between the artery above the wrist and the largest available vein in close proximity [4]. Their innovative approach remains the initial procedure of choice in patients who are candidates for long term hemodialysis.

Subsequent development of the bridge fistula, initially with reversed saphenous vein [5] and later with synthetic materials, further expanded the availability of hemodialysis to a larger

population. The introduction of polytetrafluoroethylene (PTFE) for bridge fistulae in 1976 [6] was another milestone in dialysis access surgery.

3. Haemodynamics of arteriovenous fistula (AVF)

The physiologic effects of AV fistulas can be separated into local haemodynamic effects and systemic cardiovascular effects [7].

- Local haemodynamic effects:

The effect of creating a fistula on the proximal artery is similar to making a hole in a dike. Flow in the proximal artery increases markedly in response to the sudden decrease in outflow pressure afforded by the fistula, so with forearm AV fistulas, brachial artery flow may increase 5 to 10 folds [8].

In the distal artery, the situation is not so simple. With small fistula, distal artery flow is maintained antegrade, away from the heart. With increasing fistula size, however, distal artery flow decreases until it reaches a standstill when the anastomotic length is equal to the proximal artery diameter. At this point, circus motion develops with antegrade flow during systole and retrograde flow during diastole through the fistula into the venous limbs. When the anastomotic length of the fistula communication increases, above the diameter of the proximal artery, reversed flow in the distal artery increases until it exceeds the antegrade flow [9].

- Systemic haemodynamic effects:

The immediate effect of opening a fistula is to divert blood flow away from the rest of the peripheral circulation and into a special low-resistance path directly connecting the left side to the right side of the heart. Cardiac output increases acutely via increased rate and stroke volume. Arterial pressure falls, and heart rate increases; these changes are minimal with low-flow fistulas and increase with increasing fistula flow. Cardiac work also increases [10].

4. Preoperative evaluation

4.1. Patient preparation for permanent hemodialysis access (modified from NKF, 2006 [11])

Good planning allows initiation of dialysis at the proper time with a permanent functioning access in place ready at the start of dialysis.

- Patients with a glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2 and chronic kidney disease (CKD) stage 4 should be educated about all modalities of kidney replacement therapy (KRT) options, including transplantation, so that timely referral can be made for the appropriate modality and placement of a permanent dialysis access, if necessary.
- In patients with CKD stage 4 or 5, the following policy of vein preservation should be adopted:

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– Strict avoidance of cannulation of veins of both forearms proximal to the wrist.

– When unavoidable, venipuncture should be performed in the dominant arm to preserve the non-dominant arm for AVF; or alternatively, rotation of puncture sites and sides could be used.

– Phlebocatheters should not be threaded to central veins through cephalic or basilic veins at the elbow.

– Instead, central vein catheters should be inserted into jugular veins (preferably on the right side).

– Insertion via subclavian veins is to be avoided because of very frequent subsequent stenosis.

– In cases where vein diameter/flow is the critical factor influencing the use of central veins (as when concentrated potentially caustic/toxic solutions are to be infused), one should consider using femoral veins [12].

• Patients should have a functional permanent access at the initiation of dialysis therapy:

– A fistula should be placed at least 6 months before the anticipated start of HD treatments. This timing allows for access evaluation and gives additional time for revision to ensure a working fistula is available at initiation of dialysis therapy.

– A graft should, in most cases, be placed at least 3 to 6 weeks before the anticipated start of HD therapy. However, some newer graft materials may be cannulated immediately after placement.

• Evaluations that should be performed before placement of a permanent HD access include:

a. History and physical examination:

– Arterial inflow evaluation by: pulse examination of the accessible sites in upper extremity and lower extremity when needed [13] and Allen's test for assessment of palmar arch efficacy [14].

– Venous outflow evaluation by: placing the arm in a dependent position or by placing a tourniquet on the upper arm while the patient clenches and releases the ipsilateral hand several times.

b. Duplex ultrasound of the upper-extremity arteries and veins:

– To determine the diameter of the artery as a preoperative radial artery diameter of less than 1.6 mm usually will lead to failure of the radial-cephalic wrist autogenous AV access [7].

– To assess superficial veins and deep veins for stenosis or occlusion and diameter which should be at least 2.5 mm [7].

– Conventional arteriography or magnetic resonance angiography: Used in selected cases [7].

– Central vein evaluation in the appropriate patient known to have a previous catheter or pacemaker.

(Modified from NKF, 2006 [11])

5. Different modalities of AVF

The 2006 updated version of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) urges for an increase in autogenous arteriovenous fistula (AVF) use in hemodialysis patients to a minimum of 65%, which is almost the same as the current goal of 66% raised by the Fistula First Breakthrough Initiative (FFBI).

5.1. Autogenous AVF

5.1.1. Forearm options

- Cephalic vein

a. Radial-cephalic (anatomical snuffbox) AVF:

Construction of a radial-cephalic AVF at the anatomical snuffbox mandates proper patient selection. The advantages are: proximity of the vessels and preservation of additional length of vein for cannulation. However, the disadvantages are the smaller vessel size which leads to greater surgical challenges, lower flow rate and less long term patencies than more proximal constructions [15].

b. Radial-cephalic AVF (wrist, direct or transposed, straight):

The advantages are larger vessel size, simplicity of anastomosis and lower risk of ischemic complications. The fistula can be done via various construction configurations, the most common is side-to-side and end vein to side artery (figure 1). The end-to-end was assumed to avoid ischemic consequences, however, it has the lowest flow and scarifying the radial artery can later compromise hand perfusion especially in the case of an associated progressive distal arterial occlusive disease. The advantage of an end vein to side artery configuration is minimizing venous hypertension risk. Moreover, flow and pressure in the preferred antegrade direction through the vein is increased by ligation of the distal vein and nearby tributaries. If the cephalic vein is too deep for cannulation, the vein should be transposed to a superficial location [16]. It remains the gold standard AVF.

Figure 1. End to side radial-cephalic AVF

c. Proximal radial or brachial-cephalic AVF (transposed, loop):

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When the distal radial artery is inadequate, the cephalic vein can be looped back to the antecubital region and anastomosed to the brachial or a branch artery preferably the proximal radial artery (PRA), as it lowers the risk of steal and ischemia. Transposed loop AVFs in the forearm are excellent alternatives when the distal radial or ulnar arteries are not suitable [17].

- Basilic vein

a. Radial (or ulnar)-basilic AVF (transposed, straight):

If a radial-cephalic AVF in the forearm is not feasible, and the basilic vein is suitable, the vein can be anastomosed to either the ulnar or radial artery. It is recommended to transpose the vein to the volar aspect of the forearm because the anatomic location of the basilic vein makes it vulnerable to cannulation difficulties and complications, especially infiltrations from the patient resting the forearm on the needles [18].

b. Brachial (or proximal radial)-basilic AVF (transposed, loop):

This transposed loop configuration is the same as that described for the cephalic vein above, except that the forearm basilic vein is used when the cephalic vein is unavailable [19].

- Antecubital vein

a. Gracz perforator, median cubital veins:

The use of the antecubital veins in the creation of upper arm and reverse flow AVFs is ideal. The advantages are (i) the provision of multiple outflows, i.e., into the upper arm cephalic and basilic veins in antegrade fashion, as well as retrograde into the forearm veins by limited disruption of venous valves (when desired); (ii) preservation of continuity of the major AVF venous conduit for future use or revision of the AVF; and (iii) provision of an ischemic-resistant (flow-restricting) construction due to limited size of the anastomosis and lumen of the vein. In the operation described by Gracz et al. [20], the perforating vein connecting between the superficial system and the deep brachial system is transected and used for the anastomosis to create an upper arm AVF. The median cubital or other available nearby vein may be used, depending on the anatomy. Very high patency rates (80% at 3 years) have been reported for both constructions [21].

Figure 2. Brachial-cephalic AVF

5.1.2. Arm options

- **Cephalic vein**

a. Brachial (or proximal radial)-cephalic AVF (direct or transposed):

The cephalic vein is ideally anastomosed to the artery just distal to the antecubital crease by using: an antecubital vein (as a first option), the cephalic vein itself (figure 2) or one of its tributaries all of them should be freed up distally into the forearm sufficiently to allow for a distal anastomosis into the proximal radial artery which is the inflow artery of choice or to the brachial artery (when used as inflow, the anastomosis should be limited to 4-5 mm to avoid ischemia or ischemic monomelic neuropathy). If the cephalic vein is too deep for safe cannulation, the vein should be transposed. During transpositions, it is critical to place the vein superficially and away from any incision or scars, thus allowing identification of the depth of the vein for easy cannulation. However, simple elevation and liposuction have been recently utilized when the vein is deep [22].

- **Brachial vein**

Brachial (or proximal radial)-basilic transposition AVF (1 or 2 stages):

The basilic vein is routinely transposed because there is only a short segment above the antecubital crease superficial enough for easy cannulation before the vein runs deep to the fascia. Even in very thin patients, where the vein can be seen and palpated, if the vein is not transposed, there is a danger of injuring the brachial artery during cannulation. The vein should be harvested from the axilla till below the antecubital crease for a short distance into the forearm(figure 3), in order to gain additional vein length. This additional vein length gives the advantages of: (i) having the tunnel in a lateral position without tension on the anastomosis which is very important especially in obese patients, (ii) allowing for anastomosing the vein distally to the proximal radial artery if it is suitable, (iii) important for easy cannulation as well

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as any further revisions. Some surgeons use a single incision, while others use multiple incisions. Care is needed to (i) identify and protect the median brachial cutaneous nerve, which courses over the vein; (ii) to avoid torsion of the vein by marking it with dye before dissecting it from its bed; (iii) avoid tension on the vein or kinking in its tunnel; and (iv) limit the size of the anastomosis to reduce the risk of steal-induced ischemia if the brachial artery is used as inflow. The surgery can be performed in 1 or 2 stages. In the 2-stage approach, the basilic vein is simply anastomosed to the distal brachial artery, preferably in the antecubital region just distal to the crease. The distal anastomosis is necessary to ensure adequate length of vein for the second stage. After 4-8 weeks, a duplex ultrasound or fistulogram is performed to ensure that there are no anatomic problems. The second stage is then performed by either; transecting the vein close to the anastomosis, bringing the vein through a lateral tunnel and anastomosing the transposed vein to the vein cuff or the artery at a nearby location (preferably to the proximal redial artery), depending on the length of the available vein [23] or just by simply dividing the deep fascia and subcutaneous tissue with positioning of the vein in a more superficial plane [24]. The advantage of the 2-stage procedure is that the vein becomes arterialized, more durable and can be dissected and manipulated with very little risk of injury. Also, it affords protection against the development of stenosis by waiting for arterialization before transposition, especially with respect to the fairly common "swing-point" stenosis, where the vein turns down toward the axilla [23].

There are recent reports of endoscopic basilica vein transposition [25].

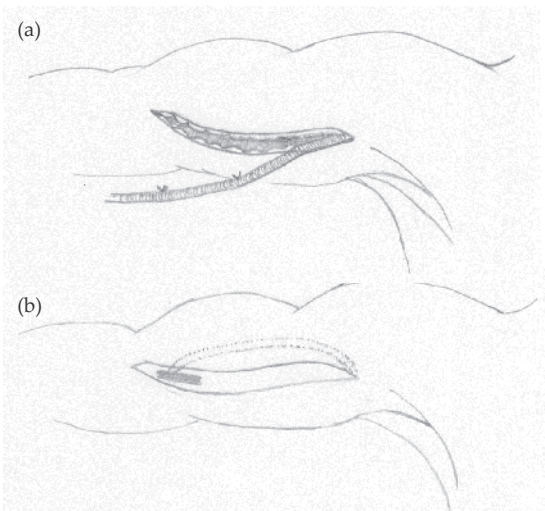

Figure 3. (a) Basilic vein harvest. (b) Transposed brachial-basilic AVF.

- Brachial vein

a. Brachial-brachial transposition or elevation AVF (1 or 2 stages):

This procedure is rather recent and usually done in 2 stages. The 2-stage approach is essential, given the small and fragile characteristics of the brachial vein(s); delaying the second stage until 4-8 weeks or more provides additional maturation time to allow this small vein to be manipulated without injury. Elevation rather than transposition may be preferred because of the limited length of vein available for cannulation if transposed. The obese patient with a big arm is probably not a candidate for this procedure, as most of the elevated vein will be used to twice traverse the considerable distance between the fascia and skin [26, 27]

5.1.3. Lower extremity options

AVFs in the lower extremity are generally reserved for patients whom all upper extremity sites have been exhausted. Reasons are: higher rates of infection and ischemia, as well as the need to preserve the saphenous veins for coronary artery bypass and other bypass procedures [19].

- Saphenous vein

a. Femoral-saphenous transposed loop AVF and superficial femoral (or popliteal)-saphenous transposed straight AVF:

The long saphenous vein can be used to either construct a thigh AVF (loop or straight configuration). In the thigh loop configuration, an incision is made below the inguinal crease. The vein is dissected through a single or multiple incisions to the level of the knee and looped back through a subcutaneous tunnel and anastomosed to the common or superficial femoral artery. In the straight configuration, the vein is anastomosed distally to the superficial femoral or popliteal artery [28].

b. Translocation of saphenous vein to upper extremity:

In the 1970s, saphenous vein was usually translocated to the upper extremity as a forearm loop. The indications were patient preference, concern about a higher infection rate in the groin region and greater risk of vascular complications associated with lower limb access. Intimal hyperplasia and stenosis at the venous anastomosis was not known at the time a problem which is avoided by performing the procedure in the thigh [29].

c. Posterior (or anterior) tibial-saphenous direct AVF:

An AVF constructed at the ankle is an analogous to a wrist AVF, it is recommended to evaluate the patient with duplex ultrasound and with arteriogram and venogram in selected cases. The posterior tibial is preferred to the anterior tibial artery for inflow because this location provides more protection for the AVF and it is technically easier [19].

- Femoral vein

a. Femoral-femoral transposed loop AVF and superficial femoral (or popliteal)-femoral transposed straight AVF:

AVF options and configurations utilizing the (superficial) femoral vein are the same as for the saphenous vein, whereby the superficial femoral vein is dissected from groin to knee and either brought through a subcutaneous tunnel in straight fashion and anastomosed to the distal

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superficial femoral artery, or brought through as a loop back to the groin incision and anastomosed to the common or superficial femoral artery. Initially reported results were not always excellent and high access flow was an important cause of complications [30].

b. Translocation of femoral vein to upper extremity:

As with the saphenous vein, the femoral vein can be translocated to the upper extremity. The potential advantages are a less risk of infection and clinically significant ischemia, compared with lower extremity access. Translocating the femoral vein with its large-diameter and very low-resistance to the brachial artery is expected to have very high flow, so the diameter of the arterial anastomosis should not be more than 4-5 mm or it is better to use the PRA for inflow [31].

5.1.4. Reverse (retrograde)-flow AVF

With reverse-flow AVFs, venous valves must be destructed to permit retrograde flow with or without antegrade flow. The proximal vein may be ligated or not (antegrade flow maintained or not). The ideal patient for a reverse-flow AVF has exhausted forearm options but still has a suitable proximal segment of cephalic or basilic vein in the forearm, with or without a suitable upper arm vein for outflow. A side-to-side antecubital construction is usually made and 1 or 2 distal valves are carefully disrupted with the vein segment dissected and visualized as the probe is passed, to prevent tearing the vein. Valve disruption can be accomplished with a probe, coronary artery dilator or a valvulotome. The retrograde pressure and flow is expected to make progressive dilatation of venous tributaries. If these small veins do not mature adequately, endovascular balloon angioplasty may be used [32].

5.2. Arteriovenous graft (AVG) for hemodialysis

The ideal vascular graft for patients on HD should be easy to handle, closely mimicking the native vessels, nonthrombogenic, immunologically inert, resistant to infection and puncture trauma, able to retain tensile strength, and manufactured at a reasonable cost [33].

5.2.1. AVGs are either biological or synthetic

- Biological grafts

a. Autogenous greater saphenous vein should have been the first option in AV bridge graft construction but has generally given disappointing results with patency rates of 20% at 2 years [34, 35].

b. Denatured homologous vein allograft.

c. Cryopreserved saphenous vein

d. Bovine heterografts such as:

– Bovine carotid artery

– SynerGraft Vascular Graft Model 100 (SGVG 100), a decellularized non-chemically cross linked bovine ureter vascular graft which provides a safe alternative for patients with a history of multiple failed synthetic grafts.

– Bovine mesenteric vein: obtained by a patented process of gluteraldehyde cross linking and gamma radiation has physiological properties similar to those of the human saphenous vein, due to its high elastin to collagen ratio [36] and is reported to have better survival than PTFE [37].

e. Human umbilical vein.

f. Sheep collagen grafts [36, 38-41].

– The Omniflow prosthesis is formed from gluteraldehyde-tanned bovine collagen, which is grown around a polyester mesh. This biosynthetic device obtained by inserting polyester mesh-covered mandrils beneath the cutaneous truncimuscle of Australian adult sheep for a period of 12–14 weeks, is stabilized using gluteraldehyde and may be prepared in straight or J- or U- curved configurations; this collagen encapsulated graft is easy to handle, with reduced thrombogenicity, low rates of infection, a low incidence of aneurysm formation and satisfactory long-term results. The current Omniflow II vascular graft has a more resistant mesh but requires delicate manipulation, avoiding cross clamping the graft with metal instruments and traction during the passage through the tunnel [42].

g. Biohybrid and bioresorbable prostheses, graft pretreatment with endothelial cell culture, methods of affixing antibiotics, anticoagulants and growth factor to graft surfaces are under investigation to enhance the results of prosthetic vascular materials, as biologic materials facilitate cell repopulation and tissue remodeling [33].

• Synthetic grafts

The commonly used synthetic grafts include Dacron. The fibrillar structure of Dacron® was expected to encourage tissue ingrowth and provide greater durability for recurrent cannulation. However, this was not seen in practice and PTFE, a fluorocarbon polymer became the prosthetic graft of choice [43]. Stretch expanded PTFE (ePTFE) is preferable to standard PTFE. Available data supports PTFE over other biologic and synthetic materials (except bovine mesenteric vein) based on a lower risk of disintegration with infection, low thrombogenicity, low tissue reactivity, prolonged patency and improved surgical handling but this concept may change in the future with introduction of tissue engineered AVG or more recent biological grafts [44].

Other new graft materials include polyurethane grafts with their self-sealing properties and reported low complication rates. The polyetherurethaneurea (Vectra graft) is suitable for early needling [45, 46].

5.2.2. Upper extremity options

• Forearm

a. Straight AVG between the radial artery at the wrist and an antecubital vein should be avoided due to the risk of early thrombosis.

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Figure 4. Forearm loop AVG

b. The forearm loop between the brachial artery and one of the available veins in the antecubital fossa is far more better option(figure 4).

c. One of the venae comitantes of the brachial artery should be used as outflow for both types rather than the superficial veins as outflow for a straight or looped forearm AVG graft, because if the basilic or cephalic veins are still available they should be used instead to construct an autogenous AVF with the brachial artery [47].

d. Straight AVG in the upper arm between the brachial artery and the axillary vein (or the proximal brachial or basilic vein) is ideal and common (figure 5).

e. Modern biological grafts are more suited for the 'O' shaped AVG with a narrow loop in the distal third of the upper arm between the brachial artery and its vena comitans or the basilic vein, because of their elasticity and compliance. This type of AVG preserve more proximal locations for potential future straight AVGs.

f. The forearm loop between the brachial artery and one of the available veins in the antecubital fossa and the straight AVG in the upper arm between the brachial artery and the axillary vein (or the proximal brachial or basilic vein) are the most popular graft configurations [48].

5.2.3. Lower extremity options

AVGs in the lower limb have generally given less encouraging results than for the upper limb, because of increased rates of infection, ischaemia, and lower patency rates. However, groin access is a useful option when upper extremities are unavailable and peritoneal dialysis has failed [28].

When implanted in the thigh, the graft can be either a straight, looped or curved configuration (figure 6) between femoral artery and either stump of GSV or femoral vein. Anastomosing AV

Figure 5. Straight brachial-axillary AVG.

graft to the common femoral vessels in close proximity to the groin has the disadvantage of a higher infection risk due to dissection through the dense lymphatic tissues. This has led to implantation of the AV graft more distal to the mid-superficial femoral vessels. This approach preserves the proximal vessels for future graft revision [49].

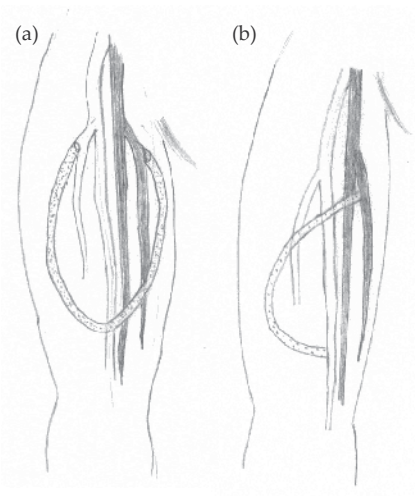

Figure 6. (a) Thigh loop AVG. (b) Straight thigh AVG.

5.3. Other less common prosthetic AV graft

- The axillary (or subclavian) artery can be used for a loop AVG, with the ipsilateral axillary or jugular vein as outflow, as well as for placing a straight AVG anastomosed to the contralateral axillary or jugular veins [50].

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- Femro-femoral suprainguinal crossover AVG between the femoral artery and the contralateral femoral vein [51].
- Long axillo-femoral grafts are prone to repeated thromboses, especially in hypotensive patients. Moreover, when large vessels, such as the axillary artery and femoral veins, are employed severe venous or arterial problems may follow AVG thrombosis [52].
- Central vein occlusion, ischaemic steal syndrome and cardiac failure may be indications for creating arterio-arterial vascular access grafts running superficially in the lower limb, or on the chest wall [53, 54].
- More heroic access configurations, such as anastomosis to the right atrial appendage through a median sternotomy and to the renal vein to bypass central venous obstruction should be avoided if possible in favour of a permanent central venous catheter [55, 56].

5.4. Guidelines for selection and placement of hemodialysis access according to (KDOQI) [11]

A structured approach to the type and location of long-term HD accesses should optimize access survival and minimize complications.

The access should be placed distally and in the upper extremities whenever possible. Options for fistula placement should be considered first, followed by prosthetic grafts. Catheters should be avoided for HD and used only when other options listed are not available.

- The order of preference for placement of fistulae in patients with kidney failure who choose HD as their initial mode of KRT should be (in descending order of preference):

a. Autogenous AVF.

1. A wrist (radiocephalic) primary fistula.

2. An elbow (brachiocephalic) primary fistula.

3. A transposed brachial basilic vein fistula

b. AVG of synthetic or biological material, such as:

– A forearm loop graft, preferable to a straight configuration.

– Upper-arm graft.

– Chest wall or "necklace" prosthetic graft or lower extremity fistula or graft; all upper-arm sites should be exhausted first.

– Patients should be considered for construction of a primary fistula after failure of every dialysis AV access.

- Enhanced maturation of fistulae can be accomplished by selective obliteration of major venous side branches in the absence of a downstream stenosis.
- Dialysis AVGs:

a. The choice of synthetic or biological material should be based on the surgeon's experience and preference, technical details, and cost.

b. There is no convincing evidence to support tapered versus uniform tubes, externally supported versus unsupported grafts, thick versus thin-walled configurations, or elastic versus nonelastic material.

c. While the majority of past experience with prosthetic grafts has been with the use of PTFE, other prosthetics (eg, polyurethane [PU]) and biological conduits (bovine) have been used recently with similar outcomes.

- Rule of 6s:

a. A fistula in general must be a minimum of 6 mm in diameter with discernable margins when a tourniquet is in place, less than 6 mm deep, have a blood flow greater than 600 mL/min, and should be evaluated for nonmaturation if, after 6 weeks from surgical creation, it does not meet these criteria.

5.5. Detection of access dysfunction: monitoring, surveillance, and diagnostic testing [11]

- The surveillance program consists of:

1. Physical examination (monitoring): to detect dysfunction in fistulae and grafts at least monthly by a qualified individual looking for: persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft.

2. Intra-access flow assessment by: Duplex Doppler Ultrasound (DDU), Magnetic Resonance Angiography (MRA), Variable flow Doppler ultrasound (VFDU), Ultrasound dilution (UDT), Glucose pump infusion technique (GPT) and Urea dilution (UreaD). Monthly in 1st 1.5 hr of treatment. The mean value of 2 separate determination (within 10% of each other) performed at a single treatment should be considered the access flow.

3. Directly measured or derived static venous dialysis pressure.

- Alarming findings deserving referral to vascular surgeon are:

a. An access flow rate less than 600 mL/min in grafts and less than 400 to 500 mL/min in fistulae.

b. If access flow 1,000 mL/min that had decreased by more than 25% over 4 months.

c. A venous segment static pressure (mean pressures) ratio greater than 0.5 in grafts or fistulae.

d. An arterial segment static pressure ratio greater than 0.75 in grafts.

e. Indicators of risk for graft rupture.

– Poor eschar formation.

– Evidence of spontaneous bleeding.

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– Rapid expansion in the size of a pseudoaneurysm.

– Severe degenerative changes in the graft material.

• Patient Education Basics [11].

All patients should be taught how to:

1. Compress a bleeding access
2. Seal the site of a central venous catheter (CVC) with ointment to keep air embolus from entering
3. Wash skin over access with soap and water daily and before dialysis
4. Recognize signs and symptoms of infection
5. Select proper methods for exercising AV fistula arm with some resistance to venous flow
6. Palpate for thrill/pulse daily and after any episodes of hypotension, dizziness, or lightheadedness
7. Listen for bruit with ear opposite access if cannot palpate for any reason

All patients should know to:

1. Avoid carrying heavy items draped over the access arm or wearing occlusive clothing
2. Avoid sleeping on the access arm
3. Insist that staff rotate cannulation sites daily
4. Insure that staff are using proper techniques in preparing skin prior to cannulation
5. Report any signs and symptoms of infection or absence of bruit/thrill to dialysis personnel immediately

6. Complications of vascular access

6.1. Failure of maturation of AVF

In general, two variables are required for AVF maturation. First, the AVF should have adequate blood flow to support dialysis; second, it should have enough size to allow for successful repetitive cannulation. Although flow and size may appear as two separate parameters, they are intricately related [57].

6.1.1. Interventions to salvage with early AVF failure

Studies demonstrated that the two most common problems observed in early AVF failure are the presence of stenosis and accessory veins. These studies have emphasized that a great majority of these failed fistulae can be salvaged using percutaneous techniques. Percutaneous balloon angioplasty and accessory vein obliteration using one of three techniques (percutane-

ous ligation using 3/0 nylon, venous cutdown, or coil insertion) were used to salvage the failed AVF. The single major complication consisted of a vein rupture with an expanding hematoma. It resulted in loss of the access. The minor complications all were hematomas that required no treatment and had no sequelae [58].

Reports have highlighted a newer technique (sequential dilation) to salvage an AVF that fails to develop because of diffuse stenosis [59, 60].

In this technique, the AVF is gradually dilated with a progressively increasing size of angioplasty balloon at 2- to 4-wk intervals until a size that is optimal for dialysis cannulation is achieved. In addition to endovascular techniques, surgical intervention has been used for AVF salvage [61].

There is a lack of prospective studies that have examined the role of surgical approach in the salvage of AVF with early failure only. The creation of a new anastomosis for a juxta-anastomotic lesion and superficialization procedures are some of the techniques that are available in this category. Inability to navigate the wire across a stenotic lesion during percutaneous approach and deep location of an AVF are some of the indications for surgical intervention [62].

6.2. Dialysis access infection

Dialysis-access-related infections are common, and often result in great cost and morbidity, may be mortality. It is the most important cause of loss of vascular catheter access and an important cause of failure of native and prosthetic arteriovenous grafts and fistula [63, 64, 65].

Diabetes seems to increase the risk of S.aureus bacteremia in dialysis patients [66].

Useful criteria for diagnosis of AV fistula infection includes, the presence of bacteremia associated with local tenderness or redness of the fistula site and no other obvious source of bacteremia, evidence of local infection at the fistula site with recovery of a pathogen by culture of draining pus or direct aspiration [67].

Prevention: The pillar of prevention is practicing meticulous aseptic technique and avoiding bleeding or hematoma when cannulating the graft. This is not only responsibility of the dialysis nurses and stuff but also the patient. Avoidance of repeated needle insertion at one particular site on the graft is also critical to eliminate complications. The presence of foreign material makes synthetic conduit especially susceptible to infection [68].

Treatment [11]:

- *Infections of primary AVFs* are rare and should be treated as subacute bacterial endocarditis with 6 weeks of antibiotic therapy. Fistula surgical excision should be performed in cases of septic emboli.
- Infection of AVG:

Superficial infection of an AVG should be treated as follows:

Initial antibiotic treatment should cover both gram-negative and gram-positive microorganisms.

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Subsequent antibiotic therapy should be based upon culture results.

- Incision and drainage may be beneficial.
- *Extensive infection of an AVG* should be treated with appropriate antibiotic therapy and resection of the infected graft material.

6.3. Thrombosis

This is the commonest cause of failure in the long term and is most often due to underlying stenosis, overdialysis leading to dehydration and hypotension, poor needling technique leading to haematoma and undue post-cannulation compression to control bleeding. The type of access and the site of thrombosis are important determinants of outcome.

Thrombosis may affect the anastomotic or post- anastomotic segments as a result of neointimal hyperplasia or may begin at a needling site. When radiocephalic or brachiocephalic AVFs thrombose at or close to anastomosis, the clot usually remains localized and run off remains patent as it has a number of natural tributaries which maintain some venous flow. This situation can be treated by a local refashioning of the AVF, anastomosing the arterialized vein to the artery at a more proximal site [69].

In contrast, thrombosis of AVFs involving transposed veins usually leads to thrombus propagation so that the entire AVF clots. This is a result of the fact that all the tributaries of the venous outflow had been ligated during the creation of this type of AVF. Successful salvage of such a clotted AVF must be attempted as soon as possible before the clot organizes. There are two choices for the treatment of the thrombosed graft: surgical and endovascular. The choice should be based on local expertise. Treatment must be timely, not delayed, and central venous catheters should be avoided. Angiography to detect venous stenotic lesions is mandatory. Venous stenosis must be corrected and all abnormal haemodynamic parameters present prior to thrombosis should return to normal [70].

Surgical correction:

The thrombectomy is usually performed with a small transverse incision at the nadir of a loop PTFE graft or at the venous anastomosis of straight PTFE grafts. The thrombectomy is then performed with a fogarty balloon catheter to extract the clot. Assessment of the presence of stenosis is made by the surgeon based on the resistance to passage of the fogarty balloon catheter or a similar dilators. More recently, intraoperative angiographic evaluation of the graft may be performed to better assess for the presence of stenoses [71].

Surgical correction of intimal hyperplasia at venous anastmosis is best managed by one of three methods depending on the extent of disease and adjacent venous anatomy:

1. Widening of the lumen with patch angioplasty.
2. Interposing a short segment of new graft material and construcing a more proximal venous anastmosis (jump graft).
3. Transferring the venous end of the graft to an adjacent vein, such as from an antecubital to the cephalic vein [72].

Endovascular therapy:

Endovascular therapy may be divided into two general categories: enzyme-mediated thrombolysis and endovascular thrombectomy [73, 74]. Enzyme-mediated thrombolysis can be subdivided into two categories:- pharmacological and pharmacomechanical.

Pharmacological thrombolysis: refers to thrombus dissolution using only the effects of a fibrinolytic enzyme. In large studies success has ranged from 58% to 68%. Complication rates have ranged from none to 85.7%. This complications included: bleeding at needle puncture sites, embolus to the peripheral artery [75] and systemic fibrinogen depletion has been routinely seen because of the large doses of enzyme used.

– Urokinase is administrated by crossed catheter technique in doses of 60,000 to > 500,000 u/hr with success rates of 75% to 93%. Urokinase offers the advantages over streptokinase of having shorter effective half-life and no antigenicity it can be readministered in cases of recurrent thrombosis [76].

– Recombinant tissue plasminogen activator has been used as thrombolytic agent for thrombosed grafts, administered at 10-20 minutes intervals with a maximum total dose of 30mg. The reported success rates have been 92% in 14 thrombosed grafts [77].

– **Pharmacomechanical thrombolysis** is composed of two phases. The first is pharmacological, consisting of enzymatic lysis. This is immediately followed by the second phase, mechanical maceration and removal of residual thrombus.

– **Endovascular thrombectomy** include pulse-spray delivery of saline [7 8], balloon thrombectomy [79, 80], thromboaspiration [81], and recently, thrombolysis using mechanical devices [82].

6.4. Vascular steal syndrome

Clinically significant distal extremity ischemia occurs in 1.6% to 8% of all individuals with a functioning dialysis shunt [83].

Risk factors include female sex, age greater than 60 years, diabetes, arteriosclerosis, multiple operations on the same limb, the construction of an autogenous fistula, and most commonly the use of the brachial artery as the donor vessel [83].

Theoretically, the presence of a large arteriovenous fistula always results in reduced perfusion to more peripheral tissues. This is evidenced by the fact that the perfusion pressure is always lower distal to an arteriovenous fistula [84].

Symptoms associated with the ischemic steal syndrome present over a broad spectrum, ranging from vague neurosensory deficits to ischaemic rest pain or tissue loss [85].

Recently, this classification was proposed [86]:

1. Stage I, pale/blue and/or cold hand without pain.
2. Stage II, pain during exercise and/or HD.

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3. Stage III, pain at rest.

4. Stage IV, ulcers/necrosis/gangrene.

Definitive diagnostic testing can be performed non-invasively by comparing digital photoplethysmographic (PPG) waveforms with and without fistula compression [85].

Steal can be limited by reducing the anastomotic length to 75 percent or less of the proximal arterial diameter, which in most patients translates length of 5 mm. Of course this must be judged carefully as very small fistulas tend to clot because of inadequate flows of less than 200 ml/min. Steal syndromes following a radiocephalic fistula are relatively unusual. The cause is thought to be diversion of the ulnar arterial flow through the palmer arches to create retrograde distal radial artery flow into the fistula with a steal of blood flow away from the digital arteries. This can easily be treated by ligating the radial artery distal to the anastomosis which effectively creates an end-to-end fistula [69].

Treatment:

- Successful treatment mandates that the surgeon recognize the existing disparity between the resistances of the peripheral circulation and the fistula.
- For many years, the most commonly suggested procedures to treat steal syndrome were: excision of a portion of the vein or graft, interposition of 4 mm ePTFE graft, banding, plicating the fistula so as to increase fistula resistance and decrease fistula blood flow. To gauge the precise degree of narrowing such that adequate peripheral perfusion is restored, investigators have used digital PPG to reach digital-brachial index of ≥ 0.6 and digital pressure ≥ 60 mmHg and residual flow ≥ 300 ml/min [83, 87].
- Rerouting of arterial inflow:

Schanzer et al. in 1988 described a novel technique termed distal revascularization and interval ligation (DRIL) (figure 7b), which offers preservation of the access with physiologic restoration of flow to the hand. A DRIL procedure involves two parts: a bypass and interval ligation of the native artery. The bypass graft is connected to the artery proximal to the access anastomosis and its outflow directed to the native artery distal to the access anastomosis. The reversal of blood flow is eliminated by ligation of the artery distal to the AV access, providing the distal vascular bed with normal perfusion pressure and flow [88].

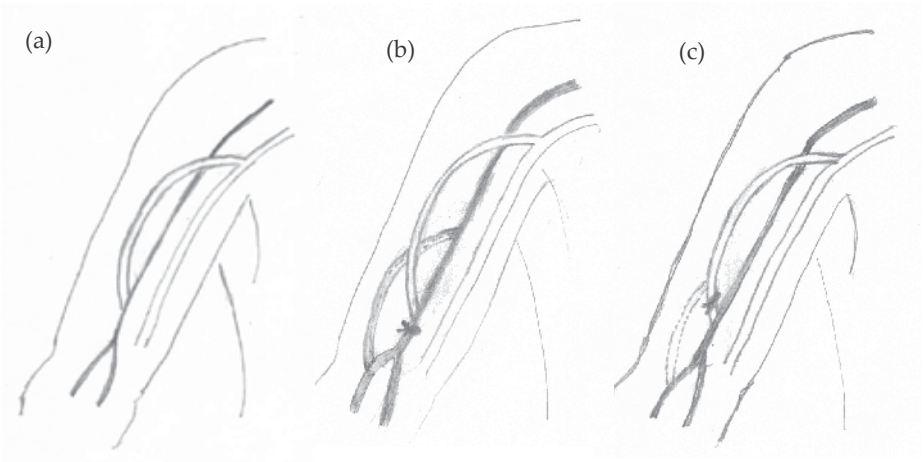

Figure 7. (a) Brachial-cephalic AVF with steal syndrome. (b) DRIL procedure. (c) RUDI procedure

Other novel solutions have focused on the basic concept of rerouting the arterial inflow. Recognizing that brachial arterial origin was a common feature of symptomatic steal, others have reported success with extending the arterial end of the access distally to smaller arteries with revision using distal inflow (RUDI)(figure 7c) and proximally to larger arteries with proximalization of arterial inflow (PAI). Each of these management solutions is based on small case series involving an uncommon but clinically significant complication of AV access. More experience is needed before an appropriate solution can be recommended [89, 90].

6.5. Haemorrhage

This occurs in the first 24 postoperative hours and may be from a specific bleeding point such as the anastomosis or from a slipped ligature. These are due to technical errors and should be avoidable. Generalized 'oozing' resulting in haematoma formation is probably more common and is a result of the functional platelet disorders and bleeding diathesis associated with uremia. This complication can be minimized by careful preoperative preparation including correction of anaemia with recombinant erytheropoietin and adequate dialysis. late hemorrhage can complicate aneurysm formation and infection which controlled by firm pressure over the bleeding point and ligation may be required in the emergency situation [91].

6.6. Aneurysm formation

False aneurysms may occur at the anastomosis when there has been an error in surgical technique or more commonly at a needling site which has been over used. These can be treated by resection with either direct end-to-end anastomosis or by the placement of a short PTFE bridge graft. The incidence of false aneurysm formation is 10% for PTFE grafts compared to 2% for autogenous AVFs [92].

- Indications for revision/repair [11]:

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AVGs with severe degenerative changes or pseudoaneurysm formation should be repaired in the following situations:

a. The number of cannulation sites are limited by the presence of a large (or multiple) pseudoaneurysm(s).

b. The pseudoaneurysm threatens the viability of the overlying skin.

c. The pseudoaneurysm is symptomatic (pain, throbbing).

d. There is evidence of infection.

- Cannulation of the access through a pseudoaneurysm must be avoided if at all possible and particularly so if the pseudoaneurysm is increasing in size.

True aneurysmal dilatation of autogenous arterialized veins are common. Often no action is required but corrective surgery is indicated if the overlying skin becomes very thin or there is evidence of progressive expansion. In some patients the whole length of arterialized vein becomes very dilated and the AVF may have to be sacrificed by ligating it [69].

6.7. Stenosis

This may-occur directly at the anastomosis, in the first few centimeters of the venous outflow from an AVF or at needling sites. Anastomotic stenosis results from either errors in surgical technique or from the development of neointimal hyperplasia. Radiocephalic AVFs can often be refashioned by creating a more proximal anastomotic site but this may not be possible for brachiocephalic or brachiobasilic AVFs. In that case a "jump graft" can be created using a short segment of PTFE to bypass the stenosis. Post-anastomotic or needling site stenoses may be amenable to treatment by percutaneous transluminal angioplasty. The disadvantage is that recurrent stenosis is common and this may require surgical revision using a prosthetic interposition graft [69].

6.7.1. Indications for preemptive PTA in stenosed autogenous AVF or AVG [11]

A fistula with a greater than 50% stenosis in either the venous outflow or arterial inflow, in conjunction with clinical or physiological abnormalities such as: reduction in flow (< 600mL/min in AVG), increase in static pressures should be treated with percutaneous transluminal angioplasty (PTA) or surgical revision.

6.7.2. Central vein stenosis [11]

Patients with extremity edema that persists beyond 2 weeks after graft placement should undergo an imaging study (including dilute iodinated contrast) to evaluate patency of the central veins. The preferred treatment for central vein stenosis is PTA. Stent placement should be considered in the following situations:

– Acute elastic recoil of the vein (> 50% stenosis) after angioplasty.

– The stenosis recurs within a 3-month period.

6.8. Lymphocele

This occurs when the lymphatic channels have been divided or diathermed. It is particularly associated with brachio-basilic fistula formation and operation in the groin. Treatment by intermittent closed drainage under-sterile condition and antibiotics cover is usually successful. Recurrent and persistent lymphocele may require re exploration and open drainage [69].

6.9. Venous hypertension

A venous hypertension syndrome may develop in which the hand distal to the fistula becomes swollen and uncomfortable with thickening of the skin and hyperpigmentation [93, 94]. Hypertension may be avoided by forming an end-to-side or end-to-end anastomosis. Ligation of the enlarged venous tributaries causing the hypertension of the distal digits may relieve symptoms while preserving the fistula. The increasing use of subclavian lines for dialysis has lead to an increased incidence of subclavian vein thrombosis or stenosis. The subsequent placement of a fistula may lead to massive arm edema caused by venous hypertension and, in women, breast enlargement [95]. Subclavian vein thrombolysis and angioplasty with stenting may allow continued use of the-fistula. This complication may also be lessened by using the internal jugular vein for central line placement [96].

6.10. Neuropathy

Ischemic neuropathy is unusual with the radiocephalic fistula and is seen mainly in diabetic patients with preexisting atherosclerotic disease and in patients with proximal site fistulas. It is characterized by the onset of severe, acute, painful weakness of the distal extremity, with wrist drop and minimal wrist flexion. This development is probably due peripheral nerve ischemia and if recognized early, fistula interception may preserve neurologic function [97].

Indeed definite thickening of the flexor synovium within the carpal tunnel is occasionally observed either in patients with a functioning shunt. The most prominent symptom of carpal tunnel syndrome in dialysis patients is painful nocturnal acroparesthession of the affected limb. The pain and numbness are in the distribution of the median nerve. In differentiating the carpal tunnel syndrome from painful uremic neuropathy, one should consider that the symptoms of uremic neuropathy are symmetric, often beginning as a burning sensation in the soles of the feet, with progressive involvement in the legs. The upper extremities are involved only after the presence of severe lower extremity disease. On examination of the median conduction velocity across the wrist it will be found to be delayed. Relief is achieved by median nerve decompression by division of the transverse carpal ligament. Some patients may achieve relief from symptoms by conservative measures such as simply moving the hand during dialysis. Using digital compression of the puncture site, rather than using a compression bandage avoids increased venous pressure [98].

6.11. Cardiovascular complications

High-output cardiac failure is a rare complication, which occurs particularly in patients who display a combination of low hematocrit and cardiomyopathy from diabetes, in the presence

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of a high-flow fistula [99]. Treatment usually involves ligation of the fistula, although banding may be attempted [100].

7. Factors affecting access patency

Patient related factors:

1. **Age:** Increasing age has no effect on fistula patency [101].
2. **Gender:** The patency of distal forearm, wrist or snuffbox AVFs is poorer in women than in men. Since, this seems to apply also to more proximal AVFs it may be unrelated to the larger vessels of men and may have a hormonal basis [102, 103].
3. **Diabetes:** There is conflicting evidence as to whether diabetes is an adverse factor for fistula patency with some authors suggesting that flow rates and patency are poorer [103], whereas others have found no effect [104, 105].
4. **Obesity:** It is more difficult to create a suitable AV fistula in obese patients because the deeper veins are more difficult to cannulate but this does not affect patency [106].
5. **Smoking:** Smokers may have poorer fistula survival [107].
6. **Thrombotic tendencies and vasculitis:** Increased fibrinogen predisposes to access thrombosis and vasculitis is a strong predictor of access failure [108].

Access related factors:

1. **Vessel size:** Small vessels have higher initial failure rates, more frequent failure to mature and poorer long-term patency [7].
2. **Access position:** More proximal AV fistulae have improved blood flow and patency but leave fewer options for access in the event of failure [109, 110].
3. **Prosthetic AV grafts:** Prosthetic AV grafts have poorer primary patency, require more revisions and have higher infection rates than autogenous AVFs. However, their patency can be improved by using a wider diameter graft or adding a vein cuff to the venous anastomosis [111, 112, 113].
4. **Fistula flow rates:** The flow rate AV fistulae the day after surgery correlates inversely with the risk of thrombosis although intraoperative flow rates are less reliable [7].
5. **Anastomotic method:** Anastomosis using non-penetrating vascular clips, which give an interrupted anastomosis with excellent endothelial apposition and less bleeding, are quicker and may have improved patencies [109, 110].

Surgeon related factors:

Surgical experience: There can be little doubt that experienced surgeons with adequate training have good outcomes [103], but well supervised trainees can produce equivalent results [114].

Postoperative follow up related factors:

1. **Access surveillance:** The use of postoperative surveillance and pre-emptive repair of detected defects has been shown to improve access survival in a randomized controlled trial [115].
2. **Early cannulation:** This is not a risk factor for fistula failure [116].
3. **Drugs:** Antiplatelet agents such as aspirin and dipyridamole prolong fistula survival and are used routinely [117 , 11 8] although a combination of aspirin and clopidogrel increased haemorrhagic complications without influencing patency in prosthetic AV grafts [11 9] Anticoagulation with warfarin reduces AVF thrombosis in patients with hypercoagulable states [120], but routine use is best avoided because of the risk of haemorrhage [121].

8. Central venous catheter for hemodialysis

Another way to get access to the circulation to perform hemodialysis is the usage of the central venous catheters.

8.1. Indications and patient selection

Central venous catheter is the preferred method for short term hemodialysis and it is also used for emergent dialysis as temporary access while a permanent access is maturing. Central venous catheter is used as a permanent access in patients who have exhausted all other options for autogenous AVF or AVG. It is the method of choice in patients who are not candidate for AVF or AVG, like patients with limited cardiac reserve, children weighting less than 30 kg, and patients with extensive peripheral vascular disease.

8.2. Catheter types

There are many commercially available percutaneous hemodialysis catheters, all are grouped into two main types; the non-tunneled and the tunneled catheters (figure 8), both are usually provided with dual lumen; one for withdrawal and the other for return of blood, but in some cases they were of three lumens, with the third one for I.V. fluids, blood products, and drug administration, as well as blood sampling. The tunneled catheters have Dacron or Teflon cuff on their shaft near the distal end which promotes tissue ingrowth in order to fix the catheter to the subcutaneous tissue, some catheters have another antimicrobial cuff distal to the fixation cuff in order to limit microbial invasion through the subcutaneous tunnel, the antimicrobial cuff is formed of porous collagen incorporating an antimicrobial agent. The non-tunneled catheters are used in patients who are planned for short term catheter dependent hemodialysis (less than one month), while tunneled catheters are used in patients who are planned for long term catheter dependent hemodialysis. They are provided in different lengths, with the tunneled catheter having longer length than the non-tunneled one to accommodate the length of the subcutaneous tunnel, and also they are available in different diameters ranging from 9

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Fr. in pediatric catheters up to 15 Fr. Most of hemodialysis catheters made of silicone or polyurethane.

The cuffed catheter is tunneled subcutaneously from the desired exit site to the site of vein entry. The non-cuffed double lumen catheters are placed by conventional Seldinger technique, while the cuffed one are flexible and required the use of rigid introducer or peel-apart sheath that is latter removed, leaving the catheter in place. The catheter is placed into one of the large central veins so the tip lies in the junction of superior vena cava with the right atrium.

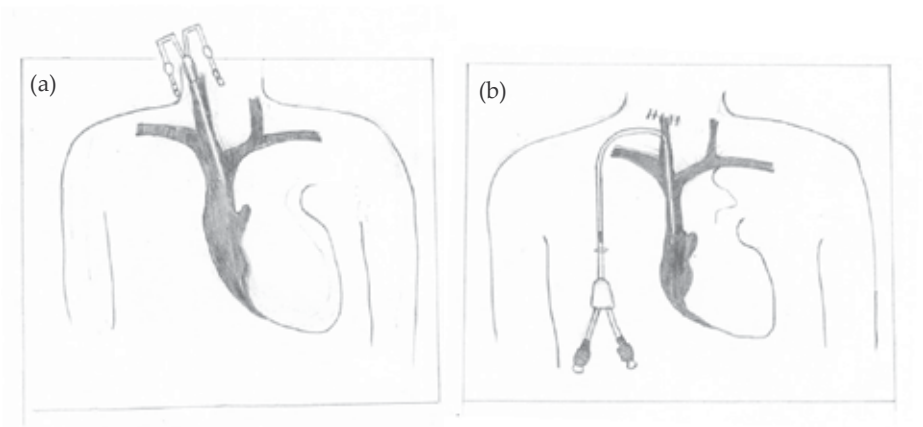

Figure 8. (a) Non-tunneled catheter in place. (b) Tunneled cuffed catheter.

Type and Location of Tunneled Cuffed Catheter Placement according to (KDOQI) guidelines [122]:

a. Tunneled cuffed venous catheters are the method of choice for temporary access of longer than 3 weeks' duration. (They also are acceptable for access of shorter duration.) In addition, some patients who have exhausted all other access options require permanent access via tunneled cuffed catheters. For patients who have a primary AV fistula maturing but need immediate hemodialysis, tunneled cuffed catheters are the access of choice. Catheters capable of rapid flow rates are preferred.

b. The preferred insertion site for tunneled cuffed venous dialysis catheters is the right internal jugular vein. Other options include: the right external jugular vein, the left internal and external jugular veins, subclavian veins, femoral veins, or translumbar access to the inferior vena cava. Subclavian access should be used only when jugular options are not available. Tunneled cuffed catheters should not be placed on the same side as a maturing AV access, if possible.

c. Fluoroscopy is mandatory for insertion of all cuffed dialysis catheters. The catheter tip should be adjusted to the level of the caval atrial junction or into the right atrium to ensure optimal blood flow. (Atrial positioning is only recommended for catheters composed of soft compliant material, such as silicone).

d. Real-time ultrasound-guided insertion is recommended to reduce insertion-related complications.

e. There is currently no proven advantage of one cuffed catheter design over another. Catheters capable of a rapid blood flow rate are preferred. Catheter choice should be based on local experience, goals for use, and cost.

In updates of 2006 (NKF-K/DOQI) (11) stated that: Ultrasound should be used in the placement of catheters, and they recommend tunneled cuffed catheters for catheter dependent hemodialysis longer than one week.

8.3. Technique of insertion

Internal jugular vein is approached by inserting the needle about one inch above the clavicle between the two heads of the sternomastiod muscle directing it toward the epsilateral nipple, another approach is achieved by inserting the needle about 1-2 inches above the clavicle under the lateral border of the sternomastiod muscle directing it toward the epsilateral sternoclavicular joint, in both approaches the patient must be supine with the head extended and tilted to the other side, the carotid artery is felt and kept medially away from the needle puncture.

The subclavian vein is approached by inserting the needle under the clavicle at the junction of its lateral third with the medial two thirds directing the needle toward the sternoclavicular joint with the patient in supine position.

The femoral vein is approached by inserting the needle at the inguino-crural crease just medial to the femoral pulsation directing the needle toward the umbilicus with the patient in supine position.

8.4. Complications

Many complications may occur during catheter placement, but they could be prevented by adopting careful maneuver, using ultrasound and fluoroscopic guidance.

Complication list include hemothorax, pneumothorax, arterial puncture, hematoma and air embolism.

8.5. Catheter related problems

8.5.1. Catheter dysfunction

This is manifested by difficulty to withdraw and/or infuse blood, if this occurs in the first dialysis session after catheter placement it is usually due to malposition or kinking and it can be corrected under fluoroscopic guidance. If this occurs in a previously functioning catheter, catheter thrombosis should be suspected. The thrombus may be intraluminal, at the tip of the catheter or rarely the catheter induces thrombosis in the vein in which it is placed. Other cause of catheter malfunction is the fibrin flap, in this condition fibrin extends from the fibrin sheath to come in front of the catheter tip acting as a valve preventing withdrawal but allowing infusion of blood.

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8.5.1.1. Prevention of catheter thrombosis

Routinely anticoagulant solution is infused inside the catheter lumen at the end of each dialysis session and it is adjusted to fill the catheter lumen (catheter lock) to prevent catheter thrombosis. The standard solution is heparin with concentrations ranging from 1000 to 10,000 u/ml, another solution is sodium citrate with concentrations ranging from 4% to 47%. In spite of the proper adjustment of the catheter lock solution to just fill the catheter lumen, some amount usually leak to the circulation [123], in case of citrate this causes no problem [124], but in case of heparin this may cause bleeding complications in susceptible patients [125]. Few studies have compared different heparin concentrations [12 6], and they found that lower concentration (1000 u/ml) is as effective as higher concentrations in preventing catheter thrombosis with less bleeding complications. Also studies comparing different concentrations of citrate solution [127, 128] found that concentrations of 4-5% is sufficient. Studies comparing heparin concentration of 1000 u/ml to citrate concentration of 4-5% solutions [129, 130, 131], showed that citrate is as effective as heparin in prevention of catheter thrombosis with the advantage of absence of liability to bleeding complications. Recently trials are going on to evaluate the use of small dose of tissue plasminogen activator as catheter lock solution aiming to obtain better results than those obtained with heparin and citrate [132 , 13 3].

The use of oral anticoagulant in the form of warfarin in therapeutic dose with the INR (1.8-2.5) is supposed to be effective in decreasing the incidence of catheter thrombosis [134, 135].

8.5.1.2. Treatment of catheter dysfunction

In case of low catheter flow, simple measures may succeed in restoring adequate blood flow such as repeated aspiration and flushing with saline, passage of guide wire through the lumen of the catheter, changing the position of the patient, and reversal of the lines (withdrawal from the venous line and return the blood through the arterial line). In case of failure of the previous measures or if there is inability to withdraw and/or infuse from both ports, lytic therapy is indicated. The thrombolytic agent is injected inside the catheter lumen and left for 30-60 min before its withdrawal. The agent commonly used is either urokinase5000 u/ml, or tissue plasminogen activator 1mg/ml, and it could be repeated. This procedure succeeded in restoring adequate flow in 70 to 90%of the cases but with high rate of recurrence [136-140]. Higher doses of urokinase were tried using infusion through the catheter rather than locking the catheter with higher success rate and less recurrence [141], provided that there were no contraindications to lytic therapy. If these methods failed to restoreadequate blood flow, then catheter exchange over guide wire will be the appropriate option.

8.5.2. Catheter infection

Infection is the most common complication of hemodialysis catheter and it is one of the leading causes of morbidity and catheter removal in hemodialysis patients. The catheter infection rate is variable and is related to the duration of use. In a prospective study including 108 patients with tunneled dialysis catheter, the rate of catheter related bacteremia was 35% in the first 3 months and 48% within 6 months [142]. Catheter-related bacteremia may cause serious

metastatic infection in 5-10% 0f patients [143] (endocarditis, osteomyelitis, septic arthritis, epidural abscess, or death). Catheter infection may be exit-site infection, tunnel infection or catheter-related bacteremia. Catheter-related bacteremia is thought to be commonly originated from bacteria in the catheter biofilm. The biofilm is formed on the catheter lumen in the first 24 hours after catheter insertion. The bacteria in the biofilm are resistant to antibiotic at therapeutic plasma concentration, but are usually susceptible to higher concentrations [144].

8.6. Prophylactic measures to prevent catheter infection

Catheter Care and Accessing the Patient's Circulation according to (KDOQI) guidelines [122]:

a. Hemodialysis catheter dressing changes and catheter manipulations that access the patient's bloodstream should only be performed by trained dialysis staff.

b. The catheter exit site should be examined at each hemodialysis treatment for signs of infection.

c. Catheter exit site dressings should be changed at each hemodialysis treatment.

d. Use of dry gauze dressing combined with skin disinfection, using either chlorhexidine or povidone iodine solution, followed by povidone iodine ointment or mupirocin ointment at the catheter exit site are recommended after catheter placement and at the end of each dialysis session.

e. Manipulating a catheter and accessing the patient's bloodstream should be performed in a manner that minimizes contamination.

f. During catheter connect and disconnect procedures, nurses and patients should wear a surgical mask or face shield. Nurses should wear gloves during all connect and disconnect procedures.

Treatment of Infection of Tunneled Cuffed Catheters

Tunneled cuffed catheter infection is a serious problem. Appropriate treatment is dependent upon the nature of the infection:

1. Apply topical antibiotics, ensuring proper local exit site care; do not remove the catheter.

2. If there is tunnel drainage, treat with parenteral antibiotics (anti-staphylococcal, anti-streptococcal therapy pending exit site cultures) in addition to following appropriate local measures. Definitive therapy should be based on culture results. Do not remove the catheter unless the infection fails to respond to therapy. If the infection fails to respond to therapy, remove the catheter and replace it using a different tunnel and exit site.

a. Catheter-related bacteremia, with or without systemic signs or symptoms of illness, should be treated by initiating parenteral treatment with an antibiotic(s) appropriate for the organism(s) suspected, usually *Staphylococcus* and *Streptococcus*. Definitive therapy should be based on the organism(s) isolated. The catheter should be removed in all instances if the patient remains symptomatic more than 36 hours. The catheter should also

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be removed in any clinically unstable patient. Preliminary reports suggest that after obtaining a bactericidal level of the antibiotic in the blood, in a stable asymptomatic patient without exit site or catheter tunnel tract involvement may be treated by changing the catheter over a guidewire plus a minimum of 3 weeks of systemic antibiotic therapy. Blood cultures should be repeated periodically during and immediately after this treatment to monitor its effectiveness.

A new permanent access should not be placed until blood cultures, performed after cessation of antibiotic treatment, have been negative for at least 48 hours.

In updates of 2006 [11]; the last recommendation has been changed: Catheters should be exchanged as soon as possible and within 72 hours of initiating antibiotic therapy in most instances, and such exchange does not require a negative blood culture result before the exchange. Follow-up cultures are needed 1 week after cessation of antibiotic therapy

Catheter-related bacteremia is diagnosed by the presence of fever in catheter- dependent patient with positive blood culture [141].

The empirical therapy should include antibiotic with broad-spectrum coverage against gram-negative organisms such as third generation cephalosporin and vancomycin in centers with frequent MRSA infection. Once the result of culture is obtained, the antibiotic is changed according to the results of the sensitivity tests, and the treatment should be continued for at least 3 weeks.

The antibiotic lock solution: Given that biofilm is the major source of catheter related bacteremia an antimicrobial catheter lock solution may reduce catheter-related bacteremia. The antibiotic lock is a concentrated antibiotic solution mixed with the anticoagulant solution and injected into the catheter lumen at the end of the dialysis session.

The antibiotic lock solutions may include the standard antibiotics or antimicrobial agents such as taurolidine and 30% citrate solution [144]. Many trials documented the efficacy of antibiotic locks in prophylaxis of catheter-related bacteremia [145, 146].

9. Portacath for hemodialysis

Portacath (totally implantable venous access system) is commonly used in oncology patients to deliver the chemotherapeutic agents and parenteral nutrition intravenously and recently it has been used for hemodialysis especially in children. The system used for hemodialysis consists of two separate or fused subcutaneously implantable reservoirs connected to double lumen catheter; one port is used for blood withdrawal and the other for blood return.

10. Translumbar inferior vena cava catheter for hemodialysis

This technique represents another option for challenging cases who did not have suitable patent central vein allowing creation of arteriovenous access or insertion of tunneled cuffed

catheter. In this technique a long tunneled cuffed catheter is inserted in the inferior vena cava percutaneous while the patient is in prone position with the aid of fluoroscopy.

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Chapter 29

Single-Needle Hemodialysis on Native Fistulae

Guy Rostoker

Additional information is available at the end of the chapter

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1. Introduction

Single-needle (SN) dialysis was first described in 1964 by Twiss, who used a time-activated mechanism with a pump and a double clamp to alternate blood through a caval catheter [1]. As a result of this publication, the technique of SN-hemodialysis on catheter has been widely disseminated and reported in publications primarily in the context of acute renal failure especially in post-operative cases [2]. In the 1980's, the work of Belgian authors allowed the development of the chronic hemodialysis technic in unipuncture particularly in the Benelux countries [3-5]. Vanholder and colleagues using a specific canula and a twin pump-head SN system showed that dialysis efficiency was at least as good as with conventional double-needle (DN) hemodialysis, based on Kt/V, the hematocrit and nerve conduction [3-4]. They also showed that the five-year fistula survival rate was 74%, a figure far better than with conventional DN hemodialysis [5]. SN dialysis failed to gain popularity, however, with the exception of the Benelux countries and recently Asia, and has been confined to specific situations such as the use of a single-lumen catheter, and when temporary and reversible problems of vascular access arise [6, 7]. Nevertheless, many nephrologists and dialysis nurses are reluctant to use SN dialysis, even in cases of problematic vascular access for fear of incidents or underdialysis [7]. The technique of SN-dialysis with a double-pump (Figure 1) must be differentiated from the use of an alternating clamp which should be reserved for the exceptional situation of termination of a dialysis session in the event of an incident on the native fistula on a simple-pump generator.

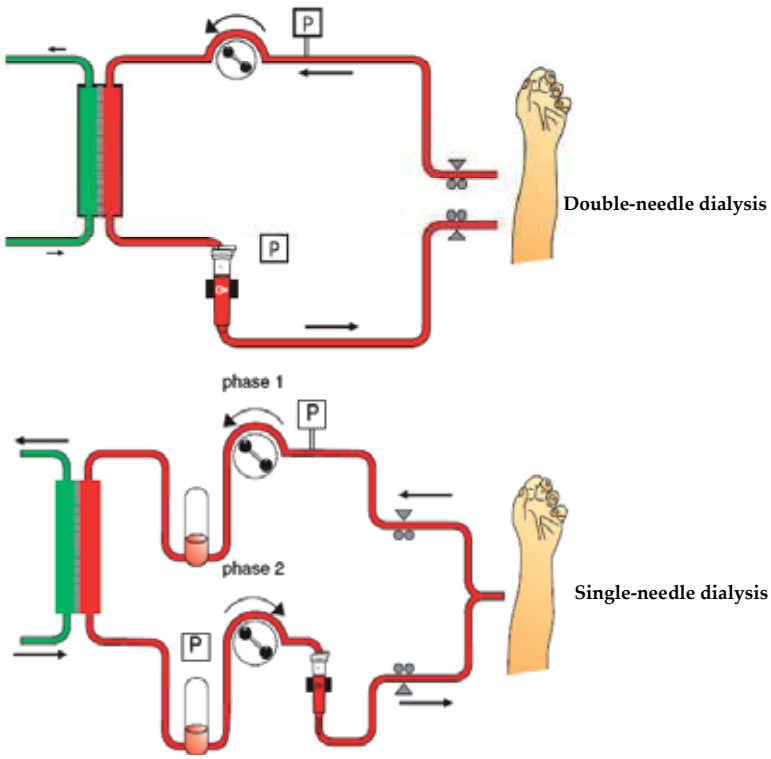

Figure 1. Diagrams of extracorporeal circuits during double-needle hemodialysis and single-needle hemodialysis according to Rostoker G. Short-term single-needle hemodialysis on native fistulae : a general review. Nephrol Ther 2010 ; 6(7) : 591-596

2. Complications of single-needle hemodialysis

The main potential hazards of SN dialysis are the same as those of conventional hemodialysis, but also include hemolysis from shear stresses between red cells and narrow needles, a higher risk of backfiltration, blood recirculation and underdialysis.

2.1. Hemolysis

The classical drama of mechanical or chemical hemolysis with violent abdominal pain and hypotension has become a very rare event in DN and SN dialysis with the current lines and pumps of generators as well as with the chemical quality of current dialysates. While subclinical hemolysis is very rare during DN-hemodialysis [8], a purely biological hemolysis can be observed in SN-hemodialysis when a high blood flow is used on a single needle of low diameter and high length, particularly when using Wallace catheters (to be avoided at all costs when unipuncture is scheduled) [8-9]. Dhaene and coworkers us-

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ing plasma lactico deshydrogenase (LDH), as a marker of mechanical hemolysis observed a significant increase in LDH during 41.6 % of the 245 SN-dialysis sessions (among 52 patients) using a 14 Gauge Wallace's catheter, as compared with 25% of the 112 SN-dialysis sessions performed with 14 Gauge metal needles [8]. Hemolysis intensity was also increased twofold with the use of Wallace's catheters [8]. In an "in vitro" hemodialysis system using calf's blood, Wachter and coworkers have also demonstrated by measuring the rate of free hemoglobin released into the plasma that mechanical hemolysis is inversely proportional to the internal diameter of the Wallace's catheters [9].

2.2. Backfiltration

The backfiltration of the dialysate to the blood compartment occurs when the pressure in the dialysate compartment is higher than the pressure of the blood compartment of the dialyzer [10]. It is a phenomenon frequently encountered in conventional DN hemodialysis ; with the use of non ultrapure dialysate, this retrofiltration of the dialysate may favor the entry of bacterial endotoxins into blood, and aggravate the micro-inflammatory state of the dialysis patients through the activation of circulating monocytes [7]. The risk of back filtration is higher with SN than with conventional DN hemodialysis due to increased pressure fluctuations resulting in lower pressure in the blood compartment [10]. This means that SN dialysis should be performed with an ultrapure dialysate [7].

2.3. Blood recirculation

Blood recirculation is defined as the reflux of dialysed blood of the venous line into the arterial line and the contamination of the arterial blood by blood which has been already dialysed thus leading to a reduction in dialysis efficiency [11]. The study of the recirculation in the central venous catheters has been widely covered in the literature [summarized in reference 11]: with double lumen catheters recirculation is estimated to average approximately 5% (with a variation of 2% to 12% depending on the type of catheter) [11]. With single lumen short femoral catheters (13.5 cm) a recirculation as high as 22% is observed; recirculation is lower (12.6 %) with longer catheters of 19.5 cm [11]. In 1993, Hoenich and coworkers observed recirculation rates with SN hemodialysis ranging from 8.8 % to 18% [12]. With modern systems of unipuncture dialysis such as the Fresenius generator 4008, Trakarnvanich and coworkers recently found an average recirculation rate ranging between 10.7 % and 12% [6]. Three factors are involved in the blood recirculation phenomenon in SN dialysis [13]: - a low flow rate in the native fistula, - a substantial dead space in the needle and the connectors, - the compliance of the lines of the dialysis circuit located between the needle and the blood pumps [13]. Blumenthal and coworkers elegantly demonstrated that a significant reduction in the rate of recirculation of single lumen catheters (from 23% to 7%) could be obtained by increasing gradually the time of blood impulse rate up to four seconds [14]. However, with the old systems of unipuncture, there was an inverse relationship between blood inflow time and the speed of pumps which limited the gain in recirculation. These works have led the dialysis industry to optimize the blood inflow time in parallel with the flow of the two blood pumps [14].

2.4. Underdialysis

Few data are available on short-term SN dialysis and especialy on the dialysis dose measured using a reliable method. Four publications have clearly shown that the technique of hemodialysis in unipuncture delivered an insufficient dose of dialysis [15-18], which fell below the recommendations of the EDTA and KDOQI [19-20]. These four publications quantified the dose of dialysis by the single-pool Kt/V [15-18] and the most recent also studied the ionic dialysance and the Kt/V provided by the dialysis monitor [18]. Wright and coworkers in the year 2000, were the first to draw attention to the importance of the method of blood sampling in relation to the circuit of unipuncture for the determination of post-dialysis urea in the single-pool method and the risk of a "dramatically optimistic" overestimation of the single-pool Kt/V (due to the contamination of the arterial blood by the recently dialysed venous blood) : among their five patients in SN dialysis, the mean Kt/V taken without precautions measured 1.7 instead of a real value of 1 [15, 21]. Vlassopoulos and coworkers have studied in 17 patients, by means of the double-pool Kt/V measured 20 minutes after the dialysis session, the influence of haemoglobin level and dialysate flow on the dose of dialysis delivered in SN and DN dialysis : with a standard dialysate flow at 500 ml/min and a mean hemoglobin of 11.9 g/dl, the Kt/V dropped from 1.26 in bipuncture to 0.82 in unipuncture [16]. Despite the increase in the dialysate flow to 800 ml/min, the increase of the hemoglobin level with Erythropoesis Stimulating Agent at 12.8 g/dl, led to a significant reduction in the double-pool Kt/V to 1.09 in bipuncture and to 0.74 in unipuncture [16]. Toussaint and Beuret studied six patients for two periods of 15 days (six dialysis sessions) and found a decrease in the single-pool Kt/V from 1.20 in bipuncture to 0.93 in unipuncture [17]. We recently reported the results of the evaluation of the dose of dialysis delivered by SN dialysis compared to DN conventional hemodialysis in eight patients studied in a prospective four-period design lasting four weeks[18]. The dialysis dose was measured by single-pool Kt/V with careful blood sampling according to Wright [15], ionic dialysance recorded 45 minutes after the beginning of the dialysis session and 30 minutes before the end of the session and Dialysis monitor-recorded Kt/V [18]. Ionic dialysance is a variable measured online by several dialysis monitors and reflects small-solute clearance during a dialysis session; it is based on conductivity measurements in the inlet and outlet dialysates and is not affected by the use of one versus two needles [22]. Ionic dialysance is as reliable as effective clearance taking into account cardiopulmonary and vascular access recirculation, and has become the preferred quality assurance parameter of dialysis efficiency [22]. The technique of ionic dialysance is also used to determine and optimize the dialysis dose delivered by double and single lumen catheters [23-26]. In unipuncture period on generator Integra, with the blood flow of 180 ml/min as recommended by the manufacturer, the ionic dialysance was measured at 130ml/min in unipuncture, 45 minutes after the beginning of the dialysis session compared to 181ml/min in bipuncture ; the ionic dialysance 30 minutes before the end of the dialysis session was measured at 122 ml/min in unipuncture compared to 171 ml/min in bipuncture ; the monitor-recorded Kt/V was also statistically reduced in unipuncture to 0.74 (versus 1.05 in bipuncture) as the single-pool Kt/V (unipuncture 0.90 versus in 1.35 in bipuncture) [18] (Figures 2, 3, 4, 5).

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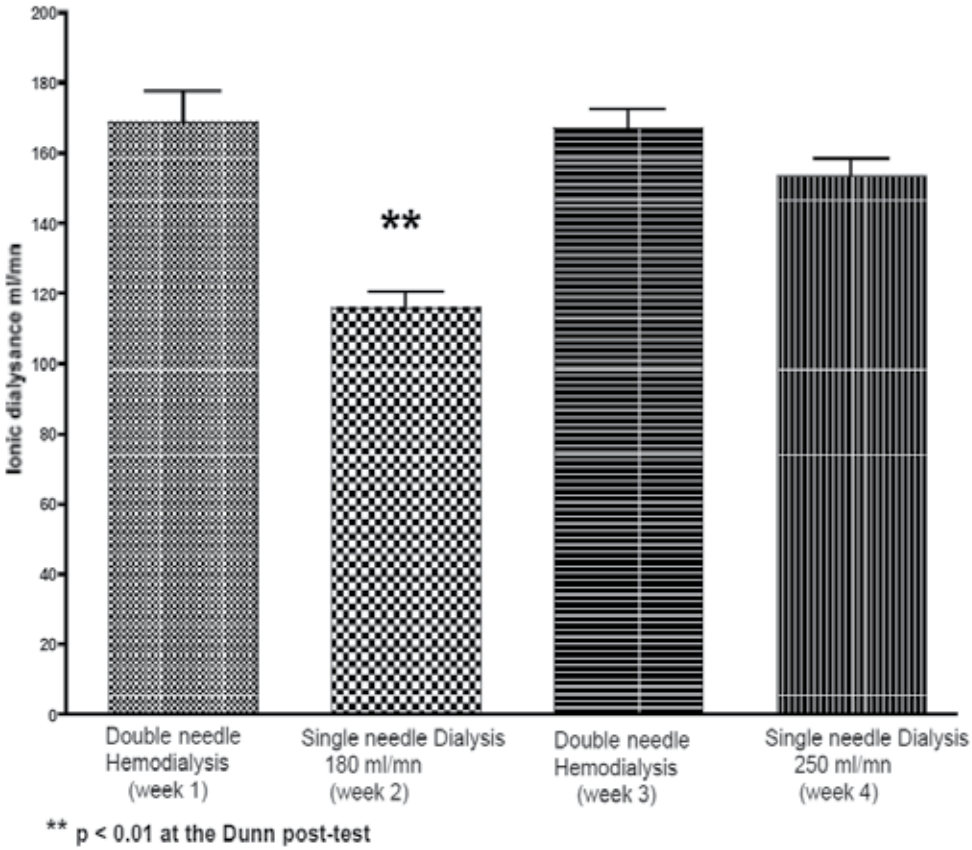

Figure 2. Ionic dialysance 45 minutes after the beginning of the dialysis session in SN and DN Dialysis according to Rostoker G et al. Improving the efficiency of short-term single-needle hemodialysis. Renal Failure 2009 ; 31 : 261-266. This figure shows the reduced ionic dialysance in SN dialysis performed according to the manufacturer's recommendations (at 180ml/min) and the improvement of this parameter by increasing the blood flow rate to 250 ml/min.

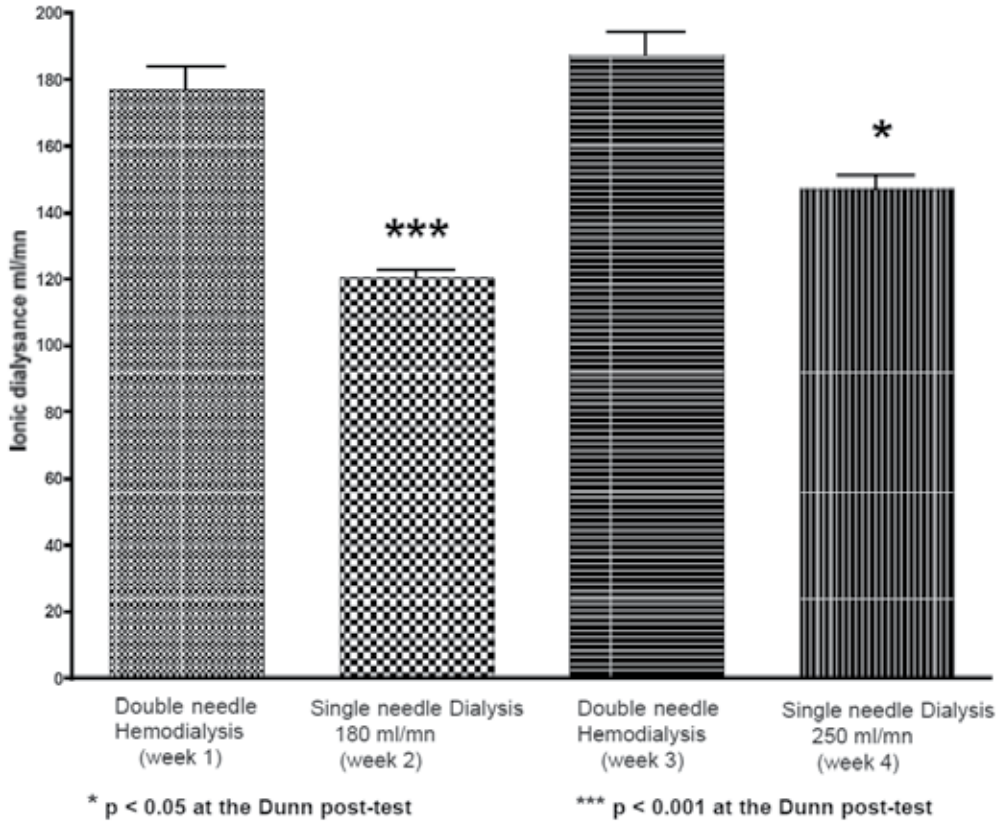

Figure 3. Ionic dialysance 30 minutes before the end of the dialysis session in SN and DN Dialysis according to Rostoker G et al. Improving the efficiency of short-term single-needle hemodialysis. Renal Failure 2009 ; 31 : 261-266. This figure shows the reduced ionic dialysance in SN dialysis performed according to the manufacturer's recommendations(at 180 ml/min) and the improvement of this parameter by increasing the blood flow rate to 250 ml/min

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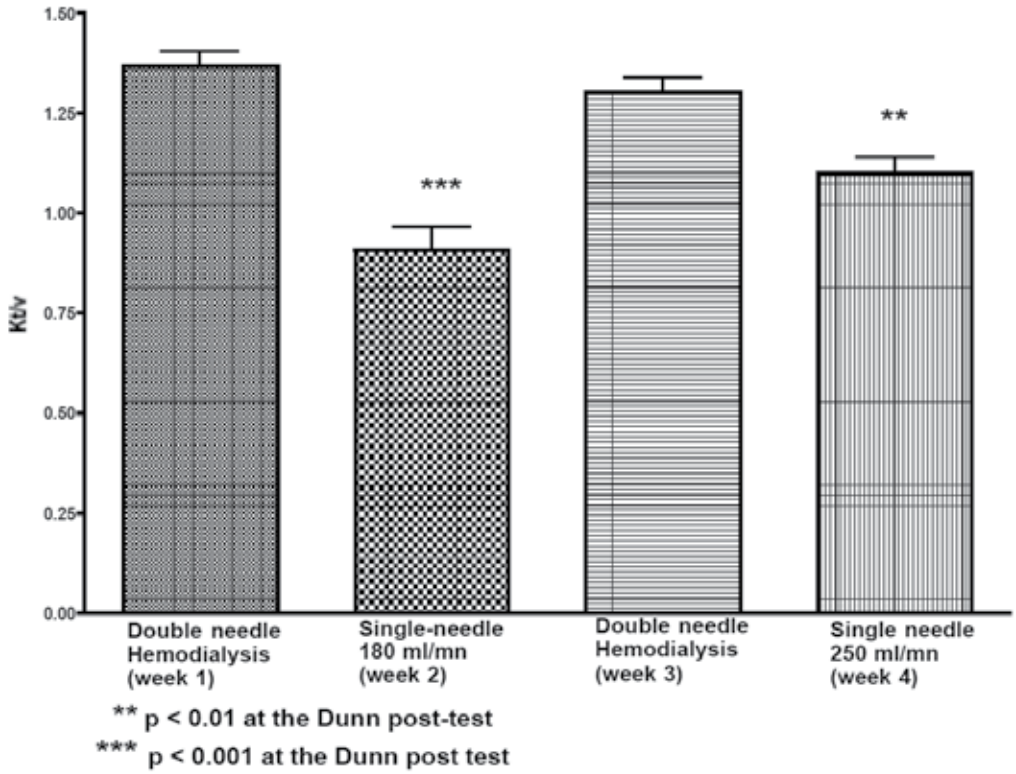

Figure 4. Single pool Kt/V in SN and DN Dialysis according to Rostoker G et al. Improving the efficiency of short-term single-needle hemodialysis. Renal Failure 2009 ; 31 : 261-266. This figure shows the reduced Single pool Kt/V in SN dialysis performed according to the manufacturer's recommendations (at 180 ml/min) and the improvement of this parameter by increasing the blood flow rate to 250 ml/min.

2.5. Increase coagulation in the dialyser

Although not formally studied, several authors have raised the problem of an increase in the coagulation in the fibers of the dialyser linked to the rheological changes induced by the technique of unipuncture and its intermittent flow and the activation of the coagulation cascade following the mechanical fragmentation of red blood cells [7, 14]. This increased coagulation may reduce the performance of the dialyzer and contribute to the reduction of the delivered dose of dialysis. The appearance of hollow fibers at the end of the dialysis session must therefore be the subject of careful consideration by nurses in the event of SN dialysis. In such circumstances, in particular when programming a transitional period of single-needle

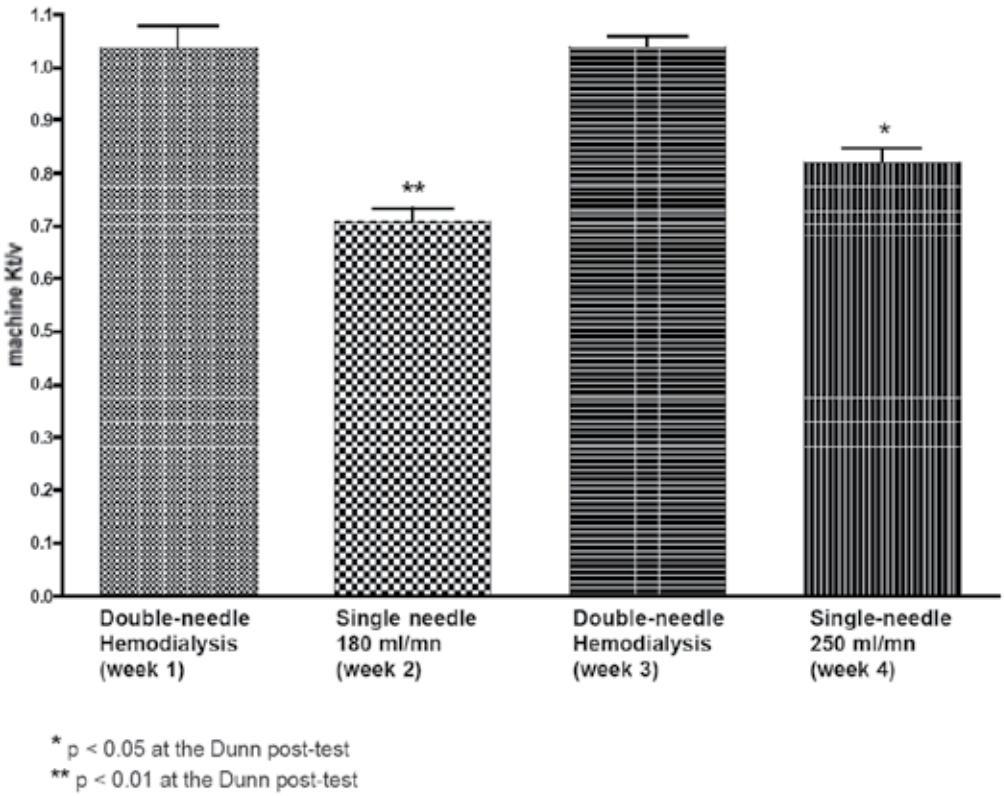

Figure 5. Kt/V provided by the integra monitor in SN and DN Dialysis according to Rostoker G et al. Improving the efficiency of short-term single-needle hemodialysis. Renal Failure 2009 ; 31 : 261-266. This figure shows the reduced Kt/V provided by the dialysis monitor in SN dialysis performed according to the manufacturer's recommendations (at 180 ml/min) and the improvement of this parameter by increasing the blood flow rate to 250 ml/min.

dialysis, it may be necessary to increase the dose of anticoagulation of the dialysis circuit or to use either dialysis membranes coated with heparin or vitamin E or a dialysate enriched in citrate. [7].

3. Optimization of dialysis dose delivered in transient single-needle hemodialysis

In 2002, Lafon showed that it was possible to significantly improve the ionic dialysance of patients treated by SN dialysis on generator Integra during the same dialysis session by increasing the flow of the two blood pumps with a vacuum threshold of -180 mmHg for the arterial pump and + 250 mmHg for the venous pump ; the ionic dialysance increased from 110ml/min in the first part of the dialysis session to 140 ml/min at the last hour of the session

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[27]. We have recently demonstrated in 8 patients (studied on generator Integra during four weeks, depending on four modalities of dialysis), that the increase of the effective blood flow at 250 ml/min (with a venous pressure < 200 mmHg and using a short 15-Gauge stainless steel needle) improved significantly the amount of dialysis delivered by the unipuncture technique and increased the ionic dialysance by approximately 20 %, the monitor-recorded Kt/V and the single-pool Kt/V by approximately 15% (Figures 2, 3, 4, 5)[18]. Trakarnvanich and coworkers have also recently shown in 10 patients, that it was possible to obtain Kt/V identical to those obtained in bipuncture by increasing the time of dialysis from four hours three times per week to 4h30 or five hours (x3/week) and by using in parallel dialysis membranes of a surface area equal to or larger than two square meter [6].

4. Indications of transient single-needle hemodialysis

4.1. Accidents of cannulation of native fistulae

The primary indication of SN dialysis is represented by cannulation-related complications of native fistula or synthetic grafts [7]. In a Dutch study, conducted in 10 dialysis centers in the Maastricht area, 120 patients newly dialysed patients were followed prospectively for the first six months after initiation of hemodialysis to evaluate the frequency of complications caused by cannulation, the frequency of use of transitional venous catheterization or the number of transient SN dialyses ; 74% of the patients had a native fistula and 26% a synthetic graft [28]. The first cannulation of the vascular access using two needles was performed on average 119 days after the creation of native fistulae and 70 days after installation of the synthetic grafts [28]. During the follow up period, only 9% of patients had not presented any accident of cannulation ; a transitional central venous catheterization was necessary in 16% of patients for an average period of 11 days for those with native fistulae and 1.5 days for those with a synthetic graft ; 24% of patients benefited from a transitional SN dialysis [28]. In multivariate analysis, the only predictive factor for successful puncture of the vascular access was the length of the cannulation route [28].

4.2. Native fistulae maturation during initiation of programmed hemodialysis

In the prospective Dutch study carried out in dialysis centers in the region of Maastricht, 51% of the cannulation accidents of native fistulae and synthetic grafts occurred during the first three programmed sessions of DN dialysis [28]. Indeed, in this study, the recommended practice was to perform initiation of hemodialysis straightaway, using the bipuncture technique. These data strongly suggest that too early and too brutal cannulation of native fistulae (and synthetic grafts) by two needles, is a source of later dysfunction of the vascular dialysis access. A Canadian team of dialysis nurses recently conducted a prospective study on the interest of the technique of cannulation by unipuncture at the initiation of hemodialysis [29]. Thirty-three new dialysis patients with native fistulae living in the London area of Ontario were therefore allocated for the first six sessions of dialysis to either SN dialysis (n= 22) or DN dialysis (n= 11) ; the criteria of judgment were the number of transitional venous catheteriza-

tions and angiographic investigations of the fistulae and number of missed dialysis sessions in the first three months after initiation of hemodialysis [29]. The number of transitional venous catheterization was reduced by 50% in the group treated by SN dialysis (9.1 % versus 18.2 % in the bipuncture group); the number of angiographic investigations of fistulae was reduced by more than 60% (13.6 % unipuncture group versus 36.4 % in the bipuncture group) ; the number of missed dialysis sessions because of problems of vascular access was similar in the two groups [29]. These two recent studies provide compelling evidence to recommend the practice of a transitional period of SN dialysis to allow the maturation of native fistulae at initiation of scheduled hemodialysis.

4.3. Other indications of single-needle dialysis

Single-needle dialysis may be proposed in situations of "rescue dialysis" such as regional dialysis with anticoagulation by citrate [30] or when bringing to term a rare pregnancy in dialysis [31]. SN dialysis has been used with success in North America, in patients in daily night dialysis presenting vascular access problems [32]. The prolonged use of SN dialysis has also been proposed for a period of several months in carefully selected patients on conventional hemodialysis with severe vascular access problems [6, 15] ; in such cases the increase in dialysis time, the use of large surface area membranes and the optimization of the blood flow are typically required [7]. In these situations, the monitoring of the dose of dialysis delivered by ionic dialysance should also be currently the rule [7]. Because data on the long-term use of SN dialysis are scarce, physicians should be cautious when using prolonged SN dialysis in selected patients.

5. Conclusions

The primary indication of SN dialysis is represented by cannulation-related complications of native fistulae or synthetic grafts. Recent data strongly suggest that the dialysis dose reliably assessed by ionic dialysance and delivered by transient SN dialysis can be improved by increasing the blood flow rate. Increasing the effective blood flow rate from 180 ml/min to 250 ml/min during SN dialysis is possible in most patients using a short 15-gauge arterial stainless-steel needle, without hemolysis, leading to improved ionic dialysance. This latter regime seems acceptable for short periods of one or two weeks. The use of a larger membrane surface area (> 2 m^2) and blood flow higher than 250 ml/min, if tolerated by fistulae, can improve the efficiency of SN and increase the dialysis dose to a sufficient level. Nonetheless, careful monitoring of the dialysis dose delivered is required during SN dialysis, as single pool Kt/V, dialysis monitor-recorded Kt/V and ionic diaysance may be far below European Best Practice and KDOQI recommendations. For longer-term SN dialysis, an increase in the dialysis time or a switch to daily dialysis is needed to obtain efficiency similar to that of conventional DN hemodialysis. Since data on the long-term use of SN dialysis are scarce, caution is warranted if SN dialysis is prolonged. Finally, recent studies have also shown that SN dialysis is a valuable option at the start of programmed dialysis on native fistulae allowing their maturation and reducing the risk of stenosis and thrombosis.

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Abbreviations

SN dialysis : Single-needle dialysis

DN dialysis : double-needle dialysis

Kt/V: fractional clearance of urea ; this is the normalized dose of dialysis, determined from the clearance of urea and reported to the patient's total water volume.

Dialysis monitor-recorded Kt/V : normalized dose of dialysis determined from the ionic dialysance and reported to the volume of total water of the patient ; the latter parameter is usually calculated using Watson's formula. Because of the overstatement by this formula of urea distribution volume, dialysis monitor-recorded Kt/V underestimate from 20% to 30% the " single pool" Kt/V.

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Chapter 30

Complications of Autogenous Arteriovenous Fistulas

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Additional information is available at the end of the chapter

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1. Introduction

Autogenous arteriovenous fistulas (AVF) are the preferred vascular access for patients with end-stage kidney disease. They are cheap and easy to construct, have excellent patency rates and require minimal maintenance by the patient and the health care staff. However, they can develop various complications, which have different rates of incidence, morbidity and mortality. Most of them threaten the functionality of the fistula and some of them even pose an immediate vital risk. We believe it is important that all health care professionals who deal with patients on whom an AVF is performed should have thorough knowledge of the types, physiopathology, risks and treatment of these complications.

Our team has performed 832 surgical constructions of autogenous AFV in the last 5 years. The number of complications that required surgical revision was 61 (7.3%). This is comparable to a 9% rate of complications reported in a study of 628 patients, by Fokou et al. in Cameroon [1]. The patients in this population have numerous comorbidities besides the end-stage kidney disease; among them, diabetes mellitus, hypertension and chronic viral hepatitis. These 4 are factors who augment the complication rate after any surgical intervention. However, the number of events requiring surgical exploration following AFV construction is relatively low, probably because of increasing experience and technical skills of vascular surgeons.

The complications can be divided in 2 categories:

1. Acute complications
2. Chronic complications

2. Acute complications

These are complications that occur in the first hours or days after the construction of an AVF and always require evaluation by a vascular surgeon.

Thrombosis of the fistula occurs when there is inadequate flow through the fistula, which leads to stasis and thrombosis. Thrombosis of the fistula occurs mostly in patients with inadequate venous run-off, i.e. history of subclavian vein catheters, multiple venous punctions with local fibrosis [2]. We do not use preoperative Duplex exam to assess the vein [3]. Local inspection at the time of surgery should be performed, and if the vein is small, fibrotic or with a visibile thrombus inside, another vein should be used. We also assess the vein by flushing it with a heparinated saline solution via a catheter; if there is resistance in advancing the catheter, injecting the solution or no backflow through the catheter, a proximal stenosis of the vein should be suspected, which leaves no alternative but using a different vein. Building an anastomosis that is too tight, restricting the blood flow, coupled with systemic hypotension can also be incriminated in acute thrombosis. We advise our patients to maintain their blood pressures in the 130-150 mmHg interval during the fistula's maturation period. Hypotension sometimes occurs during the first hemodialysis (HD) session performed after the operation, using an indwelling HD catheter. This is the reason why a newly constructed fistula should be assessed by the medical staff at the beginning and end of all HD sessions.

Introducing a catheter on the subclavian vein of an arm with a functional AVF can lead to thrombosis, either immediate or after the first HD session.

Other causes of thrombosis are extrinsic compression of the operated arm, e.g. wearing clothes with tight sleeves or sleeping on the respective arm.

In the acute setting (during the first 12-24 hours), thrombosis can be solved by surgical thrombectomy. If, on palpation, the vein is tender, pulsatile in the initial segment but with no thrill, the vein can be opened longitudinally and a Fogarty catheter passed both distally (towards the subclavian vein) and proximally (towards the anastomosis). Flushing the vein with a heparinated saline solution is mandatory. A thrill should be obtained after removing the cross clamp. There is an increased risk of pulmonary embolism associated with this procedure, making its' use subject to a very careful evaluation of the patient and close monitoring. In the past 5 years, only 3 patients were operated on for acute thrombosis of the fistula (0.3%) by our team – compared to an incidence of 2% in other studies [1]. All three cases preserved the AVF after thrombectomy.

Bleeding is the most common acute complication. Spontaneous bleedings are not uncommon in uremic patients, in whom the primary mechanisms of hemostasis are compromised, including thrombocytopenia, platelet dysfunction and von Willebrand factor's changes. Chronic anemia, which is common in uremic patients, also negatively influences the rheologic component of the platelet – vascular wall interaction. All of these factors concur to the fact that, in the postoperative setting, a bleeding is unlikely to spontaneously stop.

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Bleeding sources have several causes. There are smaller sources, with no significant hemodynamic impact, but with a continuous flow, generally overestimated by the patient and his family. These smaller sources are dermal, subdermal or from the subcutaneous tissue. If the patient undergoes a session of hemodialysis (HD) or heparination of the hemodialysis catheter shortly after the AVF has been constructed, bleeding is usually the norm. In our practice, we have observed that a delay of 36 hours between the operation and the HD session makes bleeding complications exceptional. We routinely recommend to all patients abstention from HD during this time period.

The wound is inspected, and if only a dermal bleeding point is found, with no hematoma, then the source is sutured under local anesthesia. This maneuver can be performed in the emergency room. Local digital compression or applying a hemostatic sponge generally does not stop the bleeding. Compressive dressings are to be avoided, as they can stop the blood flow through the fistula.

There are also larger sources, with a higher flow and a life-threatening potential. They are usually found at the site of the anastomosis or a slipped vessel ligature and are accompanied by a hematoma.

In the past 5 years, 4 of our 832 patients (0.5%) presented for bleeding requiring surgical exploration. In all the cases, the bleeding source was a slipped ligature on the distal end of the vein used for the AVF, with accompanying hematoma. The incision was reopened, the hematoma removed and bleeding source sutured. The wound was then flushed with an antiseptic solution and closed.

Although uremic patients are prone to bleeding due to their pathophysiological changes to the mechanisms of hemostasis, in our experience, the small number of bleedings and the fact that a "mechanical" cause is found, we believe that there is no benefit in running a series of extensive tests on these patients (thrombelastogram, von Willebrand's factor determination, clotting time etc). There is no doubt that each and every one of these patients' coagulation pathways are malfunctioning and are unlikely to spontaneously stop a bleeding. However, we feel that good surgical technique avoid bleeding in all patients.

Hematoma formation, with or without associated active bleeding, can demand surgical exploration of the wound. There are several situations that can be encountered. A hematoma with no active bleeding through the sutures may not impart on the fistula's functionality. If the hematoma is small and the AVF's thrill is present, there is no surgical indication and the patient is routinely monitored. If the hematoma is larger, and the thrill is modified or absent, the hematoma must be evacuated, followed by closing the bleeding source and AVF repermeation. Sometimes, removing the hematoma can bring back the thrill; if this does not occur, thrombectomy of the AVF or even construction of a new AVF should be performed.

Hematoma associated with bleeding with dark red blood is accompanied by an alteration of the thrill, rendering it sharp, dull, short and systolic only. Surgical exploration and hematoma removal usually turn the thrill back to normal. The bleeding source is probably a slipped ligature from the distal end of the vein used for the fistula. The volume of blood flowing from the wound can appear quite high; in this situation, the patient or untrained medical

personnel can interpret this as anastomosis disruption and can apply a tourniquet on the arm, which completely closes the flow through the fistula, making it unsalvageable. As previously stated, we have operated on 4 patients with active bleeding and hematoma. The bleeding source was found to be a slipped ligature on the distal end of the vein. In 2 patients, a tourniquet had been placed on the arm prior to presentation, so the fistula could not be salvaged, but only the bleeding stopped. In the other 2 cases, the fistula was preserved and later matured and was used for HD.

Hematoma accompanied by bright red blood oozing through the sutures has an arterial source – at the anastomotic level or a collateral arterial branch. The flow through the fistula is severely compromised due to the compression, leading to venous and possibly arterial thrombosis. After suturing the source, arterial and venous thrombectomy with a Foley catheter are performed; making sure not to injure the arterial or venous wall with the balloon catheter.

3. Chronic complications

These are complications that occur days or months after the construction of an AVF.

Thrombosis is caused by inadequate flow through the fistula, which leads to stasis. Causes of inadequate flow are discussed earlier. Other causes include intimal hyperplasia of the anastomosis, thrombosis of a venous pseudoaneurysm with consecutive thrombosis of the whole vein and extrinsic compression of the vein during its' maturation period (for example, during sleep) [4] [5]. If the patients presents promptly, an attempt to salvage the fistula can be made via a surgical thrombectomy with a Fogarty catheter [6] [7]; if the vein has aneurysmal changes, it is probably not amenable to surgical treatment. If the fistula is unsalvageable, a new one must be constructed under the protection of a temporary hemodialysis catheter.

Anastomotic pseudoaneurysm is a rare complication with severe consequences, which requires emergency surgery. In our group, 7 patients (0.8%) developed this complication. A pseudotumoral, pulsatile mass appears at the level of the incision used to create the fistula; this mass is tender, increasing in size and may be painful. The overlying skin has inflammatory and necrotic modifications. A septic process is quite always involved, which disrupts the anastomosis. The origin of the infection can be intraoperative or a clinically silent infection in a patient wearing a HD catheter. The main risk is of overlying skin necrosis with massive bleeding. Surgical exploration is mandatory. Usually, a partially thrombosed false aneurysm is found, with partial anastomosis disruption. A fragment of the pseudoaneurysm's wall is sent for a bacteriological exam and a full course of antibiotics is given after the operation.

Further action depends on the artery used for the fistula and the patient's general condition. If the radial artery is used, it is ligated; we have seen this scenario in only 3 cases and there were no ischemic complications after interruption of the radial artery. In the case of the brachial artery, which has a higher ischemic potential, the main goal is pseudoaneurysm removal and rebuilding the arterial continuity. This can be performed via a termino-terminal arterial anastomosis (as one of our patients has received) or by a venous graft interposition, using either an arterialized venous segment, or with a greater saphenous vein segment, if

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there are signs that the arterialized vein is infected. In cases with severe septic potential and aggravated general condition, the brachial artery can be ligated. Three of our patients received this treatment, fortunately without secondary ischemic events.

Venous aneurysm occurs in uncorrected hypertensive patients, months or years after fistula construction, irrespective of the fact that the fistula has or has not been used for HD (figure 1). The incidence of this complication was 3.6% (30 patients) in our group and 4.2% in the group from Cameroon [1].

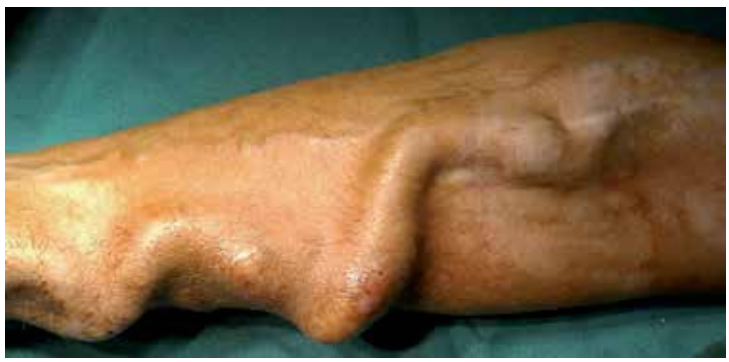

Figure 1. Aneurysm of the cephalic vein in a patient with a radio-cephalic fistula

A Doppler examination of the aneurysm shows turbulent blood flow and parietal thrombus (figure 2). The natural evolution of this complication is with total thrombotic occlusion or spontaneous rupture. Other associated processes are thrombophlebitis, infection, skin necrosis with imminent perforation and hyperdynamic syndrome[8]; these all require surgical treatment. Also, a quickly evolving aneurysm requires surgical intervention. Otherwise, the undilated segments of the fistula can be used for hemodialysis access[9].

Figure 2. Aneurysm of the cephalic vein with parietal thrombus

The fistula is ligated and a new one is constructed using a different vein. The aneurysm can be removed or left in place. Further control of blood pressure values ensures that the new fistula does not develop the same complication.

Among the 30 patients venous aneurysms in our group, we operated on 21. The fistula was ligated and a new one created with an available vein. These new fistulas developed no aneurysm once the blood pressure valued were kept in the normal range.

Venous pseudoaneurysm develops due to a common mistake made in hemodialysis services, which is repeated punctions at the same site. In time, the arterialized vein can grow to impressive sizes, develop a false aneurysm with partial or complete thrombosis. After repeated punctions, the overlying skin undergoes fibrotic changes, followed by necrosis, with a high risk of disruption and massive bleeding. This potential course of events makes surgery mandatory as soon as possible. The most common intervention is fistula ligation, followed by creating a new fistula with a different vein. In selected patients, who have no aneurysmal thrombi on Doppler exam or on palpation, a reductional plasty of the aneurysm can be performed. The entire aneurysm is exposed through a longitudinal incision, followed by proximal and distal cross clamping and wedge resection of the anterior wall of the aneurysm. The vein is rebuilt with a 7-0 Prolene continuous suture. The proximal segment of the vein can be used for HD after 36 hours and the dissected segment, after 3 weeks.

Eight of our 832 patients (0.9%) presented for venous pseudoaneurysm and were operated on immediately. We performed fistula ligation in 5 cases, followed by creation of a new fistula after 3 weeks, during which time the patient underwent HD sessions via a temporary catheter. In the other 3 cases, after assessing the pseudoaneurysms with palpation and Doppler exam, we found them suitable for remodeling and a reductional plasty was performed in the described manner.

Skin necrosis also develops at the site of repeated punctions. It occurs after superficialization of a basilic or brachial vein, if the wound had been closed with a thin layer of skin overlying the fistula (figure 3). This heals poorly between HD sessions, as it has an inadequate blood supply, and becomes even thinner and necrotic; the venous wall is also thin and very fragile. Bleeding is the risk with this complication, and can be massive, life-threatening due to the high flow through the fistula (figure 4).

Figure 3. Skin necrosis at the level of a superficalized basilic vein

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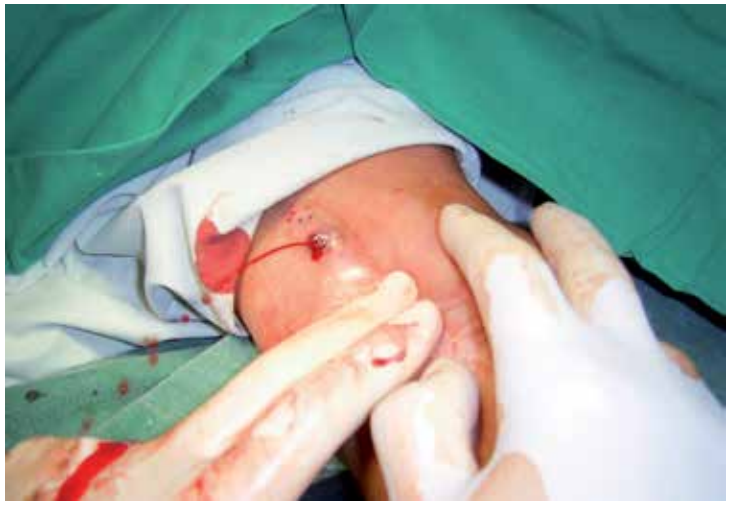

Figure 4. Bleeding from the necrotic skin area

Surgical treatment involves the bleeding point skin suture, then making a circular incision around the necrotic segment and carefully dissecting it away from the vein, without entering the vein.

Then the hemostasis can be easily performed with a 5-0 Prolene suture and the necrotic skin removed. The skin is then approximated with interrupted Prolene sutures. If bleeding occurs, the assistant compresses the fistula at the anastomotic level and proximally, on the arm, until hemostasis has been performed with interrupted 5-0 Prolene sutures. We routinely give an antibiotic regimen to our operated patients, usually 2 grams of Oxacillin per day, for 5 days.

We have seen this complication in 3 of our 832 patients (0.3%). Two of them bled from the necrotic area before presenting to the hospital. They were all operated on and made an uneventful recovery.

Hand ischemia is the most serious complication of vascular access surgery. The patients have all the clinical manifestations of chronic limb ischemia: muscular atrophy of the thenar and hypothenar eminences with functional impotence of the fingers, cold extremities, pain at rest, which becomes excruciating during HD sessions [10]. Gangrenous changes of the fingers are sometimes present (figure 5).

The patient is usually diabetic and has atherosclerotic lesions distal to the anastomosis. Blood flow is diverted through the vessel with a lower resistance, which is the vein – the "steal syndrome" [11]. Under normal conditions, when the radial artery is used for the fistula, the hand is still supplied with blood via the ulnar artery and the vascular arcades of the hand. However, there are cases when the arcades have clinically silent lesions (i.e. negative Allen test), which become significant if the distal radial artery is interrupted while constructing the AVF. This is why we attempt to maintain the distal radial artery open after creating the fistula. Hand ischemia can also occur if the brachial artery is used and is usually more serious.

Figure 5. Ischemic hand and necrosis of the fingers in a patient with a brachio-cephalic fistula

All attempts should be made to salvage the limb firstly, and the fistula, secondly. The most direct and simple technique is outflow ligation. The vein is exposed close to the anastomosis and doubly ligated with a number 5 Nylon tape. The thrill should disappear and distal perfusion is immediately improved, with quick remission of symptoms. The major drawback is that the AVF is lost for further access.

Other AVF preserving techniques aim to decrease the flow through the fistula. These are banding of the vein, prosthetic graft interposition (ePTFE nr.5) and venous by-pass using the accessory radial vein. These techniques will be discussed in the hyperdynamic syndrome paragraph.

The DRIL procedure (Distal Revascularization Interval-Ligation) has been described by Schanzer in 1988 [12]. The artery is ligated distal to the anastomosis. An arterio-arterial bypass is performed between the proximal artery (usually, the brachial artery) and the distal arterial territory (usually, the radial artery). Immediate technical success rates are excellent, with an overall reduction in ischemic events; however, if graft failure occurs, the entire distal extremity is at risk of gangrene and may require amputation [13][14].

In patients with a brachio-cephalic fistula and pseudoischemic symptoms accompanied by venous engorgement, we have found a patent accessory radial artery, which originates high in the arm, from the cephalic vein. This vein had a retrograde flow which impeded the venous outflow of the cubital region and the forearm. Ligation of this vein led to the disappearance of the venous engorgement and the ischemic symptoms.

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Hand ischemia can also have technical reasons, if the anastomosis causes reduction in diameter or even occlusion of the distal brachial artery. In this setting, the fistula is also sacrificed, this time by ligation followed by arterial reconstruction at the site of the anastomosis.

This complication occured in 7 of our 832 patients (0.7%). We were forced to ligate the fistula in 6 cases and perform vein banding in one other case. There have also been cases of ischemia associated with hyperdynamic syndrome; these cases will be discussed below.

Hyperdynamic syndrome is a consequence of greatly increased blood flow through the fistula, with consecutive volume overload of the right heart and cardiac failure. It is a relatively rare complication and can occur irrespective of the age of the fistula. It is associated with brachial artery use, which has a larger diameter and thus a higher flow (1-1.1 L/min) when compared to the radial artery (0.65 L/min) [15] [16] [17]. After the maturation period, Doppler examinations show flows of 8-10 L/min through the fistula. Local examination shows venous dilatations and the patients are restless and show dyspnea, orthopnea and sinus tachycardia [18]. Almost all of them are hypertensive, with uncorrected BP values in spite of treatment. The aim of the surgical treatment is to decrease the flow through the fistula.

Fistula closure promptly makes this syndrome disappear. However, this means that the heart has to rapidly adapt to new hemodynamic conditions (with severely decreased venous return). Transient bradycardia, hypotension and syncope can occur. With this patients subgroup, we always ligate the fistula under close monitoring (EKG, blood pressure and SpO2).

As previously stated, there are also techniques which aim to preserve the AVF. Banding the vein decreases the vein's diameter and thus increases the resistance flow and decreases the flow. The vein is dissected and encircled with a tape which is progressively tightened until the thrill becomes less intense, the heart rate drops below 100 beats/minute and the dyspnea gets clinically better. It is sometimes difficult to establish a precise amount of banding that prevents the steal syndrome but still allows fistula patency. In the setting of reduced flow that results from fistula banding, thrombosis can occur with further transient flow decrease, for example in hypotensive states [15][19]. Also, in our experience, banding offers only a momentary decrease of symptoms. For this reason, we prefer to use alternate techniques and have used this technique in only 3 patients in the last 5 years.

Prosthetic graft interposition uses a nr.5 ePTFE graft, which obviously has a much smaller diameter than the arterialized vein and thus a higher resistance. A 4-5 cm segment of the vein is dissected; 3-5 cm are removed and the graft is interposed via 2 end-to-end anastomoses. Approximating the end of the vein and the graft can be difficult, due to the difference in size. Alternatively, the vein can be left in place and the graft sutured via 2 end-to-side anastomoses, followed by ligating the fistula between the 2 anastomoses. This eliminates the size-mismatch. The surgeon must resist the urge of using a larger graft, as this does not reduce the flow in a significant manner.

To decrease flow, we have also created a venous by-pass using the accessory radial vein. This is usually found in the forearm, where it merges with the median cephalic vein, creating the cephalic vein. But there are cases when it has a high origin, in the arm, lateral to the

cephalic vein. Even after arterialization of the cephalic vein, this branch maintains a small diameter and can be used to divert the blood flow from the larger cephalic vein (figure 6).

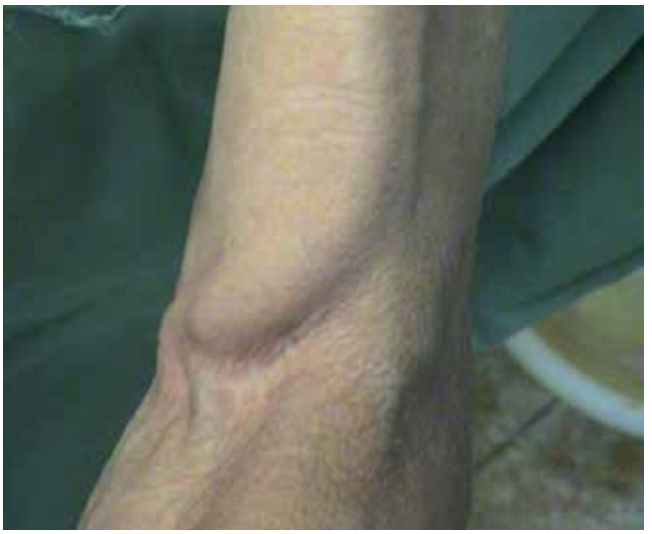

Figure 6. Accessory radial vein with a high origin in a patient with a brachio-cephalic fistula

During surgery, it is dissected from its' origin in the cephalic vein for a distance of 5 cm, then anastomosed end-to-side to the cephalic vein after the arterio-venous anastomosis. The cephalic vein is then interrupted between the newly created anastomosis and the origin of the accessory radial vein (figure 7). The patients receive one week of antibiotics after the intervention.

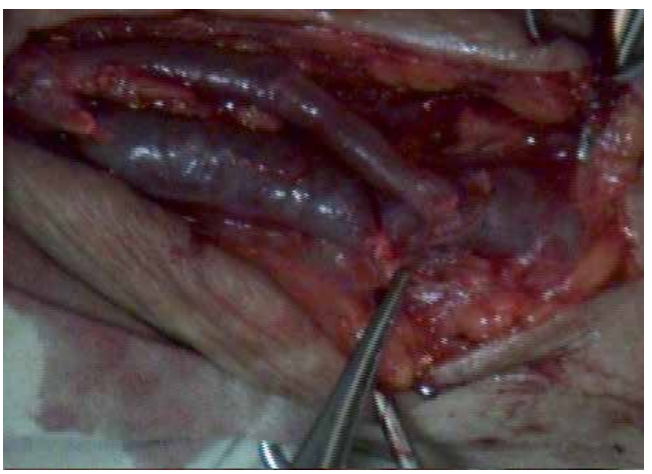

Figure 7. The anastomosis is complete and the cephalic vein is ligated distal to the anastomosis

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In 4 of our patients (0.4%) we performed a by-pass with a PTFE graft; 3 other cases (0.3%) received a venous by-pass. The results of by-pass (either using a prosthetic graft or the accessory radial vein) are very good at short and mid-term follow-up. Heart rate is maintained at less than 100 beats/minute with great clinical improvement. Doppler echography shows diminished flows, of 4-5 L/min. The fistula remains functional with no residual steal syndrome. In conclusion, the surgical treatment that we favor for hyperdynamic syndrome is venous by-pass with the accessory radial vein, whenever available; if not, graft interposition is the next option.

Hand edema is a relatively frequent, but usually transient complication in vascular access surgery. It is more frequent when the superficial veins have been used up and a brachio-brachial fistula is constructed. Venous hypertension occurs shortly after AVF creation, but it diminishes after collaterals develop and outflow improves. Outflow obstruction due to stenosis of a central vein provoked by a long-term indwelling catheter or by neointimal hyperplasia from the turbulent flow of the AVF also cause venous hypertension. Sometimes, venous tributaries become dilated, incompetent and perfuse retrograde toward the forearm and the hand, thus increasing the capillary pressure. If the hypertension does not subside, it is accompanied by the classic symptoms of a venous stasis syndrome: edema, pigmentation and ulceration. The whole upper extremity can become involved in the edema, which sometimes includes the chest wall and the breast. A rich collateral venous circulation also develops. There are rare cases when the edema is so important that it produces ischemic phenomena. Treatment consists of repair of the fistula outflow or ligation of the fistula; improvement is immediate and dramatic, with edema reduction and healing of ulcerations within 1-2 weeks.

We have seen no cases of edema requiring surgical correction during the past 5 years.

Lymphorhea is a relatively rare complication (<1% of operated patients)[7]. Patients with a thick layer of subcutaneous tissue, which has been extensively dissected, complicated with postoperative upper arm edema sometimes develop it. We have never seen it in conjunction with radio-cephalic fistula. In our experience, it is more frequent with the brachio-brachial fistula. The wound closes and heals following several (sometimes daily) sessions of HD, and frequent changing of dressings. If a septic process develops, surgical debridement and antibiotherapy become necessary.

Infection is a rare complication with severe repercussions [20]. In the past 5 years, only one of our patients developed it (0.1%). If intraoperative contamination occurs, after a short period of time the wound becomes inflamed, painful, with purulent discharge, accompanied by fever. Vascular access creation is forbidden in a patient which carries a HD catheter but presents with fever and leucocytosis; in this case, the anastomosis becomes infected due to bacteremia and is extremely susceptible to disruption. These patients should be postponed until a new catheter is implanted in a different site and the old catheter removed and its' tip sent for bacteriological examination, followed by proper antibiotherapy. The most common infectious agents encountered are *S. aureus* and *S. epidermidis*. Reinterventions for bleeding or fistula thrombosis also increase the risk of infection. The higher the number of reexploration, the higher is the chance of acquiring an infection. For this reason, we believe that the

maximum number of reinterventions is 2 in 24 hours. If the fistula is not functional after these 2 reinterventions, we wait until the incision heals before trying to create a new fistula using the same incision. Late anastomotic pseudoaneurysm formation is also a septic complication, which can develop even if the incision is healed.

If the wound shows a purulent discharge, the patient must be evaluated by a vascular surgeon. There are 2 therapeutic options. The conservative one is drainage of the collection, followed by washing with an antiseptic solution. A more aggressive option is closure of the fistula, also followed by antiseptisation of the wound. For a radio-cephalic fistula, the radial artery can be ligated without any ischemic consequences. For a fistula using the brachial artery, the fistula must be closed and arterial reconstruction performed. In the setting of acute bleeding, with fragile arterial wall, arterial ligature is mandatory; ischemic phenomena may occur, but this is not the rule.

In all cases, antibiotherapy is indicated.

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Chapter 31

Hemodialysis Access: Initial Considerations and the Difficult Patient

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Additional information is available at the end of the chapter

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1. Introduction

The population requiring hemodialysis (HD) in the United States continues to grow, with recent studies reporting over 370,000 Americans with end stage renal disease (ESRD) who are HD-dependent [1]. The creation of functional HD access is often the limiting step in utilization of renal replacement therapy (RRT). Since the 1960s, the creation of hemodialysis access has become one of the most commonly performed procedures in the United States with over 500,000 vascular access procedures performed per year [2]. This represents approximately 8% of the annual Medicare budget allocated to patients with ESRD [3]. The magnitude of the associated economic and human costs is further exemplified by the fact that up to 25% of patients with ESRD will die due to inadequate hemodialysis access [5]. This clinical situation and societal burden makes understanding the basic management steps and options for hemodialysis access of key importance to all healthcare professionals involved in the care of patients who require HD.

2. Timing of referral

There is only limited literature on the optimal timing of patient referral for placement of vascular access [6]. What has been shown is that patients with ESRD who are referred to a vascular access practitioner greater than one month before likely initiation of HD had a significantly lower chance of having a tunneled catheter as their first access option [7]. The early placement of arteriovenous access is also associated with a lower risk of sepsis and mortality [8]. At present, the Society for Vascular Surgery makes the following recommen-

dations regarding HD access: (a) Patients should be referred to vascular access surgeons for placement of permanent hemodialysis access when they have advanced renal disease defined as MDRD of <20 to 25mL/min who have elected to have hemodialysis as their choice of renal replacement therapy; (b) If upper extremity arteriovenous access is possible it should be constructed in these patients as soon as possible; (c) If prosthetic access is to be constructed this should be delayed until just before the need for dialysis [9].

3. Initial evaluation

The initial evaluation of a patient referred for HD access placement begins with an adequate history and physical examination. This aids in the determination of the most appropriate access option for the patient [10]. The initial questions should include attention to which is the patient's dominant extremity and any history of prior upper extremity interventions or symptoms of arm claudication. The physical examination should document any physical evidence that the patient has had a prior central venous catheter (CVC) and the upper extremity pulse exam as well as an Allen test (Figure 1) should be performed to evaluate the palmar arch patency. Further, the patient's chest, breast, shoulders, and upper arms should be evaluated for the presence of abnormally enlarged collateral veins which may indicate the presence of central venous occlusion or stenosis (Figure 2).

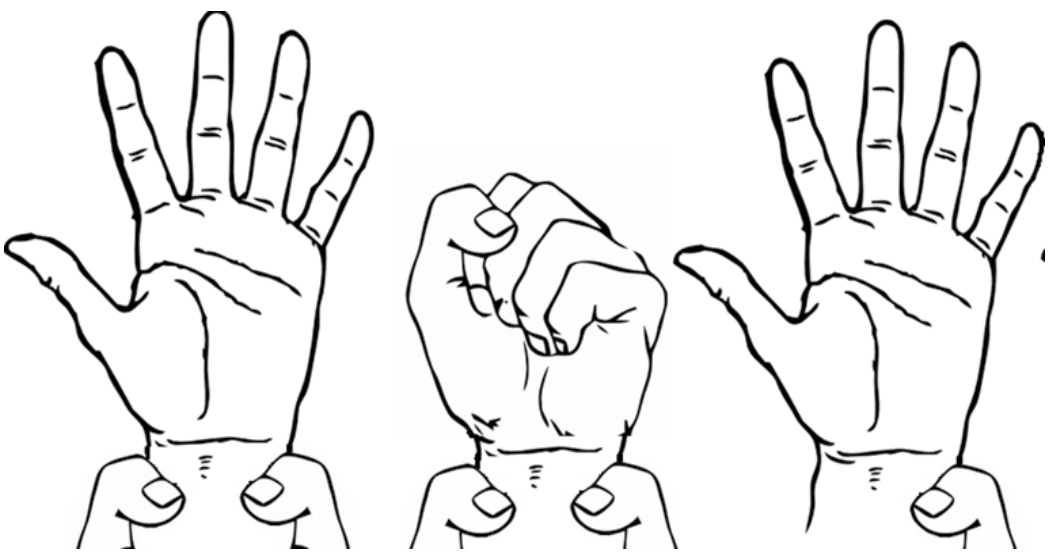

Figure 1. The Allen's test is used to assess the patency of both the radial and ulnar arteries. In this test, the physician compresses both arteries at the level of the wrist with the hand outstretched. The patient is then asked to open and close the hand into a fist several times with both arteries still compressed. The hand is then relaxed and the radial artery is released. The entire palm and digits should fill demonstrating good collateral flow. The test is repeated, with the ulnar artery being released. Again, the entire palm and digits should fill.

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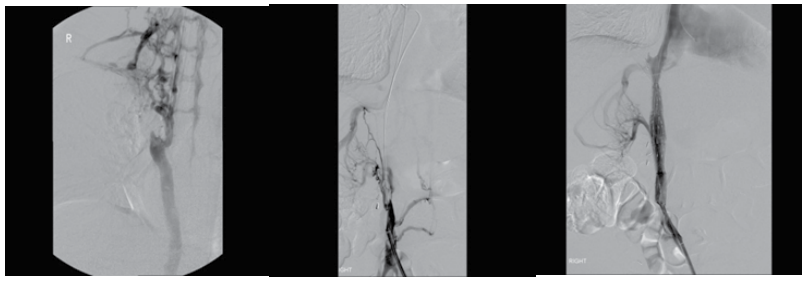

Figure 2. Superior vena cava (left) and inferior vena cava (middle) occlusion secondary to central venous catheter. The inferior vena cava underwent stent recanalization to allow future transplantation (right).

3.1. Initial evaluation: Doppler ultrasound and beyond

Two considerations are crucial when looking for an appropriate arterial target in the creation of an arterio-venous (A-V) access point. The artery selected must be capable of not only delivering blood flow at an adequate rate to support dialysis but must also have adequate flow to maintain the viability of the tissues distal to the A-V anastomosis [11]. The physical examination alone is often not sufficient to confirm appropriate vessel patency. One randomized trial demonstrated that the primary A-V fistula failure rate was as high as 25% when the pre-operative assessment depended on physical examination alone compared to 6% when noninvasive imaging was used [12]. Routine noninvasive testing should include bilateral upper limb segmental arterial pressures and Doppler ultrasound scanning or pulse volume recordings. The focus of this testing should be on documenting the following three characteristics: (a) the patient should have less than a 20 mmHg difference in systolic blood pressure between the two arms; (b) the palmar arch should be patent; (c) the arterial target should have a diameter of 2 mm or greater at the proposed anastomosis point [13, 14]. Doppler Ultrasound can further aid in identifying any stenotic arterial segments in addition to describing arterial diameter and flow [15, 16]. If any abnormalities are noted on noninvasive testing then secondary access site(s) should be considered or the patient should be referred for an angiogram [17]. Angiography is especially useful in patients with known peripheral vascular disease or in those with suspected proximal arterial occlusive disease.

The selection of an appropriate venous target is of critical importance. If there is avascular problem that is going to cause technical difficulties in the creation of an arteriovenous fistula it is more likely to be venous than arterial in nature. Routine vein mapping provides improved functionality and patency of arteriovenous fistulas as well as primary fistula formation [18, 19]. Preoperative vein mapping has further been shown to decrease the rate of unsuccessful surgical exploration (18). Color flow Doppler ultrasound is considered superior to other forms of vein evaluation as it avoids the use of nephrotoxic dyes. Further, vein mapping by ultrasound allows for evaluation of the depth in addition to size of the vessel in question [20, 21]. When the history or physical evaluation raises the concern for central venous stenosis or occlusion then venography is superior to ultrasound duplex imaging [22]. Magnetic resonance venography (MRV) has been reported as an imaging option for perio-

perative evaluation of the central venous anatomy but has not been shown to be more clinically or cost effective than standard venography [23-25].

4. Tunneled catheters

Though the present clinical guidelines attempt to limit tunneled catheters to <10% of total permanent hemodialysis access, this percentage continues to be higher at most centers [26]. Beyond this, tunneled catheters often are required to serve as a bridging therapy to maturation of some A-V fistulas and grafts. Consequently, tunneled HD catheters constitute >250,000 dialysis access procedures in the United States every year [27].

4.1. Basic options

Dialysis catheters may be divided into short- or long-term devices. The distinction between the two catheter categories has little to do with anatomic considerations and more so with catheter type and placement technique. Short-term catheters may be placed at bedside using standard Seldinger technique into the internal jugular, subclavian or femoral vein. These are usually double lumen, non-cuffed, non-tunneled catheters. To achieve the best dialysis flow rates the catheter tip, when in the subclavian or jugular vein, should be located in the superior vena cava (SVC) just above the cavoatrial junction. If femoral access is chosen, a longer catheter should be used to ensure that the tip is within the distal inferior vena cava (IVC). These short-term catheters are intended for the patient who requires acute HD access and should ideally be used for <3 weeks. The subclavian vein should be avoided to decrease the rate of central venous stenosis [28]. It should be noted that many of the temporary HD catheters are somewhat stiff and may cause some degree of trauma to the SVC, contributing to potential scar formation/stenosis. In the interest of minimizing such vascular trauma, silastic catheters can also be used in temporary capacity, without creating a subcutaneous tunnel and or burying the cuff.

Longer term external HD catheters are in general silastic double lumen catheters with felt cuffs which require tunneled placement under fluoroscopic guidance. These central venous catheters (CVC) can be inserted into the internal jugular, subclavian, external jugular or femoral veins and may be used for six months or longer due to their decreased incidence of infection [29, 30]. The right internal jugular location is preferred due to generally higher continuous blood flows available for dialysis and lower complication rates [30, 31]. Again, to decrease the risk of central venous stenosis dialysis catheters should be placed contralateral to the proposed future site of any A-V fistulas if possible [32]. Central venous stenosis appears to occur more often with the subclavian (40-50% cases) than the internal jugular insertion (up to 10%) in long-term catheters [33, 34]. Reports estimate the average 1-year catheter patency at approximately 75% [35] with most catheters lost secondary to bacteremia [32].

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4.2. Tunneled dialysis catheter placement in the difficult access patient

When standard catheter access options for HD have been exhausted in the internal jugular and subclavian positions, alternatives must be sought. The most common reasons for venous site "exhaustion" are venous stenosis or occlusion [36-38]. In an effort to reduce femoral access for placement of long-term catheters given the increased incidence of infection, and the risk of iliocaval thrombosis interfering with possible future renal transplantation, alternative upper extremity access points have been studied. Wellons *et al*, evaluated a novel method of accessing the SVC through a supraclavicular approach [39]. In their series fluoroscopic guidance was used to direct placement of the dialysis catheter at a point immediately cephalad to the head of the right clavicle into the SVC. In that study most catheters functioned from one to seven months.

Due to the development of central venous occlusion or stenosis many patients develop significant central venous collaterals. Techniques have been described whereby a wire and a snare is passed through these collaterals and attempted to be placed into a vein which can be visualized with duplex ultrasonography. Once this occurs the vascular practitioner must snare the wire into the IVC prior to passing the HD catheter using the conventional Seldinger technique [40, 41].

An alternative technique to femoral access for placing a cuffed dialysis catheter into the IVC is through a translumbar approach. Two case series described the use of this method for HD access [42, 43]. In this approach the patient is placed in the prone or left lateral decubitus position. A small incision is made approximately three centimeters lateral to the midline above the right iliac crest at the L3 vertebral level. Under fluoroscopic guidance a wire is inserted into the IVC. Under direct visualization the HD catheter is then passed in such a manner that the catheter tip is positioned at the junction of the IVC and the right atrium. For this approach preliminary data suggests that the rate of catheter thrombosis, fibrin sheath formation and infection parallel those of more traditional access sites [44-48]. The cumulative patency rate for this approach reported was 52% at 6 months and 17% at 12 months [43].

A somewhat more aggressive option for HD access is the transhepatic venous approach. This approach has been described mainly in case reports or small patient series [49-52]. The main concern regarding this approach is not its utility as a functional HD access, but rather the significant associated morbidity and mortality. In particular, the risks of catastrophic bleeding, biliary tract fistula formation, infection, hepatic dysfunction, and high rates of dislodgement make this approach too risky for most patients [53]. From a technical standpoint it requires more skills than standard venous access approaches. A guide needle is placed under fluoroscopy approximately halfway through the liver in a direction parallel to the right and middle hepatic veins and directed toward the confluence of the hepatic veins. Once an acceptable hepatic vein is engaged, a guide wire is advanced toward the right atrium. The tract is then dilated until the double lumen dialysis catheter can be placed [54, 55]. In one of the case series, the complication rate was as high as 29% with one death from massive hemorrhage [54]. This approach has a high rate of catheter malfunction requiring frequent repositioning [55]. Most authors stress that this approach should be used only as a last resort.

A hybrid device between an arteriovenous graft and catheter is the HeRO access option (Figure 3). This device type is specifically designed for patients who central venous stenosis which would prevent a fistula or graft from providing enough flow to maintain functional dialysis. The device is tunneled underneath the skin. An outflow synthetic tube is inserted into the central vein and advanced past the point of stenosis into the right atrium in order to provide continuous outflow to the system. A secondary PTFE 6mm graft component is then anastomosed to a peripheral artery.

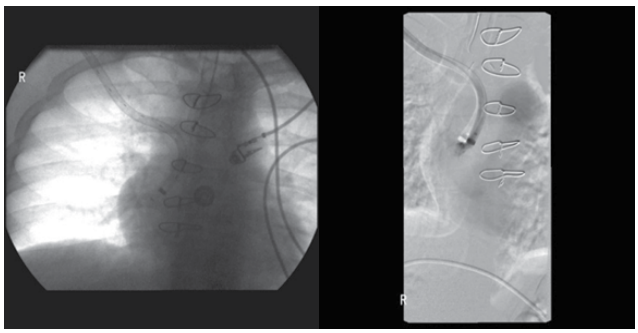

Figure 3. HeRO device with the tip at the cavo-atrial junction.

5. Arteriovenous fistulas

Of all HD access alternatives available the native A-V fistula is at present preferred. The NKF-K/DOQI guidelines have prompted the "fistula first" campaign to encourage A-V fistula as the first access option [56]. The native A-V fistula has the lowest infection rate, best long term primary patency rates and requires the fewest interventions of any type of access to remain functional [57, 58]. The society for vascular surgery makes the following Grade 1 recommendations regarding the placement of native A-V access: (a) That the access be placed as far distally in the upper limb to preserve proximal sites for future use; (b) Upper limb access sites be used first with the non-dominant arm given preference over dominant arm only when all other access opportunities are equal [9].

5.1. Forearm access

The first considerations for creation of the A-V fistula must focus on which distal vein to use. Within the forearm there are several readily attainable anatomic options: the cephalic, basilic, and antecubital veins. When considering the distal inflow options the arterial choices include the radial, ulnar and brachial arteries. The distal cephalic vein (Figure 4) is the preferred venous option due to its location and the minimal surgical dissection involved [59].

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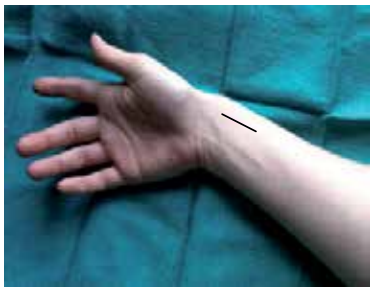

Figure 4. The anatomy of the patient guides the direct access type. The classic first option for most patients is the creation of a Brescia-Cimino-Appel Fistula, an autologous radial artery to cephalic vein fistula [4]. If one can readily appreciate the arterial pulse and vein then a single longitudinal or curvilinear incision over the anterior aspect of the wrist is used.

If however, the vein and artery are separated by too great a distance then two separate longitudinal incisions are made and the vein is ligated distally prior to being passed through a subcutaneous tunnel to create the A-V anastomosis. An additional option is the creation of the so called "snuffbox fistula" whereby an anastomosis is created between the end of the cephalic vein and the posterior branch of the radial artery located in the anatomic snuffbox. This anastomosis requires a single longitudinal incision overlying the palpable pulse of the branch of the radial artery. After these initial options have either failed or have been deemed impossible due to anatomic factors, consideration must be given to more proximal sites in the forearm. The radial artery and cephalic vein may still be a viable A-V paring more proximally but these procedures in general require transposition of the vein and will be discussed later.

5.2. Upper arm access

Upper arm access options which do not mandate either transposition or translocation procedures typically use the cephalic or antecubital veins and the brachial artery. In this situation, a single transverse incision is created and the cephalic or antecubital vein is mobilized prior to dissecting out the brachial artery. In cases where the vein and artery are anatomically remote from one another, two separate incisions are created and the vein is tunneled toward the artery prior to preforming the anastomosis. In comparison to radiocephalic fistulas, the brachiocephalic A-V fistula (Figure 5) has been shown to mature faster and has higher long term patency rates [60].

5.3. Transposition procedures

The objective of a transposition fistula is to move the vein to a more superficial position to ensure that the vein, once mature, is optimally position for safe HD cannulation. As in all other fistula formation, care must be taken to evaluate underlying anatomy and access options for the individual patient. Several options are available, each with unique limitations and technical considerations.

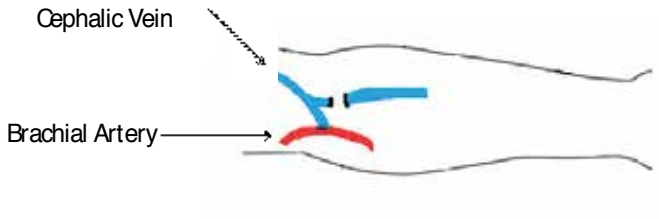

Figure 5. Diagram of brachiocephalic A-V access anatomy.

A radial artery to cephalic vein transposition may be required in the obese patient [61]. For this particular procedure, sufficient wrist inflow must be available with adequate forearm cephalic vein size which would otherwise be too deep for successful HD cannulation. In this option, the cephalic vein is identified in the wrist and mobilized to the antecubital fossa. The radial artery is identified within the distal portion of the incision. The cephalic vein, after ligation of the distal aspect, is then tunneled superficially and laterally to the radial artery to perform the anastomosis. If the distal radial artery is not amenable to create the A-V anastomosis then a similar approach may be used to mobilize the cephalic vein. However in this case, the brachial artery is identified in the proximal portion of the incision. The cephalic vein is again tunneled superficially in a forearm loop configuration to the brachial artery in order to perform the anastomosis after the distal cephalic is ligated.

A forearm fistula may still be planned if the cephalic vein is not acceptable. In this situation the basilic vein may be used, although its deeper position makes this more technically challenging. An access option may still however be planned using the basilic vein and radial artery. The basilic vein is identified in the wrist and mobilized to the antecubital fossa. The radial artery may then be identified through a separate longitudinal incision, after which the basilic vein is tunneled superficially and laterally to the radial artery to perform the anastomosis. Again, if the radial artery is not amenable for use in A-V access creation the basilic vein may be anastomosed to the brachial artery. The basilic vein is mobilized from the wrist to the antecubital fossa and the brachial artery is identified within the proximal portion of the incision or through a separate incision if necessary. The basilic vein is then tunneled superficially in the forearm in a loop configuration after the distal aspect is ligated prior to performing the A-V anastomosis. In general, the primary patency rates for brachiobasilic fistulas are higher than for brachiocephalic [62]. However, secondary patency appears to be equivocal.

If anatomic considerations preclude the use of a forearm fistula or if forearm fistulas have already failed, then attention is directed toward the upper arm. There are several upper arm transposition procedures available. Due to technical considerations, the brachiocephalic upper arm transposition is in general preferred to brachial basilic upper arm transposition access options.

In brachiocephalic upper arm transposition, the cephalic vein is identified just proximal or distal to the skin crease at the elbow and mobilized toward its origin. The brachial artery is

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identified in the distal aspect of the incision. The cephalic vein is then ligated distally. The superficial aspect of the vein is labeled to ensure that no torsion of the vein occurs during tunneling. The vein is then tunneled superficially and medially so that it comfortably aligns with the artery. If vein mapping demonstrates a cephalic vein <4 mm in diameter then this procedure may be performed in two stages, whereby the distal cephalic vein is anastomosed to the brachial and then transposed in four to six weeks [63]. The two stage approach is beneficial as the small caliber cephalic vein is relatively fragile and may be damaged by an attempted transposition procedure initially. It is felt that it is better to allow arterialization of the proximal small cephalic vein such that it becomes more robust prior to attempted transposition. A basilic vein to brachial artery approach may be performed similarly, with technical limitations again being the anatomy of the basilic vein and the required deeper dissection. Much as in the brachiocephalic transposition a two-step staged operation may be warranted [64]. The described functional patency of these two-stage brachial-basilic fistulas was 76% at one year [64]. Maturation rates for these two staged transposition procedures range from 47% to >95% [64-66]. Studies that compare brachiobasilic fistulas with upper arm grafts have generally found improved primary patency, cumulative patency, and less risk of infection for fistulas, but mixed results for other complications [66, 67].

Once standard upper extremity A-V access options have been exhausted, lower limb access may be considered. As with other non-standard access options, the literature supporting the use of distal extremities is still limited. The use of a saphenous vein loop transposition to the common femoral artery was first described in 1969 [68]. In this option, the saphenous vein is exposed and mobilized from the saphenofemoral junction to the knee. The vein may be harvested via open or endoscopic approach. Once an adequate length has been mobilized the distal component is ligated and the vein is tunneled superficially in a loop configuration so that it reaches comfortably to the proximal superficial femoral artery. Recent case series demonstrate poor maturation potential of this technique with nearly 30% of the studied patients not achieving functional maturity [69]. In those patients who do obtain functional maturity the time to secondary failure is approximately 16 months [70]. There are significant limitations with this technique that must be considered. In patients who are morbidly obese this may not be a viable option if the pannus overlaps the loop graft preventing comfortable needle cannulation. Further, the great saphenous vein does not dilate after arteriovenous creation and only veins which are greater than 3mm in diameter should be used.

If the patient's saphenous vein is not anatomically usable due to size, but a lower extremity A-V access is still required for the patient, a femoral artery to femoral vein transposition may be considered. In this approach, the femoral vein is exposed and mobilized down to the popliteal vein at the knee. The profunda femoral vein is preserved to prevent venous hypertension and compartment syndrome. The femoral vein is ligated distally at the knee and transected. The vein is then tunneled superficially through the subcutaneous tissues lateral to the vein harvest incision so that it comfortably reaches the superficial femoral artery. The reported primary and secondary patency rates for this technique at 12 months are 73% and 87%, respectively. However, in the largest reported case series for this technique, limb ischemia requiring additional surgery was common occurring in >30% of patients [71, 72]. One of

the 25 patients studied developed compartment syndrome which ultimately required an above knee amputation [71]. Further, the reported flow rates for femoral vein transpositions can be has high as 2000 mL/min [73] which requires considerable caution in the use of this technique for patients who have or are at risk for congestive heart failure.

5.4. Translocation procedures

Saphenous vein to forearm translocation procedures for development of A-V access are of mostly historical note. In overview, the saphenous vein is harvested distal to the saphenofemoral junction to above the knee. Once the vein is harvested, attention is turned to the forearm of choice. The saphenous vein is placed in a straight configuration between the radial artery and either the antecubital or the cephalic vein. The saphenous vein is then tunneled superficially between these two vessels and an anastomosis is performed [74]. Studies examining this technique are in general older and do not describe outcomes in terms of functional patency. Due to this fact comparing this technique to outcomes reported in the contemporary literature is difficult.

An alternative approach uses a translocated superficial femoral vein. It is critical in this approach that the patient's lower extremity arterial circulation is adequate to heal the wounds from the vein harvest site. In addition to vein mapping, the patient should undergo Duplex ultrasonography with segmental pressures to ensure sufficiency of the arterial system. It must also be determined that the femoral vein itself is patent and has a diameter >6 millimeters.

In this technique, an incision is made in the groin and extended along the medial border of the Sartorius muscle. The muscle is retracted laterally in the proximal thigh and medially in the distal thigh to allow for adequate exposure of the femoral and popliteal vein. The femoral vein is harvested next to the profunda vein but significant care is taken not to damage the profunda vein in order to minimize the development of venous hypertension and distal compartment syndrome. Attention is then turned toward the upper arm of choice. The brachial artery proximal to the antecubital fossa is isolated. A tunnel is then created between the brachial artery and axillary vein over the ventral upper arm. The femoral-popliteal vein is then reversed and tunneled superficially so that it reaches comfortably between the axillary vein and brachial artery. Huber *et al*. reported on the outcome of 30 saphenous vein translocations [75]. In this series, the primary, primary assisted, and secondary patency rates for the saphenous vein translocation accesses were 79%, 91%, and 100%, respectively, at 12 months; and 67%, 86%, and 100%, respectively, at 18 months. Two patients developed lower extremity compartment syndrome after the vein harvest, and nearly 30% of patients developed upper limb critical ischemia requiring re-intervention.

6. Prosthetic access

If no autogenous access options exist in the upper extremities then consideration of upper extremity prosthetic access may be considered. The additional risks of infection in prosthetic grafts are offset by the fact that prosthetic access options meet maturity for hemodialysis

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sooner than autogenous options. As with all forms of hemodialysis access options, care must be taken to tailor the surgical approach to the patient's anatomy and specific dialysis needs.

6.1. Forearm

The main prosthetic access options in the forearm, is the brachial artery to antecubital vein forearm loop access graft. In this technique a transverse incision is made proximally to the skin fold crease at the elbow. The brachial artery and antecubital vein are isolated. A 6 mm or tapered 4-7 mm prosthetic graft is then tunneled in the subcutaneous space of the forearm. This requires a small distal transverse incision to be made so that the graft may be appropriately aligned. The anastomoses are then created. A straight line prosthetic graft may also be used between the radial artery distally and the antecubital vein within the antecubital fossa. The vein is again exposed through a transverse incision distal to the skin crease of the elbow and a distal longitudinal incision is made over the pulse of the radial artery. The prosthetic graft is then tunneled superficially and laterally such that it is readily amenable to performing the two anastomoses. In general, prosthetic grafts have inferior primary and secondary patency rates and higher incidence of complications including infection and thrombosis when compared with autogenous fistula [66, 76-78].

6.2. Upper arm

Upper arm options for prosthetic graft placement are varied. The brachial artery may be used but if this is difficult owing to scar formation or prior infection, the axillary artery may be utilized as inflow. In general, the axillary or basilic veins are used with the graft in either a loop or straight configuration. Grafts in this area may be cannulated for dialysis access within 2-4 weeks sooner than native fistula formation [62]. Non-maturity failure is relatively low in patients receiving an upper arm graft with reported incidence of <10-20%.

6.3. Lower extremity access

Lower extremity prosthetic options are reserved for cases where upper extremity access options have been exhausted. The main disadvantage of the lower extremity prosthetic graft is the increased rate of infection compared to upper limb access options [79-84]. The infection rates vary from a low of 8% to a high of 41%. Further, there is an associated limb loss with the prosthetic lower extremity graft which is not observed in upper extremity graft [80-84]. The operation itself is relatively simple due to the large size and anatomic locations of the femoral vein and artery. This anatomic consideration is reflected in the relatively superior patency rates for lower extremity access grafts compared to upper limb grafts. Studies which use the standard convention established by the American Association for Vascular Surgery (AAVS) demonstrated that the secondary patency rates ranged from 41-85% at 1 year and 26-83% at 2 years [79-84]. Due to anatomic considerations, the surgical management of complications associated with this type of HD access are somewhat easier to manage than chest wall grafts and high axillary grafts. Finally, the patient has both hands free during HD which theoretically may improve their quality of life.

Lower extremity A-V graft placement is usually performed under general anesthesia. A longitudinal incision is made overlying the femoral pulse. The femoral artery and greater saphenous vein are exposed. The superior femoral artery and greater saphenous vein near the saphenofemoral junction or femoral vein (depending on anatomy) are isolated. The superficial femoral artery is preferred as an inflow option over the common femoral artery due to the presumed advantage in dealing with complications such as infection and arterial "steal" phenomenon in this artery. To perform the mid-thigh loop access, an incision is made along the medial border of the Sartorius muscle. The muscle is then retracted laterally to gain access to the femoral vessels. The artery and vein of choice are then mobilized and controlled. The graft must be tunneled over the anterolateral aspect of the thigh which helps ensure positional access for hemodialysis without the patient having to externally rotate the thigh. In general, a 6 mm graft is used though some authors describe the use of 8mm synthetic graft.

6.4. Prosthetic cervical and chest wall access

Most patients who are considered for a cervical or chest wall access procedure have already had prior central venous HD catheters and multiple upper extremity procedures and interventions. Therefore, in patients where these unusual approaches are considered it is imperative that appropriate imaging studies are performed to confirm central venous patency prior to any surgery. In addition to anatomic considerations, the dominant handedness of the patient influences the choice of right or left sided procedures much as it does in the standard A-V access options.

Prosthetic chest and cervical access reports date back to 1978 though the information regarding patency rates and complications is mainly limited to case-based evidence [85-88]. Described options for chest and cervical A-V access options include: (a) brachial artery to jugular vein access; (b) axillary artery to contralateral axillary or jugular vein; (c) axillary artery to ipislateral axillary vein loop access. The described secondary patency rates for these procedures range from 37% to 80% at two years [85-88]. Chest and cervical prosthetic access options appear to be associated with a significantly lower infection rate than those of the lower extremity. The described infection rate for these options ranges from 4% to 15% [85-88]. Further, this access option may be beneficial in patients who are morbidly obese in whom the anatomic limitations of a lower extremity access option include the size of the pannus [85]. One major disadvantage of these access options is the technical difficulty in obtaining proximal control of the axillary vessels.

7. Arterial-arterial access procedures

Arterial-arterial access procedures (Figure 6) should only be considered after all conventional options have failed. The literature describing these procedures is relatively scant and relies mainly on a few case series and reports [89, 90]. Bunger *et al*. reported a series of 20 patients who had axillary artery to axillary artery interposition with PTFE grafts [89]. These patients had a 30% re-operative rate. However, at 6 months the grafts had primary and sec-

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ondary patency rates >90%. Limb ischemia was reported in one patient whose access graft thrombosed but this resolved after thrombectomy. Zanow *et al* published a series which looked at arterial anastomoses involving axillary and femoral arteries [91]. The primary patency rates in this series at one year were >70% and >50% at three years. These access procedures have been suggested for patients who have previous access-related limb ischemia and high output cardiac failure. There are significant concerns with the arterial-arterial access options. First, the dialysis units should be aware of the nature of these patients' access and should treat each needle cannulation as an arterial stick requiring at least 20 minutes of hemostatic pressure. Second, the flow rates reported in some case series demonstrate that the arterial-arterial loop access does not appear to provide flow rates as high as standard A-V access options and therefore dialysis blood flow rates exceeding 400 mL/min may cause discomfort for the patient. Finally, this access option should not be used to infuse medications during dialysis as described by the original authors.

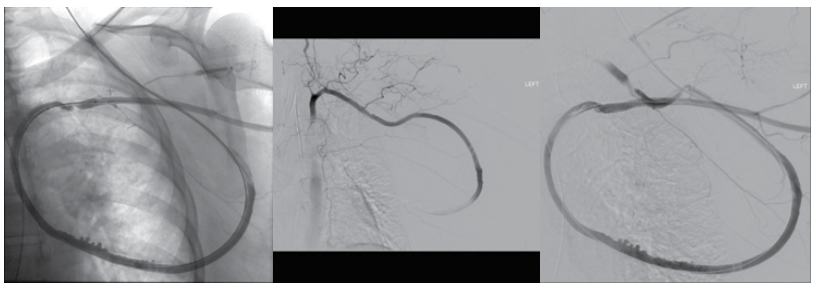

Figure 6. n example of an arterial-arteial "last resort" hemodialysis access. An arterio-arterial loop graft was placed in a patient whose venous access options had been exhausted. She later developed graft dysfunction which on angiography proved to be due to neointimal formation at the outflow anastomosis (left image). This responded well to balloon angioplasty (right-most image).

8. Complications of arteriovenous access

As with all surgical procedures care must be considered in the creation of arteriovenous fistulas. A wide variety of complications are described in the literature but the following bear special deliberation.

8.1. Access failure

The mode of failure is usually related to the type of access constructed. Catheter function is usually limited by the formation of fibrin sheaths at the catheter tip. The life expectancy of catheters, as previously mentioned, is severely limited by their propensity for infection. For both native and synthetic arteriovenous accesses the issue is very often the development of outflow stenosis leading to limited flow dynamics. Such central venous stenoses were classically treated with angioplasty or stenting. Of interest, a novel technique has been described

using radiofrequency (RF) activated wire, and snare technique for recanalization of chronic central venous occlusions in order to allow passage of HD catheters [92].

Prosthetic grafts have a higher thrombosis rate than native fistula but their functionality is often more readily returned after intervention. Intimal hyperplasia is the greatest unresolved problem in hemodialysis access. It can occur anywhere in the outflow tract and severely limits functionality and dialysis flow. It is likely the number one driving factor in primary patency failure rates after basic anatomic considerations. The literature reports a wide degree of primary patency rates and as such recognizing this critical problem rather than exact percentages is of more clear clinical benefit.

Access	1 year primary patency*
Upper Extremity Catheter	43-65%
Femoral Catheter	14%
Translumbar Catheter	17%
Transhepatic Catheter	52%
Forearm extremity AV fistula	60-75%
Upper Extremity AV fistula	64-95%
Upper Extremity AV graft	34-84%
Lower Extremity AV graft	40%

Data based on references [2, 28, 29, 31, 34, 35, 59, 60, 62, 63, 66-68, 70, 75, 77-79, 82, 84, 93-97]

Table 1. Primary 1-year patency rates of different hemodialysis access modalities.

8.2. Steal phenomenon

Ischemic lesions which result from an arterial steal phenomenon directly related to arteriovenous fistula formation (Figure 7) have become more frequent in this increasingly elderly and high co-morbidity patient population. Clinically significant steal syndrome occurs in 1% of autogenous AV distal access options verses 9% prosthetic AV graft. There are in general two distinct types of this steal phenomenon: high flow and low flow. The more readily correctible of the two is high flow steal. In this situation the fistula with a very low resistance is able to redirect or 'steal' blood from the distal anatomy creating critical ischemia of the digits. In theory, this should be readily correctable by decreasing the size of the anastomosis and reducing blood flow through the fistula [98, 99]. Recalling the physics of fluid dynamics and Poiseuille's law, one understands that the resistance of a column of fluid is in relation with the fourth power of the radius. Essentially, this requires that significant reduction in the fistula lumen's size is needed to adequately address the flow steal phenomenon. This reduction of course poses the risk of low flow, thrombosis, and destruction of an otherwise functional fistula. This can be achieved by banding the fistula's venous outflow to reduce flow demands on the distal arterial system or revising the fistula to a more distal artery itself.

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The low flow fistula requires more consideration and is significantly more difficult to address. In general, this results from stenosis of the peripheral arteries such that even normal blood flow across a fistula will create critical distal ischemia. There are only a few therapeutic options available. The first is to abandon the fistula via ligation and use a central catheter as the patient's only hemodialysis option. An alternative to this is the so called DRIL or distal revascularization-interval ligation [100, 101]. In this situation, the artery distal to the arteriovenous fistula anastomosis is ligated such that the fistula no longer feeds off the distal arterial vessels. The distal artery is then fed via an interposed segment of either vein graft or synthetic graft.

Figure 7. An example of advanced stage "steal syndrome".

Stages of Steal Syndrome	Grade	Clinical Signs
Stage I	Mild	Pale, blue or cold hand without pain.
Stage II	Moderate	Pain during exercise or hemodialysis
Stage III	Severe	Pain at rest
Stage IV	Limb Threatening	Ulcers, necrosis, gangrene

Table 2. Steal syndrome has been classified into four different stages based on the clinical impact and degree of effect on the limb in question [93]

8.3. Congestive heart failure

High fistula flow may cause hyper-circulation and thereby congestive heart failure in the already cardiac compromised patient. Hypercirculation occurs when the outflow resistance is too low. The most common cause of this is an anastomotic lumen which is too large. An additional advantage of the native arteriovenous fistula over synthetic graft is that this engorged lumen rarely occurs in native tissue [101, 102]. The only way to confirm that the fistula flow is the direct cause of a patient's increased congestive heart failure is to perform quantitative flow studies. Once a diagnosis has been confirmed, banding procedures are recommended to decrease the fistula's lumen size. These procedures have varying rates of success. If necessary the fistula should be ligated to improve the patient's outcomes after placement of a central catheter has occurred

8.4. Paget Schroetter syndrome

Paget Schroetter Syndrome or stenosis of the central veins may unfortunately be present in this patient population prior to vascular access formation. In most patients it is clinically asymptomatic prior to the demands placed upon the central veins from the arteriovenous flow dynamics. If a central stenosis is unable to accommodate the flow rates required by the vascular access point the result will be swelling of the affected limb, cyanosis, and the formation of significant collaterals. In general, central stenotic regions are the result of prior subclavian catheters [33, 103]. As with other fistula related complications, onetreatment option includes ligation of the anastomosis and the use of another limb after exclusion of bilateral stenosis. However, given the available endovascular techniques, correction with balloon angioplasty or stenting should be attempted first with surgical correction of the venous outflow stenosis also a final option [104-106]

8.5. Aneurysm

The formation of aneurysms, in A-V fistulas, is usually the result of progressive destruction of the venous vessel wall over time with replacement of normal tissue with inferior scar collagenous tissue [107-109]. Once an aneurysm has developed there is a tendency for progression due to the wall stress placed on the vessel. Wall tensile stress increases as the diameter of the vessel increases such that the larger an aneurysmal dilation gets the greater the flow dynamic changes which occur within its boundaries. Conditions which favor the formation of an aneurysm and which may be prevented include the repetitive single site puncture of a fistula for dialysis access. Also any areas of stenosis with their resultant pre-stenotic rise of outflow pressure and direct increase in tensile flow force changes will increase the likelihood for aneurysm formation. Aneurysms are cosmetically unappealing to most patients but beyond this they have the chance for significant complications including rupture and infection. Therapeutic treatment of aneurysmal disease within a fistula includes partial or complete resection and the correction of any accompanying stenosis [107-109].

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8.6. Pseudoaneurysm

Temporary HD catheters, as previously discussed, are not free of complications. The most common is of course infection, followed by central stenosis. A further and more localized complication is the formation of pseudoaneuryms. Pseudoaneuryms occur after arterial puncture. The puncture site in HD access is in general unplanned, and unintended arterial punctures do occur. When the arterial puncture site fails to seal, allowing arterial blood to jet into the surrounding subcutaneous tissue, a pseudoaneurysm may form [110]. These lesions do not have a true wall and their borders are formed by the congealed border of hematoma on subcutaneous tissue. The presentation of a pseudoaneurysm can be varied and may be as nonspecific as localized discomfort to as ominous as a pulsatile, expanding hematoma. Doppler ultrasound should be done promptly if the clinical suspicion for pseudoaneurysm is present. This allows the practitioner to characterize the anatomy of the lesion as well as its size. In general, observation is the appropriate management choice for smaller pseudoaneurysms. However, ultrasound-guided thrombin injection or surgery may be required if there is significant bleeding or the concern for limb ischemia develops. If procedural indications are not present, the practitioner may place the patient on strict bed rest, remove all optional anticoagulation, and apply focal compression. If the anatomy of the lesion is favorable then an ultrasound guided thrombin injection into the aneurysmal neck can immediately resolve nearly 75% of cases [111, 112].

8.7. AV Fistula/Graft thrombosis

The most common post procedural complication of arteriovenous fistula formation is thrombosis. The initiation of dialysis causes flow dynamic changes within the venous outflow. This stimulates intimal hyperplasia mainly at the outflow anastomosis in prosthetic grafts and potentially anywhere along the utilized vein within the native fistula [93, 113-115]. Defining why the graft or fistula has thrombosed is key to returning it to functional flow. Initially evaluation of the graft can occur within the dialysis center itself when the fistula is accessed. The fistula can be cannulated and the dialysis pump stalled. The venous needle pressure is then measured. If it is greater than fifty percent of the mean arterial pressure this is indicative of outflow malfunction. More reliable is ultrasound assessment and measurement of flow velocities across the graft. Both of these studies indicate graft malfunction and provide a tentative understanding of the abnormalities at work. Contrast imaging however gives greater anatomic information. Additionally, invasive venography provides an opportunity to treat both venous and arterial stenosis through the option of balloon angioplasty or more aggressively stent placement [116, 117]. When hybrid diagnostic and endovascular techniques fail then open operative intervention may be required to salvage the graft. Attempted thrombectomy may be done but this should also be performed in the conjunction with surgical revision of the stenotic segment. Surgical revision for fistula/graft stenosis is usually by use of an interposition graft or patch angioplasty [118].

9. Summary

Hemodialysis dependent patients require careful evaluation prior to the placement of initial and subsequent dialysis access sites. Patient factors such as age at presentation, previous history of central venous access, and long term prognosis must be factored into the consideration of HD access choice. Distal upper extremity fistulas should be attempted first unless patient factors preclude them. Only if the feasibility of native fistula options is ruled out should prosthetic grafts be used in the upper extremity. Central venous catheter HD access placement should be used sparingly and hopefully as a bridge to the maturation of native fistula or synthetic upper extremity graft. Lower extremity dialysis options should be reserved for only those patients who have exhausted upper extremity choices. Non-standard A-V or arterial-arterial fistula options should be limited to patients who have no other alternatives and should be performed by surgeons who have had experience in dealing with these more complicated procedures. Likewise, nonstandard central venous catheter placement should not be performed unless no other options for HD access are available.

I. Catheters	
	A. Internal Jugular
	B. Subclavian
	C. Femoral
	D. Translumbar
	E. Transhepatic
II. Forearm: Native Tissue	
	A. Posterior radialcephalic direct access "snuffbox"
	B. Radiocephalic anterior acces " Cimino"
	C. Radial cephalic forearm transposition
	D. Bacial cephalic forearm loop transposition
	E. Radial basilic forearm transposition
	F. Ulnar Basilic forearm transposition
	G. Bacial basilic forearm loop transposition
	H. Radial anticubital indirect femoral vein translocation
	I. Brachial antiecubital forearm indirect loopoped femoral vein translocation
	J. Radial antecubital forearm indirect saphenous vein translocation
	K. Brachial antecubital forearm indirect saphenous vein translocation
III. Forearm Prosthetic	
	A. Radial antecubital forearm straight access
	B. Rbracial antecubital forearm looped access
IV. Upper Arm: Native Tissue	
	A. Brachial cephallic direct

	B. Brachial cephalic upper arm transposition
	C. Brachial basilic upper arm transposition
	D. Brachial axillary upper arm indirect femoral vein translocation
	E. Brachial axillary upper arm indirect saphenous vein translocation
V. Upper Arm Prosthetic	
	A. Brachial axillary upper arm straight access
	B. HeRO hybrid graft
VI. Lower Extremity	
	A. Femoral vein transposition
	B. Prosthetic mid-thigh loop femoral-femoral access
VII. Chest Wall options	
	A. Axillary artery to axillary vein loop graft
	B. Axillary artery to jugular vein straight graft
	C. Axillary artery to axillary artery loop graft

Table 3. Summary of currently available hemodialysis access options

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Chapter 32

Vascular Access for Hemodialysis - Overview and Emphasis on Complications

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Additional information is available at the end of the chapter

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1. Introduction

A functioning vascular access (VA) represents a key issue in the management of patients needing acute or chronic hemodialysis (HD). However, VA surgeons, interventionists and all involved in VA creation and preservation are facing an everyday challenge, a huge one: How to meet their HD patients' VA needs. Most centers over the world are currently taking care of a steadily increasing and aging HD population, with more and more comorbidities, particularly diabetes mellitus, as well as of a growing proportion of prevalent patients with history of multiple access failures. With help of both autogenic and graft materials it has been possible to develop up to the present a wide armamentarium of VA options. However, all access alternatives are plagued with the same problems as in the past decades: thrombosis, infection, steal, etc, all of which limit their time span. In addition, anatomic sites for access creation are limited and may become exhausted. Every VA that fails brings the patient one step closer to a terminal access problem, a point where all roads seem closed. To avoid reaching this point, every VA team should be able, through careful planning and systematic application of adequate techniques for VA creation and preservation, to reduce VA-related complications to a minimum. In this chapter, a general overview of the field of VA for chronic hemodialysis in adult patients is offered where the most relevant topics are mentioned and briefly discussed. It is by no means an exhaustive review but we hope this way to convey an idea of the magnitude and complexity of the VA-related problematic and their possible solutions. We have dispensed with including details of VA history since a lot of well documented work on this issue is available in the literature.

2. Temporary blood accesses for HD

Temporary access in current nephrological praxis is synonymous with double lumen catheters whose main goal is to serve as interim VA. Emergent HD in a patient with chronic kidney disease (CKD) is the commonest indication for HD catheter insertion. It is a known fact that in most countries over the world a significant proportion, if not the majority of CKD patients starting HD do not have a functioning PVA [1]. Some of the reasons for this trend are:

a. many patients seek specialized medical care for the first time when frank uremic symptoms are present,

b. late referral to either a nephrologist or

c. to the access surgeon, etc, which do not allow for a permanent VA to be timely created.

Two types of double-lumen catheters are used for emergent acute or chronic HD:

a. non-tunneled, uncuffed (NTC) also called acute or temporary catheters, and

b. Tunneled, cuffed catheters (TC, called "permanent" catheters).

2.1. Non-tunneled catheters (NTC).

NTC are still the most commonly used catheter type for emergent HD and can be readily inserted, exchanged and withdrawn either at bedside or in a procedure at any center or outpatient dialysis facility. Although NTC are deemed to be used for a short dwell times (< 3 weeks), in some centers they are used for extended periods. Eventually, they are even exchanged for up to 2 times in case of malfunction [2].

2.1.1. Insertion technique

Typical NTC insertion method is the Seldinger technique, which consists in placing a catheter percutaneously through a guidewire [3]. Once inserted, the NTC should be firmly fixed to the skin by means of a monofilament nonabsorbable synthetic suture (polyproplylene or nylon). Multifilament, also called "braided" sutures like silk, should not be used because bacteria may hide within the interstices of the braids and this way the catheter entry site may become secondarily infected. A loose fixation of the catheter to skin causes a constant in- and outward movement of the catheter through entry site which favors bacterial colonization and infection. Dehiscent sutures lead to partial or total catheter extrusion. In case of partial extrusion, no attempt should be done to reintroduce the catheter but rather, if deemed safe, it may be exchanged over a guidewire.

2.1.2. Insertion sites

The preferred insertion site is the right internal jugular vein (IJV) mainly because in a great majority of cases it does not interfere with ulterior AV access creation on the ipsilateral upper extremity [4]. On the contrary, catheterization of the left IJV is not equally safe as the right one and is associated with left innominate vein stenosis or thrombosis [2,5]. Femoral veins are safer

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vein accesses in emergency settings particularly in patients with high risk of bleeding [6]. However, when left in place for extended periods, femoral catheters may lead to stenosis and thrombosis of the external and/or common iliac veins causing significant impairment of venous drainage of the lower limbs with mild to severe, painful edema. In transplantation candidates, external iliac vein thrombosis, which can extend up to common iliac vein may preclude ulterior renal graft placement on the affected side. With respect to subclavian vein approach, the KDOQI guidelines [7] strongly recommend its avoidance unless:

a. permanent access creation on the ipsilateral extremity is not possible because of severe arterial occlusive disease,

b. all potential access sites on the side are exhausted, or

c. when there is no other option.

Subclavian vein stenosis or thrombosis are a sequelae of 20 to 50% of subclavian vein catheters, which usually preclude ulterior use of ipsilateral arm for PVA creation [4]. Endovascular procedures like balloon angioplasty or stenting have proved useful in restoring central vein patency [8].

2.1.3. Ultrasound guidance

Real-time ultrasound guidance decreases significantly the rate of puncture-related complications in the case of IJV cannulation [9]. Landmark-guided puncture may be an acceptable alternative in experienced hands. Regardless of the employed insertion technique, in patients with history of previous IJV catheterization, checking sonographically for IJV patency (Figure 1) before making any catheter insertion attempt is strongly advised.

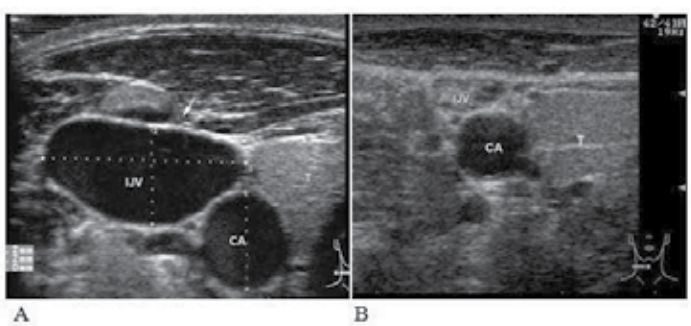

Figure 1. A) Normal ultrasound appearance of the right internal jugular vein (RIJV). (B) RIJV damage after catheterization.

2.1.4. Control chest radiographs

(for superior vena cava catheters) or an abdominal plain film (for femoral catheters) should be done to verify catheter tip position. Ideally, both posteroanterior and lateral thorax views

may be needed to better assess catheter location. Normally, catheter tip should lie at the junction of the vena cava with the right atrium so that the catheter side openings are located into the caval lumen (Figure 2). Catheter malposition (Figure 3) and puncture-related complications can also be readily diagnosed with chest radiographs in two views.

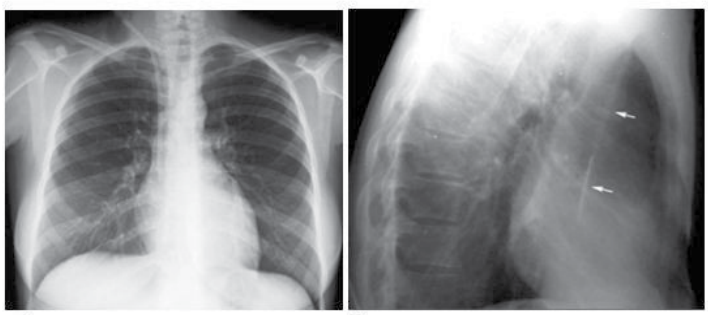

Figure 2. A) Posteroanterior chest X-ray showing normally located right-sided internal jugular vein catheter. (B) Normal lateral view of the catheter (arrows).

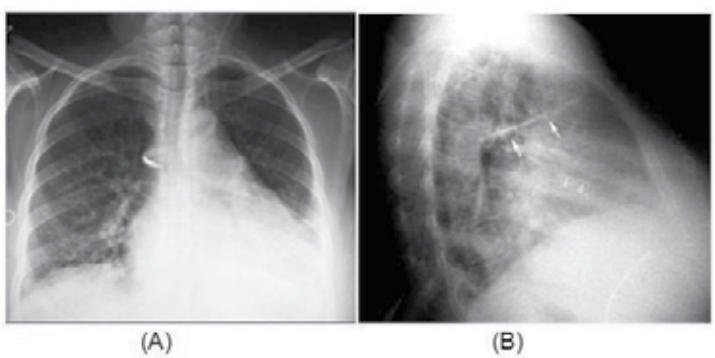

Figure 3. A) Abnormal location of a left-sided internal jugular vein catheter. Lateral thorax view (B) shows catheter tip (arrow) and side openings into the azygus vein.

2.1.5. Catheter length

The distance from insertion site to venoatrial junction may vary according to patients anatomy (height, obesity), thorax length and shape, central vein configuration and insertion route. However, as a rule of thumb, a catheter of 15-16 cm in length catheters may be adequate when placing right-sided internal jugular veins in adults. A 17.5-20 cm long catheters is required for either left internal jugular or left subclavian vein approach [10]. Femoral catheters should be 20-25 cm in length depending on insertion point and patient's physiognomy (i.e. obesity).

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2.1.6. Catheter dysfunction

NTC malfunction may be due to non-thrombotic causes like catheter misplacement, kinking, use of inappropriate catheter length and formation of pericatheter fibrin sleeve [11]. Thrombotic catheter occlusion is usually due to either intraluminal and/or mural thrombus formation. Malfunctioning catheters, except those having a fibrin sheath, mural thrombus or some evidence of infection can be exchanged over a guidewire. Biofilm formation begins immediately after catheter insertion by bacteria that has being carried by the catheter surface from skin entry site. With time, biofilm turns into a fibrin sheath o sleeve that covers side openings and adheres to the entire external surface of most catheters [12]. In advanced stage, a total extraluminal encasement of the catheter occurs causing backflow of blood which goes out through the catheter insertion orifice when dialysis pump is started. Thus, bleeding through catheter entry site only during HD indicates the presence of a fibrin sleeve and, the catheter should be removed. However, much of the fibrin sleeve may remain adhered to the vein wall after catheter removal [13] (Figure 4).

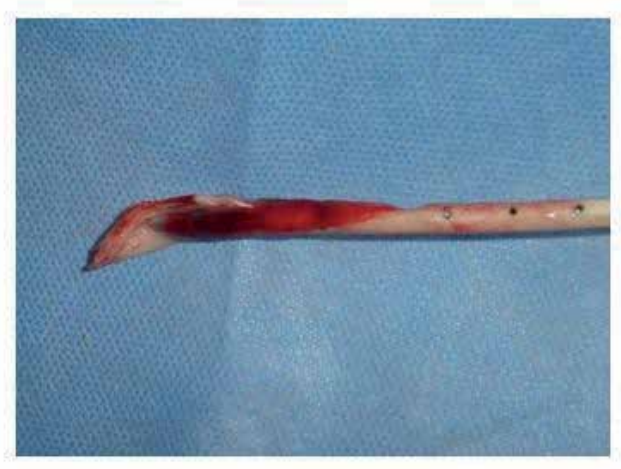

Figure 4. Catheter tip with adhered fibrin sheath.

Catheter exchange after balloon disruption of the sleeve has been reported to be a successful procedure in such cases [12]. Too short left-sided IJV or subclavian catheters may cause catheter malfunctioning as tip and side openings will lie within the lumen of the left innominate vein whose caliber and flow are lower than that of the vena cava [8].

2.1.7. Arterial Puncture

Central vein catheterization in patients with ESRD bears a higher risk of bleeding because of disturbances in platelet adhesion and aggregation. Carotid artery puncture can lead, if unadvertent, to formation of a big hematoma which can further extend in the neck and upper mediastinum causing external airway compression [14]. Mediastinal hematoma is a

rare but feared complication after unadvertent arterial puncture. Pneumothorax, hemothorax and chylothorax are complications more related to subclavian than to IJV cannulation. Femoral artery puncture can also lead to formation of huge hematomas at the groin. Retroperitoneal hematoma is also an extremely rare complication and results from inadequate puncture technique.

2.1.8. Bleeding at entry site

Bleeding around catheter entry site is most commonly due to a wide skin opening. Applying compression at entry site with sterile dressing may suffice to stop bleeding. Otherwise, the orifice can be reduced by stitching with 6x0 nylon suture which is usually effective to achieve local hemostasis. To prevent this complication, the size of the skin incision must be tailored as small as possible so that the catheter, once in place, fits tightly in the orifice. Persisting bleeding with bulging at puncture site points at a more serious cause of the bleeding and the patient should be immediately evaluated by a vascular surgeon. As mentioned before, bleeding only during HD is highly suggestive of encasement of the catheter by a fibrin sheath.

2.1.9. Catheter infection

Early infection of a new inserted catheter indicates poor aseptic conditions at the time of placement or inadequate catheter handling during HD or at home. Infected catheters may be the starting point of bacteremia and sepsis and there is an increased risk of metastatic complications, including endocarditis, septic arthritis, and epidural abscess. The relative risk of bacteremia is 7-fold higher in CKD patients with catheters than in those with an autogenous PVA [15]. Staph aureus and other grampositive bacteria like coagulase-negative staphylococcus and enteroccocus are the most commonly isolated agents in infected catheters [16]. Cultures of blood, entry site exudate and catheter tip play a key role in identifying the causative agent. Sensitivity tests to different antimicrobials with determination of minimal inhibitory concentration (MIC) are the basis for an effective antibiotic treatment.

2.1.10. Central vein stenosis and thrombosis

Despite improved catheter technology and better biomaterials, central vein stenosis continues to be the most serious middle- and long-term complication of HD catheters. Central vein stenosis may preclude permanent VA creation on the ipsilateral upper or lower extremity. Clinically, the development of superficial vein collaterals on the affected side or the development of limb swelling after ipsilateral arteriovenous access creation shoul raise the suspicion of central vein occlusion. This diagnosis can be confirmed by imaging procedures like angiotomography or MRI. In the past decades, endovascular procedures like percutaneous transluminal angioplasty (PTA) or percutaneous transluminal stenting (PTS) has proven useful and safe to recanalize occluded central veins with low rates of technical failure. However, multiple additional interventions are the rule with both treatment modalities since neither of them offer truly durable outcomes nor add to the longevity of the ipsilateral access [17]. Superior vena cava syndrome is an extreme manifestation of central vein stenosis and

results from multiple catheter insertions [18]. Femoral vein catheters may cause stenosis and thrombosis in the femoro-iliac axis precluding kidney graft placement on the affected side.

2.1.11. Postcatheterization arterial pseudoaneurysms and arteriovenous fistulas

are usually of iatrogenic origin. Some of them can close spontaneously. US guided compression has proven effective some cases. If ineffective, a more invasive treatment should be attempted. The standard approach has been surgical but currently, percutaneous endovascular implantation of covered stents has been reported to yield similar results while being less invasive [19].

2.2. Tunneled catheters (TC)

TC are made either of polyurethane, carbothane (polycarbonate-based polyurethane) or silicone. They are available in many shapes (straight or pre-curved), sizes (12-16 Fr), lengths (16-50 cm from tip to cuff) and tip forms (rounded, stepped or splitted). In addition, they may consist of either two single lumen catheters as the original Tesio catheter, which has 2 independent 10F catheters [20], or a double lumen device. All are provided with a polyester cuff favoring tissue in-growth for fixation of the catheter into the subcutaneous tunnel. TC can be either placed de novo or in exchange for a nontunneled catheter using the same insertion site without increased risk of infection [21,22].

2.2.1. Catheter insertion technique

A detailed description of all technical aspects of TC implantation are beyond the scope of this chapter. In principle, TC implantation technique is similar to that of NTC but a subcutaneous tunnel is additionally created to lodge the external segment or extension of the catheter. Catheter placement can also be done at a procedure room within the HD unit. TC offer some advantages over NTC. Tunneling from the neck to an exit site at the right or left upper chest quadrant below the clavicle brings greater comfort to patients, catheter extensions can easily be covered by dressings, concealed by clothing and, in addition, TC are suitable for outpatient management and care [23]. However, their disadvanges are many and far outweigh their advantanges [24]. In this regard, it should be underscored that tunneling does neither prevent nor make less severe central vein occlusion, which is the most feared middle- and long –term complication of all HD catheters.

2.2.2. TC infection

TC have been found to reduce the incidence of catheter-related bloodstream infection particularly when antibiotic lock is additionally used [25]. However, contrary to NTC, TC are not routinely withdrawn as first move in case of infection. Removal is only done in case of persistent infection or infection recurrence nonresponsive to antimicrobial therapy. Therefore, a major concern in such cases is the emergence of multidrug-resistant bacteria. Long-term indwelling TC are associated with five- to ten-fold increased risk of bacteremia and sepsis, significantly higher mortality risk, decreased likelihood of adequate dialysis, more frequent

hospital admissions and more frequent need for access surgeries [26,27]. It is essential to have cultures with blood drawn from catheter lumen as well as from a peripheral vein. Catheter infection can be confirmed by isolation of the same agent in both samples, particularly if the UFC count is 4-fold higher in the luminal sample than in the peripheral blood sample. Initial empirical administration of broad spectrum antibiotics should be followed by specific antibiotics when sensibility tests with minimum inhibitory concentration (MIC) data are available.

2.2.3. TC occlusion

Dysfunctional TC due to thrombotic occlusion requires administration of thrombolytic therapy to restore flow, decrease venous dialysis pressure and increase dialysis delivery. Tissue-type plasminogen activator (tPA, alteplase), is currently the only recommended antithrombotic agent for failing TC [28]. Single intraluminal instillation (in 30- 60 minutes) of low-dose (1 mg/ml) alteplase has been shown to increase catheter flow with significantly more patients achieving Qb=300 ml/min than with urokinase (5000 U/ml) (70% *versus* 35%; $P< 0.013$) and completing an HD session (93% *versus* 70%; $P =0.023$) [28]. TC are used as definite access in patients who have exhausted all options for PVA creation, cardial failure, severe occlusive peripheral disease or those with limited life span. Exceptionally, TC may be placed in unusal locations, like inferior vena cava (Figure 5) or left atrium.

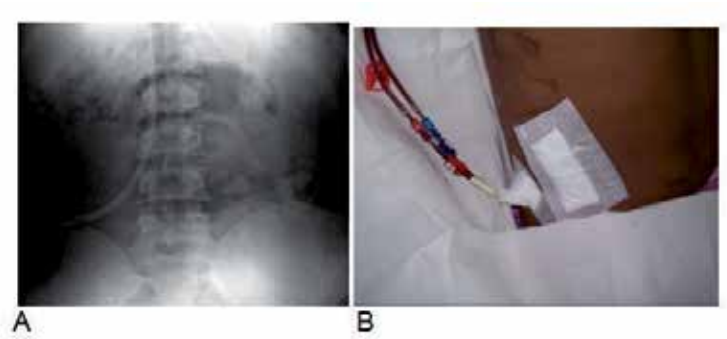

Figure 5. A) Tunneled catheter placed into the inferior vena cava. (B) Catheter being used for HD.

3. Permanent vascular HD accesses (PVA)

3.1. Measures to increase autogenic VA creation

3.1.1. Preservation of usual vascular sites for PVA creation

Preserving peripheral veins at both upper extremities (not only at the non-dominant side) as well as both subclavian veins is the mainstay for an ulterior successful PVA creation. The

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major veins of the upper extremity like the cephalic and basilic, eventually also the cephalic accessory, are the only appropriate vessels for creation of a fistula or graft and should not be routinely used for administration of fluid or medication, especially when irritating, because they may cause irreversible endothelial injury. Indiscriminate peripheral venipuncture is the first cause of loss of adequate veins for VA creation. Nursing personnel should be advised to use alternative veins like hand dorsum veins (Figure 6), the median or intermediate antebrachial vein and other minor forearm veins for intravenous fluids and medications. If there is some compelling need to use any of the major arm veins, cannulation should be done only for short periods of time, using small gauge needles, and rotating puncture sites to prevent phlebitis and thrombosis. Patients should ideally receive education about the importance of vein preservation.

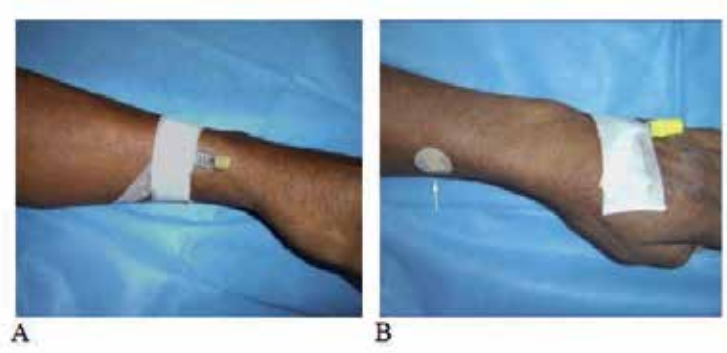

Figure 6. Preventing damage of peripheral veins. Venous cannula in the cephalic vein of a CKD patient (A) is removed and placed in a hand dorsum vein (B).

3.1.2. Optimal timing for access creation

The exact timing of placement of VA should be determined in each particular case by the rate of decline of renal function, presence of co-morbidities (i.e. diabetes, obesity), estimated time from referral to surgeon until access creation and degree of difficulty for VA creation. Avorn et al [29] found that patients referred to a nephrologist 90 days before the initiation of dialysis were approximately 40% more likely to undergo catheter placement compared with those who were seen 90 days before the initiation of dialysis.

3.1.3. Clinical evaluation of arm veins

The initial evaluation of peripheral veins is done on clinical grounds. Past access failure should be analyzed and a careful history of previous catheterizations, particularly of central outflow veins, like subclavian and innominate veins. Previous right IJV cannulation in most cases do not preclude ipsilateral access creation, except in patients developing arm edema during catheter dwell time or when enlarged superficial vein collaterals are observed on the chest wall or the neck, which is highly suspicious for significant central vein stenosis or oc-

clusion. Evaluation of the arm veins should be done by palpation with a proximal tourniquet or inflatable pressure cuff in place. This way, stenotic or thombotic segments can be easily detected. The explored outflow vein walls should be distensible all along its course with uninterrupted lumen. Collecting past history of venipuncture, presence of edema, especially if unilateral, is extremely important. Palpation of the arteries should include assessment of pulse amplitude and rhythm, as well as texture of the arterial wall all along its course. Evaluation should detect wall hardening, plaques or absence of pulse. Allen's test should be routinely done in all cases.

3.1.4. Ultrasound mapping of the vessels

Color Doppler ultrasound (CDU) is usually a complementary diagnostic tool in the setting of VA planning. It should be used to further assess pathologic findings obtained at clinical evaluation. CDU can corroborate or exclude underlying vein stenosis and thombosis, arterial plaques, etc. Hemodynamic parameters like vessel diameter, arterial flow pattern and flow measurement can also be readily assessed. Minimum artery diameter for successful autogenous AV access creation at forearm ranges from 1.5 mm and 2.0 mm although 2.0 mm seems to be a more acceptable limit in adults [30,31]. In addition to measuring arterial diameter, it is of utmost importance to exclude calcification of the media, which precludes surgical opening of the artery, or the presence of proximal atheromas which would reduce inflow. Typical arterial flow pattern is shown in Figure 7.

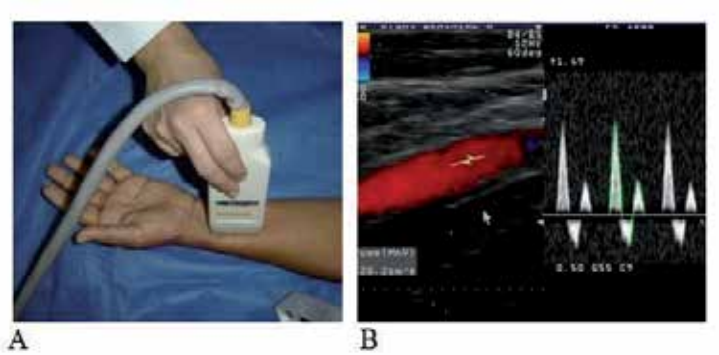

Figure 7. Doppler ultrasound of the radial artery (A) showing nomal triphasic flow pattern (B).

Venous system can be evaluated sonographically for continuity and absence of strictures. To this end, CDU scans should be done with a distal tourniquet in place to distend the outflow vein. Evaluation of the basilic vein at upper arm is only possible with CDU since this vein is located below the brachial fascia in most of its upper arm course. Arm diameter in obese patients may limit access site selection. CDU may also dictate the need for primary or staged vein elevation in case of too deep lying outflow veins.

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3.1.5. Additional imaging studies

A central vein imaging procedure is necessary to exclude subclavian or innominate vein stenosis or thrombosis in patients with history of subclavian or left internal jugular vein cannulation, especially if catheter infection occurred or when vein collaterals are visible on skin over the chest. To circumvent the need for central imaging procedure, it is advisable to select in first instance the contralateral upper extremity for access creation, if the vessels are appropriate, in those patients with history of subclavian vein cannulation only on one side. Likewise, former left IJV cannulation requires that innominate vein stenosis or occlusion be excluded before ipsilateral VA creation.

3.1.6. Order of preference for VA creation

The sequence of VA creation should, ideally, be individually tailored with clear preference for native vessels, exhausting first more distal VA options bilaterally before considering creating a proximal one. The sequence of preference is:

1. radiocephalic fistula (RCF),

2. ulnarbasilic fistula (UBF),

3. brachiocephalic fistula (BCF)

4. brachiobasilic (BBF) or brachiobrachial fistula and

5. brachioaxillary straight graft (BASG).

Eventually, placement of a forearm graft, in preference in straight configuration, may be evaluated before moving to an autogenous upper arm access [32]. If graft placement is decided, the graft/vein anastomosis should be performed below the elbow crease in order that both cephalic and basilic vein at upper arm remain intact for ulterior access procedures.

3.1.7. Preoperative clinical protocol

Some basic clinical, hemodynamic and laboratory parameters should be systematically evaluated in patients scheduled for VA surgery [32]. Patients should be in their dry weight, afebrile without evidence of catheter infection or elsewhere, no signs of cardiac insufficiency nor pericardial effusion, normal range heart rate and rhythm, minimal BP 110/70 without orthostatic hypotension. Regarding laboratory data, normal WBC and platelet count with Hb levels above 8 g/dl are essential. Too high hematocrit levels can make the patient more prone to access thrombosis. In such cases, transient epoetin reduction should be considered. Coagulation tests like bleeding time, TP and TPT should be within normal range. Serum albumin should be 3.0 mg/dl or higher. Prothrombotic medication (methilprednisolone) should be tapered to 10-15 mg daily before performing access surgery. It is very important that antithrombotic agents (ASA, clopidogrel, davigatran), anticoagulants (low-weight heparin, warfarin) are stopped at least 5 to 8 days before surgery.

3.1.8. Operative technique

A detailed operative technique for each access type would be beyond the scope of this chapter. However, It can be never stressed enough that, for successful VA creation, surgical procedures should be done under stringent aseptic conditions, using appropriate surgical instruments, sutures and a meticulous technique. AVF not requiring general anesthesia, like forearm fistulas and BCF, may be performed on an outpatient basis in a procedure room located within a renal unit, Access procedures requiring axillary nerve block or general anesthesia should be performed in a conventional operating room keeping the patient hospitalized for a short observation period. Vein collaterals should be ligated to allow for better maturation. Ligation of tributary veins like hand dorsum veins in case of RCF and cephalic accessory vein in case of BCF may prevent retrograde flow once the runoff vein has enlarged and increased its flow. The recommended anastomosis technique for arm fistulas is side-to-end. However, for forearm fistulas, side-to-side anastomosis, turned into a functional side-to-end anastamosis by juxta-anastomotic ligation of the distal venous limb (Figure 8), may be an equivalent alternative which has an additional advantage: the anastomosis size can be tailored regardless of the diameter of the vessels.

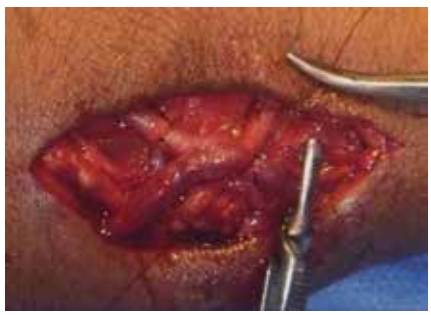

Figure 8. Side-to-side anastomosis turned into a functional side-to-end by juxta-anastomotic ligation of the distal venous limb.

In case of BBF creation, subcutaneous transposition of the arterialized basilic vein is mandatory since it runs in most of its upper arm course beneath the deep fascia and would otherwise not be amenable to safe cannulation except in its short distal postanastomotic segment [33]. In addition, the basilic vein is crossed in part of its upper arm course by branches and filaments of the medial antebrachial cutaneous nerve. Aneurysmatic dilation of the postanostomic segment of BBF is commonly observed when superficialization is not performed owing to the fact that the arterialized vein is being "clamped" proximally by the deep fascia. Superficialization of the vein usually requires either a long incision or multiple short incisions in the medial aspect of the upper arm. However, a new endoscopically performed superficializacion technique has been described recently [34]. Some authors recommend doing superficialization as a two-stage procedure [35].

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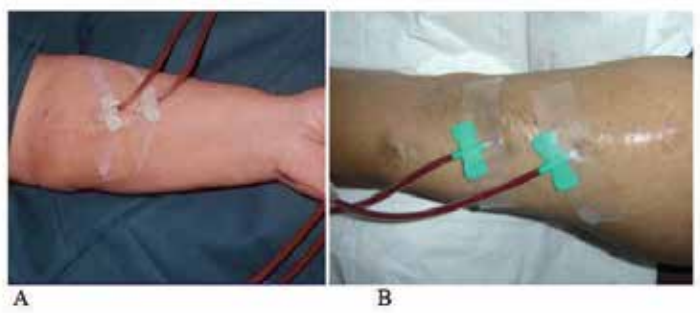

Figure 9. RCF (A) and BCF (B) with staged superficialization of the cephalic vein.

3.2. Basic types of PVA at upper extremities

3.2.1. Autogenic

RCF, also called Cimino or Brescia-Cimino fistula, is by far the best type of HD access. It offers the longest and easiest to puncture vein segment, lowest venous dialysis pressures, higher primary function rates, as well as better long-term survival. Snuff box fistula, a distal variant of RCF which may be created at the basis of the thumb, can be performed if the caliber of the vessels at this location is appropriate. UBF, another autogenic VA type in the forearm, was first described by Hanson et al as early as 1967 [36]. UBF is an optimal VA alternative with good survival rates [37] which has not yet been included in the KDOQI recommendations probably under the argument that the posteromedial course of the basilic vein along the forearm is inconvenient for cannulation. However, in our experience, UBF does not need transposition to be successfully cannulated (Figure 10).

Figure 10. Ulnarbasilic fistula being used for HD. Note that transposition of the arterialized basilic vein is not necessary for safe cannulation.

BCF and BBF with vein superficialization are the the two basic autogenic fistula variants at upper arm. If the basilic vein is found to be inadequate, one of the brachial veins may be used instead [34]. Other access options like Gracz fistula, or bidirectional (reverse) fistulas offer no additional advantages over other conventional fistulas [38].

3.2.2. Prosthetic grafts

In the forearm, arteriovenous grafts (AVG) are placed in either straight or loop configuration [39]. Inflow artery of straight grafts may be either the radial or the ulnar artery. Inflow artery of forearm loop grafts is the brachial artery. Outflow veins are usually antecubital veins. As stated earlier, the graft/vein anastomosis should be located in preference below the elbow crease. At upper arm, the most common AVG variant is the brachioaxillary graft. Since adhesion between the graft and subcutaneous tissue may last up to 3 weeks, it is advisable waiting until after that time has elapsed to start cannulation. The shorter waiting time for starting cannulation is one of the advantages of AVG over AVF. The expanded PTFE (ePTFE) remains still the most commonly used graft material. Biological prostheses are of limited availability, usually more expensive and of variable size and quantity [39].

3.3. Basic types of PVA in the thigh

They should be attempted only when all options in the upper extremity are exhausted.

3.3.1. Femoral vein transposition

It is an autogenous AV access in the thigh which is created between the femoral artery and the transposed common femoral vein. It has good patency rates but a higher risk of distal ischemia [40].

3.3.2. Sapheno femoral arteriovenous fistula

It is created by anastomosis of the distal femoral artery and the great saphenous vein (Figure 11) which is subcutanously transposed to allow cannulation. Access survival is acceptable [41].

3.3.3. Saphenous Loop

It is also an autogenous alternative whose inflow is provided by the proximal femoral artery at groin level. It requires frequent endovascular procedures owing to vein stenosis. Only 70% of all new created saphenous loop are functional with a 16-months survival rate [42].

3.3.4. Femorofemoral ePTFE loop graft

This AVG type is created at the groin using the common femoral artery as inflow, or at mid-thigh level using the superficial femoral artery instead [39,43]. Infection rate of thigh graft is higher than that of upper arm accesses.

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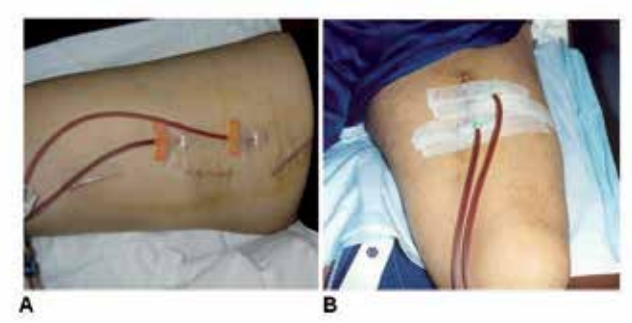

Figure 11. A) Saphenofemoral arteriovenous fistula. (B) Arterioarterial HD through a superficialized femoral artery.

3.4. Timing of first puncture

Ideally, mature AVF should have the following characteristics to be safely punctured: discernible vein margins, flow greater than 600 mL/min, vein diameter at least 0.6 cm and should be located no more than 0.6 cm deep [8]. Too deep lying arterialized cephalic veins, particularly in obese patients, can be superficialized either along its forearm course in case of RCF or along its upper arm course as in the case of BCF. (Figure 9). Since superficialization is an extensive, surgically complex and time-consuming procedure, we recommend to perform it as staged procedure on a case-by-case basis once the impossibility to cannulate the new access has been established. Superficialization of the vein can be done by surgical transposition [44], by single lipectomy [45] (or suction-assisted lipectomy [46]. Maturation time of BBF is about 8 weeks. Adequate puncture technique and care is the clue to prolonged VA survival. Cannulations can help to widen the caliber of the arterialized vein on condition that puncture sites are rotated. Lack of needle rotation may favor the development of aneurysms at neddling sites. However, some authors recommend the buttonhole cannulation and report less complications and interventions using this technique [47].

4. PVA complications

4.1. Immediate and early postoperative period

Complications in the immediate and early postoperative access complication are bleeding, thrombosis and infection. CKD patients are more prone to bleeding, but this complication is totally preventable with careful surgical technique. Significant bleeding associated with skin bulging at the operative site always requires surgical revision.

4.1.1. Thrombosis

is the commonest complication of PVA in the immediate and early postoperative period. Even using an impeccable surgical technique and in the presence of both adequate vessel

anatomy and optimal hemodynamic parameters, the risk of thrombosis remains high in the first minutes or hours after access surgery. Arterial wall incision done for anastomosis is in principle an arterial injury causing exposure of subendothelial elements as collagen and laminin which initiates a cascade of cytochemical and cellular events leading to platelet recruiting, adhesion and activation at the anastomosis site. Platelet activation together with thrombin generation results in thrombus formation [48]. In addition, chronic renal failure per se is a procoagulant state with multiple concurrent hemostatic abnormalities [49]. Some comorbidities like old age, obesity, diabetes, atrial fibrillation and hypertension could also contribute to enhance prothrombotic conditions. Therefore, close surveillance of fistula function, particularly in high risk patients, should begin just after unclamping of the vessels and continue after wound closure during the immediate and early postoperative period. Initially, a discontinuous sometimes high-pitched bruit may be heard over the anastomosis but in the following minutes or within the first hour it should turn into a continuous bruit which is the normal auscultatory finding in a well functioning fistula. In addition, fistula bruit must increase in intensity to a maximum in the first hours, remaining then stable. Decreasing fistula bruit, particularly during the first minutes or the first hour may herald impending thrombosis. Careful intravenous fluid and heparin administration may avert definite fistula thrombosis in a great majority of cases. In the event of complete bruit disappearance, a gentle massage can be done over the anastomosis area until the fistula bruit reappears. This massage can be repeated more than once if necessary [32]. Persistent discontinuous flow associated with pulsations instead of thrill over the outflow vein may point at an underlying outflow impairment.

4.1.2. Postoperative infection

in a new created VA needs aggressive therapy particularly because the anastomosis site is almost always involved and may rupture leading to acute, eventually life-threatening bleeding requiring urgent VA ligation. Infection is more common in AVG than in AVF [50]. Factors favoring infection are intraoperative contamination, poor wound care, diabetes, steroids, etc. Similarly as in NTC and TC, most episodes of infection are due to gram positive bacteria in particular, S. aureus. Infection at the anastomosis site may lead to fistula ligation or graft excision.

4.2. Late postoperative/precannulation period

Thrombosis in this period is most commonly due to hypotension after HD. The nursing staff should be strongly advised to always measure standing blood pressure (BP) before allowing a patient going back home after finishing HD session. If BP is found to be less than 110/70, the patient should be placed immediately in recumbent position until BP improvement. Tight circular bandages or dressings should be avoided. Since a new created AVF or AVG may cause a variable decrease in peripheral vascular resistance, antihypertensive drug dosing may eventually need to be adjusted. A bit higher median arterial pressure than usual (100-110 mmHg) should be tolerated in the first 10 days after surgery. Patients should be advised to keep their arm elevated to reduce local edema and decreased wound suture tension.

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Mild to moderate edema is not uncommon but it normally subsides within the first 3 weeks after surgery. In case of persistent or worsening edema, venous hypertension syndrome owing to an underlying central or peripheral vein occlusion should be suspected. Arterial steal is another complication that may also become clinically apparent during this period. Both the latter complications will be addressed in detail later in this chapter.

4.3. Lack of maturation

As mentioned earlier a mature autogenous access requires

1. an adequate diameter (> 6 mm),
2. discernible margins,
3. adequate access flow rate (>500 ml/min) and
4. it must be sufficiently superficial (<0.6 cm deep) to permit accurate, safe cannulation.

Blood acces flow increases dramatically within 24 hours of autogenous access placement and reaches most of its maximum flow within 3 to 6 weeks [51,52]. Average flow rates vary according to access site and type. Mean forearm fistula fistula flow is 784 ± 623 ml/min, upper arm fistula 1400 ± 850 and prosthetic graft 1270 ± 604 [53]. Similarly, most of the increase in access diameter is achieved within 4 to 8 weeks of autogenous access placement [54]. It has been estimated that about one quarter to one third of AVF fail to mature [55]. Causes of lack of maturation are poor arterial inflow (inadequate vessel diameter, proximal atheroma, juxta-anastomotic occlusion of the proximal arterial limb, anastomosis of small size, chronic hypotension), juxta-anastomotic vein stenosis (probably resulting from intraoperative prolonged venous clamping), lack of ligation of tributary and collateral veins, venous intimal or media fibrosis not allowing vein diameter to enlarge. The usefulness of endovascular or surgical procedures to improve flow and promote AVF maturation should be evaluated in each particular case.

4.4. Postcannulation complications

4.4.1. Hematoma or infiltration

Infiltration are common complications. They may be confined to subcutaneous tissue looking like ecchymotic lesions or be the result of subaponeurotic bleeding, when the needle crosses the vein lumen leaving an orifice in the posterior vein wall [56]. In the latter case, skin bulging is seen without significant ecchymosis. Hematomas may eventually either become secondarily infected, cause significant stenosis or turn into pseudoaneurisms.

4.4.2. Pseudoaneurysm (PA)

PA are typical puncture-related complications of both AVF and AVG. The trigger event is usually a wall laceration due to a traumatic cannulation with subsequent hematoma formation around the vessel or a leak at the anastomosis site leading to hematoma formation [57].

The size of the hematoma may vary widely and is one of the determinants of final PA size. Inadequate compression at puncture site favors further hematoma grow. PA may be located either subcutaneously or subfascially depending on where the hematoma was located. Once hematoma is formed around the fistula vein or graft, it will be progressively eroded in the course of few days by the pressure of a blood jet going out through the wall defect, which will later become the PA neck. Finally, a cavity or sac can be observed within the hematoma, connected to the fistula vein or graft lumen by the PA neck (Figure 12). PA can develop in both AVG and AVF. US guided compression of the PA for 30 minutes [58], or US guided direct thrombin injection into the PA sac have been used as primary options [59]. However, in case the latter measures fail or when PA is rapidly enlarging, revision is required. Surgical revision has been the standard approach to treat PA. However, endovascular treatment using covered stents insertion to exclude PA has been successfully used to treat such complications [57,60]. This method has proven safe and effective and the results has been encouraging, however it requires a specialized institution and the procedure-related costs are high. Surgery should be used in preference in case of wide-neck PA or when a significant skin bulge or mass is observed. Infection is a contraindication for endovascular procedures. In case of secondarily infected PA, the best way of action is to ligate the access in a definite manner.

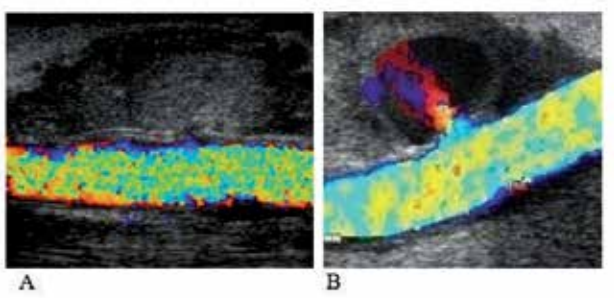

Figure 12. A) Perigraft hematoma. (B) Doppler ultrasound show formation of pseudoaneurysm following hematoma cavitation.

4.4.3. Aneurysms

Different than pseudoaneursyms, aneurysms are widened or enlarged segments of the arterialized vein that may develop at puncture site or at the anastomosis. Aneurysms may reach significant sizes and exhibit small saccular areas with thin wall which may cause, if ruptured, serious bleeding, Aneurysms usually limit puncture sites and can be the starting point of infections and thrombus formation. In selected cases, surgical plication may be attempted to reduce aneurysm size on condition that a proximal stenosis of the vein is excluded [61]. Otherwise, ligation of the access is the only option.

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4.4.4. Puncture site Infection

Infection can develop at puncture sites, poor aseepsia, hematoma formation or infiltrations being predisponent factors. Most commonly isolated agents are grampositive bacteria, particularly S. aureus and coagulase-negative staphylococci [62]. AVF or AVG infection should be always viewed as an emergency condition that require hospitalization since it may ultimately lead to access rupture with bleeding, sepsis, endocarditis and other metastatic infections. Aggressive empirical antibiotic therapy should be started until culture results are available. Strict adherence to aseptic and antiseptic protocols by the nursing staff and patient's education are instrumental in preventing access-related infections.

4.4.5. Stenosis

Luminal stenosis may range from mild to severe and can develop at any site along the AVF or graft (anastomotic stenosis, peri or postanastomotic stenosis, puncture-related stenosis, stenosis at the site of former venipunctures and venous outflow stenosis). While anastomotic or puncture-related stenosis point at surgical failure or inadequate puncture technique, perianastomotic stenosis in AVF and venous outflow stenosis at the graft-vein anastomosis are due primarily to neointimal hyperplasia [63]. Other possible causes of postanastomotic stenosis might be venous wall damage induced by clamping and excessive denudation of the vein. The diagnosis of luminal vein stenosis can be accurately done in a great majority of arteriovenous fistulas by physical examination alone [64]. CDU or other vascular imaging techniques should be used to confirm the clinical diagnosis of stenosis. Treatment of stenosis is either surgical or endovascular (balloon dilatation or stent placement) and the results depend largely on the size and type of the stenosis. The KDOQI Guidelines [7] recommend that stenoses in prosthetic or autogenous accesses should be treated prophylactically with percutaneous transluminal angioplasty or surgical revision if the stenosis is 50% of the lumen diameter and is associated with clinical abnormalities. Early detection of fistula vein stenosis can be achieved by applying the KDOQI static intra-access pressure surveillance protocol which consists of serial calculations of the normalized arterial and venous segment static intra-access pressure ratios or indexes. Arterial index values > 0.43 in AVF or > 0.75 in AVG are suggestive of significant stenosis [65]. Index calculations and normal range values are described in detail in the respective KDOQI recommendation [7].

4.4.6. Neointimal hyperplasia

of the runoff vein is a special type of stenosis which has been subject of extensive research. Cumulative patency of AVG largely depends on the development of neointimal hyperplasia at the graft/venous anastomosis. Therefore, prevention of this complication would contribute to prolong AVG survival [63]. Research has been focused on how to eliminate or inhibit the two main pathogenetic factors involved in the development of this complication: Shear stress and the subsequent endothelial cell proliferation. Shear stress has long been pointed as the main cause of neointimal proliferation as proved in experimental flow models. Some modifications in graft configuration have been shown to reduce shear stress, particularly on the bed of graft-vein junction, like helical ePTFE grafts which swirl blood flow across the graft-

venous anastomosis reducing endothelial stress [66]. Another way to limit neointimal hyperplasia is reducing venous outflow turbulence either by modifying the graft-vein anastomotic angle inserting grafts with angled venous end [67] or with the so called Y-Split AVG (Prolong™) that bifurcates shortly after arterial end and reunite just before the runoff vein anastomosis [68]. *Inhibition of endothelial cell proliferation* has been achieved on the one side by embedding allogeneic aortic endothelial cells in a gelatin matrix (Vascugel™), which is placed around the vessel at the time of AV access creation. Preliminary studies have been promising but further research is needed [69]. On the other side, it has been long known that increased nitric oxide levels inhibit the intimal hyperplasia of grafts [70]. In this regard, worthmentioning is the interesting work by Luo et al [71] who evaluated the efficacy and safety of an adenoviral vector encoding the carboxyl terminus of beta-adrenergic receptor kinase in a pig model of arteriovenous PTFE graft failure. The authors found that locally applied gene therapy reduced significantly neointimal hyperplasia in the graft/vein anastomosis.

4.4.7. Access recirculation

Access recirculation occurs when dialized blood having already passed through the dialyzer, instead of returning to circulation via the proximal "venous" needle, is redirected toward the distally placed arterial needle and reenters the extracorporeal circuit. The explanation is that flow of the extracorporeal circuit exceeds that of the VA whose minimal range should be between 300 to 450 mL/min [72]. Recirculation results in dialysis delivery being less than that prescribed. The most common cause is stenosis of the outflow vein which can ultimately lead to access thrombosis owing to significant intraaccess flow reduction. Other causes to be excluded are poor arterial inflow, close proximity of the needles and inverted lines. Complementary imaging methods like Doppler ultrasound, venography, angioresonance, etc, can locate site and determine degree and extension of the stenotic segment, measuring access recirculation is a valuable tool to estimate the percentage of recirculation and help to establish the indication for surgical or endovascular interventions. Recirculation may be measured either by urea-based or non-urea based methods like ultrasound dilution, potassium dilution, ionic dialysance, glucose infusion and thermal dilution [73]. Percentage recirculation can be calculated by the traditional urea-based method according to the following equation: [Systemic BUN-arterial blood line BUN/Systemic BUN-venous blood line BUN] x 100. Consistency of the urea-based methods is poor for surveillance for access stenosis, in part because of arteriovenous (cardiopulmonary recirculation) and venovenous disequilibrium [74,75] but if the percentage recirculation is >10% stenosis should be suspected. Other methods which eliminate the effect of disequilibrium have different thresholds, such as > 5% for ultrasound dilution [76].

4.4.8. Arterial steal syndrome (ASS)

Also referred to as HD access-induced distal ischaemia (HAIDI), ASS is a rather uncommon complication and occurs in 2.7–4.3% of AVG and 1% of AVF [77,78]. It may appear early after surgery or in the postcannulation period. Symptoms range from only pain and coldness during dialysis to digital necrosis. It may develop shortly after surgery or years afterwards.

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Patients at risk are diabetic and those with severe peripheral occlusive disease. ASS may be classified in 4 stages [79]:

Stage 1: Retrograde diastolic flow without complaints; steal phenomenon;

Stage 2: Pain on exertion and/or during HD;

Stage 3: Rest pain and

Stage 4: Ulceration/necrosis/gangrene.

The diagnosis of steal syndrome is made clinically, color Doppler US and complementary imaging procedures. Measuring finger pressure before and after fistula vein or graft compression is a very helpful diagnostic manoever in patients with steal syndrome. Using the digital brachial index (DBI), Goff et al [80] identified patients with a DBI of <0.45 as having a significant risk for ASS. Treatment of ASS is surgical and has two main objectives: increasing or restoring distal limb flow and maintaining access patent. Surgical interventions to obtain symptoms relief in SS are of two kinds:

a. Revascularization and

b. Banding.

The more severe forms require excision or removal of the affected tissue.

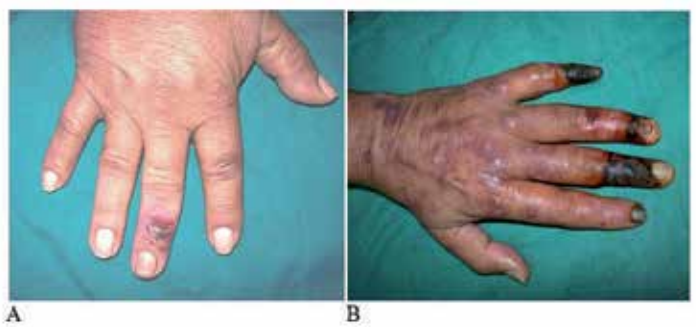

Figure 13. A) Steal syndrome with painful necrotic ulceration of the middle finger. (B) Stage 4 steal syndrome.

4.4.8.1. Revascularization techniques

a. Distal revascularization with interval ligation (DRIL) was first described by Shanzer et al [81] as early as 1988 and consists in placing an arterioarterial bridge that bypasses the anastomosis site. In addition, a juxta anastomotic ligation of the distal limb of the artery is done. It has been long viewed as the gold standard procedure.

b. Proximalization of the arterial inflow: First, the distal original arteriovenous anastomosis is closed and the artery repaired using an interposition graft. Secondly, the outflow vein is anastomosed to a bridge graft (autologous or else) which is in turn anasto-

mosed to a more proximal site of the artery. This procedure is useful in cases with low fistula flow [82].

c. Revision Using Distal Inflow (RUDI). In this technique the original anastomosis at the brachial artery is ligated and the outflow vein is anastomosed more distally to either the radial or ulnar artery just below the bifurcation using a bridge graft (autologous or ePTFE). The basic principle is that the distal artery has both lower diameter and flow [83].

4.4.8.2. Banding

The main objective of banding is to increase postanastomotic outflow resistance by narrowing the lumen of the outflow vein or graft so as to reduce outflow and increase distal arterial flow. Banding may be achieved either by placing a *narrowing suture* near the anastomosis site [84], by *plication* of a short postanastomotic stretch [85] or by tapering [86]. Flow reduction in either technique is measured by means of intraoperative pulse volume recording or by measuring access flow with a flow meter [87]. Among the banding techniques, the minimally invasive limited ligation endoluminal-assisted revision (MILLER) for treatment of dialysis access-associated ASS is one of the most simplest to perform and offers excellent results [88]. In this technique one or two sutures are placed 1-3 cm after the anastomosis using an inflated endoluminal angioplasty balloon, which is retrogradely inserted more proximally, to size the final luminal diameter of the outflow vein.

4.4.9. High-output heart failure

It is a rather uncommon complication which can easily be overseen [89]. Excessive shunting of the access, anemia and underlying heart disease are triggering factors. Surgical banding [90] may relieve symptoms, but in case of persistent manifestations, definite ligation is the only remaning option.

4.4.10. Venous hypertension syndrome (VHS)

VHS is a relatively common complication of AV accesses, particularly AVF and consists of a painful edema, redness and warmth of the affected skin area that appear after VA creation that may affect, depending on the site of the outflow stenosis or occlusion, either the entire upper extremity or may be circumscribed to forearm, hand, or skin segments overlying the fistula. The stenotic site represents a formidable barrier against arteriovenous flow originating a steady rise of the intraluminal pressure distally to the stenosis. The increased intraluminal pressure is in turn transmitted backward to the superficial or subcutaneous vein system producing the typical symptoms of VHS (Figure 14). In patients with longstanding VHS skin pigmentation occurs as well as other manifestations observed in chronic venous insufficiency like vein collaterals, small varicosities and even ulcerative lesions. The mechanism of hyperpigmentation is possibly similar to that of chronic venous insufficiency where both a moderate hypermelanosis and dermal hemosiderin deposits can be seen microscopically, derived from the breakdown of red blood cells that have extravasated through damaged capillaries and smaller vessels are [91]. Diagnosis of VHS is made clinically and should

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be complemented by imaging procedures like ultrasound, flebography, angiotomography or angioresonance. The main advantage of the two latter procedures is that small dosis of contrast media are used. Treatment options are: Ligation of retrograde veins, endovascular or surgical procedures or definite access ligation.

5. Last resort PVA (complex VA options)

5.1. Subcutaneous transposition of peripheral arteries

The purpose is to perform an arterioarterial hemodialysis. The arteries reported to be used this way are: the superficial femoral [91], the brachial [92] and radial artery [93].

5.2. Arterioarterial grafts

Desperate case access option that has been performed as axillary-axillary chest loop (preferred type) or femorofemoral loop. Reported primary and secondary patency at 3 years were 54% and 87%, respectively [94].

5.3. Anterior chest wall (body wall) prostetic accesses

These are a particular type of VA. The axillary artery is anastomosed by means of an ePTFE graft to either the ipsitaleral axillary vein, internal jugular or femoral vein. Loop configuration of the graft at the upper chest is the typical configuration when either the axillary or the ipsilateral internal jugular vein is used [95]. If the contralateral axillary vein is used as outflow, ePTFE configuration in the form of a collar or necklace is placed. Mickley et al [96] described a novel AVG using the axillary artery as inflow and the right atrium as outflow in cases with superior vena cava occlusion.

Figure 14. A) Venous hypertension syndrome developing after a brachiocephalic fistula creation (B) Angiotomography showing right innominate vein occlusion.

6. Alternatives to PTFE graft material and new trends in the field of PVA creation

6.1. Xenografts

Xenografts are more expensive than PTFE grafts, a fact which limits their use in spite of their proven better patency rates and lesser frequency of complications compared to PTFE graft [97-99]. Two types xenografs are commercially available:

a. The bioingeneered bovine carotid artery (Artegraft™) which has been in use since 1970 and

b. the bioengineered bovine mesenteric vein (Procol™).

6.2. Hybrid prosthetic devices

The Hemoaccess Reliable Outflow (HeRO™) Vascular Access Device (Hemosphere, Inc., Minneapolis, MN) has emerged as a valuable, innovative alternative to tunneled catheters (TC). Early results suggests that bacteremia was significantly less frequent for the HeRO device than for TC being its secondary patency (> 72.2%) quite close to that of PTFE grafts [100-102]. According to the description by Katzman et al [102], this device consists of a 6-mm straight ePTFE upper arm graft serving as cannulation segment, whose distal end is anastomosed to the brachial artery and the proximal one is attached by means of a titanium-made crimp ring to an also subcutaneously placed, 5 mm inner diameter, silicon catheter ("outflow component"). The catheter may be introduced endovascularly or inserted into the internal jugular or subclavian vein utilizing the Seldinger technique The catheter tip should lie at the cavoatrial junction.

6.3. Early stick grafts (ESG)

Their main advantage is that they can be used 24 hours after placement and would avoid using NTC and TC preventing catheter-related morbidity and costs. Some of the ESG have resulted from modifications introduced to the original ePTFE like the *Trilaminate composite construction ePTFE* (Flixene™) which would have reduced hole bleeding, being ideal for early use [103] or the gelatin-coated ePTFE (Vascutek™). The gelatin would make subcutaneous graft placement smoothly preventing tissue trauma and thus allowing early graft cannulation. However, with the latter a high incidence of perigraft hygroma has recently been reported [104]. Other ESG are made of polyurethane urea (Vectra™) which is an antithrombogenic material with an impermeable middle layer. The graft would seal rapidly after decanulation being thus ideal for early use [105,106]. A really innovative development as graft material in the future is the endothelialized polyurethane grafts (NanoVasc™) which has a biomimetic scaffold allowing for endothelial cell ingrowth. The results of animal studies are encouraging [107].

6.4. Tissue engineered vascular grafts (TEVG)

The creation of AVG using TEVG technology is really very promising. Some are created by seeding autologous bone marrow-derived mononuclear cells onto biodegradable tubular scaffolds constructed mainly from derivatives of the extracellular matrix or using allogeneic or canine smooth muscle cells grown on a tubular polyglycolic acid [108]. Other TEVG grafts are created from autologous fibroblasts and endothelial cells obtained from small skin and vein biopsies. The grafts are implanted without synthetic scaffolding [108].

7. Comorbidities and vascular access creation

As stated in the introduction paragraph, during the past two decades, HD population has become increasingly composed of patients of advanced age and/or suffering from comordibities like diabetes, hypertension, chronic hypotension, dyslipidemias, occlusive artery peripheral disease, malnutrition, etc. In this population the risk of VA loss or malfunction is extremely high, particularly when two or more comorbid conditions coexist.

7.1. Diabetics

are prone to complications like occlusive arterial disease which limits their access options and, in a significant proportion of them, the primary access has to be created at upper arm due to severe atheromatous changes of distal arteries. The risk for development of arterial steal syndrome in patients of this group is elevated. In addition, a subset of diabetic patients suffer from chronic hypotension, orthostatic hypotension, etc., owing to autonomic neuropathy or cardiac failure. Access thrombosis is very common among those patients and, in many of them, a TC for chronic HD or CAPD are often the only remaining option.

7.2. Chronic hypotension

defined as interdialytic systolic pressure of less than 100 mmHg without cardiac function impairment, affects 5 to 10% of HD population. Its pathophysiology is not well understood but the mechanism of hypotension seems to be a reduction of the peripheral resistances with poor response to midodrine and other vassopresor agents [109]. In these patients frequent VA thrombosis are observed. The creation of upper arm fistulas has been recommend as primary access choice in such cases [110].

7.3. Elevated lipoprotein and hypoalbuminemia

have been associated with AV access thrombosis [111]. In addition, serum albumin is a known marker of nutritional status in HD patients. Hypoalbuminamia is associated with malnutrition and the latter, in turn, may lead to poor wound healing, infection and subsequent VA loss [112]. Hyperhomocysteinemia has also been found by some authors to be a risk factor for VA thrombosis and suggest decreasing levels before performing any VA [113]. Others, on the contrary, found no association between risk for thrombosis and hyper-

homocysteinemia [114]. Further studies are necessary to clarify whether lowering plasma homocysteine concentrations may prevent VA failure in HD patients.

7.4. Patients with systemic lupus erithematosus (SLE)

Patients with SLE on HD are at increased risk of vascular access thrombosis as compared to non-SLE patients because of the high prevalence of the so called, antiphospholipid antibodies, namely, anticardiolipin antibodies and lupus anticoagulant among SLE patients. [115 - 117]. Lupus anticoagulant is actually a prothrombotic agent which precipitates the formation of thrombi in vivo. In addition, SLE patients on chronic HD receiving high dosis of oral steroids, may have an elevated risk of VA thrombosis and infection and, for this reason, steroid dosis should be reduced before performing VA surgery.

8. Conclusion

The ideal AVG, which can be created with graft materials similar to the patient's own vessels is yet to be invented. However, a lot of progress has been done. The best example is TEVG technology which are showing us a complete new world in the realm of HD accesses in the future. Likewise, early stick grafts are undoubtedly unvaluable developments which have raised special attention because they could obviate the need for a bridging NTC or TC. However, before resorting to all that panoply of innovative developments whose extensive use would otherwise represent a serious financial burden for any health care system, there is a lot that can still be done. Catheters have been a necessary evil but one step in the right direction is avoiding or minimizing their use in the years to come. To reach this goal, increasing predialysis construction of autogenous fistulas is the only way out of the current trend. Applying autogenic-oriented VA plans is another crucial step that could help to substantially decrease the use of grafts. Additionally, but equally essential measures are complications prevention through patients' education, continuous staff training and timely-performed VA preserving interventions. Certainly, we will continue finding patients with very difficult access who will benefit from all those innovative AV types described in this chapter. Yet, it would not be far from the truth to state that the VA needs of the overwhelming majority of our patients could be met with a simple autogenous fistula if timely done, adequately punctured and optimally cared.

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Chapter 33

Catheter-Related Sheaths (CRS): Pathophysiology and Treatment Strategies

Robert Percarpio, Elizabeth T. Chorney and Andrew R. Forauer

Additional information is available at the end of the chapter

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1. Introduction

Despite the emphasis on arteriovenous fistula creation in patients requiring renal replacement therapy, catheter-based hemodialysis remains a valuable access option that allows for immediate initiation. They continue to serve as an important option for chronic kidney disease (CKD) patients who are: (a) awaiting a permanent AV access creation or maturation, (b) in need of acute hemodialysis, (c) have exhausted traditional access routes, and (d) those suffering from graft infection or extravasation episodes [1].

Catheter-related sheath (CRS) formation, previously referred to as the "fibrin sheath" is a well documented physiologic reaction occurring between the catheter, vein wall, and blood elements. The incidence of central venous CRS formation is reported to occur in 42%-100% of central venous catheters [2-5]. The sheaths can be asymptomatic or result in a number of complications including withdrawal occlusion, medication extravasation, thrombosis, infection and in rare cases pulmonary embolism. Repeat catheter removal and replacement, or loss of an access route is not infrequently the end result of catheter related sheath formation. It is important for those clinicians caring for CKD patients to be aware of the clinical and imaging manifestations of CRS and understand the interventions that can be used to mitigate them.

The goals of this chapter are to review the existing literature on CRS in animals and humans, to provide a current, coherent explanation of the composition of the CRS and how they form, and describe the clinical manifestations and treatment options that are available

2. A brief history of central venous catheters and catheter-related sheaths formation

The first catheterization of a central vein was performed in 1733 by an English clergyman named Stephen Hales who fixed a glass tube to the left jugular vein of a mare to measure venous pressure [6,7]. It wasn't until the late 1920's that Werner Forssmann performed the first documented central venous catheterization in a human when he passed "a well oiled 4F ureteric catheter" through his left antecubital fossa and into this heart. Remarkably, Forssmann then climbed several flights of stairs to the x-ray department to visualize his catheter placement [8,9]. Decades passed and it was not until the 1970's that the central venous catheter became widely available [10].

One of the earliest descriptions of CRS covering a central venous catheter described a "fibrin sleeve" published in the French literature in 1964 by Motin [11]. A number of subsequent studies referred to the central venous catheter related sheaths as a fibrin sleeve and fibrin sheath [2,3,5]. More recently, the work of Xiang et al. more accurately described the CRS as cellular-collagen tissue covered by an endothelial layer. Fibrin was described a component of an early physiologic response to the catheter that consists of pericatheter thrombus, but the CRS itself is not composed of fibrin [12]. Subsequent papers by these authors and others reinforced the concept of CRSs representing a spectrum of thrombosis and thrombus organization [13-16].

3. Clinical implications

The most common manifestation of CRS is catheter dysfunction. This interrupts the patient's medical therapy, may require intervention ranging from thrombolytic infusion to catheter removal or exchange, and may have long lasting implications such as loss of specific venous access locations. Extravasation of fluids or intravenous medication is a less common but certainly significant complication that can result in tissue loss and necrosis. Thrombus that forms on the CRS or the CRS itself can on rare occasion become dislodged and embolize to the pulmonary circulation. Finally, there have been reports that the presence of the sheath is a risk factor for catheter-related bacteremia and infection.

When dysfunction is present, the patient is commonly referred for radiographic evaluation of the catheter. A radiograph or fluoroscopy of the chest is performed to document catheter tip position. Contrast injection of a normal, functioning catheter should show contrast exiting the end-holes and filling a substantial portion of the vein lumen distal to the catheter tip. When a sheath is present, contrast will track in a retrograde fashion along the catheter. The contrast will then "spill" out into the vein lumen via gaps or fissures in the sheath.

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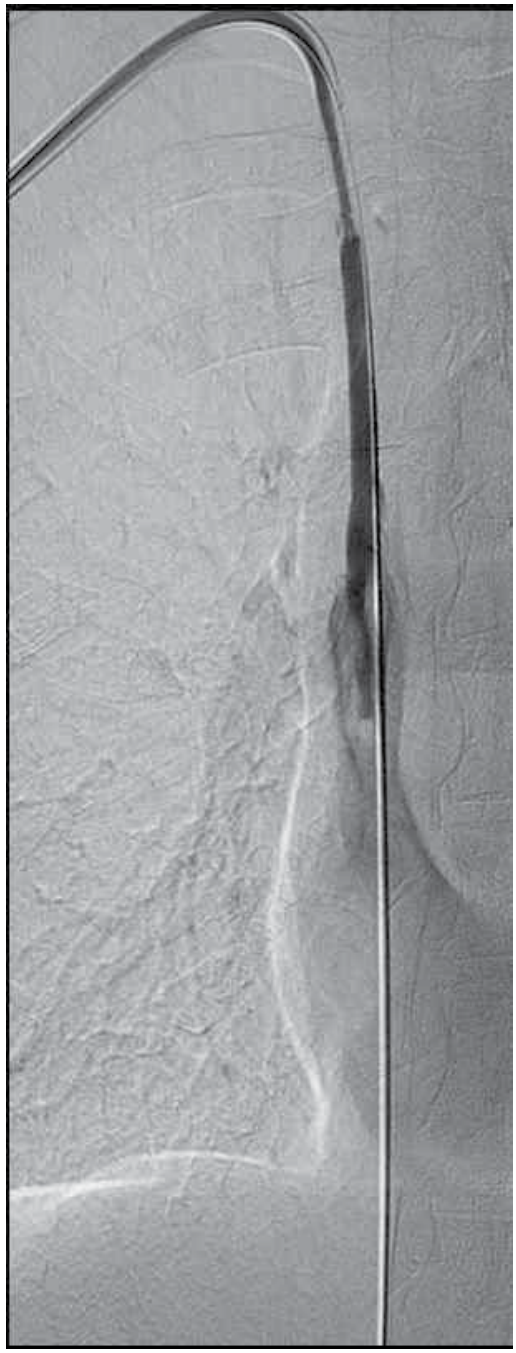

Figure 1. Catheter injection under fluoroscopy. The existing catheter has been pulled back approximately 10 cm and then injected. Contrast fills a well developed sheath considerably narrower than the expected diameter of the superior vena cava. A guide wire has been advanced through the other catheter lumen and is positioned in the inferior vena cava in preparation for exchange.

4. Histopathology of catheter related sheaths

By the middle of the 20th century, central venous catheters were being placed with subclavian and jugular approaches and used for intravenous infusion [6]. The presence of a tissue-like covering was reported after catheters had been indwelling for relatively short periods of time. An early description of this coating appeared in the French literature in 1964 [11]. Since that time, the covering has been referred to as a fibrin sleeve [2,3], a sleeve thrombus [4], a sleeve [12], and—the most recognized phrase—a fibrin sheath [5]. The reported frequency of this observation ranges from 42% to 100% [2-5]. Although there are a number of articles in the literature that are concerned with the clinical aspects of CRS; a minority of these focus on the sheaths' histopathologic features and microscopic development.

An often-referenced article [2] describes the findings at autopsy in 55 patients with subclavian vein catheters. In that study, sheaths were identified in all specimens, even as soon as 24 hours after catheter insertion. Microscopic evaluation was reported to reveal a predominately fibrin makeup, "with no evidence of endothelialization or organization." The sleeve was observed, in many cases, to be adherent to the adjacent vein wall.

Well into the 1990s, descriptions of a catheter-related sheath consisting of "fibrin and thrombocytes" [17] or a "layer of investing fibrin and proteinaceous material" [18], could still be found in the literature.

Later, two reports offered a more detailed microscopic and histologic description. In 1996, a study [19] was performed in which small-caliber silicone catheters were inserted in 15 rats. The catheters were placed via a jugular approach, and the animals were sacrificed at 3, 7, and 60 days. Catheter-related thrombus, with points of attachment to the vein wall, was observed in the earliest group. The thrombus underwent changes typical of organization at the 7-and 60-day observation points and evolved into what was described as a "dense fibrous connective tissue containing numerous spindle-shaped fibroblasts" [19].

In a second, larger study [12], again performed in a rat model, catheters were placed via the jugular vein in 123 animals. Histologic changes were studied at catheter indwelling times that ranged from 1 day to 6 months. A true pericatheter thrombus was identified in all animals within the first 3 days after catheter insertion. A transformation occurred from pericatheter thrombus to a more cellular structure composed of collagen with smooth muscle and endothelial cells; this latter structure appeared 1–4 weeks after catheter placement.

Three kinds of catheter-associated thrombus have been described [14]. The first variety is a mesh-like thrombus that bridges the vein wall and catheter. This is thought to evolve into the mixed cellular and collagen catheter-related sleeve described by these authors in an earlier report [12]. A second, nonorganized form of thrombus has been termed "sleeve-related thrombus" and is found on the distal aspects of the indwelling catheter itself. This variety has no attachment to the vein wall and is histologically and physically separate. Last, mural thrombus is found on the vein wall adjacent to the distal intravascular aspect of the catheter. This thrombus undergoes organization and is thought to become incorporated into the vein wall. It is uncertain why a thrombus at a particular location develops into a cellular bridge instead of incorporating into a vein wall, although catheter motion may influence this process [20].

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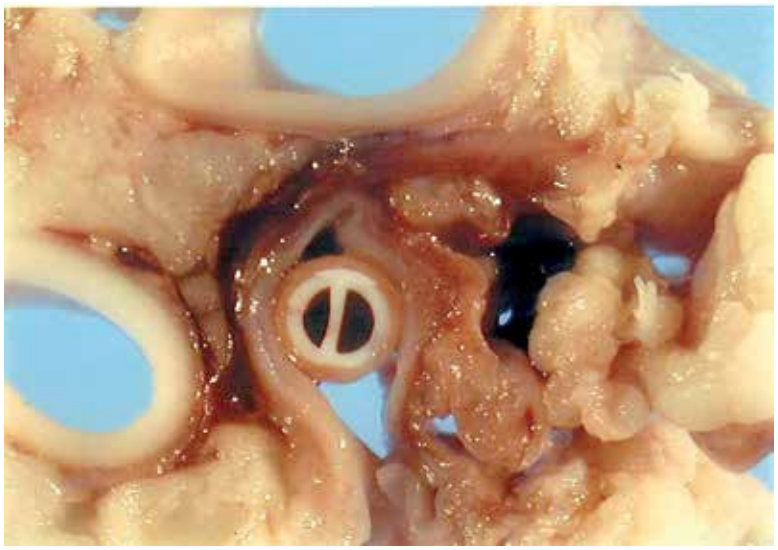

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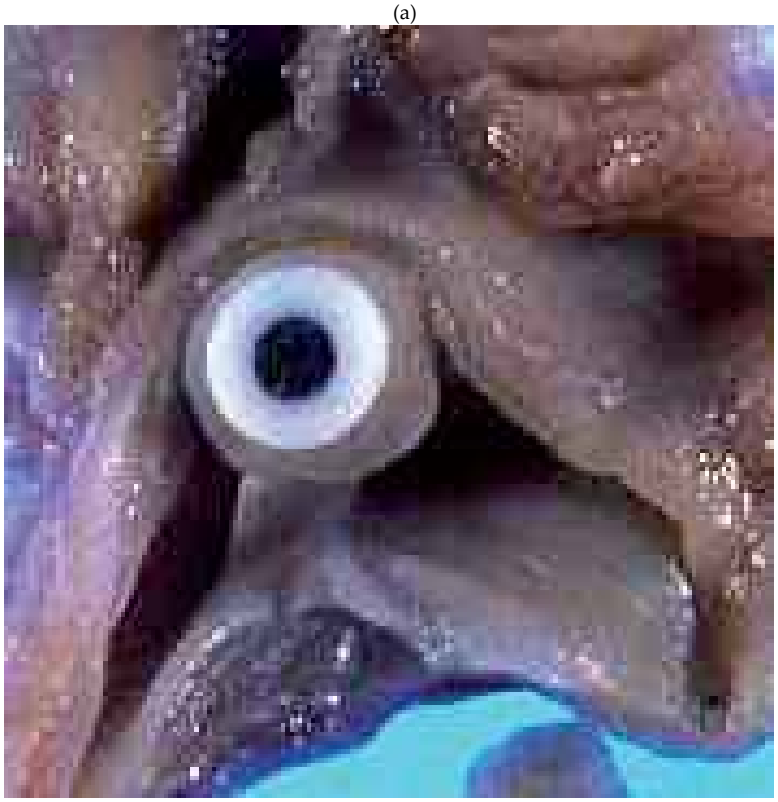

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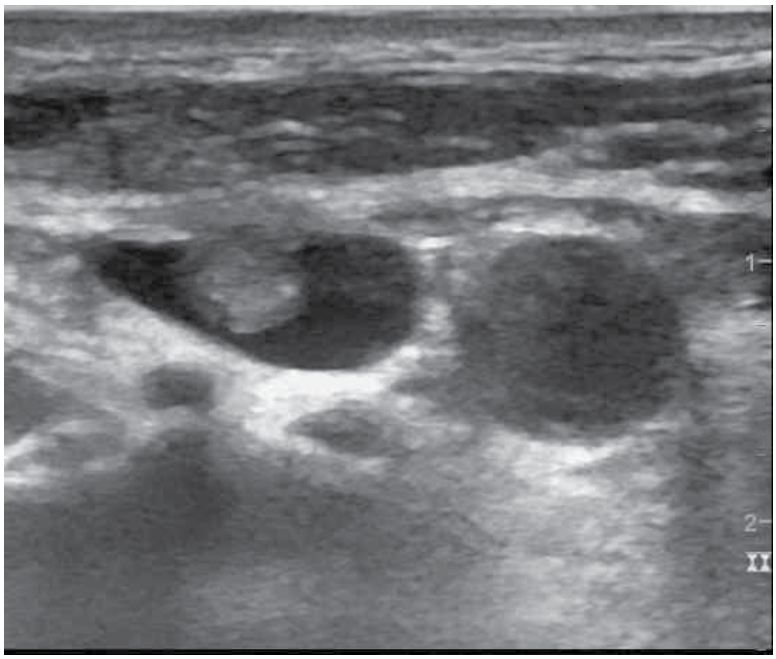

(c)

Figure 2. a)Gross photograph of a well developed, circumferential catheter-related sheath (CRS) that formed in a swine vena cava after only seven days indwelling time. b)Catheter-related sheath from a human autopsy specimen. The sheath is well developed and there is a prominent pedicle-like attachment to the vein wall. c)Ultrasound (US) image of a catheter-related sheath (CRS). Transverse US image from the base of a patient's neck prior to insertion of a tunneled hemodialysis catheter. There is a rounded structure attached to the anterior jugular vein wall representing residual CRS. A previous tunneled catheter had recently been removed secondary to infection.

In a large animal model (swine), Forauer et al [16] examined CRS formation at 7, 14, 30, and 45 days after catheter insertion. This confirmed the cellular nature of the sheath including endothelial and smooth muscle cells; see Figure 3. These cell populations were not randomly present; the smooth muscle cells assumed a typical orientation to the vessel lumen with the long axis of the cell oriented with the circumference of the vessel. The smooth muscle cells were also involved in neovascularity of the sheath, forming small lumens lined with endothelial cells. The endothelial cells formed a monolayer covering the external portion (vascular lumen aspect) of the sheath that was indistinguishable from adjacent vein wall intima.

The development of the catheter-related sheath is postulated to begin with thrombus that develops after trauma associated with the catheter insertion procedure [3,21]. Local trauma occurs at the venotomy site. Factors contributing to thrombus formation include disturbance of normal flow through the venous segment and stasis that occurs between the catheter and the vein wall. Other locations of trauma occur at foci of friction of the catheter against the vein wall or catheter tip impact against the vein wall and in segments where catheters lie in acute angles within the course of the vein [20,21]. In addition, acute or chronic (organized) thrombus has been confirmed in catheter stripping specimens [13].

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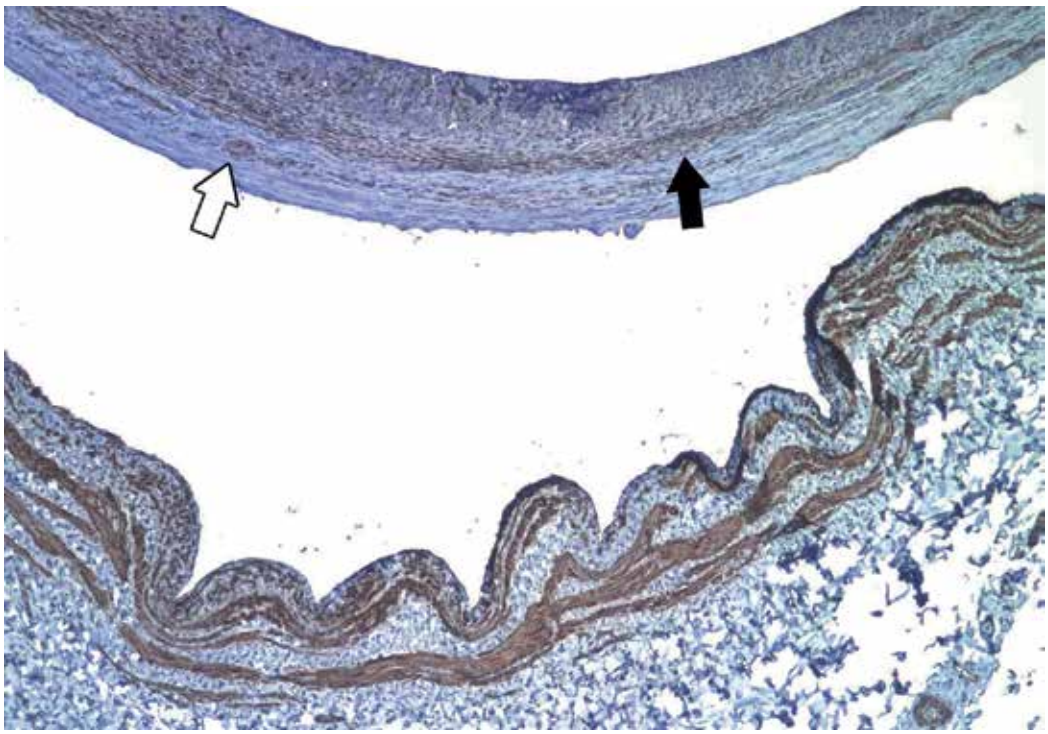

Figure 3. Low-power (x50) micrograph demonstrating smooth muscle cells in the catheter-related sheath. Immunohistochemistry (anti-smooth muscle stain, 1:50) highlights positive staining smooth muscle cells, seen as brown, in both the vein wall and throughout the sheath (solid arrow). A circular arrangement of smooth muscle cells is present in the sheath (open arrow), representing neovascularization within the sheath.

The role of catheter-tip trauma and associated thrombus formation has been examined, also in a swine model [20]. Silicone catheters with or without a 0.018-inch wire stabilizing loop at the distal indwelling tip were inserted, and their tips were positioned in the distal aspect of the superior vena cava. In the group in which catheter tips were stabilized by the wire loop, there was only a mild increase in vein wall thickness without vein wall thrombus. In the control group (without the stabilizing loop), mural thrombus formed at the site of local vein wall trauma caused by catheter tip motion. This thrombus subsequently underwent organization and resulted in vein wall thickening and intimal hyperplasia. The organization of intravascular thrombus involves an infiltration by smooth muscle cells and the development of a vascularized connective tissue that includes collagen, smooth muscle cells, and endothelial cells [22,23]. Inflammatory cells are also known to be involved in venous thrombosis [24].

The process of catheter-related sheath formation is a dynamic and ongoing response of the components of the vein wall to the catheter and associated thrombus. The sequence of the steps of sheath formation is similar among animals and humans. Inflammatory, endothelial, and smooth muscle cells are involved in this response, and these are all biologically active cell types. Findings support the hypothesis that a pathologic process occurs when thrombus organizes adjacent to a synthetic scaffold—a catheter. This process differs from intravascular

thrombus formation because the presence of the catheter within the vessel lumen allows the process to continue with only limited focal vein wall contact.

The role of medical comorbidities, such as diabetes mellitus and hypercholesterolemia, in the formation of CRS has not been well evaluated. A small randomized study evaluating the occurrence of late malfunction in tunneled hemodialysis catheters did note a trend toward late catheter malfunction (either thrombosis or CRS formation) in patients with diabetes, but this did not reach statistical significance (p=0.054) [25]. Several series focusing on peripherally inserted central catheters and non-tunneled internal jugular central venous catheters have shown no clear relationship between diabetes or hypercholesterolemia on thrombotic complications [26-28]. The specific role of hypercholesterolemia in CRS formation has not been addressed.

5. Clinical manifestations of the CRS

While this process can remain clinically silent, there are many clinically important sequelae to sheath formation. These include withdrawal occlusion, total occlusion of the catheter [29], vein thrombosis [4,17,30,31], infusate extravasation [30], pulmonary embolus at catheter removal [2,4], and predisposition to infection [32-34]. Vessel thrombosis can also result in loss of the venous access route- a sobering prospect for a patient requiring long-term renal replacement therapy.

The first indication that a CRS is present is often the ability to flush or inject, but the inability to aspirate from a catheter, termed withdrawal occlusion. This occurs when a CRS encases the tip of a catheter and effectively forms a one-way valve [35]. Additionally, defects or rents in the CRS may allow infusion while not providing sufficient area to aspirate; see Figure 1. This persistent withdrawal occlusion results in chronic catheter dysfunction and poor flow rates. It can also result in the serious complication of medication extravasation [36]. Medication extravasation can result in significant morbidity with administration of chemotherapeutic agents. The infusate injected into the catheter exits the end-hole, tracks retrograde between catheter and the sheath and can follow this path back to the venotomy and into the soft tissues; see Figure 4. The patient may experience pain, inflammation, and tissue necrosis.

The thrombotic complications of pericatheter thrombus formation resulting in a catheter related sheath can lead to stenosis or frank occlusion of the veins anywhere along the indwelling path of the catheter. Intraluminal and mural thrombosis may also contribute to catheter dysfunction and complete venous thrombosis. The catheter dysfunction secondary to intraluminal thrombosis may also present with persistent withdrawal occlusion secondary to a “ball–valve” effect within the catheter lumen [37], and may likely manifest resistance to antegrade flushing as well. Mural thrombi may partially or completely block a vein and are often asymptomatic, but may present with arm, neck, head or jaw pain, numbness of the ipsilateral extremity, erythema, phlebitis or venous distension [37]. In the extreme, the patient may display symptoms of superior vena cava syndrome.

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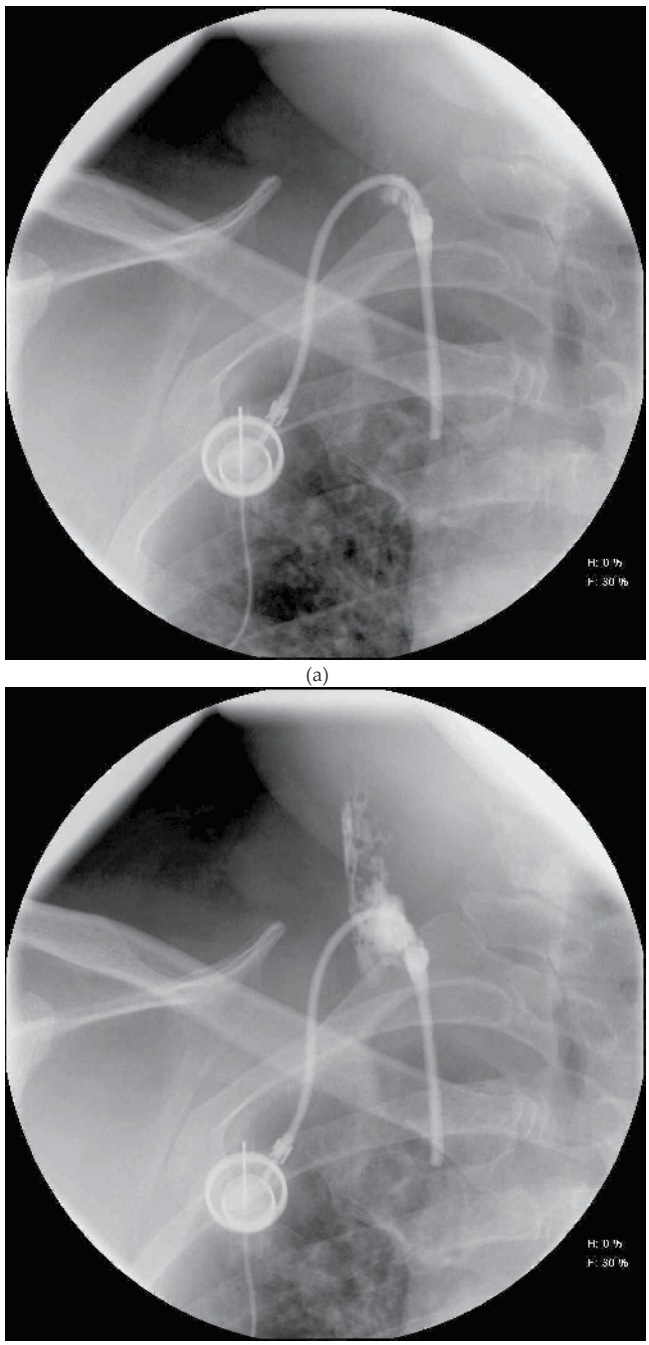

(a)

(b)

Figure 4. Catheter-related sheath causing soft tissue extravasation. a)Early and b) late images from a contrast injection of a right sided chest port. No contrast is observed exiting the distal end-hole of the post catheter. The contrast tracks retrograde along the catheter and exits in the soft tissues of the neck at the level of the venotomy.

CRS and pericatheter thrombus has also been implicated as a risk factor for infection. Mehall et al. established that CRS significantly enhanced catheter related infection and bacteremia. It was postulated that the sheath provides a surface for bacterial attachment and source of septic emboli [34].

Cases of CRS being dislodged into pulmonary vasculature have been described [4,38]. However, this complication appears to be rare or clinically insignificant given the relatively small volume embolic burden and the bridging of cellular tissue with the vein wall.

6. Clinical interventions and management

6.1. Thrombolytic therapy

An initial, conservative approach to patency restoration is the use of thrombolytic agents. Thrombolytic therapy for treatment of hemodialysis catheter malfunction due to thrombosis or CRS has been used for decades. Two basic protocols have been employed: indwelling ("lock") catheter treatments and infusion therapies. Indwelling or "lock" treatments involve administration of a volume of thrombolytic agent which only fills the catheter lumen for a variable amount of time. Infusion treatments involve the infusion of variable doses of thrombolytic through the hemodialysis catheter over several hours.

Multiple different thrombolytic medications have been used with the two methods above in varying doses over the years. Urokinase was the agent of choice for both protocols until its withdrawal from the North American market in 1999. It was reintroduction to the market in 2002. To date, it is the only thrombolytic agent to be directly compared with percutaneous catheter related sheath stripping (PCRSS) in a prospective randomized trial. In 2000, Gray et al found no significant difference in primary patency between urokinase infusion and PCRSS [39]. Low dose (5000 to 9000 units) indwelling treatments have had mixed results in the literature with successful return of catheter function ranging from 14% to 95% [40]. More recently, positive results with high dose urokinase (25,000 to 100000 IU) indwelling treatments have been reported by Donati et al with recanalization rates up to 100% [41].

Since urokinase was withdrawn from the market in North America, several other thrombolytic agents have been evaluated. Multiple published reports and a clinical trial have shown alteplase to be effective and safe [42-45]. There is evidence that alteplase yields similar or better results compared to UK [46-48]. Although less studied, reteplase has also been shown to be safe and effective but no direct comparison has been made to the more commonly used thrombolytic agents [49,50]. Tenecteplase has also been shown in Phase III trials to be safe and effective in the treatment of dysfunctional catheters [51,52]. Newer thrombolytic agents such as recombinant-urokinase, afimeprase, and anistreplase are currently under investigation [53].

Because the composition of the CRS has a significantly cellular component, the efficacy of thrombolytics must be attributed to interaction with the associated thrombotic elements that are present.

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6.2. Percutaneous CRS stripping and other mechanical interventions

Mechanical interventions have also been employed as a treatment for CRSs which result in occlusion or decreased blood flow rates. Such interventions include catheter exchange and PCRSS with balloon disruption. Although sheath stripping is used less frequently in favor of catheter exchange at many institutions, an understanding of the technique is important.

Treatment of occluded central venous catheters by some method of mechanical disruption has been described in the literature as early as 1983 using a straight guide wire advanced through the catheter lumen via a Y-valve under simultaneous constant suction with 100% success [54].

In 1995, Knelson et al [55] described two techniques (a wire only and separate snare technique) for PCRSS. Eleven of the patents had either a J-tipped wire or tip-deflecting wire advanced through the catheter until the curved tip just excited the catheter end, after which it was rotated several times until contrast injection under fluoroscopy demonstrated patency. Alternatively, a snare technique was employed via right femoral vein access. Here, a nitinol loop snare was advanced 5cm over the catheter with the aid of a 6-F guiding catheter, closed and retracted under moderate tension stripping off the sheath surrounding the catheter. Nineteen of the twenty treatments were successful with a mean duration of satisfactory function following intervention of 150 days.

Subsequent retrospective studies have reported high technical success rates [56-59], but with less promising durable clinical results with 45% and 28% primary patency at 3 and 6 months respectively [58]. A study specifically evaluating HD catheter flow rates post stripping yielded more disappointing results: the average flow rate fell below host the institution's standard by the fifth hemodialysis session [56]. Suhocki found primary and secondary mean patency at 3 and 4.5 months respectively [59]. Johnstone found at 6 months primary and secondary patency rates of 40% and 60%, respectively [60]. In 1999, Brady et al [61] prospectively found median post-stripping patency of 89 days(i.e., 3 months).

In 2007, Reddy et al [62] described a new "internal" snare approach as opposed to the "external" approach from a femoral vein. Here, a nitinol wire was bent in its mid portion 180 degrees resulting in a loop. The loop was then advanced through the proximal lumen until and then was tightened down on the distal portion of the catheter snaring it. The looped nitinol wire was also advanced though the distal lumen. Multiple passes were made in each lumen often resulting in clot/sheath removal. Disruption of the CRS was attributed to two mechanisms of action: the stripping action of the snare over the distal lumen and the deformation/expansion of the catheter as the snare is advanced. Nine internal snare procedures were performed in seven patients who had failed pharmacologic lysis with 100% technical success. With the internal snare procedure, there was a 100% patency at 8 weeks and a mean patency of 108.5 days without complication.

In 2002, Angle et al [63] published a five year retrospective analysis of 115 patients with 340 tunneled hemodialysis catheter fluoroscopic evaluations of which underwent one of five interventions: conservative management (aspiration/flushing), tip-deflecting guide wire manipulation, catheter exchange, PCRSS with a snare via femoral approach, and thrombolytic

infusion. Failure rates at 30 days using the five management strategies above ranged from 24% to 62%. PCRSS had the lowest 30 day failure rate of all the methods evaluated.

There have been two prospective trials comparing the effectiveness of different techniques on the dysfunctional dialysis catheter. In 2000, Merport et al [64] performed a randomized prospective clinical trial comparing the effectiveness of over-the-wire catheter exchange versus PCRSS over 37 encounters in 30 patients with malfunctioning hemodialysis catheters which demonstrated 1-month patencies of 93% and 31% respectively. Estimated costs were lower in the catheter exchange group.

In 2000, Gray et al [39] performed a randomized prospective clinical trial comparing the effectiveness of PCRSS with a femoral snare approach versus 250,000 U urokinase infusion over 4-hours. Forty-five day primary patency rates for PCRSS and urokinase infusion were 35% & 48% respectively and were not statistically significant (p=.2).

6.3. Other alternatives

Hemodialysis catheter exchange with or without CRS balloon disruption with has been well described with comparable or improved outcomes compared to PCRSS [64-68]. This procedure is performed by placing guide wires through the existing catheter into the superior or inferior vena cava, freeing the retention cuff from the surrounding tissues using blunt dissection, and removal of the catheter. Disruption of the CRS can be accomplished by advancing a modest diameter (6-8 mm) angioplasty balloon catheter and performing inflations along the previous course of the catheter; see Figure 5. A new catheter is then advanced over the guide wires and through the existing subcutaneous tunnel. When performed using strict sterile technique, there is no increased risk for infection. This strategy has the advantage of preserving the existing venous access site. The less invasive nature of this procedure is responsible for its current widespread application.

Endoluminal brushing of occluded hemodialysis catheters during thrombolysis has been reported with success [69]. This technique targets only the inner lumen of the catheter, not the external CRS.

6.4. Catheter material, coatings and shape

A multitude of tunneled hemodialysis catheters have been marketed over the years with differences in catheter material, tip shape, number of side holes and surface coatings with the hope of reducing complications. While the effects on infection rates and thrombosis of these different catheter types have been studied, rigorous examination of different catheter types on CRS formation is less well understood.

Catheter material has traditionally been variants of either silicone or polyurethane. More recently carbothane has been introduced allowing for greater catheter wall strength and resistance to certain chemicals. In vivo studies of catheter material with regard to thrombogenicity and platelet adhesion have had mixed results showing both no difference between polyurethane and silicone [70] and lower thrombogenicity with polyurethane [71]. Unfortunately, these studies did not evaluate the relationship between thrombogenicity and CRS formation.

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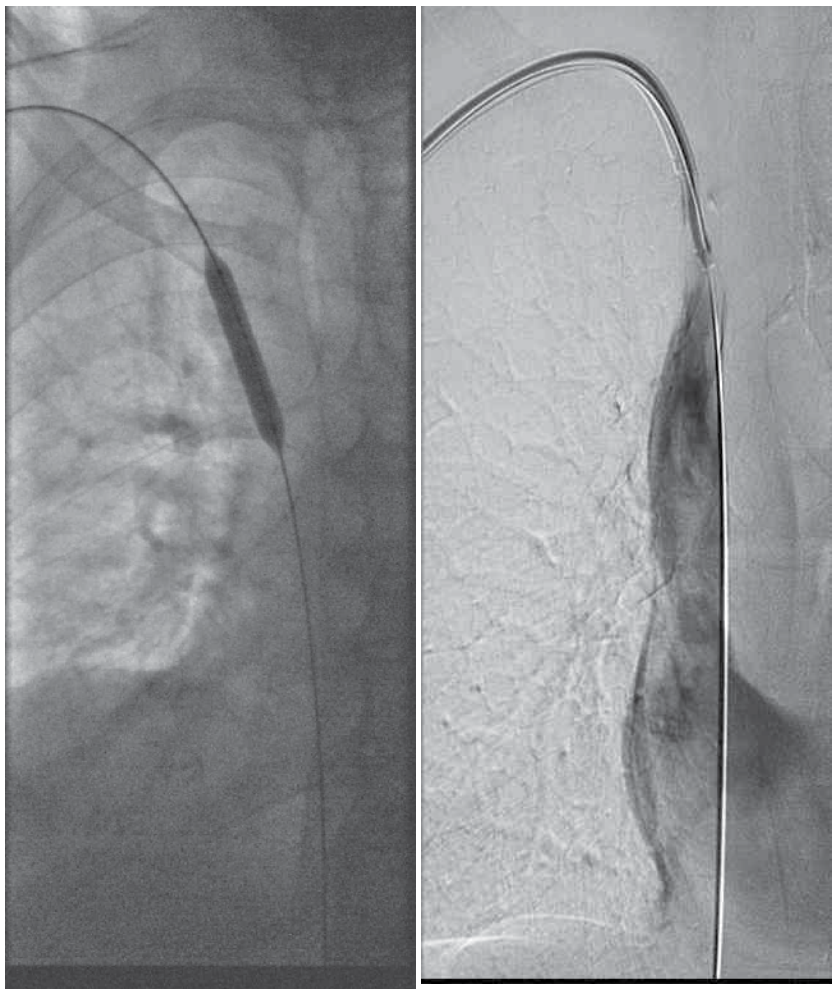

(a) (b)

Figure 5. Balloon disruption of a catheter-related sheath (CRS). a) Inflation of an over the wire angioplasty balloon to disrupt the sheath.b) Post balloon disruption contrast injection. The full lumen of the superior vena cava is now opacified.

A variety of antibiotic and antithrombotic catheter-bound coatings have been developed to prevent infection and thrombosis. As expected, studies have shown that heparin-coated central venous catheters can reduce central venous catheter thrombotic complications [72,73]. A retrospective study published in 2009 evaluated the differences in primary patency between heparin-coated and uncoated hemodialysis catheters. Primary patency at 30 and 90 days demonstrated a slight trend favoring the heparin-coated catheters, but the results did not reach statistical significance ($p=0.08$) [74].

Variations in catheter tip shape, number of lumen and number of side holes continue to evolve with promises of decreased recirculation, rates of thrombosis and improved flow rates. A

randomized prospective evaluation of three catheter configurations- paired catheters, split tip catheters, and stepped lumen catheters was published in 2001. Despite different design and arrangement of side holes or lumens, all three catheters had similar survival times and flow rates [75]. In 2008, Kakkos et al attributed differences in tip shape to the significant improvement in 90 day primary assisted patency of the Tal Palindrome Ruby (Covidien; Mansfield, MA, USA)) catheter compared to the HemoSplit (Bard Access Systems; Salt Lake City, UT, USA) tunneled catheter, 94% versus 71%, respectively [76]. This difference persisted at 180 days.

6.5. Future directions

Considerable effort in current interventional cardiovascular research is focused on drug-eluting coatings for stents [77]. These coatings consist of cytostatic or cytotoxic agents that target cell populations involved in stent related restenosis. The characterization of the cellular basis of catheter-related sheath formation may initiate further developments in the area of catheter technologies [78] that could include the development of materials with or without coatings that prevent, retard, or eliminate the sheath.

7. Summary

Catheter-based hemodialysis remains an important option for many chronic kidney disease (CKD) patients. In addition to catheter-related infections, CRS formation is responsible for a significant proportion of catheter dysfunction. It is a dynamic and on-going response of the vein wall to the catheter and the associated thrombus. It involves biologically active cell types and there are many similarities with the process of thrombus organization. There have been numerous methods developed to restore catheter function; thus far, none have provided consistent long term, durable results.

Nomenclature

Chronic kidney disease (CKD), catheter-related sheaths (CRS), percutaneous catheter related sheath stripping (PCRSS)

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Chapter 34

Arteriovenous Fistula or Catheter: Creating an Optimal Vascular Access for Hemodialysis

Joëlle Cridlig, Michèle Kessler and Thanh Cao-Huu

Additional information is available at the end of the chapter

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1. Introduction

Hemodialysis has been used for half a century and is often proposed as the first support treatment for patients developing end-stage renal disease, more frequently than peritoneal dialysis and kidney transplantation. For a large part, the success of hemodialysis depends on the success of the vascular access, whether achieved with an arteriovenous fistula or a central venous catheter. Survival of the vascular access often determines the patient's survival, emphasizing the importance of carefully preserving the often limited stock of available vascular tissue. The purpose of this chapter is to review the different possibilities for vascular access for hemodialysis, from planning to construction, including a discussion on the importance of complementary explorations for complex situations or complications. Clinical cases will be presented to illustrate how multidisciplinary management can meet the challenge of desperate "last chance" situations, providing lifesaving solutions for our patients.

2. Vascular access for hemodialysis: Background

Vascular access should enable obstacle-free blood flow for the extra corporeal hemodialysis circuit with appropriate inflow and outflow pressures (Figure 1). In addition, vascular access should not cause any deleterious consequences for the patient such as limb ischemia related to steal phenomena, stasis edema or compressive effects (for instance in the head and neck) due to a peripheral or central stenosis blocking venous backflow. An excessive flow rate can compromise cardiac function. Several types of vascular access are available, with two modalities: catheter and fistula. In the past, the first hemodialysis systems used an external shunt made by inserting canulas into an artery and a vein (lower or upper limbs), for

example the Thomas shunt [1], creating an extracorporeal circulation. In the sixties, improved techniques allowed the creation of the first arteriovenous fistula (AVF), an anastomotic bypass between an artery and a vein [2]. AVFs may be positioned on the upper limb or the lower limb, proximally or distally. Single or double-flow central venous catheters may also be inserted into the large veins of the neck or thigh, with or without tunnelization.

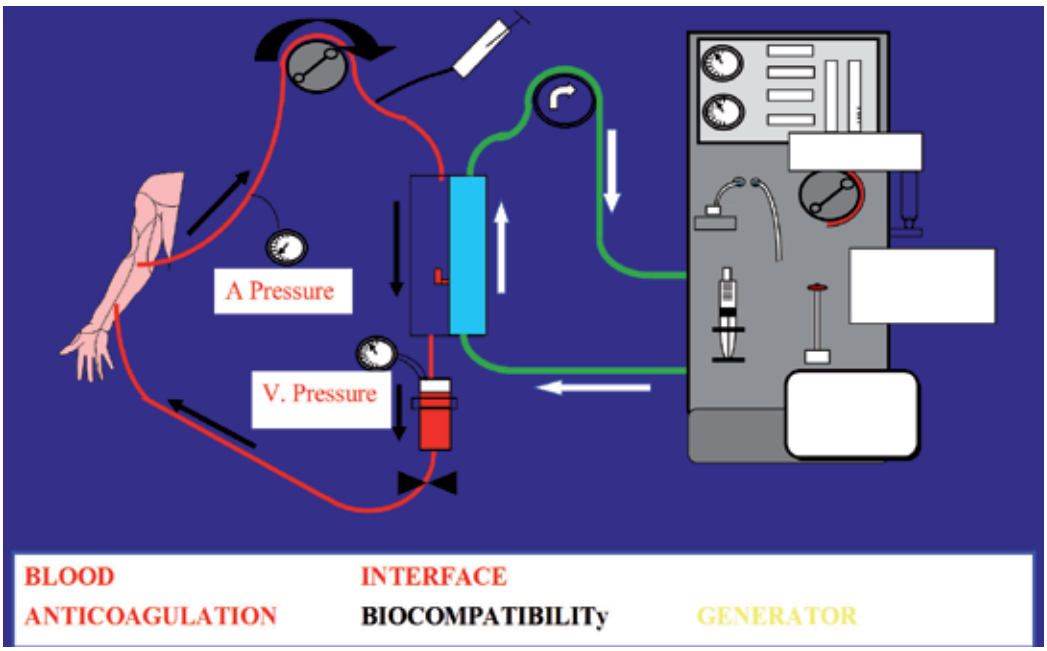

Figure 1. Hemodialysis circuit (From T. Cao-Huu with permission)

3. Catheter or arteriovenous fistula (AVF): The rationale

A central venous catheter may be used for vascular access in emergency situations in patients unprepared for hemodialysis or if an intercurrent event, for example thrombosis of the AVF, infection or any situation contraindicating the usual access, occurs in a patient already on hemodialysis. Insertion of a central catheter has the advantage of offering immediate high-flow vascular access but should, according to the guidelines issued by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI), be used in less than 10% of patients [3]. Data from the United States Renal Data System (USRDS) however revealed that in 2009 more than 80% of patients started dialysis with a central catheter. Practices in Europe and the United States differ as shown by the DOPPS study which, after adjustment for confounding factors, compared vascular access practices, focusing on particular

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factors associated with use of a native AVF versus graft or catheter [4]. The prevalence of native AVF use was found to be 80% in Europe versus 24% in the US. At dialysis onset, 66% of European patients had an AVF (including 2% with a prosthetic graft) versus 15% in the US [24% prosthetic graft). Patient referral patterns, nephrological follow-up and the type of vascular access used are directly related: closely monitored patients are better prepared for dialysis. There is also an economic element, related to general population access to healthcare [5].

It is argued that more complications occur with a catheter than with an AVF [6-10]. A review of the literature confirms the superiority of the native AVF over prosthetic material or catheters. Longer life, fewer mechanical complications (thrombosis, stenosis), and lower infectious risk are advantages of the native AVF. It is the recommended vascular access, and should be considered as the gold standard [3][10][11].

Quality-of-life [12] and morbidity-mortality risk, especially in the elderly [13], are directly related to the type of vascular access first used for dialysis. There is a real advantage if the first vascular access is a native or graft AVF [14]. Survival is also improved [15].

A central catheter may however be quite useful for temporary (or permanent) vascular access in particular situations: living-donor graft involvement; short life expectancy (cancer); waiting for an AFV to mature; permanent access despite a highly deteriorated vascular system; heart failure; severe arteriopathy with risk of steal phenomena [16]. For the congestive heart failure patient, preemptive construction of an AVF has been shown to be a source of decompensation[17].

4. Choosing a vascular access for hemodialysis

4.1. Catheter

4.1.1. Types used

Catheters have been carefully designed to respond to the needs of the dialysis patient. Prerequisites include appropriate flow rate and clearance quality (diameter, separate branches, multiperforated tip), physical resistance (flexibility/rigidity, composing material: silicone, polyurethane…), tolerance (internal medium, blood/material interactions, surfacing processes), and cosmetic acceptability. Portacaths and tunnelization have been used since 1987, greatly reducing the risk of infection by increasing the distance between the point of entry into the central vein and the point of exit through the skin [18] (Figure 2).

To access central veins, priority should be given to jugular (and secondarily infraclavicular) puncture to reach the superior vena cava, first on the right side, and secondarily on the left side. Access to the inferior vena cava, via a femoral or translumbar puncture, should always be a second-intention procedure.

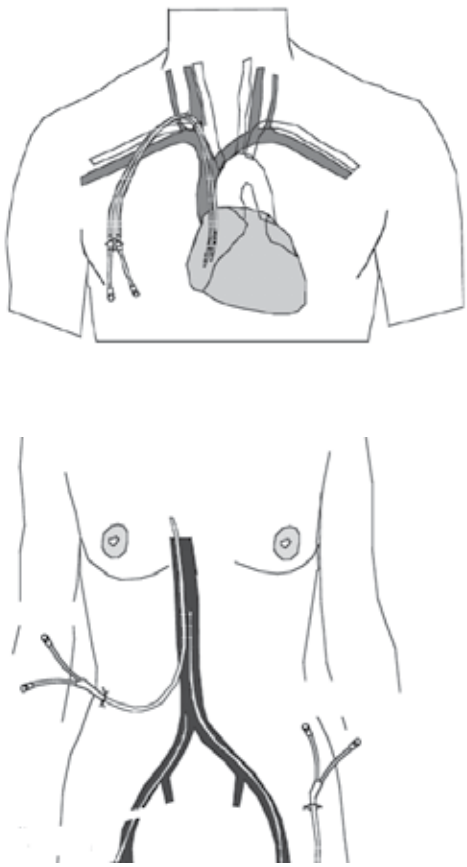

Figure 2. Example of a cuffed catheter (From B. Canaud with permission)

4.1.2. Technical modalities

There are a certain number of clinical prerequisites for catheter insertion. Attention must be given to the patient's history of vascular access and potential problems or anomalies, the risk of stricture often revealed by collateral circulation, and the presence of edema.

Ultrasound guidance has a proven impact on reducing the risk of complications [19]. The pitfalls of blind puncture (anatomic variations or unknown strictures or thrombi) may be avoided. This may be especially important in catheter-naïve patients or those with a past history of vascular access.

Hemostasis should be checked. Treatments (anticoagulants) and specific clinical features (hemodynamic situation, respiratory function, general status) should be noted before attempting to position a central catheter.

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A chest X-ray may be useful during catheter insertion but in general is obtained in the radiology unit after completing the procedure. Local practices depend on available facilities (catheter insertion feasible in the radiology unit?).

Catheter maintenance is a multifactorial process. Rigorous aseptic manipulation is the rule. Different types of impregnated locks can be proposed depending on the objective [20]: anticoagulation, fibrinolysis, anti-infectious or anti-septic effect (tauludine, citrate). The debate continues concerning the longevity of non-tunnelized catheters: guidelines vary from 1 to 3 weeks. These catheters are however often used for much longer periods of time. It is also generally accepted that tunnelized catheters should be a temporary option while waiting for the maturation of an AVF, although clinical practice may dictate using them as the permanent vascular access (AVF unfeasible, frail elderly patient) [21].

4.1.3. Acute complications

Different types of acute intra-operative complications are noted: hemorrhage, traumatic arterial or venous puncture with vessel laceration, pneumothorax, hemothorax, air embolism, dysrhythmia, neurological injury, malposition [22-24].

4.1.4. Long-term complications [25]

Long-term complications are usually related to the duration of use and insertion [26] and in general affect the quality of dialysis. According to the KDOQI, catheter dysfunction is defined as blood flow <300ml/min and blood pressure >250 mmHg [3]. There are many causes related to mechanical problems or clot formation. Mechanical obstruction may arise if the catheter is folded or malpositioned (a catheter is considered to be too short or too long depending on the position of the tip in relation to the right atrium). Clotting may result from a blood-material interaction leading to progressive formation of a fibrin sheath around the catheter. Blood clots may also form at the tip of the catheter because of perturbed blood flow or microtrauma. This is the leading cause of catheter dysfunction [27].

Infection is another important complication. A venous catheter constitutes a portal with the inherent risk of colonization and dissemination. In the chronic hemodialysis patient, it is the leading source of infection [28], which in turn is the leading cause of morbidity and mortality [29].

Central veins repeatedly exposed to catheters may develop zones of stenosis [30]. The hypothesized pathogenic mechanism would involve repeated microtrauma injuring the endothelium, turbulent blood flow, local uremic context related to the renal failure, chronic inflammation, and activation of the coagulation cascade. The use of the left side would have an impact since the catheter has to be longer and local anatomic conditions are less favorable (compression). Similarly, complications would be more common after infraclavicular puncture compared with jugular puncture due to the anatomic configuration.

4.2. Arteriovenous fistula

4.2.1. Types used

Several types of AVF are proposed (Figure 3), using different upper or lower limb arteries and veins, with or without a graft (straight forearm graft, looped-shape graft). Beyond vessel quality and the patient's past history and clinical situation, the only limitation for fistula configuration appears to be the creativity of the nephrologist and surgeon [31] (Figure 4).

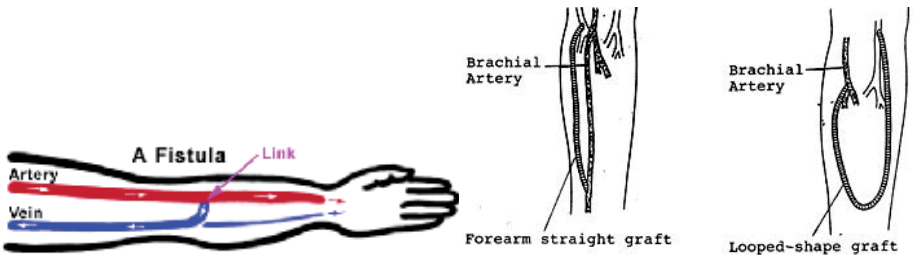

Figure 3. Native and prosthetic arteriovenous fistulas (from T Cao-Huu with permission)

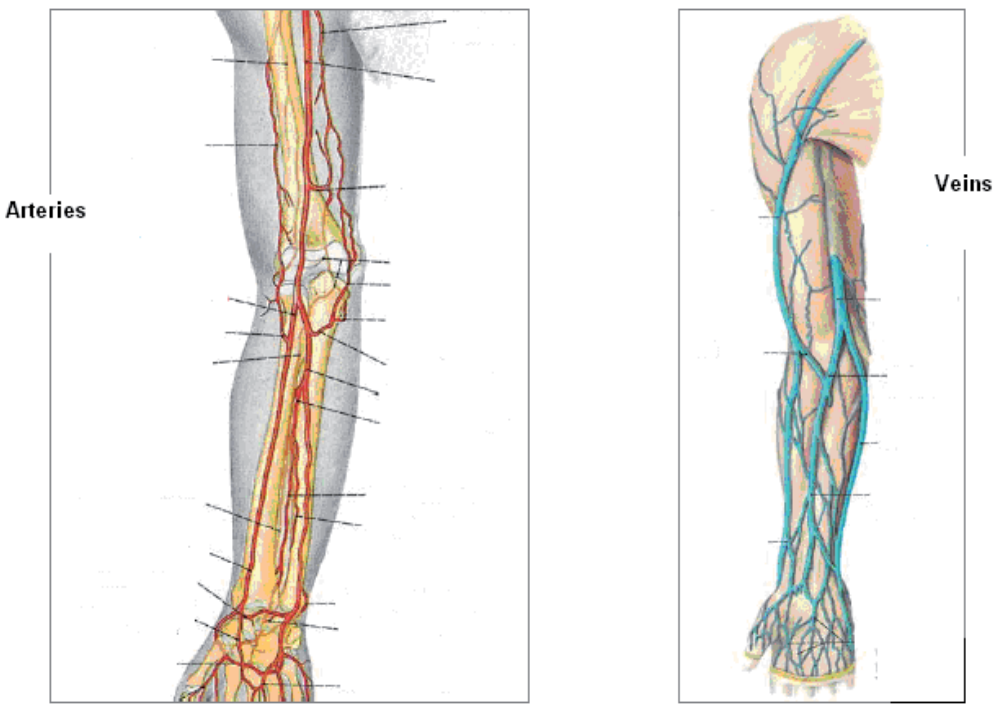

Figure 4. Map of forearm vessels (from T Cao-Huu with permission)

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One question often raised is whether the patient's endogenous vasculature or a prosthetic graft should be preferred. Most clinicians prefer to reserve prosthetic grafts as a second intention option after failure of one or more native AVF, or if the existing vascular network is unusable, as a first intention proposal. The advantage is that native AVFs mature more rapidly and offer easier more effective surgical access should a thrombotic event occur [32]. One retrospective study found that the risk of access failure is higher with a graft compared with a native AVF [33], both for first and second intention accesses. Greater longevity, better quality and fewer surgical revisions are all advantages of the native AVF over the graft [34]. If a native AVF is not feasible, a graft would be superior to a central catheter in terms of complications, although opinions have varied [36]. The Flixene graft composed of synthetic material (PTFE) is easy to puncture. To date, there has not been any clinical study comparing mechanical complications with Flixene and vascular grafts.

4.2.2. Technical modalities

The construction of a vascular access for hemodialysis is a crucial event affecting the patient's quality-of-life and survival. European and American guidelines have been issued [37][38].

Several parameters and pre-operative explorations must be taken into account [38][39]:

- Patient characteristics: genetic background, age, dominant hand, spare vessels, co-morbid conditions (diabetes, arteriopathy), status of venous network, prior attempts to form an access, presence of a pacemaker, coagulation disorders, heart failure (risk of decompensation if the fistula flow rate is too high), possibility for anesthesia, patient education, future renal transplantation (waiting list, blood group, anti-HLA immunization, projected living-donor graft);
- Physical examination: vessel map and vessel characteristics [40], signs of collateral circulation or edema suggesting possible strictures, Allen maneuver to search for steal phenomena and other vascular functions [41];
- Imaging findings: ultrasound, computed tomography angiogram;
- Biochemical parameters would also have an impact although formal evidence is lacking [42];
- Physician experience and training (nephrologist and surgeon) also affect outcome [43].

A recent study showed that according to the responding nephrologists, selection criteria for AVF candidates are quite variable. No consensus has been reached concerning the appropriate indications and contraindications for creating an AVF [44].

4.2.3. Acute complications

Early complications are mainly related to the operative procedure and include hematoma, operative site infection, defective wound healing, and neurological problems.

4.2.4. Long-term complications [45]

Complications occurring late are also quite variable: retarded maturation requiring collateral ligation to favor development; need to change the site of anastomosis; a vein too deep for puncture (e.g. superficialization of a humerocephalic AVF); bleeding; ischemia related to steal phenomena; flow rate too high for cardiac output requiring a smaller caliber or a DRIL procedure); aneurismal or necrotic lesions related to puncture; thrombotic events and strictures of the AVF itself or of the central veins. No direct link between daily dialysis sessions and complication rate has been demonstrated [46]. Infection is also a serious complication, sometimes diffusing to multiple sites (endocarditis, spondylodiscitis).

4.2.5. Good clinical practices for AVF [38][37]

As a rule, a good AVF will exhibit optimal development. This means avoiding complications and treating those which do develop early. It also means limiting the risk of thrombosis and stricture by avoiding the use of venous access in emergency situations. The site chosen for the AVF should be as distal as possible in order to facilitate puncture and spare more proximal veins for later use if needed. The AVF should be on the dominant side.

What is an ideal AVF? According to both the American [38] and European [37] guidelines, the first-intention AVF should be native and distal. Case-by-case decision making nevertheless determines the optimal configuration: e.g. a proximal fistula because of an insufficient distal network; a distal fistula to avoid high flow rate in a patient with heart failure; a synthetic graft or a central venous catheter in a patient with poor vessel quality.

When should the AVF be constructed? Considering past experience and available evidence, concerted action has been undertaken in several countries to increase the proportion of first-intention AVFs used for hemodialysis vascular access [47-49]. No consensus has been reached concerning the optimal position for the AVF in the end-stage renal disease dialysis patient. The decision depends on how fast the kidney disease progresses, and the availability of healthy arterial and venous tissue. In the emergency context, a temporary access may have to be created rapidly, followed by a final configuration determined later: position of the permanent vascular access, option for peritoneal dialysis, etc[37].

When can an AVF be punctured? According to the KDOQI [3], indicators of optimal maturation include flow rate >600 ml/m and 6-mm inner diameter. In clinical practice, operator skill greatly affects the decision to use an AVF or not, and consequently, its longevity. Good clinical practices focus on local hygiene and puncture technique (button-hole puncture, compression after needle withdrawal). Care must be taken to avoid infections, aneurysms or necrotic tissue and strictures. Several studies have compared the use of the button-hole option versus a rotation of the puncture points. Results have been discordant concerning the advantages and disadvantages of the two methods (pain, ease of puncture, infection rate) [50, 51]. There is also the question of the number of needles. Unipuncture can be useful if the fistula cannot be punctured readily or if it is too short to insert two needles. It can also be a solution if a bipuncture venous catheter cannot be inserted. Well performed, unipuncture can enable good quality dialysis, with equivalent morbidity and mortality compared to the bipuncture

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technique. Data are lacking concerning a potential reduction in the complication rate with unipuncture.

How should the AVF be monitored? Various methods can be used to check vascular access function and detect the development of complications: physical examination, education of patients and nurses, venous pressure, blood recirculation and flow rate, clearance (kt/v), duplex Doppler, CTangiogram, or fistulography, which can be performed with or without compression, particularly to identify steal phenomena. Combining these explorations often provides complementary information. The KDOQI proposes a basic algorithm for monitoring these elements [38]. A software based on impedancemetry combined with tomography angiography is an innovative technology allowing study of flow rates and pressures within the AVF and thus early detection of potential complications [52].

5. Multidisciplinary management: Key to success

Nephrologists, radiologists, and vascular surgeons working together to find the most appropriate solution for each individual patient, before, during and after construction of the vascular access is the key to success. The goal is to achieve the best possible vascular access which will survive as long as possible.

In the following sections, we present a few examples of patients referred to our center with a failing vascular access. These 'desperate' cases illustrate how audacious solutions may be found for lifesaving vascular access.

5.1. Catheter failure

5.1.1. General statement

Catheter failure generally occurs in patients who have had several catheters or when AVF is no longer feasible. Mechanical complications are however becoming less and less common because of the greater flexibility and longer stability provided by the new materials: polyurethane and silicone. Neither material has proven superiority over the other [18].

In the past, immediate withdrawal was the rule when infection developed in a catheter-bearing patient. This is still the basic attitude for non-tunnelized catheters. If however the catheter is tunnelized, most clinicians now consider that a probabilistic antibiotic regimen can be initiated in combination with aseptic wash-out (skin orifices, subcutaneous tunnel). An antibiotic lock is also useful. If the course is unfavorable (poor control of infection markers, secondary spread), the catheter must be withdrawn rapidly [53].

In general, for a non-tunnelized catheter, thrombus-related complications (clot formation within the catheter, fibrin sheath) are treated by withdrawal. For a tunnelized catheter, thrombolytic agents (urokinase) are often used. Short-term results have been satisfactory, but long-term results less so [54]. To prevent recurrence, thrombolysis may be associated with oral anticoagulants or antiplatelet agents, but to date no real indication has been identi-

fied in this context and no consensus can be established from the currently available studies. There is no evidence supporting the efficacy of preventive treatment for AVF or central vein thrombotic events or strictures [55]. Salvage (mechanical extraction of a fibrin plug or blood clot) can be attempted with angioplasty equipment and balloons. Results have been promising [56, 57]. The KDOQI recommends extraction with catheter replacement [3].

For stenosis of the central veins, percutaneous angioplasty, with or without stenting, is preferred, especially for recurrent stenosis [58].

5.1.2. Illustrative cases: Failing vascular access due to multiple strictures of the central veins and catheter dysfunction

Case n° 1: a large number of old thrombi obstructing the central veins and preventing catheter insertion. The problem was solved using a novel interventional radiology technique performed in cooperation with the vascular surgery team.

A 52-year-old obese woman with diabetes was referred for failing vascular access after loss of a kidney graft subsequent to non-compliance. Over the last five years, 12 central catheters (jugular and femoral access) had been used for dialysis. All attempts to fashion an AVF, on the right and on the left, had failed. The most recent central catheter was tunnelized but failed due to thrombi in both brachiocephalic venous trunks (Figure 5). Several dilatation attempts had failed.

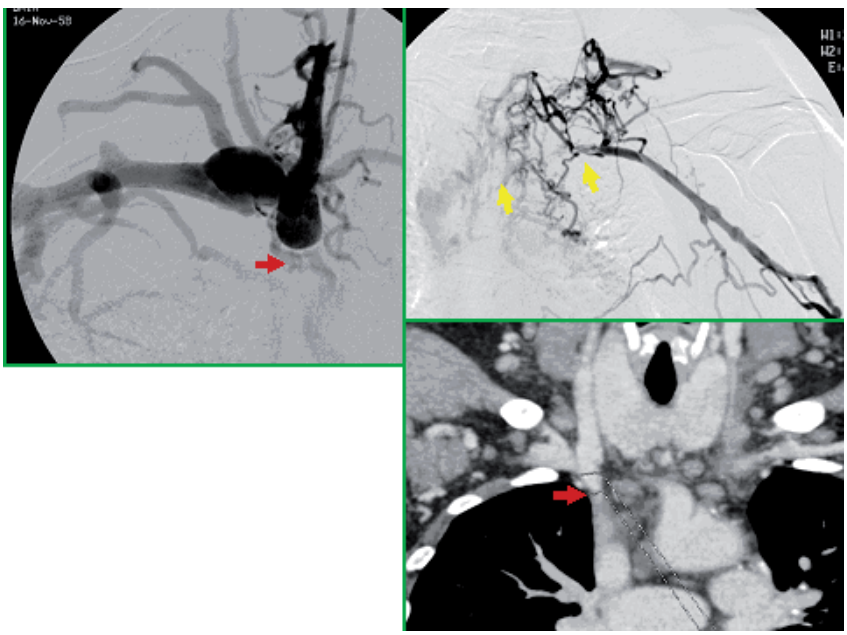

Figure 5. Thrombi in both brachiocephalic venous trunks; one was recent and long (yellow arrow); the older one was shorter (red arrow) (From T.Cao-Huu with permission)

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The patient was referred with a tunnelized left femoral catheter complicated by a long thrombus in the right femoral vein. Imaging showed patent right subclavian and right cephalic veins so that a homolateral upper limb AVF would be feasible. In order to maintain the hemodialysis after constructing the AVF and waiting for it to mature, another angioplasty procedure was attempted to overcome the 1-cm obstruction in the right brachiocephalic trunk. Using an innovative "rendez-vous" technique, probes inserted via the femoral and jugular veins were passed through the obstruction and joined to dilate the stricture and insert a stent then a catheter. The procedure was performed under general anesthesia by a radiologist with a vascular surgeon back-up if necessary (Figure 6 and 7).

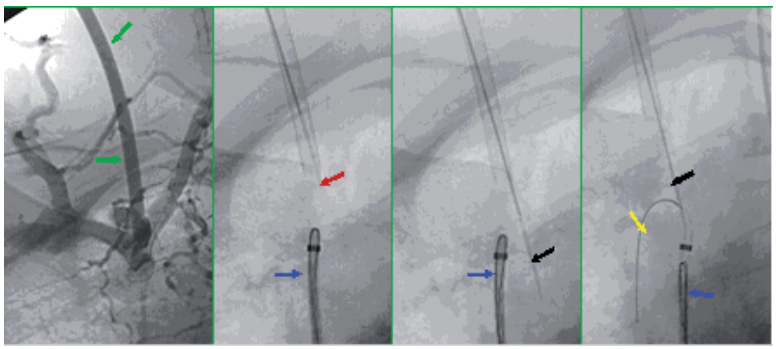

Figure 6. Dual access (10F) via the right common femoral vein and the right internal jugular vein. The right internal jugular probe was positioned on the superior aspect of the obstruction (green arrows). A lasso catheter was inserted via the femoral access up to the inferior aspect of the obstruction (blue arrows). Biplanar analysis showed the proximity of the two probes. A Chiba 23G needle (black arrows) was inserted via the jugular probe to puncture the thrombus. A 0.0014 In (yellow arrow) guidewire was fed through the Chiba needle and captured by the inferior lasso. (From T.Cao-Huu with permission)

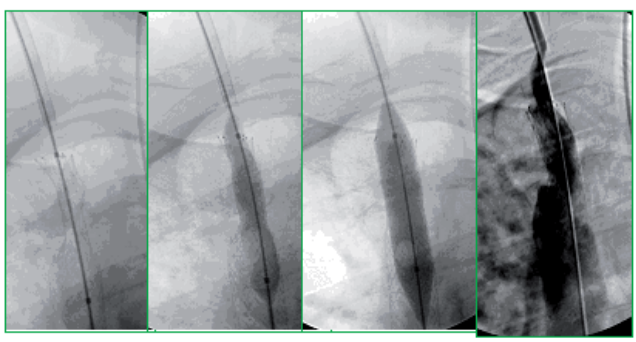

Figure 7. After 8, 10, and 12 mm balloon dilatations ⇒ 12-cm self-expansive stent completed with a 12-mm balloon. (From T.Cao-Huu with permission)

This patient was dialysed on her cuffed catheter and died about one year later, from a coronary disease.

Case n° 2: a problem of central venous stenosis solved by dilatation (and stenting) then secondary catheter insertion.

A 23-year-old patient who had developed cutaneous graft-versus-host disease after a bone marrow graft for leukemia was referred for calciphylaxia and very poor general status. At admission the work-up showed poor dialysis parameters and low flow rate from a left radial-radial native AVF. There were multiple arterial and venous strictures and a risk of hand ischemia. The angiogram visualized very frail calcified forearm arteries and thrombi in the left cubital artery, the left jugular vein, and the right brachiocephalic venous trunk. A multidisciplinary meeting with radiologists and vascular surgeons led to the decision to attempt stenting the right brachiocepahlic venous trunk to insert two tunnelized catheters after dilatation (Figure 8).

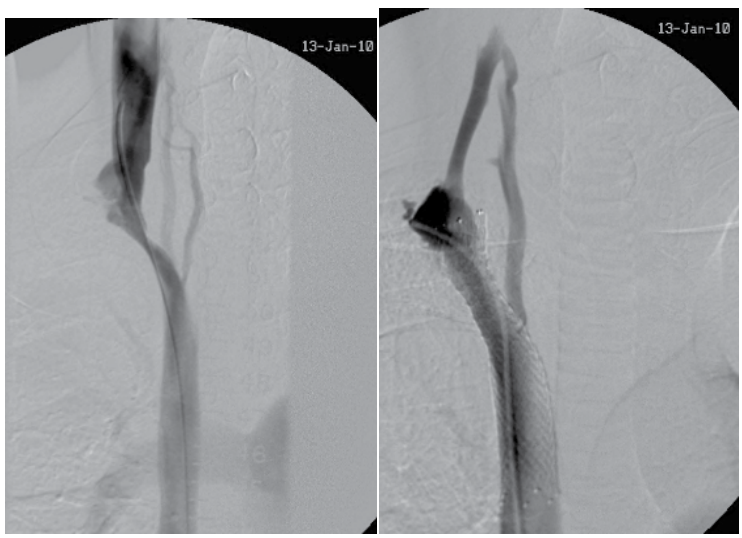

Figure 8. Angioplasty and stenting of the stenosed right brachiocephalic venous trunk. (From T.Cao-Huu with permission)

The angioplasty was successful allowing intensified hemodialysis and associated treatment of the calciphylaxia (disodium thiosulfate) in preparation for renal transplantation, considered as an "emergency" procedure due to the failing vascular access and the calciphylaxia. Outcome was favorable, both for the kidney graft and the calciphylaxia.

5.2. Fistula failure: Multiple stenoses affecting the upper limb venous network and both central veins

Treatments for aneurismal complications, late fistula maturation, ischemia or high flow rate are well known and will not be discussed here. This chapter will focus on stenotic complications involving the fistula itself or the central veins and situations of failing vascular access

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in patients who often have had a long history of successive attempts to create functional vascular accesses.

5.2.1. General statement [59]

Evidence in the literature on patients prepared for hemodialysis with an AVF is formal: after adjustment for confounding factors, AVF survival is inversely proportional to the number of interventions needed to render it usable [60].

Two cases in our center have illustrated the negative impact of catheter-related stenosis of the central veins on vascular access. Treatment relies heavily on interventional radiology [61, 62].

In addition to the imaging explorations mentioned above, stenosis of the AVF can be detected clinically by measuring fistula flow rate during dialysis [63]. Patient and caregiver education is essential here. Invasive diagnostic procedures are not recommended per se and increase the cost of treatment, but if a stenosis is suspected clinically, further explorations should be undertaken to prevent the development of significant thrombosis [64]. To date, studies have been unable to demonstrate any difference in the long-term outcome of the fistula between surgery for thrombosis and pre-thrombotic treatment [65].

Angioplasty is the treatment of choice for fistula stenosis; stenting is optional. Various types of material have been tested. Ultra-high pressure balloons or cutting balloons can remove the atheroma from the vessel wall mechanically, but with the risk of vessel tears. Metallic stents can be coated with different surfacing agents to improve their longevity. Self-expandable stents are successful in only one-third of cases, but with no real impact on long-term AVF survival [66, 67].

A recent review [68] detailed the different phases of the interventions: angioplasty for stenosis of pre-thrombotic AVF and thrombectomy for thrombotic AVF (pressure or mechanical removal depending on the nature of the thrombus) followed by angioplasty if an associated stenosis is identified; systematic exploration of the central vascular network in order to avoid missing any stenosis-favoring stricture accessible to angioplasty. Short-term pharmacological treatment (anticoagulant, antiplatelet agents) may be useful.

5.2.2. Illustrative cases: Steal syndrome and last chance access

Case n°1: chronic hand ischemia in a 77-year-old patient with upper limb arteriopathy.

A Distal Revascularization Interval-Ligation (DRIL) (Figure 9) procedure was performed to reperfuse the distal arteries and save the fistula. Revascularization was achieved with a radial-radial bypass combined with ligation of the radial artery. It allowed a long term fistula, hand and patient survival. Other types of revascularization (e.g. prolongations) can also be proposed.

Case n° 2: extensive central venous stenosis involving the vena cava combined with intracardiac thrombotic formations treated with interventional radiology, avoiding thoracotomy for major heart surgery and preserving the vascular access.

This 56-year-old patient on chronic hemodialysis for uropathy subsequent to multiple trauma (traffic accident) had already had several central catheters and distal AVFs when he was referred to our unit for low flow rate in the right forearm gortex graft with central vein thrombus involving the superior vena cava. The final decision was to combine heparin with radiologic angioplasty because of the high risk of heart surgery. The successful intervention illustrates how the potentially serious consequences of a long history of vascular accesses can be resolved. This patient is still on hemodialysis, on his goretex graft that well work.

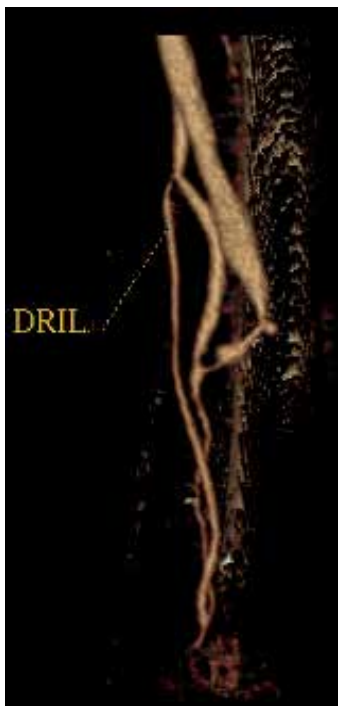

Figure 9. DRIL. (From T.Cao-Huu with permission)

Case n° 3: a young patient with recurrent fistula stenosis compromising the last dialysis access available.

This 26-year-old patient on hemodialysis since childhood for malformativeuropathy had had a kidney transplant before returning to hemodialysis due to non-compliance with drug regimen. He had a right tunnelized catheter for hemodialysis because successive attempts to fashion an AVF had failed. Thrombi developed bilaterally in the internal jugular vein, in the left brachiocephalic venous trunk and in the superior vena cava. Multiple episodes of catheter dysfunction occurred requiring successive replacements, complicated by repeated infections. Despite the very poor venous network and a very frail cubital vein, the vascular surgeon successfully created a right cubital AVF after repeated procedures to carefully dilate juxta-anastomic strictures. Hemodialysis was continued for more than two years via this

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fragile fistula while waiting for the progressive development of the basilic vein and subsequent construction and maturation of a humerobasilicgortex bypass. Despite recurrent stenosis with thrombus formation favored by a fold in the graft assembly at the elbow, the patient's hemodialysis protocol was conducted successfully until a second kidney graft could be implanted. This graft has a favorable outcome, but the patient has lost his fistula. This case illustrates the important contribution of an experienced vascular surgery team capable of creating a fistula with very little viable tissue.

The long term prognosis of these "difficult" patients is not easy to evaluate. With time these patients have also a high cardiovascular risk and even if an access for hemodialysis is successfully created, some of them died from a cardiovascular event. It reflects the links between the vascular deadlock and the global vascular risk.

6. Conclusion

Vascular access is vital for end-stage renal disease patients on hemodialysis. Many solutions are available, but careful decision making is crucial. A good vascular access could be defined as one avoiding serious complications and multiple surgical and radiological interventions. There is always a risk of complications, but with an adequate physical examination, appropriate imaging and multidisciplinary management involving the nephrologist, the interventional radiologist and the vascular surgeon, an optimal solution can be found to prolong the life of an existing access or fashion an ingenious new access, even for the most desperate "last chance" cases. A few cases observed in our center illustrate this need for a multidisciplinary approach to patient management, focusing not only on vascular access itself, but also its complications and their prevention.

It is clear that before opting for a central catheter, an arteriovenous fistula should be attempted whenever feasible, even for the most difficult cases. The optimal moment to create the arteriovenous fistula remains a difficult decision which can be made only after global assessment of all potential candidates, i.e. not only patients scheduled for prolonged hemodialysis but also those followed for kidney failure, keeping in mind the major objective of preserving the vascular network.

At the present time, the most innovating development remains the arteriovenous fistula conceived by Brescia in 1966. There has been no change in this gold standard, but there has been in our patients who have become older and frailer, a real challenge for multidisciplinary teams.

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Section 5

Quality of Life and Exercise

Chapter 35

Renal Rehabilitation: Present and Future Perspectives

Masahiro Kohzuki

Additional information is available at the end of the chapter

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1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. In patients with CKD, exercise endurance, measured as maximal oxygen uptake (VO_2 max), etc. is lowered and this phenomenon becomes more distinct as the renal dysfunction advances. Poor physical condition and skeletal muscle wasting are associated with CKD. This is due to the combined effects of uremic acidosis, protein-energy malnutrition and inflammatory cachexia, which lead to and are further aggravated by a sedentary lifestyle. Together, these factors result in a progressive downward spiral of deconditioning.

Renal rehabilitation (RR) is coordinated, multifaceted interventions designed to optimize a renal patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. RR includes five major components: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling. Present and future perspectives of RR is addressed in this chapter.

2. Physical inactivity in CKD patients

Physical inactivity is well recognised as a major health issue in today's society. Regular exercise is important in maintaining health and preventing chronic disease, it is increasingly accepted as a valuable therapeutic intervention in many long-term conditions.

Patients with end-stage renal disease (ESRD) on maintenance haemodialysis have very high mortality, and yet higher mortality risk has been reported for sedentary hemodialysis patients [1]. As well as being a strong cardiovascular risk factor, physical inactivity is associated with increased risk of rapid kidney function decline in CKD [2].

Unfortunately the role of physical activity in renal disease has been largely overlooked and provision of exercise advice and rehabilitation programs for kidney patients lags well behind that of cardiology and pulmonary services. Levels of physical exercise among CKD patients with hemodialysis are low. Regular exercise frequency varied widely across countries and across dialysis facilities within a country.

3. The effect of regular exercise in dialysis CKD patients

The positive effects of physical exercise reported in the general population may be highly relevant for ESRD patients. Increased physical activity has been associated with improved ability and capacity to perform activities in everyday life, occupational tasks, health-related quality of life and survival. Therefore regular exercise is recommended to this population.

Results from an international study of haemodialysis patients indicate that regular exercise is associated with better outcomes in this population and that patients at facilities offering exercise programs have higher odds of exercising. In DOPPS study, overall, 47.4% of participants were categorized as regular exercisers. The odds of regular exercise was 38% higher for patients from facilities offering exercise programs ($P = 0.03$) [3].

In DOPPS study, regular exercisers had higher health-related quality of life, physical functioning and sleep quality scores; reported fewer limitations in physical activities; and were less bothered by bodily pain or lack of appetite. Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms. In models extensively adjusted for demographics, comorbidities and socio-economic indicators, mortality risk was lower among regular exercisers (hazard ratio = 0.73 [0.69–0.78]; $P < 0.0001$) and at facilities with more regular exercisers (0.92 [0.89–0.94]; $P < 0.0001$ per 10% more regular exercisers) [3].

A systematic literature search was completed in August 2010 to identify randomized, controlled trials of exercise training studies in hemodialysis patients. A subsequent meta-analysis was conducted and the search repeated in December 2010 [4]. Fifteen studies, yielding 565 patients were included. Baseline, peak VO_2 values were 70% of age-predicted values, exercise intervention patients improved post-training peak VO_2 to 88% predicted. Exercise training produced 26% improvements in eight studies that reported peak VO_2. Equivocal results for change in short-form 36 health questionnaire scores were reported post-training. Significant improvements in lean body mass, quadriceps muscle area, knee extension, hip abduction and flexion strength were also reported [4]. They did not find any deaths directly associated with exercise in 28,400 patient-hours and no differences in withdrawal rates between exercise and control participants. Exercise training for 6 months or more conveyed larger improvements in peak VO_2 than shorter programs. Therefore, Exercise training is safe and imparts large improvements in peak VO_2, and heart rate variability in hemodialysis patients[4].

Moreover, a growing evidence base suggests that exercise training in patients with hemodialysis improves in VO_2max, left ventricular function, cardiac sympathetic and parasympa-

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thetic disharmony, malnutrition-inflammation-atherosclerosis syndrome, anemia, sleep quality, anxiety, health-related quality of life, activities of daily living, shunt size, Kt/V and mortality [5]. In contrast, a recent randomized clinical trial failed to show further benefits of additional resistance exercise on long-term somatic protein accretion above and beyond nutritional supplementation alone [6]. Further research is necessary to both understand the observed lack of obvious benefits and strategies to improve the exercise regimens in patients with hemodialysis.

4. Low implementation rate of exercise therapy or rehabilitation for patients with visceral impairment

Therefore regular exercise is recommended to haemodialysis patients.

The problem of exercise therapy or rehabilitation for patients with visceral impairment such as renal or cardiac impairment is a low implementation. Because the beneficial effects of rehabilitation on exercise capacity, quality of life, and prognosis (mortality) in patients with visceral impairment have been established, the low implementation rate of rehabilitation implies that patients are kept away from the established benefits of rehabilitation by reasons unrelated to the patient conditions. Thus, efforts should be made urgently to increase the implementation rate of rehabilitation.

Why, then, have exercise and rehabilittaion not been broadly applied? For example, the cardiac rehabilitation (CR) program usually consists of three stages: the acute stage (phase I), subacute stage (stage II) and maintenance stage (phase III). Phase III CR is recognized as a community or home-based program committed to encourage exercise and a healthful lifestyle with the goal of minimizing the risk of recurring cardiac problems (secondary prevention). A recent study [7] demonstrated that the participation rate of phase II CR to be 12% in the Japanese Circulation Society (JCS)-authorized cardiology-training hospitals (TH) and 5% in all the hospitals in Japan. Major reasons for not implementing CR were lack of staff, equipment and space, and the absence of the approval for the CR facility standards [7]. However, THs are usually large-sized, general hospitals which would be expected to have sufficient staff, equipment, and space. In addition, 73% of THs that had been approved for specific intensive care did not have an approval for CR despite their ability to fulfill the CR facility standards indicates that there should be reasons other than the CR facility standards for the non-implementation of CR in these hospitals [7].

Ades et al [8] reported that by multivariate analysis, the strength of the physician's recommendation for participation was the most powerful predictor of cardiac rehabilitation entry in patients after acute myocardial infarction (AMI) or coronary bypass surgery. Thus, physicians' reluctance or lack of proper understanding to use CR after AMI might be the reason for the low implementation rate of CR in Japan. Since the CR facility standards in Japan has been loosened in 2004,2006, and 2010, the motivation of physicians and hospitals would be a critically important factor for the implementationof CR [9].

5. Barriers to exercise participation among dialysis patients

The recently published Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines on management of cardiovascular disease state that, "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" [10].

Delgado et al. [11] administered a 30-item survey regarding exercise counseling to nephrologists attending the American Society of Nephrology (ASN) meeting in 2007. In multivariate analysis, older nephrologists (OR; 95% CI) (3.3; 1.2–9.0) and those more physically active (5.5; 2.0–14) were more likely to ask and counsel patients about physical activity (PA). Opinions associated with less counseling behavior included lack of confidence in ability to discuss PA. Multivariate comparison to previous respondents before the guidelines showed current nephrologists were not asking and counseling more. Despite the guidelines, counseling behavior has not increased. Published guidelines are insufficient to reach younger nephrologists [11]. They also reported that dialysis patients were interested in physical activity [12]. They reported that the majority of participants strongly agreed that a sedentary lifestyle was a health risk (98%) and that increasing exercise was a benefit (98%). However, 92% of participants reported at least one barrier to physical activity. The most commonly reported barriers were fatigue on dialysis days and non-dialysis days and shortness of breath. In multivariate analysis, a greater number of reported barriers was associated with lower levels of physical activity. Lack of motivation was associated with less physical activity. Endorsement of too many medical problems and not having enough time on dialysis days were also associated with less activity in adjusted analysis [12].

Perhaps a larger barrier to implementation of exercise programs in the dialysis population is the lack of a clearly defined "best" program. The location of the exercise training is also an important factor influencing adherence. In HD patients, intradialytic programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on nondialysis days [13]. Dialysis facility efforts to increase patient physical activity may be beneficial. Studies of the barriers to patient participation in exercise and to provider assessment and recommendations are needed so that more widely generalisable interventions can be developed.

6. The effect of exercise training in predialysis CKD patients

There is increasing evidence of the benefit of regular physical exercise in a number of long-term conditions including chronic kidney disease (CKD). However, this evidence has mostly come from studies in end stage patients receiving regular dialysis. It should be noted that the majority of published studies were small and enrolled patients were undergoing hemodialysis. Relatively few studies have included patients with stage 1 to 4 CKD, which limits the generalization of findings to predialisis CKD patients.

It is also necessary to consider the influence of exercise on renal functions because acute exercise causes proteinuria and subsequent reductions in both the renal blood flow and glomerular filtration rate. It has also been demonstrated clinically that sudden exercise decreases renal function. There are few reports on the influence of chronic exercise on renal function and there is little information about the effect of exercise on predialysis CKD patients. The optimal intensity and duration of exercise for patients with chronic renal failure has not yet been formulated.

Recently, it is reported that exercise therapy for 12 weeks significantly improved the anaerobic metabolic threshold and high-density lipoprotein cholesterol (HDL-C) levels, and estimated glomerular filtration rate (eGFR) in patients with cardiovascular disease (CVD) and CKD [14]. Change in eGFR correlated significantly and positively with change in anaerobic metabolic threshold and HDL-C. Exercise therapy correlates with improving renal function in CVD patients with CKD through modifying lipid metabolism. Therefore, exercise therapy could be an effective clinical strategy to improve renal function.

7. The effect of exercise training in animal predialysis CKD models

Also, there are few reports about the effect of exercise on renal function in animal models of chronic renal failure. We have been published several papers in this field recently.

First, we assessed the renal effects of moderate chronic treadmill exercise in a remnant kidney model of spontaneously hypertensive rats (SHR) with 5/6 nephrectomy and also assessed the effects of exercise and antihypertensive therapy on renal function [15]. The rats were divided into four groups: (i) no exercise (Non-EX); (ii) moderate exercise with treadmill running (20 m/min, 0 grade incline for 60 min) (EX); (iii) EX with an angiotensin converting enzyme (ACE) inhibitor, enalapril (2 mg/kg per day, i.p.); and (iv) EX with an angiotensin receptor antagonist, losartan (5 mg/kg per day, i.p.), for 4 weeks. Chronic EX significantly attenuated the increase in proteinuria and significantly protected against increases in the index of glomerular sclerosis (IGS). Both enalapril and losartan with EX significantly decreased blood pressure, and further decreased the IGS. In the stepwise multiple regression analysis, only antihypertensive drug remained in the model as a significant predictor of IGS. In contrast, exercise, antihypertensive drug and mean systolic blood pressure remained in the model as a significant predictors of mean proteinuria. These results suggest that exercise does not worsen renal function and has renal-protective effects in this model of rats. Moreover, the antihypertensive therapy has additional renal-protective effects in this model of rats.

Second, we assessed the renal and peripheral effects of moderate to intense chronic exercise as well as the effects of the combination of chronic exercise and enalapril (ENA) in 5/6-nephrectomized Wistar-Kyoto rats [16]. The rats were divided into six groups according to the following treatment: 1) no exercise (C); 2) ENA (2 mg/kg/day, subcutaneously); 3) moderate exercise with treadmill running (20 m/min for 60 min/day, 5 days/week) (EXm); 4) intense exercise with treadmill running (28 m/min for 60 min/day, 5 days/week) (EXi); 5) EXm

+ENA; and 6) sham operation (S). The rats were then treated for 12 weeks. Both chronic exercise and ENA blocked the development of hypertension, blunted increases in proteinuria, reduced serum creatinine and blood urea nitrogen, and improved IGS and the relative interstitial volume of the renal cortex (RIV). Moreover, IGS and RIV in the EXm+ENA group were the lowest among all other nephrectomized groups. Furthermore, EXm+ENA enhanced capillarization as well as the proportion of type-I fiber in the soleus muscle. These results suggest that EX and ENA have renoprotective effects. The findings also suggest that EXm+ENA provided greater renoprotective effects than those of ENA alone, and that EXm +ENA had some additional peripheral effects without any complications in this rat model.

We also assessed the renal protective effects of treatment with moderate exercise (EX; 20 m/min for 60 min/day, 5 days/week), with EX plus angiotensin II receptor antagonist olmesartan (OLS), with EX plus calcium channel blocker azelnidipine (AZN), and with the three together in 5/6-nephrectomized Wistar Kyoto rats for 12 weeks [17]. EX, EX+OLS, EX+AZN, and EX+OLS+AZN showed decreases in the serum creatinine (Scr), an index of glomerular sclerosis (IGS), the relative interstitial volume of the renal cortex (RIV), the number of ED-1 (monoclonal antibody) positive cells (ED1(+)) and the glomerular expression score of alpha-smooth muscle actin (alpha-SMA(+)). EX+OLS, EX+AZN, and EX+OLS+AZN blocked the development of hypertension, increased the number of Wilms' tumor-1 (WT-1) positive cells (WT1(+)); EX+OLS and EX+OLS+AZN blunted the increases in proteinuria. In particular, blood urea nitrogen (BUN), ED1(+), alpha-SMA(+), WT1(+), IGS, and RIV in the EX+OLS +AZN were the lowest among all the nephrectomized groups. In the results, simultaneous treatment of EX, OLS, and AZN showed renal protective effects in this rat model suggesting that the treatment may affect the macrophage infiltration to the glomerulus, the fibroblast accumulation in the glomerulus, the mesangial activation, and the podocyte differentiation.

Finally, we assessed the renal and peripheral effects of chronic exercise in a rat model of diabetic nephropathy (Goto–Kakizaki rats) and the benefits of combined exercise and losartan [18]. The rats were divided into four groups: (i) no exercise (control); (ii) exercise with treadmill running; (iii) losartan; (iv) exercise plus losartan, and the rats were treated for 12 weeks. Losartan and exercise plus losartan significantly decreased systolic blood pressure (SBP). Exercise, exercise and losartan, and losartan blunted the increases in proteinuria. IGS and RIV of the renal cortex were significantly improved in the exercise, exercise and losartan, and losartan groups. The IGS, expressions of ED-1 and a-smooth muscle actin in the glomerulus were the lowest, and the number of Wilms' tumor was the highest in the exercise plus losartan group. The endurance, the proportion of type I fibre and capillarization in the extensor digitorum longus muscle were greater in the trained groups. These results suggest that both exercise and losartan have renoprotective effects, and the combination of exercise and losartan provided greater renoprotective effects than losartan alone, and may affect macrophage infiltration, mesangial activation, and podocyte loss in this model of diabetic nephropathy. It is also suggested that exercise has a specific renoprotective effect that is not related to SBP reduction, and can enhance endurance without renal complications.

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Exercise training does not always show renoprotective effect in any animal models of predialysis CKD. For example, we reported that exercise training did not show renoprotective effect in Thy-1 nephritis model and adriamycin-induced nephritic syndrome model [19,20].

In summary, these results suggest that exercise training may have renal protective effects in some animal models of predialysis CKD.

8. What is renal rehabilitation?

Moreover, we have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (RR). We define RR as, “RR is coordinated, multifaceted interventions designed to optimize a renal patient’s physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. RR includes five major components: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling.” [21]. The first step to successful RR is ensuring that the clinical prerequisites of anemia control, adequate dialysis, exercise, a well-functioning vascular access, and proper nutrition are in place. The Life Options Rehabilitation Advisory Council (LORAC) developed a comprehensive approach to RR, based on the "5E's:" Encouragement, Education, Exercise, Employment, and Evaluation [22].

9. Adding life to years and years to life

Medical science basically aims to "Adding Years to Life" by increasing life expectancy. Rehabilitation generally aims to "Adding Life to Years" by helping patients with impairment achieve, and use, their full physical, mental and social potential. However, recent growing evidence suggests that rehabilitation for patients with visceral impairment such as cardiac, renal and pulmonary impairment can not only improve exercise performance and quality of life, but also increases survival [23]. Therefore, modern comprehensive rehabilitation for patients with visceral impairment does not simply aim to "Adding Life to Years" but “Adding Life to Years and Years to Life“ which is a new rehabilitation concept [23].

10. Conclusion

In RR, we should improve not only quality of life but also biological lifespan in patients with CKD. RR is a feasible, effective and safe secondary prevention strategy following CKD, and offers a promising model for new field of rehabilitation. Future RCTs should focus more on the effects of exercise training and rehabilitation programs as these subjects and exercise types have not been studied as much as cardiovascular exercise. Moreover, efforts should be made urgently to increase the implementation rate of the RR.

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Chapter 36

Exercise Therapy – Additional Tool for Managing Physical and Psychological Problems on Hemodialysis

Andrea Mahrova and Klara Svagrova

Additional information is available at the end of the chapter

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1. Introduction

Chronic renal failure (CRF) is a progressive and untreatable disease which is associated with numerous complex metabolic and hormonal changes leading to a development of consequent complications which further change function of all organ systems [1]. CRF has several stages. The last one is known as the end-stage renal disease (ESRD). The renal function at this stage has to be replaced by either hemodialysis (HD) or peritoneal dialysis (PD). Such treatment is a life saving method but it does not completely substitute function of healthy kidney [2]. Therefore the best solution for all patients is kidney transplantation. Certain level of physical fitness of all patients on the waiting list for the transplantation is necessary for both successful transplant surgery as well as high quality of life (QoL) with the transplanted kidney. Long-term inactivity prior the kidney transplantation and most importantly during the dialysis treatment leads to diminished physical fitness of dialysis patients who most often suffer from muscular atrophy, low capacity of musculoskeletal system, bone and joint diseases, or system nervous malfunctions [3].

ESRD patients often suffer from other diseases. Associated lifestyle changes typically affect motor and cardiovascular systems. Complications associated with deterioration of those systems have negative impact on the renal disease itself and consequently results in diminished QoL. In fact HD patients' mortality is caused by cardiovascular diseases from 50% (atherosclerosis, ischemic heart disease, and hypertension) [4-7].

Physical load is less tolerated by HD patients as the disease progresses without the influence of the renal disease type [8]. Deligiannis [7] and Kouidi [9] found that patients with CRF have maximal oxygen consumption decreased by 50% as compared to healthy but sedentary population. Complications associated with motor system include bone, joint, and muscular problems caused by renal osteodystrophy which is typical for long-term CRF patients. Other

complications typical for CRF patients and dialysis treatment include anemia, diabetes mellitus, lipid and protein metabolic disorders, uremic myopathy and neuropathy, malnutrition, or all cause peripheral neuropathy [10, 11, 12]. Long-term HD patients often suffer from peripheral vascular disease, dialysis amyloidosis, cerebrovascular complications, immunodeficiency, infections, malignant diseases, etc. [2]. All those complications limit patients' physical fitness and occupational capacity [7, 13]. Decreased physical activity is characterized by functional failures of motor system (back pain, spinal blocks, joint pain) and is associated with limited joint range, muscular shortages, decreased muscular power and endurance, stability disorders, gait changes, or coordination failures [14, 15, 16]. Also one of the most frequent disturbing symptoms of HD patients is pain [17-20]. As a result of above mentioned complications HD patients prefer sedentary lifestyle. Most of those complications and its relationship with physical activity will be described in detail in the following chapters.

Both age of HD patients as well as their quality of life has been improved by a modern technology of dialysis treatment however it is still not comparable with healthy population [21]. HD patients are stressed by a burden of a life threat by untreatable condition typical for patients with chronic conditions such as CRF. In addition HD patients must respect strict dialysis regime (dialysis procedure 2 – 3 times per week for 4 -5 hours). Therefore HD patients often suffer from anxiety, inferiority, and depression [3, 22, 23].

Despite variety of causes leading to limited physical activity of HD patients we have a reason to conclude that earlier mentioned restrictions can be positively influenced by appropriate physical activity. International literature provides evidence that regular physical activity may effectively improve overall status of HD patients (in detail later). Regular physical activity is crucial component of active lifestyle not only among healthy population but also among those with chronic conditions. Certain volume and intensity of physical activity is an effective tool to improve QoL among chronically ill patients and should be a vital part of non-pharmacological complex treatment. Physical activity is currently considered a common part of multidisciplinary approach that consist except for medical treatment also consultations with dietologist, psychologist, and sometimes even social worker. However services of physiotherapists who could propose appropriate physical activity programs for patient on dialysis are still rather rare. Physical activity – passive or active – defined by volume, intensity, and content represents subsequent treatment. Important is also its psychosocial effect which can positively influence performance of everyday tasks by increased self-confidence, assertive behavior, clear thinking, ability to deal with problems and with the disease, etc. [24].

The goal of this chapter is to emphasize meaning of physical activity among patients on dialysis. The key benefit of regular physical activity in HD patients is to maintain self supported life and independence that is especially important for the elderly patients. The chapter is focused on the description of selected factors influencing physical and mental fitness and presents various ways of appropriate itradialytic and interdialytic physical exercises. In addition it includes description of physical activity programs developed to improve fitness status before and after kidney transplantation.

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2. Body

2.1. Problem statement

The issues of physical activity programs realization and its influence on quality of life among ESRD patients on dialysis is still discussed topic. In the past 40 years it has been conducted many trials focused on testing the effects of physical fitness among ESRD patients on dialysis, and describing overall benefits of regular physical activity on fitness and mental status [25-47]. The goal of all studies was to offer patients with the interest to include physical activity into daily routines an appropriate fitness program that can be performed during hemodialysis as well as in their free time. Offered programs included both individual and group conditioning exercises.

During the evaluation of the effect of activity programs it has been found that the exercise was a brand new experience for most of the patients and that it was often perceived as a motivating factor to maintain physically active even between dialysis procedures [33, 40, 48, 49]. Although the attendance rate of physical activity programs was found somewhat lower in the classes offered between the dialysis. Also early termination was more often observed in the interdialysis classes [48, 50-52]. The most common causes of the early termination included problems with transportation to the classes, lack of free time between dialysis procedures, lack of motivation, and fatigue. Organized physical activity represents for the majority of patients the only chance to perform regular physical activity. Also organized physical activity is known to be more motivating, guarantees expert supervision and heart functions monitoring. There are number of studies conducted to evaluate a use of individual physiotherapy interventions for those with motor system disorders due to dialysis and after kidney transplantation [14, 53-58]. Those studies provided clear evidence that the role of the physiotherapist is absolutely crucial in the multidisciplinary care team working with HD patients. The goal of physiotherapy tailored to HD patients´ needs is to optimize physical fitness necessary for safe and long-life mobility and independence with the effort to eliminate dependence on the others for as long as possible [55]. It is important to emphasize substantial financial savings associated with more independent living caused by adequate physical fitness and with a reduction of the use of pharmacotherapy due to decreased blood pressure. According to Miller [59] a year savings of one HD patient can reach 885 USD only for pharmacotherapy expenses.

2.2. Application area

As mentioned earlier ESRD patients on dialysis cannot tolerate physical load as effectively as healthy population. Actually the toleration is decreased by 50%. Also they experience lower muscular power, motor system failures, etc. This all together leads to preferred sedentary behavior which was supported by many research studies published in the past 20 years [3, 7-9, 21, 36, 40-47, 49, 55, 59-61].

This chapter is focused on the description of selected factors (complications) associated with ESRD and renal dialysis treatment (RDT), especially those affecting physical fitness of HD

patients. Special attention is paid to motor system disorders. Its symptoms negatively impact patients´ abilities and are often accompanied by the first signs of polymorbidity. Yet many conditions can be effectively treated in its early stages by for example regular physical activity which consists of both active and passive techniques.

There is also a huge area dealing with quality of life of ESRD patient. The problematic will be discussed only briefly although it would deserve whole chapter.

Most of the health complications associated with the ESRD and the dialysis treatment do not allow medical personnel to focus attention just on individual systems. The approach must be multidisciplinary. Knowledge of individual conditions typical for HD patients can help to improve the overall cure management and overall approach to the kidney patients. Because individual co-morbidities are interrelated, relevant issues will be discussed across following chapters.

2.2.1. Impact of selected factors of physical fitness in HD patients

It is important to keep in mind specific rules of physical activity performance among HD patients that are associated with identified limitations and to adjust the intensity and type of physical activity if necessary [36, 62-65].

The most limiting factors of aerobic capacity are: increased concentration of "uremic toxins" in blood, anemia, metabolic acidosis with developed muscle malfunction, uremic myopathy, uremic polyneuropathy, hypercalcemia, cardiovascular abnormality, or hypokinesis [9, 36, 66, 67]. Maximal exercise load at deconditioned HD individuals is only at 51% of population norms and the most limiting factor is muscle fatigue which is closely related to injury and breathlessness. Therefore exercise intensity close to anaerobic threshold, dynamic exercises with heavy weight, or exercises involving rapid intensity changes are not recommended for HD patients. On the other hand aerobic activities characterized by low secretion of lactose are beneficial. Interruption of exercise or immediate intensity decrease are recommended when breathlessness, muscle fatigue, or heart rate above training levels are experienced.

Factors negatively impacting aerobic fitness are: reduced cardiac function due to low trainability and decreased heart rate response to exercise load, low transport capacity of blood for oxygen due to developed anemia, diminished muscle function due to uremic myopathy and atrophy. The cause of diminished physical fitness among HD patients is impaired metabolic activity of skeletal striated muscle due to: depletion of adenosine triphosphate (ATP), depletion of energetic substance such as glycogen, limited oxygen exchange, acidosis, intracellular electrolyt disorders, and constant muscle tissue loss caused by catabolic processes. Oxygen distribution to exercising muscles is decreased due to a combination of low cardiac function (limited chronotropic reaction to physical loading) with low transport capacity of oxygen (anemia) and low utilization of energetic substances (enzymatic blockage and detraining). Physical fitness of HD patients is influenced by muscle weakness (reduced ability to utilize energetic substances), uremia, deconditioning, and decreased heart response (due to polyneuropathy) to physical activity [68].

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2.2.2. Anemia and physical fitness

Common accompanying signs of physical activity are diminished blood transport capacity for oxygen, premature onset of muscle fatigue, lowered performance, diminished maximal oxygen consumption, etc. Anemia is accompanied by metabolic adaptation of the organism to a lower oxygen supply which negatively impacts the reaction to physical activity. Inadequate oxygen supply to mitochondria is the cause of insufficient anaerobic energy metabolism even at lower intensity levels. Therefore the increased metabolic acidosis and lungs´ ventilation followed by breathlessness is further developed in HD patients. Patients´ reaction is characterized by high heart minute volume influenced by high heart rate at almost normal levels of the end-systolic volume. The levels of anaerobic threshold, maximal oxygen consumption (VO_{2max}), maximal vessel oxygen as well as other relevant factors affecting physical fitness and efficiency are seriously decreased.

Ulmer et al. [69] points out decreased working capacity by 50% due to anemia, especially immediately after the dialysis procedure. Long-term changes of complete blood count among ill individuals are associated with oxidative metabolic changes. Therefore high intensity activities and explosive sports or exercises are inappropriate for HD patients with anemia. It is crucial to monitor side effects of physical activity such as fatigue, nausea, breathlessness, or head pain and to adjust intensity if necessary. Aerobic performance of HD patients can be improved by gradual endurance training.

2.2.3. Hypertension and physical fitness

As mentioned earlier most of the HD patients suffer from hypertension. According to published studies reviewed by Parsons et al. [61] 50-90% of HD population has a level of blood pressure higher than 140/90 mmHg. Physical activity is always accompanied by increased heart rate and blood pressure which produce higher demand of heart to a supply of blood and oxygen. Such phenomenon is among hypertonic patients even increased therefore blood pressure reaches undesirable levels during physical activity as well as resting. Thus the antihypertensive pharmacotherapy is often required despite its negative impact on the reaction of cardiovascular apparatus on physical activity. It is absolutely crucial to know all drugs and customize the actual type and intensity of physical activity according to individual needs.

Several indicators such as heart rate (HR), blood pressure, (BP), subjective perception of physical activity and its intensity measured by Borg scale are regularly monitored during physical activity [70, 71]. It is impossible to use a classical calculation of maximal heart rate and subsequently training heart rate (220 minus age multiplied by 60-70%) due to present complications and medication [72]. Intensity of physical activity must be determined individually based on the results of prior objective and subjective testing and constantly controlled by the Borg scale [70, 71]. Static strength exercises are not recommended for patient with hypertension. Breath holdings combined with static and dynamic exercises of high intensity, sudden position changes, or exercising with hands above head is strictly forbidden. Heart rate of individuals using beta blocators is during physical activity significantly lower as compared to healthy population without the use of such medication. Any physical activity is

strictly contraindicated for patients with rest arrhythmia, tachycardia, or bradycardia without obvious reasons.

However results of various studies conducted to evaluate the influence of physical activity on lowered blood pressure provide inconsistent conclusions. For example Hagberg et al. [30] found that blood pressure can be lowered from 155 mmHg to 135 mmHg after only 3-months conditioning intervention. Deligiannis et al. [73] found similar but moderate decrease of blood pressure, from 145/87 to 136/79 mmHg. Interestingly Ridley et al. [74] and Miller et al. [59] found significant decrease of antihypertensive pharmacotherapy consumption after just 3-months intervention although their research did not support the results of the two previous studies. Similar results were provided by Miller et al. [59]. In his research study on average 36% of patients reached decreased amounts of antihypertensive pharmacotherapy which lead to economic savings of 885 USD per patient per year. On the other hand research studies conducted by Parsons et al. [61], DePaul et al. [75] and Cappy et al. [76] did not support such positive findings. According to their results only 3-months intervention does not ensure significant decrease of blood pressure or the decrease of antihypertensive pharmacotherapy consumption. The question is whether the length, intensity, and type of physical activity as presented in the studies are sufficient or not.

2.2.4. Atherosclerosis and physical activity

Failures of lipid metabolism are often presented among ESRD patients. One of the main risk factors of atherosclerosis is insufficient physical activity which is very common for HD patients. Research studies [29, 68, 77] conducted to evaluate effect of 6-9 months training on lipid metabolism in HD patients provided evidence that exercise decreases levels of triacylglycerol (TGC) to 25-39% and increases plasmatic high-density lipoprotein (HDL) to 22-23% (hypertriglyceridemia and lowered level of HDL might be caused by decreased function of lipoprotein lipases) [78]. Nevertheless it is necessary to consider possible negative consequences of the high demand on circulation during the physical activity. Physical activity is associated with accelerated blood flow. In accordance with hydrodynamic law the speed of the flow – both laminar or turbulent - has specific pressure demands on the vessels´ walls. Regardless the speed turbulation always occurs in the bending or branching of for example coronary vessels. Therefore the highest demand on the vessels´ wall is presented right there. It is assumed that the increased speed during for example physical activity causes high demand on the vessels´ wall at the identified areas. This is especially thru when atherosclerosis is presented. In such cases it is required to adjust physical activity appropriately. However physical activity is a very effective prevention to atherosclerosis.

2.2.5. Diabetes mellitus and physical activity

It is absolutely crucial to check the level of glykemia before a start of any physical activity. The risk of hypoglycemia or hyperglycemia is high among decompensated diabetes individuals during physical activity. Physical activity recommendations should be followed when indicating physical activity in HD patients [62-64, 79].

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2.2.6. Malnutrition and physical activity

Malnutrition increases the risk of morbidity, mortality, and diminished quality of life among renal disease population [80]. Malnutrition, muscle tissue loss, and muscle fatigue are closely related to lower physical activity levels of HD patients [81-83]. Also malnutrition is associated with the retention of „uremic toxins" which further supports suppression of protein synthesis and stimulates its catabolism processes [16]. Symptoms such as loss of active muscle tissue, muscle atrophy, and muscle fatigue are closely related to protein metabolism malfunctions. It is important to consider that similar losses naturally occur with age. Therefore the effort to maintain muscle tissue and power for as long as possible is especially important for HD patients because the majority of them is over 60 years and the issues of independence and self supported life are very real [84, 85].

Several studies [13, 37, 86-88] suggest that the muscle power (resistance) training represents the most effective way how to support lipid synthesis in muscles, reduce their catabolism, and support hypertrophy of muscle fibers. Kouidi et al. [13] and Sakkas et al. [88] conducted many studies about muscle fiber morphology (m. gastrocnemius, m. quadriceps femoris) in HD patients during regular physical activity. They found that 6-months intervention courses may reduce an atrophied tissue from 21% to only 2%. Also studies focused on issues of nutrition status in HD patients and the effect of physical activity provide clear evidence that regular physical activity is beneficial as soon as after 3-months of training [76, 89, 90].

2.2.7. Hypokinesis and physical fitness

Limited physical activity – hypokinesis – has negative impact on physical fitness in HD patients. One of the causes might be the fact that those patients spend 600-1000 (4-6 weeks) hours per year sitting or lying during dialysis procedure which is in most cases required 3 times per week for 4-5 hours [36]. It has been published that due to this fact 30 years old patients have working capacity only at 75%, 30 to 60 years old at only 57% and over 60 years old at only 40% of healthy population norms.

In 1981 Gutman et al. [26] conducted study evaluating quantity of physical activity and independence in activities of daily living (ADL) in 2191 HD patients. It was found that only 60% of study participants were completely or partially independent of outside help. Another 20% were independent only at home environment and remaining 20% were completely dependent on the help of others. According to Kouidi et al. [40] HD patients are interested to participate in long-term organized physical activity programs and their adherence is in general high. The authors concluded that after 4 years of the study duration those HD patients who fully completed interdialysis physical activity program reached great results. 70% of them experienced increased oxygen consumption during the physical activity, 53% of them could participate in longer physical exercises, and 52% of them improved their anaerobic thresholds. On the other hand those HD patients who dropped of the program experienced rapid loss of physical fitness and muscular strength after only 4 weeks. According to life-long experiences of Daul and Schäfers [49] the organized exercise sessions during dialysis are the only effective way for the majority of dialysed patients how to regularly participate in physical activity.

2.2.8. Hemodialysis procedures and physical fitness

Lichtenbelt et al. [91] compared the values of working capacity, cardiac output, heart rate, vessels´ volume, or arteriovenous oxygen extraction in intradialytic and interdialytic exercise programs and did not find the difference. Arterial volume of oxygen increased during maximal physical activity faster among patients in the intradialytic exercise program as compared to the patients in the interdialytic exercise program. Hemodialysis itself does not cause acute response on the exercise except for trivial influence on hemoconcentration. Barnea et al. [92] did not find any difference in working capacity immediately prior and 12 hours after the dialysis. One of the possible explanations of a speedy secretion of "uremic toxins" during hemodialysis seems to be the physical loading. There are several studies [61, 76, 93, 94] focused on the effect of physical loading during hemodialysis on levels of urea in serum and in dialyzer. The indicator of evaluation of hemodialysis success is the Kt/V ratio (K = clearance of urea in dialyzer in ml/min; t = time of dialysis in minutes; V = volume of total body fluids which is equal to 60% of patient's weight). Cappy et al. [76] and Kong et al. [93] provided evidence that the Kt/V ratio can be increased by 13% after regular physical activity during hemodialysis. This increase is caused by higher blood flow through the working muscles. Parsons et al. [61] focused his research on the effect of 8-weeks physical activity program during hemodialysis on the more effective removal of uremic toxins. Also the effect of the program on working capacity and the subjective quality of life in HD patients was evaluated. It was found that the program slightly increased level of urea in dialyzer but the Kt/V ratio remained the same.

Due to the motion of body fluids during the dialysis and associated changes in the blood pressure the most appropriate and optimal time for physical activity during hemodialysis is considered the second hour of the treatment. Physical activity is not recommended at the beginning of the treatment because of high extracellular volume and possible increase of blood pressure. On the other hand the end of the treatment (fourth hour) is known for increased risk of hypotension events and cramps [61, 62, 95].

2.2.9. A-v shunt and physical fitness

A-v shunt requires special care during physical activity. It is not recommended to wear watch or bracelets on the arm with the a-v shunt. A-v shunt should be protected from rubbing by sterile gaze also during swimming or other water activities. Any contact sports with the risk of falling or being hurt as well as sports for couples involving hands holding are not recommended. Also lifting of heavy objects should be avoided. On the other hand exercises with light objects such as overballs, light balls, and blow up balls are appropriate. Activation of the arm with a-s shut supports blood flow, improves vessels´ elasticity and function of the a-v shunt in general. Although it is not recommended to test heart rate in the area of a-v shut it is possible to do so in the case of peripheral nervous system disorders. Otherwise hand palpation on the arm with a-v shut is not accurate because of false values of diastolic blood pressure.

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2.2.10. Skin changes, bleeding and physical fitness

Skin of most HD patients is frail and sensitive to injury. In addition healing is significantly worsened among diabetics. Increased bleeding is enhanced by antithrombotic treatment, thrombosis due to uremic changes, and vessel´s wall frailty. It is recommended to avoid all activities that may lead to skin damages.

2.2.11. Uremic myopathy, polyneuropathy and muscular activity

Daul et al. [36] provided evidence that loss of muscular strength may be caused by a degenerative change in muscle cells which is known as uremic myopathy. Additional research [96] discovered a hypertrophy of anaerobic fiber type I. in HD patients. In the most recent studies that use p-magnetic resonance spectroscophy was found out that except for morphological also metabolism functional changes occur in the muscles of dialysed patients [97, 98]. The most affected are muscles of lower extremities where the decline can reach 50-70% and where the muscle fatigue is the most apparent [99, 100]. Lower extremities are also affected by uremic polyneuropathy and muscular atrophy. At the same time sensitivity and coordination disorders are also often detected [36]. Physical activity should be focused on systematic strengthening of low extremities muscles. Other consequences of uremic stages are in detail described in the following section Motor System Disorders.

3. Motor system disorders

Prevalence of musculoskeletal complications which is already common in the population increases with longer life expectancy of HD patients [14, 55, 101]. Together with other complications musculoskeletal issues are responsible for rapid deterioration of functional abilities necessary for independent living and consequently diminished quality of life.

So far many research studies focused on motor system disorders in dialyzed patients have been recently published not only abroad [55, 101-103] but also in the Czech Republic [1]. In the following text are individual motor system disorder presented according to the most recent research findings. Table 1 at the end of this chapter presents discussed motor system disorders (MSD).

Common symptoms of such disorders include pain, limited dynamics, diminished muscular strength, early onset of fatigue, diminished sensitivity as well as other symptoms. The causes of all symptoms are often interrelated. Most of the disorders are caused by structural changes due to uremic stages but other causes such as sedentary lifestyle and other restrictions associated with renal dialysis treatment have been recognized and described. With the regard to multifactorial etiology relevant disorders are organized into groups according to location of the individual disorder as follows: disorders affecting whole motor system, joints, bone tissue, muscle tissue, peripheral nervous tissue, and other remaining disorders.

3.1. Disorders affecting whole motor system

Dialysed patients have extremely low physical fitness and endurance. A primal cause has not been discovered so far but important factors negatively influencing fitness have been recognized and include anemia, uremic myopathy, decreased utilization of oxygen by working muscles [3, 13, 104] and sedentary lifestyle so common for HD patients [105].

Fatigue is in general described as weakness, feeling of exhaustion, and lack of energy [106]. It is one of the most often occurred problems among dialysis patients [107]. Fatigue prevalence reaches 60-97% and may be even 3 time higher as compared to healthy population [108]. Physiological and psychological causes of this fatigue are hypoparathyreoidismus, uremia, anemia, depression, diminished quality of sleep, psychosocial stress, physical inactivity [106], muscle energetic metabolism disorders, diminished central activation, muscle contraction failures, and neuromuscular transmission – symptom of uremic polyneuropathy and myopathy (in detail described later) [108].

Specific type of fatigue often presented among dialysis patients is so called postdialysis fatigue [109]. Its development is caused by many factors which can influence its level and duration. It is possible to ease symptoms by increased frequency of dialyses procedures [110]. The most important factor seems to be a level of daily habitual activity – less activity means stronger fatigue [109]. Fatigue is the most frequent obstacle to physical activities [111]. It is a very complex problem which from the point of view of nephrology requires multidisciplinary approach. However this field still suffers from lack of research focused on pathogenesis and adequate treatment [106]. Pharmacotherapy includes prescription of erytroprotein and other similar drugs controlling anemia [112, 113]. Effective non-pharmacological approaches are represented by endurance training during hemodialysis [114], yoga [115], or acupressure [116].

Another often very disturbing disorder detected in dialysed patients is a back pain – most often low-back pain or lumbar pain [58]. Illness of certain organs evocated by nociceptive stimulation has a characteristic pattern of reactions in the motor system - not only in the correspondent innervations segments but practically in the whole motor system [117, 118]. Then we are talking about so called visceral pattern [117]. Such changes may become a factor that keeps the problems such as in most cases pain presented [117]. Except for typical pain that most of us know as renal colic it is typical also already mentioned low-back pain [118]. Subjective difficulties depend on the range and stage of the illness [119]. Approximately 36% of patients suffer from low-back pain which is often associated with stability failures, muscle weakness, arterial hypertension, bone disorders, and cerebrovascular disorders [58]. One of the most frequent disturbance symptoms in dialysed patients is pain [17-20]. Pain associated with locomotor system disturbances reduces the functional capacity even in healthy population. Pain in combination with polymorbidity leads to a fast overall deconditioning and total functional capacity reduction [55] and consequently diminished QoL.

However this area of expertise still lacks the knowledge gained in research studies, especially the treatment methods are still underdeveloped [58]. Within physiotherapy intervention

the most appropriate techniques appears to be a soft techniques, mobilization in blocked segments as and other blockages and spasms, electrotherapy treatments (solux, diadynamic streams, TENS), and reduction of defective movement stereotypes. Available medication includes salicylates, non-steroid antirheumatics, and analgetics. Myorelaxats are considered only rarely in most serious cases and just for short period of time [117].

Dialysis-related amyloidosis is a special kind of amyloidosis which attacks individuals in a long-term dialysis [120]. Patophysiology based on dialysis-related amyloidosis is storing of special kind of lipids (amyloid) in bone tissues, synovial, tendons, and peripheral nerves. Over 50% of patients suffer from dialysis-related amyloidosis after 20 years of dialysis treatment [121]. Consequently complications are detected mostly at motor system and include: cystic nidus in bone tissue, carpal tunnel syndrome, hands´ tenosynovitis, destructive spondyloarthropathy, monoarthritis, polyarthritis and also periarthritis, spinal canal stenosis, cervico-occipital psedotumors, pathology fractures and so on [121-125]. Therapeutic approaches consist of prevention of the development as well as further progression, symptomatic therapy (conservative treatment, orthopedic interventions and physiotherapy), use of biocompatibility of peritoneal dialysis fluids [101] and of course kidney transplantation [121, 126, 127].

3.2. Joints disorders

Dialysis-related arthropathy is a syndrome specific for long-term dialysed patients and is described as a result of dialyses amyloidosis (see above) – sedimentation of amyloid protein in joint tissue [128]. Symptoms are observed at some patients between 4th and 5th year of dialysis but most often the symptoms develops as late as after 15 years of dialysis [125, 129]. From the clinical point of view the disease is manifested by pain and stiffness of large and small joints on both sides, movement limitations, pain and stiffness of hands and axis joints, and spine canal syndrome [122, 125, 128, 130]. Rare exacerbations of inflammation mostly in metacarpophalangeal joints may resemble acute inflammation arthritis which can result in trigger fingers or even spontaneous tendon ruptures [128, 129]. In addition this disease can attack at about 20% of patients spinal vertebrae which is known as destructive spondyloarthropathy [131], especially in sub-axial and lumbar area [122, 127, 132, 133]. In case of spine canal syndrome and destructive spondyloarthropathy the symptoms are treated by chirurgical decompression which is rather conservative approach. Acute monoarthrithis may be treated by non-steroid antirheumatics, corticoids, or by joint replacements [122]. Crystal-induced arthropathy due to sedimentation of elementar phosphat crystals is also considered a significant cause of acute joint inflammation among renal disease patients [122].

3.3. Bone tissue disorders

Kidney plays an important role in regulation system of bone and mineral metabolism [134]. Renal disease patients suffer from four different types of bone disorders which are together called renal osteodystrophy [135, 136]. Bone changes follow imbalance of basic elements

such as phosphor, aluminum [126], fluor, and strontium [137]. Production of those elements relies on several factors such as calcium-phosphor homeostasis, type of renal disease, or frequency and quantity of potentially toxic drugs. Renal osteodystrophy often worsens according to a renal disease progression, during hemodialysis, and culminates, in case of transplantation, at early post-transplant stage [135]. Renal bone diseases start simultaneously with ESRD when glomerular filtration reaches 50% of the original level. At the same time about 50% of the patients have abnormal bone histology [138]. Increased levels of alkaline phosphatase combined with high overall level of parathyroid hormone signify onset of the disease [139]. Around 70% of all dialysed patients suffer from some bone disease characterized by higher number of fractures [138] which can be even 3-4 times higher than in healthy population [140, 141]. Spontaneous fractures of ribs, ankles, vertebrae, leg, wrist and hip are the most typical [140]. Those fractures can be also caused by dialysis-related amyloidosis [125] which slightly differs from renal osteodystrophy by the presence of healing process [124]. Shiota et al. [142] describes spontaneous tendons ruptures in long-term dialysis patients usually where the tendon is attached to the bone because it causes bone frailty at the precise spot [142]. Except for earlier mentioned bone disorders long-term HD patients face high risk of osteoporosis due to age, sedentary lifestyle, nutrition, post menopause among women, or due to prior transplantation, or steroid treatment [138]. Bone mineral density measured by T-score was found in 79% of patients in lumbar vertebrae and in 59% of patients in femoral neck [139]. Lower bone mineral density was found in older dialysis women [143]. Bone mineral density should be regularly tested among all patients after they reach 3 years of the dialysis treatment because it is a great early indicator of bone fractures [140]. Patients with one of the bone disease should be supplemented by bisphosphonates - drugs that influence bone structure and mineralization [135]. Physical activity involving jumps with higher risk of fall or contact sports with a danger of potential crash are not recommended. Among individuals suffering from end stage form of renal osteodystrophy any group exercise involving walking or running should be totally avoided. Instead physical activity such cycling, swimming, water exercise in general, sitting exercise, or cycling ergometer training is highly recommended. The goal of physical activity is to support production of the bone cells and strengthen the bone structure. At the end it is important to mention that weight-bearing exercise supports successful treatment [144].

4. Peripheral nervous tissue disorders

Uremic peripheral polyneuropathy is one of the most common neurological complications in CRF [103, 145, 146]. The most plausible causes are abnormalities in peripheral nerves such as axial degeneration accompanied by secondary demyelization [145, 147]. Prevalence of uremic polyneuropathy is according to the most recent studies high. It reaches 60-100% among all CRF patients [148] and 87% among dialysed patients [149]. Neuropathy in general thrives at the glomerular filtration (GF) below 12ml/minute. This disease has a slow start and its development takes months. It is typically characterized by distal symmetric process more obvious on the lower extremities rather than the upper extremities [148]. This disease

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is accompanied by muscle weakness and atrophy, areflexia of deep tendons reflexes, changes or total loss of sensitivity, and gradual spreading of neurologic deficit [146, 150]. However the symptoms may be stabilized during the dialysis treatment [146]. It is recommended to maintain serum K(+) within the normal range between individual dialysis procedures [148]. Pharmacotherapy has many side effects and in hemodialysis patients it is not effective [105]. A total recovery can be observed after successful kidney transplantation [146] but only if degeneration did not reach the advanced stage and if most of the axons were not damaged [151]. Noteworthy more than 50% of the ESRD patients suffers from neurological complications caused by diabetic peripheral polyneuropathy. This problematic is in detail discussed elsewhere [152, 153].

Sensitivity of peripheral nerves is increased during uremia. That is why individuals with ESRD have higher risk of mononeuropathy. Nervus ulnaris and nervus medianus are the two nerves that are affected the most often [154].

All dialysed patients with hand paresthesia are recommended to electrophysiology examination [155]. Carpal tunnel syndrome is treated by a surgery [126, 155-158] which is also used for ulnar nerve blockages especially when the conservative treatment is not effective and when the motor deficit is still worsening [159]. Kidney transplantation is considered to be the best preventive approach [126, 156].

Within physical activity application the attention should be paid to diminished concentration ability, restrained reaction of the organism on physical load, rapid onset of fatigue, motor coordination and fine motor skills malfunctions, muscle atrophy, disposition of orthostatic collapse especially during position changes, and diminished perspiration. Fatigue increases the risk of falling during the exercise. A risk of high blood pressure is increased during the coordination overload. HD patients often suffer from overheating, increased hear rate and even tachycardia, or risk of hypotension and collapse due to diminished perspiration. Both subjective and objective sighs of fatigue should be constantly monitored during physical activity. Physical activity session should be immediately terminated in case of failure of coordination and concentration. It is recommended to gradually train gait (on flat surfaces, off road, with obstacles, and with sudden changes of direction) in case of the presence of peripheral polyneuropathy, sensation, and coordination failures in low extremities. Recommended is also a correction of muscle atrophy by systematic strength training. HD patients vulnerable to orthostatic collapse should avoid sudden position changes or long-term standing. Due to low perspiration it is not recommended to perform high intensity physical activity. In case of high outside temperatures the intensity should be decreased even more, important is also a proper clothing, skin color and heart rate monitoring.

5. Muscle tissue disorders

Functional and structural muscle abnormalities in ESRD patients due to uremic state are in general called **uremic myopathy**. Hypothetical patophysiological factors are anemia, mito-

chondrial metabolism disorders and abnormal oxygen transport [160]. Morphological muscle changes of uremic patients consist of muscle atrophy, diminished endurance and fitness, and rapid onset of fatigue [98]. Usually are observable at levels below 25ml/min GF and progression advances together with decrease of renal function [160]. Overall prevalence estimation is 50% of dialysed patients [161]. Another factors influencing reduction of muscle tissue in uremic patients includes: sedentary lifestyle, hypertension, diabetes mellitus [160], uremic peripheral neuropathy [13, 147] as already described, and so called MIA syndrome (Malnutrition – inflamation – atherosclerosis) which can limit energy supply to muscles. Most studies are based on bioptic examination of muscle and clinical findings. Electromyography examination and muscle enzymes are usually within normal range. Specific treatment of uremic myopathy does not exist. Important is prevention by high-permeable dialysis membranes or by kidney transplantation [160]. Several studies found that some improvement can be achieved by aerobic training, prevention, treatment of secondary hyperparatyreoidism, dietary changes, renal anemia treatment by erythropoietin [160, 162, 163], or vitamin D supplementation [164]. Over 65% of dialysed patients complain about muscle problems due to **mineral metabolism disorders** [165]. It is necessary to distinguish between uremic myopathy and other malfunctions caused by water and electrolyt collapse [166]. Another disease affecting uremic muscle is a **progressive parathyreoid myopathy** which itself is a great indicator of parathyreoidectomy [167]. Muscle inflammation or so called **fokal myositis** can be detected during repetitive muscle pains of low extremities [168].

6. Other disorders

Restless leg syndrome is a disorder associated with uremia [154]. It is a senzomotor neurological illness characterized by constant leg motion, unpleasant feelings in lower extremities such as itching, burning, nipping, twitching, pain, and worsening of those feeling while resting (before falling asleep or at night) with occasional relief after activity performance. Etiology among dialyzed patients is unknown but it is assumed that relates to peripheral neuropathy, ESRD [154], and diminished physical activity [169]. Prevalence of the syndrome differs across studies form 10-30% [170], 58% [171] or 60% [172]. Higher prevalence is associated with diabetes mellitus, supplementation by Ca^{2+} antagonist, and dialysis treatment duration [171]. Individuals suffering from this syndrome are not able to rest, have low quality of sleep, suffer from insomnia and depression, and are under constant emotional stress [154, 173]. Patients on dialysis should focus for example on anemia reduction and supplementation by dopamine agonist. Attention should be paid to drugs´ side effects [174]. Physical activity, especially aerobic and strengthening exercise 3 times per week can reduce symptoms by 39% [175]. All symptoms disappear only few weeks after successful transplantation [174].

Another neurological complication includes several types of uremic involuntary movements due to encephalopathy, medication, or structural lesion [154]. Some studies describe flapping tremor (asterixis), action myoclonus-renal failure syndrome [154], uremic twitch-convulsive syndrome [176], chorea [177], etc.

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Group of disorders according to impacted tissue	Name of disorder	Subgroups
Whole motor system	Low exercise capacity	
	Fatigue	Muscle fatigue Post-dialysis fatigue
	Reflex visceral pattern	Pain - most common is Low Back pain Muscle spasms, trigger points Decreased Joint Flexibility Joint blocks Disorders of Stability Defected Movement Stereotypes
	Dialysis-related Amyloidosis	Bone tissue Synovial tissue Ligament tissue Peripheral nerve tissue
Joint tissue	Dialysis-related Arthropathy	Shoulders, knees, etc.
	Infectious Discitis	
	Crystal-induced Arthropathy	
Bone tissue	Renal osteodystrophy	Spontaneous bone fractures Spontaneous ligament ruptures
	Osteoporosis	
Peripheral nerve tissue	Uremic Peripheral Polyneuropathy	
	Diabetic Peripheral Polyneuropathy	
	Mononeuropathies	n. ulnaris, n. medianus, some cranial nerves
Skeletal muscle tissue	Uremic myopathy	
	Mineral metabolism malfunctions	
	Progressive Parathyroid Myopathy	
	Focal myositis	
Others (non-classifiable into groups)	Uremic restless legs syndrome	
	Uremic Involuntary Movements	Asterixis (flapping tremor) Action myoclonus-renal failure syndrome Uremic twitch-convulsive Chorea

Table 1. The Motor System Disorders (MSD) in Dialysis Patiens [18].

7. Quality of life of HD patients

Perception of ESRD individuals differs according to psychological, social, and medical point of view. Many different approaches how to deal with psychological and social issues and dialysis treatment have been developed and are further improved. All approaches are consistent in the opinion that dialysed patients carry a great burden and that the most important goal of all involved personnel is to ease this burden [2].

Dialysis patients as any other chronically ill individuals are exposed to a great deal of stress related to the life threatening situation. Significant component of the stress is a total dependence on medical devices, hospital and medical personnel which may be more stressful then the life threatening situation itself. The value of independent life is sometimes so strong that it is impossible to deal with the treatment which often results in depression, aggressive behavior, self destruction behavior, etc.. Dialysis procedure itself is very stressful because it involves fear from the connection to a dialyzer, pain and other related complications. Worry some are also potential failures of dialyzer, inability to predict process of dialysis, fear from the presence of other patients during complicated cases, etc.. The stress of dialysis patients is strictly specific due to various disease symptoms and demanding treatment. Other stresses typical for HD patient are as follows: loss of close persons, diet restrictions, free planning restrictions, increased time and space needs, dependence on the others, loss of physiological functions (urinations, sexual activity), increased aggression and constant threat of death.

Even dialysed patients are interested in quality of life, wisdom, and dignity. Important moment that improves patients´ quality of life is their participation in social activities, social interaction, and other consequent pleasures. Social network represents important support system that helps to live satisfactory life despite the disease [178]. Without the support system patients usually experience more complications, are more often hospitalized, and as a result of worsened health status they eventually prematurely die [179].

In fact quality of life and physical activity are closely associated. Physical activity can be perceived as a basic tool for socialization because the group stimulation typical for physical activity participation is very effective. The most important is social interaction which is absolutely crucial for all humans. Unique experiences achieved during physical activity, game or sport are positive distractions from permanent pressure of a “serious” life. Many studies concluded that physical activity is unavoidable component of healthy lifestyle and very effective tool that can release negative symptoms of the stress. Protective effect of physical activity is based on various mechanisms on various levels of psychical and somatic regulation. Well known studies provide clear evidence that physical activity can improve quality and length of life. Physical activity programs are secondary components of complex treatment [3, 10, 14, 15, 21, 28, 37, 38, 40, 48, 180].

Physical activity can significantly ease depressive and anxiety symptoms, strengthen self-confidence, improve sleep, improve adaptation to stress, improve social interaction, support of social re-integration, etc.. Important part of regular group physical activity is participants´ mutual understanding and social integration [181]. Despite all benefits it is relatively diffi-

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cult to change lifestyle habits and up to date daily routines even for healthy population. This is especially thru for dialysis patients due to among others fear of further worsening of the situation. Therefore intense motivation is required. But in general it is possible to conclude that physical activity significantly improves quality of life of dialysed patients and reduces mortality.

7.1. Importance of physical activity for elderly dialysis patients

CKD has recently been recognized as a number one chronic diseases primarily affecting the elderly [182]. Coresh et al. [183] found an increased prevalence of CKD among individuals over 70 years from 38% to 47% in the period from 1999 to 2004. According to US Renal Data System from 2008 the median age of a new dialysis patient is now 65 years. The fastest growing group is over 75 years. In renal patients advancing age was found to be independently associated with higher scores on the physical dimensions of Sickness Impact Profile [184].

Crucial indicator of quality of life among older patients is the degree of their independence and maintenance of the ability to continue living at their homes for as long as possible. All measures that may reduce the risk of complications and at the same time increase or maintain independence are very much welcomed from the patient as well as from society point of view. According to Kutner and Jassal [185] it is a great clinical challenge to identify factors that can support functional status of elderly dialysis patients. It has been clearly documented that regular physical activity has positive effect on the overall functional and psychosocial status of RDT patients of all ages [36, 42, 56, 185, 186]. The consensual aim of most of earlier mentioned studies was to include the appropriate form and amount of physical activity for patients who express the will to improve their physical fitness. Sedentary and already dependent elderly patient on RDT represents a great burden and expenses for health care and medical personnel [187]. Kutner [188] and many others suggest that some form of regular physical activity in routine care is a key opportunity to enhance functioning and well-being of elderly renal patients. Regular physical activity could improve elderly renal patient's physical parameters such as strength, balance, mobility and therefore potentially lower the risk of falls [189]. Also dimensions of person's HRQOL can be significantly improved by regular physical activity. Cycle exercise during dialysis is safe even in older HD patients with multiple co-morbidities [190]. It results in walking ability improvements and lower extremities muscle strength gain. Exercise in later life is a great way of social interaction and also a way to meet new people and thus to reduce loneliness [187]. The major goals of rehabilitation and physical activity programs for older patients are as follows: maintenance and improvement of overall physical fitness with the regard to the actual level (it is not necessary to reach the pre-disease stage but rather to maintain or improve fitness within actual capacities); improvement of mental status and mood; identification of areas of functional fitness that are weakened and thus are subjects for the therapy; group low intensity activities – exercises focused on stability corrections, joint flexibility improvements – walking (on the flat surface, off road, with help, without help); stretching exercises; isometric strength exercises – during dialysis; individual exercise program with respect to the results

of entry tests; pain monitoring; overall improvement of physical fitness of elderly patient – reduction of the need of assistive home care.

7.2. Importance of physical activity for kidney transplantation preparation

Certain level of physical fitness is necessary for dialysed patient on the waiting list for transplantation not only to guarantee successful surgery but to ensure high quality of life after the transplantation. Overweight is one of the risk factors that may complicate kidney transplantation. BMI over 35 is considered a contraindication to a surgery. The kidney transplantation itself is associated with a development of specific side effects (cause by immunosuppression) that includes increased appetite, increased fat tissue storage, etc. which all together leads to further weight gain. Long-term inactivity prior the transplantation and during the dialysis treatment results in reduction of physical fitness. Significant improvement of working capacity and tolerance of physical activity appears at the first year after the transplantation but only when prescribed physical activity intervention is strictly followed [186, 191, 192]. To participate in the post-transplant intervention appears to be much easier for those who already participated in physical activity programs prior the transplantation.

8. Used methods

8.1. Selection of tools that can be used for evaluation of physical fitness and quality of life in HD patients

8.1.1. Recommended examination before the initiation of regular physical activity of HD patients

Application of appropriate tests and proper examinations are necessary in order to avoid possible risks that are associated with physical activity of ESRD patients on dialysis treatment. Type, amount, and intensity should be individually indicated with the respect to the results of prior evaluation. The suggested physical activity should be also consulted with the physician in charge who should be able to provide additional information regarding patient ´s health status. Important is basic anamnesis (ESRD courses, co-morbidities, pharmacotherapy), specific dialysis anamnesis (frequency and duration of dialysis session, duration of dialysis treatment, acceptance of dialysis treatment).

It is important to test actual potassium concentration before any physical activity recommendation. Too high or too low concentration may have fatal influence on heart rhythm because physical activity itself is associated with a lactate production in working muscles and a secretion of potassium ions which together significantly increases the potassium concentration. This is the reason why it is so important to know actual potassium level prior any activity. In addition the potassium level is also stimulated by beta blocators. Hypokalemic patients are threatened only rarely. The concentration of potassium in blood rapidly decreases after physical activity but because of the prior increase caused by physical activity there is a risk of developing tachycardia. Border values where physical activity is not recom-

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mended are: in hypokalemia < 3.5, in hyperkalemia > 6 mmol/l. High intensities or sudden ends of exercise without gradual calming are not recommended at all for those patients.

Actual status important for individual intensity indication should be examined by available motor and fitness test (for more details see below). Kinesiology assessment which includes examination of joint flexibility, muscle strength, muscle shortages, coordination, motor stereotypes, sensation, etc. can be used [193]. Prior physical activity experience and actual fitness level (before and after enrolment into dialysis group) are also important factors that should be considered for physical activity recommendations. In this case simple inquiry and interview are methods commonly used to collect needed information.

Important is also an assessment of body composition and nutrition status of the patients. Various methods such as isotope dilution, hydro densitometry, potassium level examination, neutron activation analysis, or BMI can be used. Another appropriate non-invasive method to evaluate body composition is a multifrequent bioimpedance analysis (BIA). Questionnaires evaluating quality of life such as KDQOL-SF36, SQUALA, WHOQOL, etc. are also appropriate for assessment of psycho-social status.

8.1.2. Indication of physical activity

Regular physical activity is especially beneficial for HD patients with motor and cardiovascular limitations. Indication includes: diminished physical fitness, joint flexibility disorders, weakened muscle strength, coordination disorders, renal anemia, renal osteopathy, arterial hypertension, carbohydrate metabolisms disorders and diabetes mellitus, lipid metabolism disorders [36]. Other details such as indications to the test termination or contraindication to the test execution are presented e.g. in publications of Daul et al. and ACSM [36, 63].

8.1.3. Contra-indication of physical activity [36, 62, 63, 194]

Total contraindications include malignant arterial hypertension (240/120 mmHg), resting decompensated hypertension (200/100 mmHg), unstable angina pectoris, heart failures, serious heart rate disorders without medication therapy, acute lung emboli, arterial events, advanced aortic stenosis, serious lung hypertension, acute illness (acute myocardial infarction, inflammations such as myocarditis, thrombophlebitis, fever, thyrotoxicosis). Partial contraindications include hyperkalemia > 6 mmol/l, hypokalemia < 3,5 mmol/l, serious renal osteopathy, serious uremic polyneuropathy, unstable angina pectoris, less serious heart rate disorders, some of the inborn or acquired valve malfunction, post myocardial infarction states, decompensated diabetes mellitus, patients reluctance to cooperation).

8.1.4. Possibilities of physical fitness testing in HD patient

There are several available tests of physical fitness appropriate for HD patients. The actual selection of the most suitable one depends on many factors such as motor ability and skills, actual health status, technical equipment, available space, and personnel experiences of the laboratory. The following list contains only the tests that are currently used and that proved

to be suitable for HD patients (Senior Fitness Test Manual, 6-minute walking test, Balke-Naughton treadmill test).

8.2. Senior fitness test manual [195]

Senior Fitness Test (SFT) was developed to evaluate components of physical fitness that are necessary for everyday activities performance among individual over 60 (to 90 years) years which is perfectly appropriate also for younger but chronically ill or physically impaired patients. The test battery evaluates muscle strength, aerobic endurance, flexibility, and dynamic stability. The individual tests are safe to perform, fun to execute, and the battery has a sufficient validity (0,8) and reliability. Importantly the testing does not require demanding technical equipment and large space and it is usable in the field settings. The SFT includes following tests: Sit to stand, Arm-curl, 2-minute Step test, Sit and Reach, Back Scratch, Up and Go, 6 minute walk test. According to the authors the battery evaluates "functional fitness" that has been defined as a minimal level of physical fitness that is necessary for independent performance of everyday activities safely and without undue fatigue. Results can be compared with the population norms presented at the SFT manual.

8.3. 6-Minute walk test

Although this is one of the test from the SFT battery it is commonly used separately in a clinical practice as well as in research studies conducted by Orcy et al. [46], Golebiowski et al. [190], Ragnarsdóttir et al., Bulckaen et al. and Reboredo et al. [196-198]. The result of the test is a number of meters that a tested person can walk with maximal effort in precisely 6 minutes. The test should be performed in a tunnel or outside where it is not required to turn during the whole test. During testing instructor walks 3-4 meters behind the tested person and measures the distance. Rest heart rate (HR), breath frequency (BF) and blood pressure (BP) are examined before the test execution. The degree of effort is evaluated immediately after the test completion by Borg scale [70, 71] and by earlier mentioned indicators (HF, BF, BP). Those are examined once again approximately 3 minutes later.

8.4. Balke-Naughton treadmill protocol

Another appropriate test for HD patients is Balke-Naughton treadmill protocol which is a submaximal intensity test executed on a treadmill [65]. Submaximal intensity is again determined by patient´s subjective evaluation or objectively by heart rate. It is a gradual test with incline of 1,5°. Starting speed is set up at 2, 2.5 or 3 km per hour and is increased by 1 – 2 km per hour. Duration of each stage is 5 minutes with 1 minute of a rest break between the stages. Blood pressure is taken during each break approximately 20 seconds after the end of the stage. Spiroergometric indicators such as VO_{2max} are taken during walking. Also Borg scale is used after the completion of each stage [70, 71]. Classical rest indicators such HF, BF, BP, and subjective perception of intensity are assessed prior the testing. In addition it is recommended to monitor both rest and post-activity electrocardiograph for at least 5 minutes. Also heart response to each stage should be administered.

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8.5. Bicycle treadmill test

Bicycle treadmill test according to WHO protocol is another test requiring submaximal intensity [8, 36, 61]. Submaximal intensity is again determined by patient´s subjective evaluation or objectively by heart rate. Starting power output is set up at 25W and is increased by 25W each 2 minutes until maximal fatigue. HF, BF, BP are monitored 30 seconds before the end of each stage. Patient evaluates subjective intensity by Borg scale [70, 71] after each stage. HF, BF, BP is assessed prior the testing. Also it is recommended to administer rest electrocardiograph and to monitor heard response during each stage. Post-testing electrocardiograph, HF, BF, BP as well as subjective perception of intensity should be assessed after the test completion. The most common cause of the test termination among HD patients are pain and muscle weakness of lower extremities [36] followed by cardiovascular complications characterized by a significant increase of blood pressure.

8.6. Subjective evaluation of exercise intensity

Subjective intensity evaluation by Borg scale [70, 71] is applied when objective methods such as for example lactate concentration, spiroergometric indicators such as $VO_{2,}$ VO_{2max} or HR and BP are not accurate due to medical therapy (beta blocators). Borg RPE („Rating of Perceived Exertion") scale was developed to evaluate subjective perception of intensity. The combination of both subjective and objective evaluations during physical testing provides unique information about patients´ response to a physical testing and the tolerance to physical stress. RPE scale is a standardized tool to assess effort of tested person regardless age, gender, and origin. Basic presumption of clinical application is that perceptual and physiological responses are linear during various types and intensities of physical activity. This presumption can be used especially in testing of cardiac or HD patients with frequent cardiovascular complications that prevent them from maximal or submaximal effort exercises or tests. Results of Borg scale are valuable especially when the patient is treated by beta blocators because such group of drugs increases maximal oxygen consumption which in turn increases intensity of physical activity. RPE values between 12 and 13 corresponds with 60 – 70% VO_{2max} and 16 corresponds with 85% VO_{2max} [62, 199].

8.7. Possibilities of evaluating quality of life in HD patients

Quality of life can be evaluated by both subjective and objective approaches. However patient´s subjective evaluation of own perception of the given situation, ability to actively participate in work, family and social life, and the overall satisfaction is absolutely crucial for evaluating and understanding of the quality of life [179]. The best tool currently available is the scoring system known as Health Related Quality of Life (HRQOL) [200]. The HRQOL score is one of the crucial factor influencing strategic decisions about the treatment and overall approach to the patient as well as nosologic unit [200]. HRQOL consists of standardized questions and answers which enable to effectively evaluate patient´s health status. There are three types of questionnaires to assess quality of life – HRQOL [200] - Global assessment. This type provides general quality of life evaluation without a possibility to identify dysfunctions in individual areas or domains (physical, emotional, vitality, etc.). Generic

type enables to identify details and actual differences between individual population groups which permit to compare individual specifics or similarities in the area of quality of life. On the other hand specific type is explicit for certain disease. It was developed to analyze the disease progress in time. Although the types are separated they often overlap. All the three types are in general accepted. Example is questionnaire SF- 36 (Short-form 36 Health Subject Questionnaire) which can be both global and generic. Other examples of generic assessments include: Karnofsky Performance Status Scale, Activities of Daily Living (ADL), Sickness Impact Profil (SIP), Time Trade-Off (TTO), SF 36. SIP identifies impact of the disease on health profile of patients. TTO enables to evaluate impact of the disease on working ability and independence [200]. Specific questionnaires were developed for individual diseases. Kidney Disease Questionnaire - KDQ is the most often one used in dialysed patients [179]. Features of both generic and specific questionnaire are presented in Kidney Disease Quality of Life Instrument (KDQOL) which also includes SF – 36. WHOQOL-BREF [201] and KDQOL-SF36 can be also used for evaluation of selected parameters HRQOL [202, 203]. So called European standard of Results for 8 components (domains) of HRQOL can be used for evaluation of SF-36 questionnaire results [204, 205].

9. Physical activity programs suitable for HD patient

Kutner and Jassal [185] created an entry and follow up criteria for integration into integrated care programs consisting of dialysis, and active short-term and long-term rehabilitation. The entry criteria include: active participation of motivated patient in rehabilitation program (active and voluntary cooperation), future potential of actual functional status improvement, activity of daily living (ADL), social interaction, and cognitive status. The follow up criteria include: cooperation of medical personnel on treatment adjustment, cooperation of dialyses nurses, multidisciplinary approach, long-term health status showing signs of improvements – positive reaction to impulses.

9.1. Priority goals of physical activity programs

Priority goal of physical activity program for dialysed patients is maintenance or improvement of physical fitness in order to support overall independence on other persons´ help, social re-integration, work re-integration of individuals in productive age, and chances to live a life of healthy individuals. Both individual and group physical activity programs must respect uniqueness of each participant, prior physical activity experiences, actual physical fitness status, recommendation of physician in charge, and must not threaten ones health. Physical activity programs should include activities leading to maintenance or improvement of joint flexibility and muscular strength, compensation of muscle disbalances, renovation of dynamic stereotypes necessary for independent living, correction of muscle coordination disorders, and improvement of cardio-respiratory fitness. Additional benefits of physical activity include improvement of mental tolerance (self-confidence, self-evaluation, solving stressful situations), improvement of overall independency, better dealing with the disease and the treatment (shortened hospitalization, decreased morbidity and mortality), more enjoyable work and lei-

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sure activities, and enhanced dealing with the change of social roles in the family, work and society in general [8, 36, 49]. To satisfy all mentioned goals of physical activity programs is especially important for older patients, the majority of dialysed population.

9.2. Types of physical activity programs

Physical activity programs can be divided into group and individual exercises and, according to the timing within the complex HD treatment, into intradialytic and interdialytic physical activities. Each activity program is unique due to different acceptance of the complex treatment and the disease itself. German expert in nephrology divided physical activity programs into several groups according to the specific focus on individual components of physical fitness [36]:

Conditioning training: the goal is to maintain or improve overall fitness with the special attention to a development of basic motor abilities. Training includes exercises to improve joint flexibility, muscle strength and endurance, motor coordination and general physical condition.

Conditioning-endurance training: the goal is to improve cardio-respiratory fitness and to ease complication associated with ESRD and HD treatment (lower BP, carbohydrates and lipid metabolism optimization, etc.). Specific activities include all cyclic exercises (walking, jogging, cycling, etc.). HD patients should strictly follow individual intensity recommendation.

Strength training: the goal is to improve overall muscle strength, increase muscle volume, reduce atrophy of muscle fibers, support mineralization of the bone tissue, correct muscle disbalances, etc. Specific activities include resistance exercises and exercises with equipment such as weights, thera-bands, heavy bags with sand, etc..

Balance-coordination training: the goal is to correct coordination disorders and balance disorders which are associated with peripheral and central nervous system diseases. Specific activities include both individual and game based group exercises, exercises with balance equipment (overball, physioball, soft pad, etc.) and with gymnastic apparatus (bench, balls, ribstall)

Breath training: breath exercises are important for training of correct breathing stereotype which can be severely impaired among chronically ill individuals. The goal is to learn all types of breathing, coordinate breathing movements, harmonize function of organs, release overall tension, and optimize mental functions (stress, anxiety, and fear reduction).

Relaxation training: relaxation exercises are important part of physical activity programs of HD patients. Those exercises should be performed at the end of training session or individually. The goal of relaxation is to calm down all body processes, to release muscle tension in overloaded muscle groups, harmonize psychical functions, reduce risk of stress situations, re-gain strength and energy. Several relaxation techniques such as Schultz autogenic training, Jacobson progressive relaxation, or music are commonly used. Another example is Feldenkreis method which is based on body perception.

Following physical activity variations may be included in individual physical activity program:

Bed exercises during hemodialysis: the exercise is focused on a development or maintenance of joint flexibility and muscular strength on the one free upper extremity (without a-v shunt) and both lower extremities, breathing exercises, training of cardiovascular fitness using bed side ergometer.

Exercises after dialysis (inpatient or outpatient): includes the same exercises as during hemodialysis with employment of all positions except for back laying and sitting position and the arm with a-v shunt. The exercise is focused on: relaxation and stretching of overloaded muscle groups, training of movement coordination and movement stereotypes, breathing and relaxation exercises.

Off-hemodialysis exercises (outpatient): includes of cyclic aerobic physical activity focused on overall physical fitness improvement. Final selection is made individually in accordance with patient´s actual status and desires.

Following group exercises may be included within **group physical activity program**: water exercises, swimming, and outdoor activities such as walking, Nordic walking, games (petanque), relaxation, etc.

Physical activities and sports [72] such as badminton, walking on stairs, running, canoeing, rowing, fencing, skiing, table tennis, softball, volleyball, basketball, dancing, skating, tennis, squash, etc. are recommended for overall physical fitness improvement.

9.3. Individual phases of physical activity programs

Fundamentals of long-term physical activity among HD patients are the adaptation of motor and cardio-respiratory system to physical activity and training. The physical activity program is usually divided into several phases because of the presence of cardio-vascular complications. This is the same for other chronic conditions such as ischemic heart disease or acute myocardial infarction [36]. Individual phases differ by overall duration as well as duration of individual parts within the program (for details see Table 2.). However individual phases are interrelated and may be mixed. Also important role plays personality of each patient. Precise duration of individual phases is not presented because it is not described in the available literature [8, 36, 62, 63].

9.4. Timing of physical activity programs within complex hemodialysis treatment

Participation in physical activity in HD patients is also recommended between dialyisis when the organism tolerates the physical load the best. According to the available literature the most effective is one day after the dialysis treatment or immediately after the dialysis [36, 62]. During those periods patients´ water and electrolyte metabolism are stabilized. However earlier mentioned recommendations are individual because few individuals may suffer from high ultrafiltration leading to a pressure decompensation. On the other hand inappropriate physical activity timing is between the two hemodialysis, especially the second

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or the fourth day after the treatment (among patients with 1 – 2 hemodialysis per week), or at the same day of the procedure or immediately before the procedure (among patients with 3 or more hemodialysis per week). Those periods are typical for accumulation of body fluids in the organism and decompensation of water and electrolyte metabolism. Interestingly physical activity seems to be beneficial and well tolerated during the hemodialysis procedure. Physical loading during the dialysis is often the only chance to participate in regular physical activity for most patients because they lack any extra time needed for preparation for the physical activity session including commute time [49]. The best timing for physical loading is during the second hour of the dialysis due to body liquids movement and changes in blood pressure. On the contrary the beginning and the end of the dialysis are inappropriate because of high extracellular volume and often increased blood pressure. This risk of hypotension events and cramps is too high [61, 62, 95]. The first responses of cardiovascular system to exercise become obvious after one or two months of regular intervention. But substantial improvement in physical fitness among HD patient occurs after six months or even one year of regular participation in physical activity program. Any termination of physical activity causes rapid decrease of physical fitness which is noticeable in few weeks and speeds up the progression of the disease [8, 40]. This is the main reason why it is so important to stay physically active for as long as possible.

Phase	Program duration	Focus	Type of physical activity	Intensity	Exercise session duration
Adaptation phase	2-3 weeks	Explanation of advantages and risks of PA; Motivation to participate in either group or individual PA programs.	Simple exercises developed to improve joint flexibility and muscle strength, and to correct muscle shortages; Training of breath and exercise coordination; Training of own body perception and body responses to exercise; Conditioning exercise enriched by breath gymnastics; Beginning of easy cardio-respiratory training using passive forms of bicycle egrometer (bed-side ergometer or bicycle ergometer with added electromotor.	Borg RPE scale 7-9, 30-50% of VO_{2max}.	15-30 minutes

Development phase	Several months (10 – 12 weeks)	Follows the adaptive phase and further develops practiced exercises; Emphasizes muscle strength (resistance training using own body weight) and muscle endurance; Stretching exercises; Training of movement coordination and cardio-respiratory fitness; Breath and relaxation exercises performance;	Simple arm movements; Vascular and respiratory gymnastics; Exercises maintaining or renewing muscle balance; Joint flexibility and muscle strength; Exercise and breathing coordination – increasing number of repetitions; Active interval cardio-respiratory training using bed-side ergometer, bicycle ergometer; walking and jogging (off-dialysis); Relaxation and breath exercise.	Gradual intensity increase by prolonged duration of the session or higher number of repetitions; Borg RPE scale 10-12 50-60% of $VO_{2max.}$	40-60 minutes
Stabilization phase	Follows the previous phases and continues for as long as possible	Motivation to regular PA participation; Group exercises integration; Both ambulatory and home off-dialysis PA	Games and group sports; Conditioning, coordination and strengthening exercises used as follows: a) adaptation phase – exercises to maintain or re-new muscle balance, joint flexibility, muscle strength (using equipment and apparatuses), exercise and breathing coordination – duration of the phase is 20 minutes; b) development phase – active training of cardio-respiratory fitness using bed-side ergometer, bicycle ergometer, walking and jogging (off-dialysis)	Gradual intensity increase by prolonged duration of the session, incorporation of new exercises and more challenging versions of used exercises, strength exercises using various equipment and apparatus; Interval forms of cardio-vascular training are substituted by endurance forms with gradual increase of	**60-90 minutes**

				exercise duration; Borg RPE scale 12-13 60-75% of VO_{2max}.	

* PA: physical activity

Table 2. Individual phases of physical activity program for HD patients – intradialytic and interdialytic exercise

9.5. Organization of physical activity session for HD patient

Each session (group or individual) consists of three basic phases [33, 48, 52, 199]: a) warming-up b) main part – adaptation and development; c) Final part (cool down) – for details see Table 3. Duration and intensity of each session is set up individually based on actual condition of participants or group of participants.

9.6. Indication for termination or intensity cutback during physical activity session [8, 63]

Indications for lowering intensity include dizziness, faintness, sudden increase of breathing frequency, shallow breathing, increase of HR above training values, articulation and speech failures, nausea, chest pain or pressure, joint and muscle pain, skin color change (sudden redness), paleness in the lips and nose areas, cold perspiration [8, 63].

Indications for termination are described at ACSM´s Guidelines for Exercise Testing and Prescription [63].

10. Research course

10.1. The focus of our research and used methods

Lately (2007-2012), our research has been focused on the evaluation of the effects of regular physical activity on functional status and quality of life during hemodialysis. Since 2010 we have also paid our attention to identification of possible ways to improve functional status and quality of life in patients at the early stages after kidney transplantation. This chapter provides information about research studies that were conducted within two grant projects titled "Quality of the life in renal dialysed individuals of the Czech Republic and the possibilities of their affection through an exercise intervention" 2007-2009 Registration number 406/07/P443 and „Muscle metabolism after kidney transplantation: early exercise intervention, selective nutrition and gene polymorphism“ 2009-2011 IGA MZ CR 173 (NS-10518-3/2009).

The major goal of our research studies was to introduce and apply intradialysis physical activity program and to evaluate its effect on physical and mental status and quality of life in

Organization of physical activity session				
Session part	**Warming-up**	**Main Part**		**Final Part**
		Adaptation part	**Development part**	
Focus	Body warm-up; Injury prevention; Stimulation of cardio-respiratory function; Coordination of CNS processes; Body preparation to muscle work out.	Development of joint flexibility, muscle strength, overall stretching and relaxation of muscle groups with tendency to shortages; Training of coordination; Coordination of exercise and breathing; Respiratory and vascular gymnastics.	Aerobic endurance training.	Overall cool down of the body; Muscle relaxation and stretching of loaded muscles groups; Harmonization of overall physical and mental status.
Types of PA	Simple complex exercises improving joint flexibility; Various types of walking; Simple stretching exercises; Games; Bicycle ergometer and so called bed side bicycle ergometer.	Complex exercises improving joint flexibility; Muscle strength and endurance improvement (resistance training; training using own body weight; dumbbells , theraband, gym equipment, etc.) Bicycle ergometer („bed-side" ergometer); Various types of walking, Nordic walking, low aerobic activities, running, swimming, etc.; Special games that attractively develops complex abilities and motivate HD patients.		Exercise without loading; Stretching exercises; Breathing and relaxations methods (Feldenkreis, Jacobson, Schultz); Use of music (or talking); Yoga, power yoga, Pilates.
Intensity	Bellow recommended training HR values Borg RPE scale 7-9.	At recommended training HR values 50-75 % of VO_{2max}; Borg RPE scale 10-13		Bellow recommended training HR values Borg RPE scale 8-9
Duration	5 – 10 minutes (in accordance with individual physical fitness and actual PA program phase).	20 – 60 minutes (in accordance with individual physical fitness and actual PA program phase).		5-10 minutes (in accordance with individual physical fitness and actual PA program phase).

* PA (physical activity)

Table 3. Characteristics of individual phases of physical activity session during hemodialysis

HD patients. Specific aims were to assess actual functional fitness and quality of life of the Czech HD patients, to evaluate prevalence of motor system disorders among HD patients, and to compare the results with healthy population. One of the studies was focused on eld-

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erly patients. Another study compared group of HD patients with patients after kidney transplantation. Results were published in both Czech and international journals and presented at international conferences/congresses [19, 207-214].

The criteria for inclusion in the studies were:

1. Previous medical examination and recommendation
2. Age over 18 years
3. Previous HD treatment for at least 4 months
4. Physical and mental ability to complete fitness tests and fill out HRQOL questionnaires
5. Positive attitude to physical activity
6. To be able to participate in exercise program at least twice a week
7. Expected inclusion in HD treatment program for another at least six months

The criteria for exclusion from the studies were:

1. Any significant cardiovascular, neurological and orthopedic complications
2. To miss more than two weeks of the program
3. Termination on the own request or because of transplantation, presence of medical complications or death

In 2009 we conducted three studies focused on the effect of regular physical activity during hemodialysis on physical fitness and quality of life among selected patients. It was a quasi-experiment in all three cases. Randomization process was avoided because of limited number of the study participant. Also all participants were volunteers. Informal consents were sign by all participants prior the study. All of the patients were examined by a nephrology expert who approved participation in the program. Test such as Senior Fitness Test Manual [195] and hand dynamometry test [215] as well as standardized quality of life questionnaires WHOQOL-BREF [201] and KDQOL-SF36 were used for evaluation of selected parameters. HRQOL was compared to preliminary norm for the Czech population of 45 years and older [202, 203]. So called European standard of Results for 8 components (domains) of HRQOL was used for evaluation of SF-36 questionnaire results [204, 205]. Descriptive analysis and non-parametric Wilcox signed-rank test was used for statistical analysis. Level for statistical significance was set up at $p \leq 0.05$.

Following physical activity program was applied among all study participants and all described criteria and recommendations were met. Exercise intensity during hemodialysis did not exceed aerobic HR and was applied during second and third hour of hemodialysis procedure as suggested by ACSM [62] and Daul et al. [36, 49]. Exercise sessions were led by trained personnel of dialysis unit. Course of each session was in detail described at prepared protocols. Each exercise session was led individually and the personnel monitored HR, BP and sign of fatigue. Exercise was terminated in the case of decompensation or sudden worsening of health status. Maximum of three patients participated in the program at the same

dialysis session due to organizational reasons (approximately 30 – 40 minutes of physical activity for each patient). Intensity of exercise was based on results of the three tests. The recommended intensity was always within submaximal range which is 60 – 70% of the maximal HR. Also objective intensity measured by Borg scale [70, 71] was monitored and did not exceed RPE of 12 – 13. Exercise sessions were performed at least two times per week. Interval form of physical loading was used for those who did not have prior physical activity experience or those who did not exercise for a long time. Also at the very beginning less number of repetitions as well as very low intensity at 30 – 50% of maximal HR or RPE of 7 - 9 was applied. Both volume and intensity were gradually increased. Periods of physical loadings were increased while rest periods were decreased; also number and used types of exercise as well as number of repetitions were increased and so forth. Very useful appeared to be an in-cooperation of relaxation and breathing exercises. Physical activity program consisted of adaptation and developing phase. Adaptation phase was performed for two months and consisted of: introduction and explanation of advantages and risks associated with physical activity in HD patients; joint flexibility training; stretching of shortened muscles; maintenance or improvement of muscle strength without use of equipment; vascular gymnastics; coordination of breathing with exercise; respiratory gymnastics; training of own body perception and body responses to exercise. Duration of each session was 20 – 30 minutes. Development phase was performed for four to six months and consisted of: further improvement of adaptation phase´s exercises, higher number of repetitions and extension of exercise session to 45 – 60 minutes, exercise with equipment. Any complications that would harm participants were not observed.

10.2. Overview of individual studies

Study 1 [206]: Mixed sample of 15 hemodialysis patients participated in the study (men – N = 7; average age = 67,9 ± 17.8 years; average duration of dialysis = 34 months; women – N = 8; average age = 65.0 ± 11.6 years; average duration of dialysis = 32.5 months). Functional status and QoL were evaluated before and after the intervention. Only the improvement in 2-minutes step test among women was statistically significant ($p<0.04$) - 50% improvement was observed. Performance on the rest of the test was improved but the results were not statistically significant. Quality of life remained the same in most of the cases. However some of the domains such “physical activity”, “vitality”, and “mental health” showed a tendency to improvement. Quality of life was at the bottom of healthy population norms prior the intervention. After the intervention it was close to the population average values. Improvement was observed among patients who exercised regularly.

Study 2 [207]: This study was conducted to evaluate effect of organized intradialytic physical activity on the health related quality of life among 44 hemodialysis patients (average age = 66.5±14.3 years; average duration of dialysis = 27 months). The majority of patients were over 60 years. From those under 60 years was 8 men (mean age = 48.5±7.2 years) and 7 women (mean age = 49.0±11.0 years). Quality of life was evaluated before and after the intervention. HRQOL was assessed by SF-36 and the results prior the intervention showed that the only one domain where the HD patients were comparable with the healthy population

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norms was the domain of EWB-mental health. The results of the rest of the domains were much poorer as compared to the healthy population norms. Quality of life was slightly improved after the intervention however the results were statistically insignificant.

HRQOL was assessed by WHOQOL-BREF. The domain of "physical health" was lower as compared to the healthy population norms. The rest of the domains were comparable or at least at the lower level of the normal range. The domain "mental health" improved significantly after the intervention. The improvements in the rest of the domains were observed but unfortunately the differences were not statistically significant.

In general we can conclude that the strongest tendency for improvement in SF-36 was observed in the RE "restrictions due to emotional problems", SF "social functioning", and PF "physical fitness" domains. In WHOQOL-BREF the same tendency showed only the domain "mental health". The experiences gained in the study demonstrated that in general older patients over 60 years are interested in the physical activity program participation. Between 60-75 years it was 9 men (average age = 66±4.0 years) a 9 women (average age = 70±3.7 years); and over 75 years it was 8 men (average age = 80±3.4 years) a 3 women (average age = 84±4.2 years). It was also found out that the majority of study participant had a prior experience with physical activity.

Study 3 [208]: The goal of the study was to provide comprehensive overview of ESRD, dialysis treatment, and associated complications and to present the results of the study project in the participating dialysis units in the Czech Republic. Study sample consisted of 44 HD patients (25 men, average age = 66.0 ± 14.1 years; 19 women: average age = 67.0 ± 14.7 years) from three dialysis units. However data from only 27 – 32 participants were analyzed. Three participants died, three had kidney transplantation and six were excluded due to worsened health status. Motor performance was analyzed among 12-16 men and 9-12 women. Those participated in both pre-tests and post-tests. HRQOL was analyzed only among 35 patients (without gender separation). Results of motor performance measured by Senior Fitness Test [195] were compared to the population norms according to age categories separately for men and women. Improvement in more than half cases was observed in men in five out of seven tests. Statistically significant improvement was observed in "chair sit and reach test" ($p = 0.04$). However it is important to know that the significance might be questionable due to a low number of participants. The rest of the improvements might have not been statistically significant but it is very likely that they were important from the personal point of view (clinically significant). Women improved only in the two tests – "back scratch test" and "step-test". The improvements were observed in more than half women. HRQOL measured by SF-36 prior the intervention showed that the HD patients performed comparably with the healthy population norms except for one domain of EWB "mental health". Performance in the dimensions of PF "physical functioning", GH "general health" and RE "restrictions due to emotional problems" was significantly lower as compared to the healthy population over 45 years. Also worse performance on QoL tests was observed in the rest of the dimensions: BP "body pain", EF "vitality", RP "restrictions due to physical problems" and SF "social functioning". After the intervention some of the domains of quality of life were improved but the difference was too low so it was insignificant.

HRQOL measured by WHOQOL-BREF showed that in comparison with the healthy population the domain of "physical health" is very poor. The lower range of the population norm was reached in the domain "mental health" prior the intervention. But after the intervention, in was significantly improved so it reached the average levels of the healthy population in the Czech Republic. In the domain "social relationships" the results before and after intervention were within the normal range. On the contrary the domain of "life conditions" was even above the normal range therefore the quality of life in this area is slightly better as compared to healthy population regardless the intervention. However the results have to be interpreted with great care due to a low number of participants.

In general it can be concluded that patients who participated in the intervention program during HD dialysis show the highest tendency for improvement in the following SF-36 domains: RE "restrictions due to emotional problems", SF "social functioning" a PF "physical functioning" and one WHOQOL-BREF domain of "mental health". Any complications that would harm participants were not observed.

Study 4, 5 [19, 210]**:** The goal of the study was to verify the fact that motor system disorders (MSD) are also a common complication associated with ESRD in the Czech Republic and that the prevalence is higher as compared to the healthy population. Overall aim of the study was to spread general knowledge about motor system disorders among dialysis patients and to incorporate appropriate physiotherapeutic methods into complex care and therefore to improve patients´ quality of life. Prevalence of MSD in healthy population was compared to the prevalence of MSD in dialysed patients. The study sample consisted of the total of 27 subjects (16 men/11 women, 28-86 years, average dialysis = 44.8 ± 53.6 months; MSD prevalence 81.5 %).

Assessment of selected indicators was divided into three parts so duration of testing did not exceed 45 minutes. Assessment included following tests: anamnesis, kinesiology testing, stand on the two weights test, spinal functional examination, back palpation, deep stabilizing spine system examination, neurologic examination of lower extremities sensation, breathing stereotypes examination, and sit-stand test. Anamnesis data were collected using a questionnaire consisting of questions relevant to MSD. The actual selection of the questions was based on the available literature [118, 119, 216]. Questionnaire also contained questions about dialysis treatment, regular physical activity, and daily routines. Anamnesis data were then completed from the internal database of the dialysis unit and from the interview with the physiotherapist in charge. Our results were also compared with the results of international studies. The total of 26 individual (96%) were able to walk independently at the time of testing. Out of those individuals 10 were able to walk maximally 1 – 4 km without resting. The most common complication was hypertension (21 patients, 78%). MSD were found in 22 out of 27 subjects (81,5%). The most common MSD was arthritis (6 patients, 22%) and diabetic polyneuropathy (5 patients, 18,5%). The most common symptom was pain (22 patients, 81,5%), followed by limited ability to move and back pain (17 patients, 63% in both cases). The most damaged part of the body was spine (17 patients, 63%).

The prevalence of MSD was significantly higher as compared to the healthy population ($p < 0.05$). Unfortunately this was thru even when comparing data of elderly population ($p <$

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0.05). Our results correspond with the results of international studies. This study was published in the two journals with different aims. One was a rehabilitation journal for strictly physiotherapy expert readers and the other one was sport science journal. In addition the results were presented at nephrology and sport congresses [209, 210, 212].

Study 6, 7, 8 [209, 212-214]**:** This project was focused on musculoskeletal system disorders (MSD), functional capacity and quality of the life in patients on renal dialysis treatment (RDT).The results of the study address the prevalence of MSD among HD patients.

While the first part of the project was strictly descriptive, the second part of the project was an intra-group experimental comparative study. Thus the project included two phases: diagnostic and interventional. Group 2 – ESRD patients N= 67 (34 males/33 females; mean age 64±15yrs; RDT 39±56.4 months). Aim: to prove positive effect of regular exercise program on functional and psychosocial condition of HD patients. All participants completed 6-months conditioning program during each HD. Senior Fitness Test - SFT [195] was used to evaluate functional fitness. Hand dynamometer test – Handgrip [215] was used to assess the maximum static-power capacity which is not included in SFT. We always tested non-fistula arm. To evaluate the effect of the exercise therapy, especially its influence on HRQQL, the standardized questionnaire SF-36 Bref [202] was used in the pre-tests as well as post-tests. Also so called European standard of Results for 8 components (domains) HRQOL was used [204]. Firstly we compared results of our patients with population norms and secondly we compared results of the pre- and post-tests. Descriptive analysis and non-parametric Wilcoxon signed-rank test ($p \leq 0.05$) was used to data analysis.

The number of patients decreased at the end of the study to N = 49 (73.1 % of the original number). 18 participants (26.9 %) were excluded from the overall evaluation due to the following reasons: presence of significant cardiovascular, neurological and orthopedic complications; termination of the exercise program for more than two weeks; termination on the own request or because of transplantation, medical complications or death. The only statistically significant difference between pre- and post- test was observed among female group in Sit to stand test ($p=0.04$). The improvement for the rest of physical fitness tests was not found statistically significant. However 50% of the improvements ware observed in four out of seven tests. Among male group, despite the fact that none of the pre- and post- intervention differences were not found statistically significant, at least 50% of the improvements were observed in four out of seven tests. The improvement of quality of life measured by SF-36 was found statistically insignificant. There was a strong but not statistically significant increase in the two HRQOL components: RE- Emotional limitations of Roles and EV – Vitality. Based on our results, we can assume that the most important components in patients' everyday life are independence and well-being. The results of the study were published in two journals and presented at one conference. One journal is for expert medical personnel working with ESDR patients and the other deals with sport science among elderly.

Study 9 [211]: The goal of the study was to evaluate the physical fitness among randomized group of 50 individuals (19 women and 31 men, average age 54.2±11.7 years) at early stages after the kidney transplantation (1 – 6 months). Senior Fitness Test (SFT) was used to evaluate physical fitness. The study results were compared with the population norms and with

the results of 61 long-term hemodialysis patients (30 men, 31 women, average age **65.2±13.1 years**) by statistical analysis ANCOVA. Covariate was patients´ age. The group of patients after the transplantation performed better as compared to long-term hemodialysis patients (in five out of six tests $p \leq 0.05$) but did not reach levels of healthy population.

The total of 39% patients after the transplantation were bellow or at the lower level of the population norms in overall fitness. For endurance it was 84% and for flexibility only 16%. SFT proved to be an appropriated testing tool for physical fitness evaluation among renal patients at the early post-transplant stage. The SFT can be also used in the later stages for further comparisons. In addition it can be used as a motivating factor for physical activity participation.

Study 10 [214]**:** The goal of the study was to assess an impact of regular exercise and nutrition intervention on physical fitness and the quality of life (QoL) in the first year after kidney transplantation (Tx). Group of patients: (M/F, 11/10, age 59.1±10.8 yrs/ 57.0±8.4 yrs; 69.9±25.4/65.1±17.8 days post-Tx), randomized into 4 subgroups: exercise (E), exercise + nutrition (E+N), nutrition (N), control (C). For testing the physical fitness and QoL we used the "Senior Fitness Test Manual" and KDQOL-SF™ questionnaire. Exercise intervention focused mainly on the joint mobility, muscle strength, nimbleness, dynamic stability, and cardio respiratory endurance (3 times/week; 60 minutes; 6 months). Nutrition intervention included substitution with keto-amino-acides. Results were analyzed using the non-parametric Wilcoxon and Kruskal-Wallis Test.

Both physical fitness as well as QoL in the first year after Tx improved in all patients. Statistically significant differences in the dynamics of physical fitness were observed in 1- 4^{th} months post Tx in four out of six tests ($p \leq 0.01$) and in 1 - 8^{th} months post Tx in five out of six tests ($p \leq 0.05$). The greatest improvement in physical fitness was achieved by the E+N group followed by N, E and C groups. QoL improved in the groups E+N and N in seven out of eight dimensions, however the results were statistically insignificant. The combination of an exercise and nutrition intervention was the most effective.

11. Status and further research

Our laboratory is focused on the evaluation of physical and mental fitness of both hemodialysis patients as well as patients at early stages after kidney transplantation. Foci of our attention are effects of regular physical activity on physical fitness and quality of life of hemodialysis patients. As a result of our efforts unique intradialytic physical activity program has been developed and applied in the clinical practice. The program is among other focused on strengthening of lower extremities. It has been proven that the program is well tolerated and accepted by the majority of the patients and, most importantly, that it has a potential to improve most of the components of physical fitness and quality of life. However the improvements were not in most cases statistically significant. Negative effects were not identified. It is important to note that the results of our research studies have to be interpreted with a great care. The reasons are low research sample sizes and non-existence of control

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group. On the contrary the major goal was not to prove the changes itself but to improve life of dialysis patients by individualized care. Health status of HD patients can rapidly change due to a number of typical complications which in turn negatively affect physical fitness and thus quality of life. In accordance with available international research our studies provided additional evidence that physical activity during hemodialysis does not threaten health status of these patients. In can be concluded that positive effect of physical activity on physical fitness, especially lower extremities muscle strength, have been proven. Although the improvements of quality of life were not statistically significant it can be said that they were clinically significant and that regular physical activity has a great potential to improve quality of life, especially the domains of "physical functioning", "vitality" and "mental health". Due to advanced age of the majority of HD patients (over 60 years) it seems important to focus exercise programs on the maintenance or improvement of muscle strength since it rapidly decreases with age and the disease progress. According to ACSM [194] and Shephard [217] muscular strength decreases 15 – 20% per decade after 50 years. This reality negatively impacts the ability to move and to perform activities of daily living independently. Certain level of muscular strength among persons over 60 years is crucial for activities such as stair climbing, getting in and out of the public transportation or bath tub, carrying groceries, lifting objects, etc. [218]. Decreased muscle strength of lower extremities is one of the essential predictor of future locomotion problems [219, 220].

In the National Kidney Foundation Disease Outcomes Quality Initiative guidelines it is suggested that lifestyle issues such as physical activity should be seen as cornerstones of the therapy. Physical fitness in adults with chronic kidney disease (CKD) is greatly reduced so it negatively impact ability to perform activities of everyday life and occupational tasks [221].

Research studies dealing with the issue of physical activity among ESRD patients and its effect on quality of life suggest various durations of intervention programs (from 6 weeks to 4 years). However the rule "longer, better" can be applied in this case. Regarding quality of life, at least 12 weeks intervention is needed [33, 39]. The improvement is the most obvious in the domains related to physical functions. On the other hand changes in mental domains require longer interventions. Off course that the level of improvements depend on duration of the intervention, its content, volume, intensity of loading and timing with respect to hemodialysis [52]. Combination of various types of physical activity and various intensity result in greater benefits and stronger adherence to physical activity [9, 48, 52]. Adherence to physical activity of HD patients is also determined by their health status, dialysis stage, and motivation. Important factor of the success is a practical cooperation between physiotherapist and medical personnel which is well documented in number of studies [8, 39, 49]. Although advantages of intradialytic physical activity are well documented in both national and international literature, the intradialytic exercise is still quite rare in the clinical practice. Most of the early studies have been applying aerobic type of physical activity using bed-side ergometer [39, 40, 48, 50, 61, 222]. About two decades ago other types of physical activity such as joint flexibility exercises, muscle strength and endurance exercises, balance exercises, overall coordination exercises, coordination of breathing and exercise exercises or relaxation techniques started to be tested in many research projects. As mentioned earlier the goal

of our studies was to spread the general knowledge of the benefits of physical activity among HD patients, nephrologists and physiotherapist. Selected diagnostic tools used in the international literature were proven to be appropriate for the use in the Czech Republic settings. So far physical activity programs are not an option in most Czech dialysis units although the results of our projects proved that such program are beneficial and safe. Dialysed patients have higher risk of prevalence of MSD therefore the physiotherapeutic interventions are more than appropriate. The issues of MSD among dialysis patients are not sufficiently recognized by medical care representatives. Discussed issues were very well captured by Perryman and Harwood [55] who said that painful complications of motor system limit even healthy individuals. In combination with polymorbidity of dialysis patients the presence of pain may lead to deconditioning and overall decrease of functional abilities. Physiotherapist can help dialysis patients to reach safe and long-term mobility. Thus the role of physiotherapist is in multidisciplinary care absolutely crucial [55]. The major goal of the care of motor system of dialysis patients is to ensure long-term independence and self-support and thus postpone the need of other person´s help which at the end significantly increases the cost of care. Although the kidney transplantation is so far the most effective treatment it does not ensure immediate re- integration into ordinary life. It is important to inform patients that certain level of physical fitness is one of the most important factors influencing successful treatment [223]. The patients after kidney transplantation have better levels of fitness as compared to the patients on the dialysis but it still does not reach normal levels of healthy population. The most diminished component of physical fitness is aerobic endurance and the best is flexibility. The appropriate physical activity intervention should be a standard part of medical care of those patients. Unfortunately, with the respect to its specific requirements, it is not available type of care. The presence of someone who would lead and inform patients, monitor their health status and correct performance (type, intensity, etc.) is necessary to ensure the appropriateness of the physical activity. But needed experts such as physiologist, sport physician, rehabilitation specialist are not part of the nephrology team in the Czech Republic as well as abroad. Also commonly used tests of physical loading such as spiro-ergometry evaluations (maximal oxygen consumption, maximal heart rate, etc.) are not always appropriate for HD patients. Simple and easy to understand evaluations of physical fitness may ensure patients that the physical activity is effective and thus it can increase their motivation to remain physically active [224, 225]. SFT proved to be a great example. It is considered an alternative evaluation of physical fitness among dialysis patient although it was originally developed to assess functional fitness among elderly [195].

As already stated all study participants were volunteers. It rises a question whether the interest level in the active participation and thus the opportunity to actively influence own health can be reflected in overall QoL evaluation or not. In our opinion it certainly can. The reason for this might be an individual psychological attitude (if he/she is an optimist or pessimist), level of subjective over-estimation or under-estimation of actual health condition (at the time of testing), interest in exercise activities, etc. Patients´ motivation plays an important role in QoL evaluation. The professional nursing staff must explain to HD patients the

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benefits and also potential risks of the exercise activities and to emphasize their significance for complex treatment.

As mention throughout the text regular physical activity should be essential part of active lifestyle among chronically ill dialysis patients. Appropriate exercise proved to be a great tool to improve quality of life and therefore it should be part of the complex treatment. Independence on other is desirable among all persons, especially the older ones. Physical activity participation represents an active approach in care of own body and should be always emphasized and supported. With the regard to still increasing number of older HD patients, it is important to include physical activity programs into a complex care. Equally important is to spread the knowledge about physical activity benefits in HD patients as much as possible.

12. Practical examples of individual exercises appropriate for HD patient

12.1. Intradialytic Exercise Program (IEP)

The available literatures focused on recommendation and application of physical activity program during hemodialysis procedures is sparse [8, 36, 226]. Any physical activity should be performed between 2nd and 3rd hour of the hemodialysis procedure. Indicators such as HR, BR and BP should be monitor at regular intervals. The arm with a-v shunt is relaxed and lying down. This arm is not activated during the exercise. Physical activity starts slowly and the intensity, number of repetitions and exercise duration is gradually increased according to individual needs of each patient. Shorter exercises are preferred at the early stages of intervention. Patients should wear comfortable clothing. It is recommended not to eat at least one hour prior the exercise session (excluding diabetics). Recommended drinking depends on the amount of urination. It appears to be useful to set up individual goal before each exercise session (for example to learn two new exercises and repeat those five times or to climb stairs instead of using elevator). After mastering the goal a new more challenging goal should follow. All exercises should be performed slowly with great concentrations while strictly maintaining proper position. Important is a regular breathing without holding it in. It is useful to remind patients who are not used to physical activity that exercise is often accompanied by muscle pain, joint pain and muscle fatigue, especially on the day after the exercise session. Those symptoms are not very common right after the session and sometimes they can be postponed for another few days. There is no need to worry. The body is adapting to exercise so the symptoms become less and less obvious until they disappear completely. Important is not to terminate regular exercises because every start is hard. It is recommended to perceive exercise as a pleasant addition to daily routines. Individual exercises are selected according to patients´ preferences. Pain should not be suppressed at any time. Whole process of exercise session should be documented in prepared protocols. Also resting days should be monitored together with the reason of inactivity. Filled up protocols are important for the feedback which is necessary for the future physical loading plan. All earlier mentioned indicators (HR, BR and BP) are continuously monitored during physical activity session and all eventual deviations to normal conditions are documented. Prior the

beginning of the exercise, patients are provided with information about actual content of the session and factors leading to the exercise termination. Patients are again reminded not to use the arm with a-v shunt. It is recommended to perform few exercises using this arm after the dialyses although the area of a-v shunt should be always avoided. Equipment such as light balls or overballs are suitable for loading the a-v shunt arm. The exercise should be slowed down when patient experiences any of the following symptoms: difficulties with breathing, lack of breath, heavy perspiration, abnormally high HR (or abnormally low HR). Exercise should be avoided on very hot or humid days or when patients do not feel well. Cramps, muscle pain or abnormal feeling one hour after the session signalize too challenging exercise. In that case the exercise is immediately terminated. If symptoms such as dizziness, nausea, cramps, serious fatigue, chest pain, irregular HR are presented, physician in charge should be contacted.

Good physical fitness is a prerequisite for promoting good quality of life and can prolong survival of hemodialyzed patients. The beneficial effect of regular physical activity on the overall fitness and mental status of hemodialyzed patients has been reviewed in detail in a number of studies [21-43, 221]. Specific benefits of regular exercise in hemodialysis include:

- in terms of **physical fitness**: increased exercise tolerance; improved overall functional status of the motor system; normalization of the lipid profile (HDL cholesterol, triglycerides, and so on); normalization of insulin tolerance and metabolism; power training muscle protein synthesis and inhibition of protein catabolism; improved hypertension control → reduction of the risk factors of cardiovascular complications and their decreased incidence → reduced morbidity and mortality rates.
- in terms of **psychological fitness**: improved control of depression and anxiety; improved mood, self-confidence; improved management of sleep disorders; improved nutrition and appetite; improved adaptation to stress, workload, and out-of-work activities; improved social interaction, support of return to work and improved social interaction; reduced dependence on others.

The mainstay of our intradialytic exercise program are activities leading to maintenance or improvement of joint flexibility and muscular strength, compensation of muscle disbalances (overloading and shortening of muscle groups), renovation of dynamic stereotypes necessary for independent living, correction of muscle coordination disorders, and improvement of cardio-respiratory fitness.

Individual exercises and variants thereof have been developed so they can be readily performed during hemodialysis. Long-term repetition and extension of the main part of the physical activity session will help improve the above components of physical fitness. By offering the patient a chance to maintain or improve their physical fitness, active elimination of musculoskeletal system-related complaints makes the patient aware of their independence and self-sufficiency as well as their potential contribution to promoting their physical and mental health and improving their quality of life.

Joint mobility (flexibility) is a physical feature whose development affects a man's functional capacity. As regards performance of physical activities, flexibility is a variable characterizing

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the status of the muscular system and, in combination with other variables, characterizes a body's functional status [227]. Joint mobility is closely associated with the status of the muscular system or, more exactly, with balanced muscle stretching and strengthening referred to as muscle balance. A shortened muscle or a muscle group may restrict the extent of joint movement. A certain extent of joint mobility is critical for proper performance of a movement and may also affect muscle strength. Weakened muscles are unable to move properly through the desired movement pattern, which is why ancillary muscles become involved in the movement and may subsequently become unnecessarily overloaded. Adequate muscle strength is crucial for maintaining or strengthening a patient's current movement ability and skills. Muscle strength can be obtained or enhanced by power exercise. Special attention should primarily be given to strengthening weakened muscle groups or those showing a tendency to wasting (phasic muscles, e.g., abdominal, gluteal muscles). While muscle strengthening is of critical importance for the elderly, muscle strength is a factor limiting self-sufficiency and self-care not only in that particular patient population. Attention should be given to strengthening of lower limb muscles but, also, of all muscle groups as a whole. Before starting a program of strengthening weakened muscle groups and during it, consideration should also be given to stretching muscle groups with a tendency to shorten, and those with a higher resting tone to maintain the upright posture. Balanced stretching and strengthening of muscles based on their tendency to shorten or waste will not only contribute to developing and maintaining their current abilities and skills as well as enhancing the level of self-care and self-sufficiency, it will also prevent the development of so-called muscle imbalance experienced by most – not only those suffering from chronic disease or elderly – patients. When performing individual exercises, emphasis should always be placed on the respiratory phase. Proper coordination of movements and breathing is critical not only for the correct performance of a movement but, also, for adequate oxygen supply to the working muscle.

12.2. Example of intradialytic physical activity session [228]

Our exercise program gives only several examples of exercises that can be helpful in developing components of physical fitness. The exercises have been selected from a large set of exercises designed for the hemodialysis patient. The whole exercise set along with the respective illustrations is available in a publication [228] by Svoboda and Mahrová (2009).

Characteristics of individual phases are presented below. Individual exercises are focused on upper or lower extremity movements (arms or legs) separately. All exercises can be combined using arms and legs at the same time. When combining the exercises, coordination of all movements becomes more difficult, therefore, the focus on proper execution is crucial.

The defined number of repetitions is recommended, however, it does not have to be strictly followed. Adjusting the repetitions according patients´ subjective feeling during the exercises is recommended. The exercise unit may start with lower number of repetitions, which may be gradually increased with respect to the enhanced fitness.

Starting position (the position the exercise starts with) - SP

Warming-up:

1. **SP:** Back-lying position, arms are alongside the body.

Movements: Wrist circling, alternately in both directions. See Figure 1.

Repetitions: 6-8 times to the right, then to the left, separately.

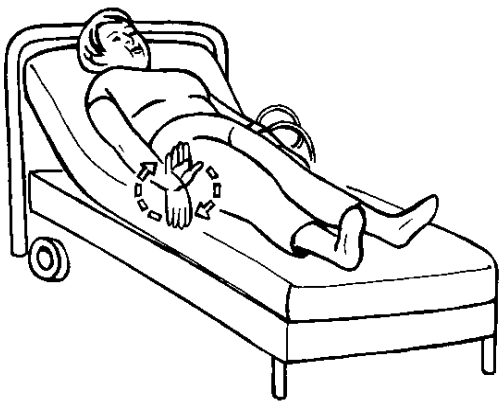

Figure 1.

2. **SP:** Back-lying position, arms are alongside the body with palms facing upward.

Movements: While breathing out, bend your arms at the elbows with palms touching the shoulders. See Figure 2.

Repetitions: 6-8 times

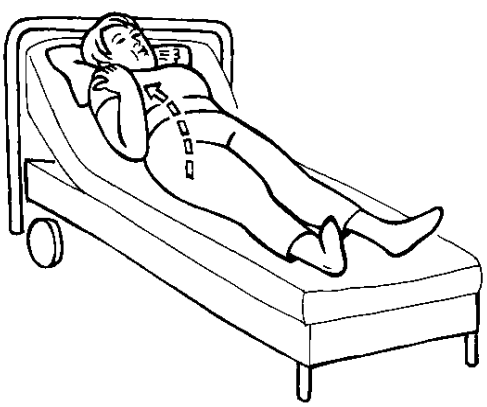

Figure 2.

3. **SP:** Back-lying position, the arms is flexed with palm on the shoulder („wing“).

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Movements: Shoulder circling, alternately in both directions. The shoulder of the arm with the AV- fistula performs circling while adducted. **Note:** Do not hold the breath. The arm moves upward while breathing in, and downward while breathing out. See Figure 3.

Repetitions:6-8 times

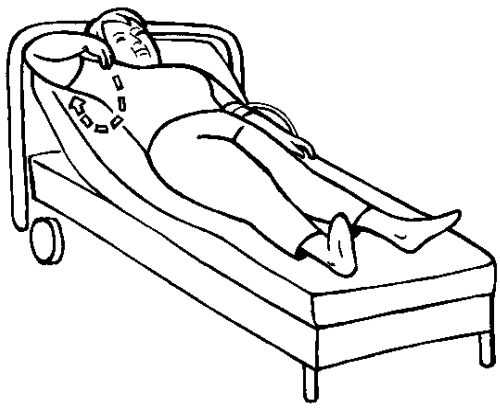

Figure 3.

4. **SP:** Back- **Repetitions:** lying position, legs are hip-width apart, arms alongside the body.

The goal: Vascular gymnastics – supports blood circulation in deep veins.

Movements: Flex the tips of your feet towards the shins, breathe out, stretch the tips and breathe in. *Alternative:* Alternately flexing and stretching the tips of the feet. See Figure 4.

Repetitions: 6-8 times

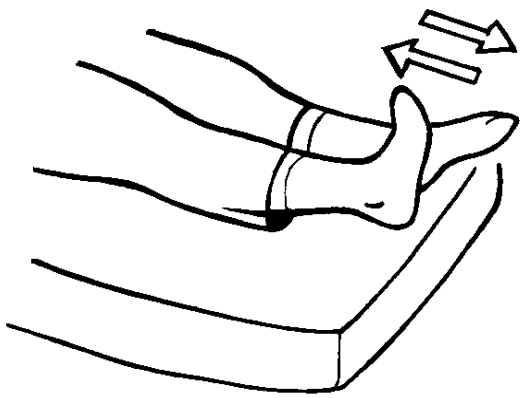

Figure 4.

5. **SP:** Back-lying position, arms are alongside the body.

Movements: Bend the knees alternately, breathe in, go back to the starting position and breathe out.

Note: Do not hold the breath. Do not bend both knees at the same time.

Alternative: Bend your knees, breathe in, stretch your legs upward, breathe out, bend your knees again, breathe in, go back to the starting position while breathing out („triple-flexion"). See Figure 5a, 5b.

Repetitions: 6-8 times

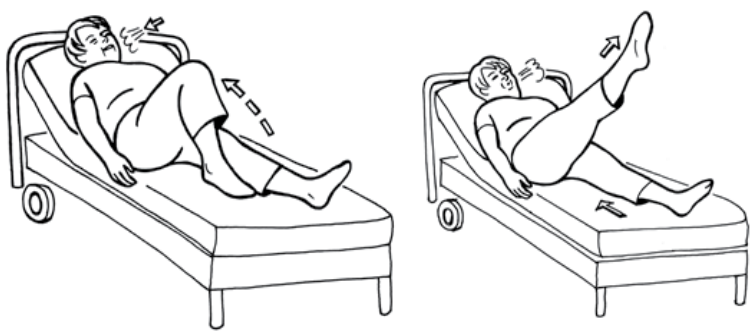

Figure 5.

6. **SP:** Back-lying position with knees bent, arms are alongside the body.

Movements: Keep your lower back flat on the floor while breathing out, legs alternately perform the bike riding movements. Alternately use the right and left leg. **Note:** Do not hold the breath. Do not sag. See Figure 6.

Repetitions: 6-8 times

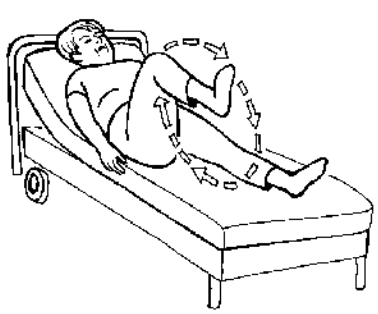

Figure 6.

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Main Part:

The main part can be divided into three individual sections focused on increasing the joint range movement, stretching and strengthening part. Execute the joint range movement enhancing exercises only when the movement is felt comfortable. Do not exercise against the pain. The stretching exercises should be associated with the feeling of comfortable muscle pull, never do the exercise against the pain. The strengthening exercises should be executed slowly with gradual muscle pull that is felt comfortable. Aids: Thera-Bands® (various flexibility, yellow, red, green and blue thera-bands are recommended), physio-big ball, overball, small soft balls, dumbbells (0.5 kg, 1kg, 2 kg).

Enhancing Joint Range Movements – the exercises are the same as those used in the warming-up phase, the number of repetitions is higher.

Muscle Stretching

1. **Muscle group:** Muscles of the whole body

SP: Back-lying position, arms are alongside the body.

Movements: Stretch your arms upward, reach out, breathe in, release and breathe out. *Alternative:* Alternately stretch diagonally just one leg and one arm. **Note:** Do not hold the breath. Do not sag. Do not lift your shoulders. See Figure 7.

Repetitions: 6-8 times

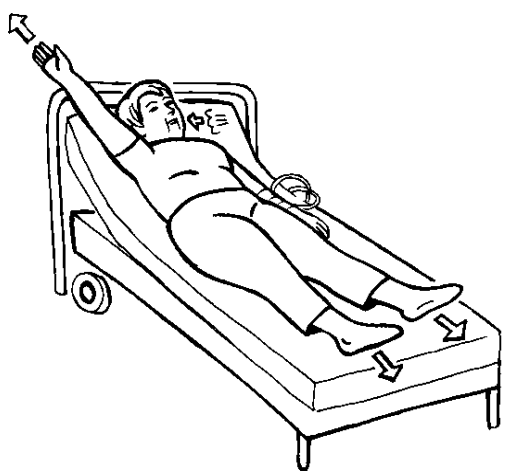

Figure 7.

2. **Muscle group:** Neck extensors

SP: Back-lying position, knees are flexed with feet flat on the floor, arms are alongside the body.

Movements: Breathe in, stretch your neck and head in line with the neck spine while breathing out, the chin is pressed towards the chest ("double chin"). **Note:** Head rests on the floor or on a pillow. See Figure 8.

Repetitions: 2 – 4 times, hold the stretched position for 10 – 15 seconds.

Figure 8.

3. **Muscle group:** Neck muscles – trapezius muscles

SP: Back-lying position, knees are flexed with feet flat on the floor, arms are alongside the body, shoulders pushed downward.

Movements: Breathe in, and while breathing out tilt your head by sliding the head on the floor alternately to the right and left. The ear is pulled towards the shoulder, shoulders are pushed downward. You must feel the muscle pull beginning below the ear through the neck towards the shoulder on the stretched side of the body. **Note:** Do not turn the head to the side. See Figure 9.

Repetitions: 2 – 4 times, hold the stretched position for 10 – 15 seconds.

Figure 9.

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4. **Muscle group:** Gluteal muscles, muscles on the back of the thigh

SP: Back-lying position

Movements: One leg is flexed at the knee, arms clasp below the knee as you breathe out, the leg is pulled towards the chest. The other leg reaches out as much possible while remaining on the floor. Return to the starting position while breathing in, perform the same to the other side. **Note:** Do not pull the leg using the arm with the A-V fistula, do not hold the breath, do not lean your head backward, and do not lift your legs off the **floor.** See Figure 10.

Repetitions: 2 – 4 times, hold the stretched position for 10 – 15 seconds.

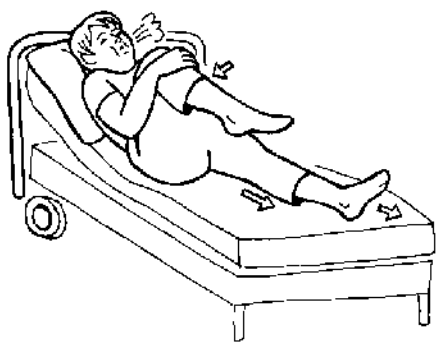

Figure 10.

5. **Muscle group:** Gluteal muscles, outer thigh muscles, low back

SP: Back-lying position, legs are flexed and crossed, arms are alongside the body, slightly to the sides.

Movements: Breathe in and while breathing out, tilt both legs to the side, alternately to the right and left. **Note:** Scapulas remain flat on the floor, do not lean your head backward, do not sag, do not hold the **breath.** See Figure 11.

Repetitions: 2 – 3 times, hold the stretched position for 10 – 15 seconds.

6. **Muscle group:** Spinal erectors, deep muscles of the back (rotators)

SP: Back-lying position, arms are alongside the body.

Movements: Breathe in, put your right leg across the left while your head to the opposite side and breathing out. The lower leg is supported against the left thigh, the left arm is supported against the outer side of the right thigh. Alternate the left and right leg.

Note: Scapulas remain flat on the floor. See Figure 12.

Repetitions: 2 – 4 times, hold the stretched position for 10 – 15 seconds.

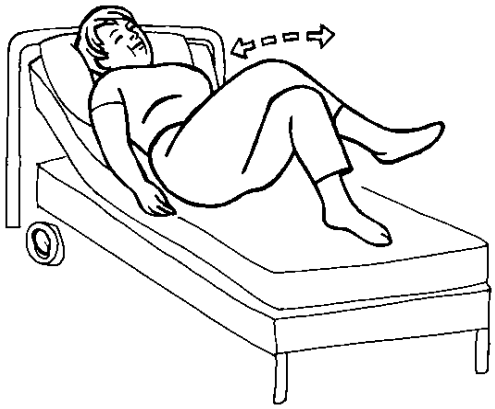

Figure 11.

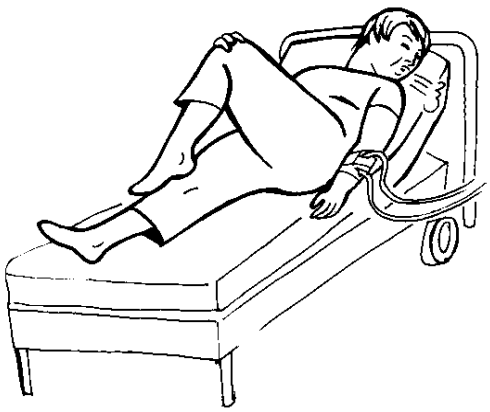

Figure 12.

7. **Muscle group:** Inner thigh muscles

SP: Back-lying position, knees are flexed with feet flat on the floor, arms are alongside the body or stretched to the side.

Movements: Breathe in, lower your knees to the side towards the floor while breathing out, soles remain connected. **Note:** Do not hold the breath. Do not sag. See Figure 13.

Repetitions: 2 – 4 times, hold the stretched position for 10 – 15 seconds.

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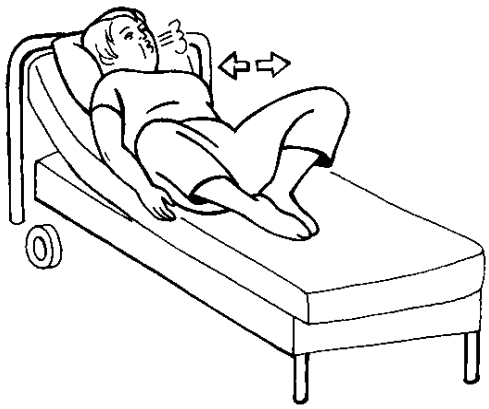

Figure 13.

Muscle strengthening

1. **Muscle group:** Straight abdominal muscles

SP: Back-lying position, knees are flexed with feet flat on the floor, arms are alongside the body.

Movements: Tighten your abdominals while breathing out, keep your low back flat on the floor, lift your head, shoulders and scapulas up from the floor, push your shoulders downward, tips of the feet are flexed towards the shins, look above your knees to the distance. See Figure 14. **Note:** Do not hold the breath. If your abdominal muscles are weak, lift your head only, scapulas are flat on the floor.

Repetitions: 6-8 times, hold for 2-3 seconds.

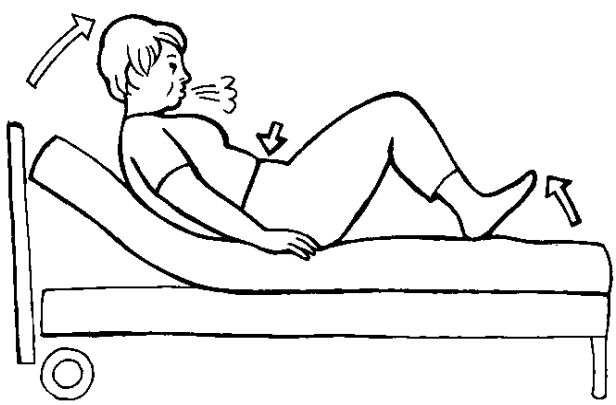

Figure 14.

2. **Muscle group:** Straight abdominal muscles

SP: Back-lying position, legs are bent approximately at 90 degrees at the hip and knee joints, the little ball is on your lower legs, arms are alongside the body.

Movements: Roll the ball on your lower legs back and forth, breathe regularly. See Figure 15. **Note:** Use only soft, small balls.

Repetitions: 6-8 times.

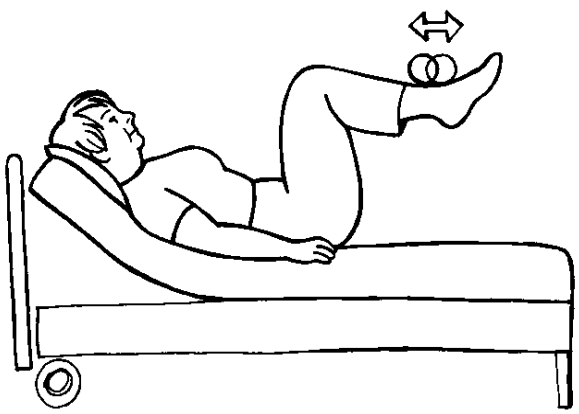

Figure 15.

3. **Muscle group:** Muscles of the back of the thigh, gluteal muscles

SP: Back-lying position, knees are flexed with feet flat on the floor, arms are alongside the body with palms facing the floor.

Movements: Tighten your glutes while breathing out, low back is flat on the floor, continue with lifting your low back from the floor, slowly, vertebra by vertebra up to the scapulas, breathe in, and gradually go back to the starting position while breathing out. *Alternative:* The movement can be divided into 2, 3 phases, hold the muscle contraction. See Figure 16.

Note: Do not hold breath, the movement is executed slowly with slight arm support.

Repetitions: 5-8 times, hold for 2-3 seconds.

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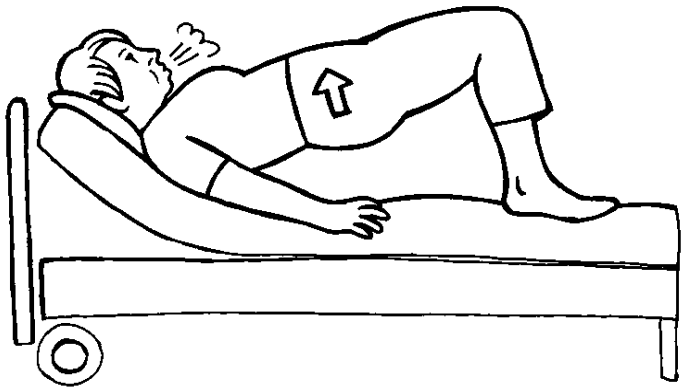

Figure 16.

4. **Muscle group:** Outer thigh muscles

SP: Back-lying position, knees are slightly flexed, arms alongside the body. The Thera – Band® is above the ankles.

Movements: While breathing in, slightly lift one leg off the floor and tilt the leg to the side while breathing out. Repeat the same with the other leg. *Alternative:* The movement can be divided into 2-3 phases, with hold of the muscle contraction. See Figure 17.

Note: Knees can be supported by a roll, or a rolled mat. Low back is flat on the floor. To ensure the leg is tightened, flex the tip of the exercised leg towards the shin.

Repetitions: 6-8 times.

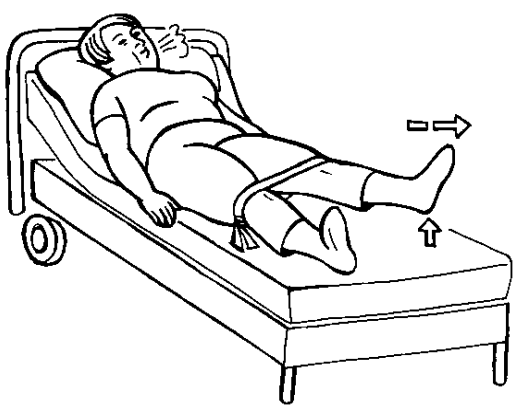

Figure 17.

5. **Muscle group:** Inner thigh muscles

SP: Back-lying position, knees are slightly flexed, arms alongside the body. Put an overball or a rolled blanket in between your knees.

Movements: While breathing out push the knees and thighs toward each other, release while breathing in. **Note:** Knees can be supported by a roll, or a rolled mat. The arm with the AV fistula must not press against the floor. See Figure 18.

Repetitions: 6-8 times.

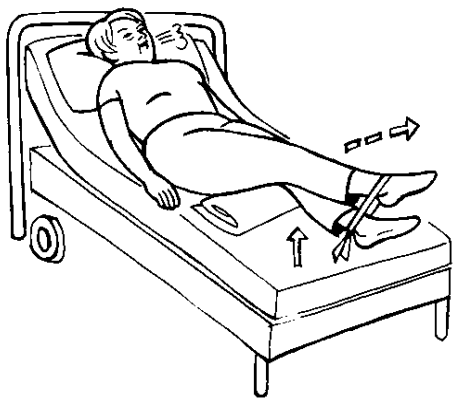

Figure 18.

6. **Muscle group:** Hip flexors, front thigh muscles

SP: Back-lying position, knees are slightly flexed, arms alongside the body. The Thera –Band® is above the ankles.

Movements: Lift one leg off the floor while breathing out, perform the same with the other leg. **Note:** Knees can be supported by a roll, or a rolled mat. The arm with the AV fistula must not press against the floor. See Figure 19.

Repetitions: 6-8 times.

7. **Muscle group:** Shoulder girdle muscles

SP: Back-lying position, knees are slightly flexed with feet flat on the floor, arms alongside the body. The Thera –Band® is attached to the bedside or an armchair.

Movements: While breathing out, the arms raise and pull the Thera-band up and forward, release while breathing in. *Alternative:* The movement can be divided into 2-3 phases, with hold of the muscle contraction. See Figure 20.

Repetitions: 6-8 times.

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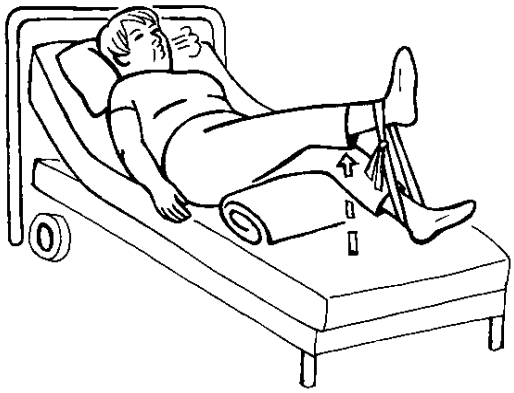

Figure 19.

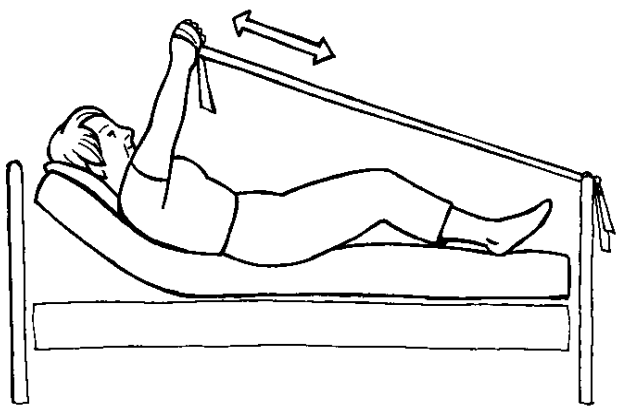

Figure 20.

8. **Muscle group:** Outer shoulder muscles

SP: Back-lying position, knees are flexed, arms alongside the body. The Thera –Band® is attached to the bedside or an armchair.

Movements: One arm (the one without the A-V fistula) is stretched to the side at the shoulder height. The arm slides on the floor. *Alternative:* The movement can be divided into 2-3 phases, with hold of the muscle contraction. See Figure 21.

Repetitions: 6-8 times.

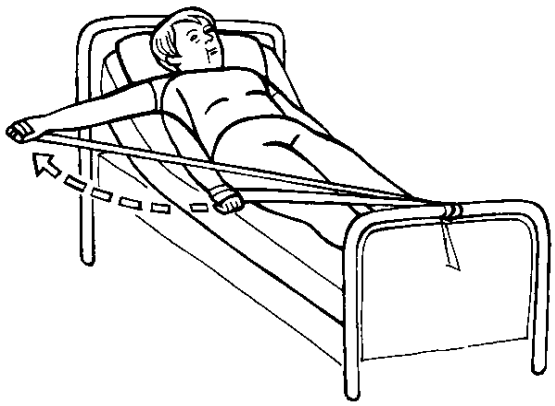

Figure 21.

9. **Muscle group:** Latissimus dorsi, rotator cuff muscles

SP: Back-lying position with knees flexed, one arm (the one without he A-V fistula) is raised upward. The Thera –Band® is attached to the bedside or an armchair.

Movements: The arm pulls the Thera-Band down from the upward to the forward position. *Alternative:* The movement can be divided into 2-3 phases, with hold of the muscle contraction. See Figure 22.

Repetitions: 6-8 times.

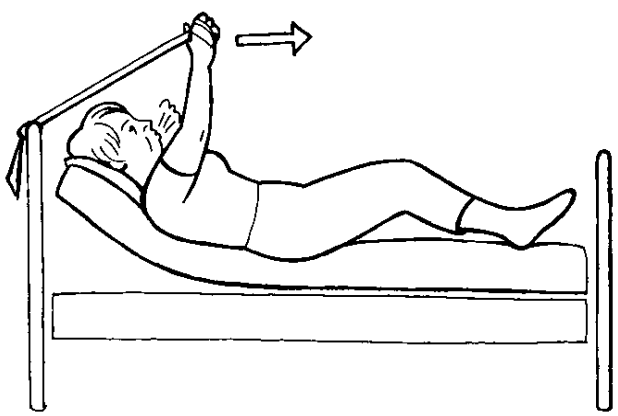

Figure 22.

10. **Muscle group:** Biceps

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SP: Back-lying position, knees are slightly flexed with feet flat on the floor; arms are alongside the body with palms facing upward. The Thera –Band® is attached to the bedside or an armchair.

Movements: Flex your arm at the elbow while breathing out and go back to the starting position while breathing in. *Alternative:* The movement can be divided into 2-3 phases, with hold of the muscle contraction. See Figure 23.

Note: The upper arm remains in contact with the floor.

Repetitions: 6-8 times.

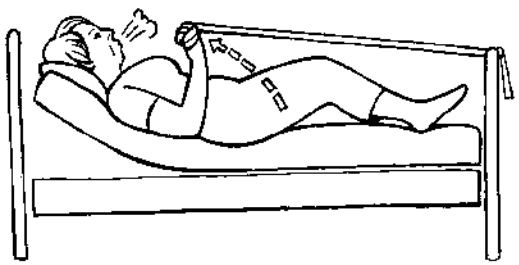

Figure 23.

The Final part:

The final part should be focused on stretching the exercised muscle groups. Complementing this part with some relaxation music is beneficial and recommended. Heart rate should be taken at the end of the exercise following the cool-down phase. The heart rate should be approximately the same as before starting the exercise, which corresponds to a normal resting heart rate.

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Chapter 37

Quality of Life in Patients Undergoing Hemodialysis

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Additional information is available at the end of the chapter

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1. Introduction

Quality of life (QoL) is a broad multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life [1]. What makes it challenging to measure is that, although the term "quality of life"has meaning for nearly everyone and every academic discipline, individuals and groups can define it differently. Philosophers were concerned with the nature of human existence and defined the "good life", ethicists debated the shift in health-care decision-making for the concept of "sanctity of life" to "QoL" and social utility, environmentalists have placed emphasis upon attributes and conditions of the physical and biological environment, economists were concerned with the allocation of resources to achieve alternating goals, psychologists considered human needs and their fulfillment, where as sociologists have advanced a social systems approach in which indicators of QoL are seen as variables in the total system and its subsystems. Physicians focused on health- and illness-related variables and nurses, on keeping with the discipline's holistic approach, took the broadest view in defining life quality, yet because of their frequent preoccupation with the physiological status, they tend to contaminate their operationalization of the concept with disease-specific items [2,3]. And within these disciplines, scientists have defined QoL from different perspectives, such considerations as objective indicators, subjective view, life goals, needs satisfaction, and components of life. WHO defines Quality of Life as individuals perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment [4,5].

Although health is one of the important domains of overall quality of life, there are other domains as well—for instance, jobs, housing, schools, the neighborhood. Aspects of culture, values, and spirituality are also key aspects of overall quality of life that add to the complex-

ity of its measurement [6,7]. Nevertheless, researchers have developed useful techniques that have helped to conceptualize and measure these multiple domains and how they relate to each other [8].

Health-related quality of life (HRQoL) was adapted from the more general and wide-ranging concept 'quality of life'. The concept of HRQoL and its determinants have evolved since the 1980s to encompass those aspects of overall quality of life that can be clearly shown to affect health—either physical or mental [9]. Health-related quality of life is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. It goes beyond direct measures of population health, life expectancy and causes of death, and focuses on the impact health status has on quality of life [10,11].

In the field of medical research, medical sociologist and scientists were concerned with evaluating aspects of life that are affected by disease or treatment for disease, hence, the term health-related QoL were used and included as a criterion for determining the outcome of illness and treatment [12,13].

HRQoL refers to the physical, psychological and social domains of health that are unique to each individual [3].Each of these domains can be measured by the objective assessments of functioning or health status and the subjective perceptions of health. Other valued aspects of life exist that are not generally considered as "health," including income, freedom, and the environment. It has been defined as follows: "HRQoL is defined as the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy" [8]. Another definition is "HRQoL can be defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by a patient" [14]. Lehman, Rachuba and Postrado (1995) also suggested that "HRQoL is the optimum level of mental, physical, role, and social functioning, including relationships, and perceptions of health, fitness, life satisfaction, and well-being" [15]. And Bird et al. (2000) defined HRQoL as: "the degree to which valued aspects of a person's life have been influenced, positively or negatively by health and/or health-related interventions such as medical care" [12].

Over the years, consensus has been established that HRQoL is a multidimensional concept. As such, HRQoL is generally divided into 3 domains: physical, social, and psychological (Guyattet al.1993, Testa MA & Simonson DC, 1996). In the physical domain, perception and observation of normal or disrupted corporal functioning, such as mobility, pain, and nausea, are evaluated. In the social domain, the performance of societal functions is studied; these include activities of daily living and responsibilities in and out of the home, such as those associated with family, friends, and colleagues. In the psychological domain, mental and emotional functioning—for example, patients' concerns, distress, and mood—are examined [4,6].

Briefly, HRQoL refers to the subjective perception of the effect of a disease or its treatment on one's health and overall QoL. It includes physical, psychological, and social dimensions of health as assessed by the patient. It is clearly influenced by the individual's beliefs, life experiences, personality, and expectations [6]. Emphasizing the inherently subjective nature

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of HRQoL is important. The physical dimensions of health (eg, disabilities, impaired physical strength) can be assessed "objectively" through either healthcare personnel or different instruments. These measurements provide information about the patient's "health status" or "functioning." HRQoL, on the other hand, assesses how the presence of the disease's physical symptoms, such as impairment of physical functioning and reduced stamina, affect one's overall well being, life satisfaction, or QoL. This means that two individuals with either similar physical health or equal severity of the disease could have vastly different HRQoL. Evidence accumulated over the last 10–15 years has clearly demonstrated that HRQoL measurements correlate with "objective" measures of physical health and predict traditional "hard outcomes" (ie, hospitalization and mortality) [16]. They also add additional information to the assessment of the overall well being of patients with chronic medical conditions. Clinicians and public health officials have used HRQoL and well-being to measure the effects of chronic illness, treatments, and short- and long-term disabilities. While there are several existing measures of HRQoL and well-being, methodological development in this area is still ongoing.

Recently there has been growing recognition of health-related quality of life as an important indicator of the quality of care for patients with various illnesses. Monitoring patient-reported outcomes (PROs) including self-reported mental and functional health of individuals with chronic disease states is important for assuring optimal disease management and patient satisfaction. The subjective or self-reported state of well being, as it relates to the health condition, also known as "health related quality of life", is a core PRO measure in individuals with End stage renal disease (ESRD). QoL may also serve as a prognostic measure and predictor for such other outcomes as survival.

In order to understand the relationship among the disease, its treatment, and HRQoL, the concept of illness intrusiveness must be understood. Illness intrusiveness was introduced to represent illness-induced disruptions to lifestyles, activities, and interests that compromise QoL [17]. Conceptualized as a facet of the chronic disease experience common across conditions, illness intrusiveness is a fundamental determinant of HRQoL. The central hypothesis is that disease (ie, pain, fatigue, disability) and treatment factors (ie, time required for treatment, untoward side effects) indirectly influence subjective well being and HRQoL through their effects on illness intrusiveness. For example, depriving the individual of the gratifying consequences of psychologically meaningful activities could affect the patient's HRQoL. Psychological and social factors act as moderator variables that influence both the magnitude of illness intrusiveness, which is occasioned by disease and treatment factors, and the degree to which illness intrusiveness compromises QoL [18].

2. Quality of life of hemodialysis patients

Over the past few decades, quality of life research endpoints have emerged as valuable research tools in assessing the outcome of therapeutic intervention in chronic diseases [19]. End stage renal disease is one such chronic disease causing a high level of disability in dif-

ferent domains of the patients' lives, leading to impaired QoL [20,21]. The availability of various renal replacement therapies (RRT) has reduced the severity of symptoms and resulted in longer survival of ESRD patients [22]. Hemodialysis therapy is time-intensive, expensive, and requires fluid and dietary restrictions. Long-term dialysis therapy itself often results in a loss of freedom, dependence on caregivers, disruption of marital, family, and social life, and reduced or loss of financial income [23]. Hemodialysis alters the life style of the patient and family and interferes with their lives. The major areas of life affected by ESRD and its treatment includes employment, eating habits, vacation activities, sense of security, self-esteem, social relationships, and the ability to enjoy life [24]. Due to these reasons, the physical, psychological, socioeconomic, and environmental aspects of life are negatively affected, leading to compromised QoL [25].

Survival of ESRD patients has been largely improved nowadays because of medical progress, advanced technology, and beter patient care. Accumulated data in the recent decade show that health-related quality of life markedly influences dialysis outcomes. Attention thus needs to be focused not only on how long but also on how well ESRD patients live [26]. Compared with the general population, ESRD patients treated with hemodialysis have significantly impaired HRQoL [27].

Evaluation of HRQoL in patients with chronic diseases is becoming very important. HRQoL assessment helps to plan the individual strategy of treatment, to determine the efficacy of medical intervention, and to evaluate the quality of medical care. In comparison with HRQoL of the general population, it provides the opportunity to evaluate the psychological burden of chronic disease, and the effect of specific treatment [28].Some studies have shown international differences in HRQoL of ESRD patients treated with hemodialysis [29, 30].

An increasing number of professionals feel that HRQoL assessment is essential to evaluating quality and effectiveness of ESRD patient care, comparing alternative treatments and RRT modalities, improving clinical outcomes, facilitating complex rehabilitation of ESRD patients, and enhancing patient satisfaction. Several authors have suggested that regular HRQoL monitoring become part of regular ESRD patient assessment and incorporated into the continuous quality assurance and quality improvement systems [31,32].

ESRD is a life-threatening disease that leads to numerous and severe symptoms and complications. These severe comorbid conditions will have a major impact on the affected patients' HRQoL. RRTs are able to alleviate, but they are very intrusive and cure neither the disease nor its symptoms. Patients suffering from ESRD need RRTs to survive, but they also expect to achieve a certain level of well being. In industrialized countries achieving survival is not enough for a treatment to be considered "successful" unless it also yields an appreciable gain in HRQoL [33,34]. Thus, the results of studies suggest that the QoL of hemodialysis patients is considerably impaired compared to that of the healthy subjects, especially with respect to the physical, psychological and social relationship domains [35,36]. In a previous DOPPS study, lower scores in several measures of HRQoL, particularly PCS, were found to be strongly associated with higher risk of death in Japan, Europe, and the United States [16]. Other studies have shown that patients on hemodialysis have a poor health-related quality of life (HRQoL) and present with complications such as depression, malnutrition, and in-

flammation. Many of them suffer from impaired cognitive functioning such as memory loss and abnormally low concentration, as well as other unhealthy physical, mental, and social aspects of life that can, and do, affect even the simplest activities of daily life [37,38]. On the other hand, many researchers emphasize that an improvement in HRQoL reduces the complications associated with this disease, or at least makes them more tolerable [39]. Therefore, it is useful to determine the level of renal function related to the decreasing point of HRQoL for the adequate intervention to enhance HRQoL in time. Improving QoL and other PROs in the dialysis patient population has evolved as a goal for renal replacement therapy.

3. Factors associated with health-related quality of life in patients under going hemodialysis

End-stage renal disease patients undergoing hemodialysis (HD) has a considerable impact on the functional status and health-related QoL perceived by the patient as it is accompanied by symptoms that affect daily life [40].Over the years, several studies have assessed HRQoL in different ESRD populations. These reports reveal numerous sociodemographic, clinical, and psychosocial factors that are associated with impaired HRQoL.

Sociodemographic factors: It has been repeatedly demonstrated patients undergoing hemodialysis that female patients consistently report worse HRQoL than men [40,41]. Women had lower QoL scores than men, as already reported by the studies [42,43]; this may be explained by women's multiple domestic tasks and responsibilities that, unlike men, they cannot circumvent [44]. Also, one potential explanation may be the more negative disease perception and the increased prevalence of depression in women. Moreno et al.,(1996) in their multicenter cross-sectional study [36], and Sesso et al., (2003) in their prospective cohort study, also found that higher socioeconomic level was significantly related to better QoL [45]. A lower social status, characterized by lower education, worse financial situation, or lack of employment, has also been consistently associated with impaired QoL [41,46]. This association is important, as vocational and educational rehabilitation could substantially improve HRQoL. The association of age with HRQoL is quite complex and illustrates the complexity of the QoLconcept.Some studies conducted in different countries also demonstrated that age was strongly inversely associated with the physical domain scores [25].As age increases in the elderly, physical function of the body decreases [46-48]. The subjective QoL for elderly patients, however, varies depending on their expectations and beliefs. It could be surprisingly good compared to their younger counterparts [49].

Clinical factors: Several clinical factors are strongly associated with HRQoL in hemodialysis patients. The underlying kidney disease leading to renal failure, the presence and severity of diabetes [50,51] and comorbid conditions in general [49,52] and congestive heart failure in particular predict impaired QoL [53]. Anemia is highly prevalent in patients undergoing HD and is associated with adverse clinical outcomes and diminished HRQoL [54-59]. The most prominent symptoms of anemia are fatigue, dyspnea, and diminished sense of well-being. Less common symptoms include difficulty concentrating, dizziness, sleep disorders, cold in-

tolerance, and headaches [60]. Walters et al. (2002) assessed health-related QoL, depressive symptoms, anemia, and malnutrition at hemodialysis initiation and found that 56% of the sample group (422) had a hemoglobin levels less than 10g/dl [38]. Chronic inflammation, presence of malnutrition, and different medications' side effects have been reported to predict worse HRQoL [31]. However, it is important to note that the different comorbidity indices are used to measure comorbid burdens, and clinical and sociodemographic factors only explains a fraction of HRQoL variability.

Duration of dialysis plays an important role affecting QoL in dialysis patients. According to Vasilieva (2006), in linear regression analysis, duration of dialysis was a significant independent predictors of the low physical component score (PCS) in hemodialysis patients [61]. A similar observation was made by Anees et al. (2011); duration of dialysis had a reverse correlation with QoL. As duration of dialysis increases, QoL of dialysis patients deteriorates [62]. In another study, QoL was better in hemodialysis patients with a duration less than 8 months than patients with a dialysis duration more than 8 months [63].

Psychological/psychosocial factors: Several psychosocial factors have also been shown to strongly predict HRQoL scores. The expanding awareness about objective parameters and their impact on HRQoL is complemented by few studies on subjective symptoms and their influence on HRQoL in CKD [64-66]. The symptom burden that these patients struggle with include, fatigue [59,64,65], cognitive difficulties [59,64], sleep disturbances [34,59,64,67], sexual dysfunction [59,64], pain and depression [59,64,65], most of which are interlinked [65,67. While larger studies on pre-dialysis ESRD patients are lacking, existing ones confirm the negative impact of these symptoms on HRQoL [34,59,66].

In relation to psychological status, the a study by Mollaoglu (2004) indicated that two third of ESRD patients in Turkey had depression and found an association between depressed mood and health-related QoL [63]. The higher depression scores the lower health-related QoL scores. She explained that as a direct influence of chronic renal insufficiency on health-related QoL. Another study indicated that the mental health was significantly higher for patients treated in the United States than in Europe [68]. In another study by Jofre, Lopez-Gomez &Valderrabano (2000) who reviewed the factors affecting the QoL of renal failure patients, they found that the prevalence of depression is within 70% in the dialysis population using Beck Depression Inventory (BDI), they also indicated that depression has a significant impact on the perception of QoL [40]. Anxiety is another psychological response to hemodialysis patients and is related to the awareness of one's illness and the sense of dependency on the machine. Patients are concerned about the unpredictability of the illness and the disruption of their lives, they are chronically ill and fear dying [24].

Body image is also affected by dialysis treatment, making patients feel different, unattractive, and ill at ease within their own bodies. Access surgery often results in multiple scarring, involving the arms and chest. A fistula which is regarded as "very good" by dialysis staff can be seen as a horrible disfigurement by the patient, who may try to conceal it from friends and the curious stares of strangers. Many feel embarrassed in front of their partners and feel that nobody could find them attractive anymore [63,64].

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Anxiety, loss of control, body image and sexual problems, social support, and unemployment are all factors that strongly influence QoL in hemodialysis patients. The utmost significance of these factors is further underlined by the fact that many of them are modifiable. Unfortunately, little attention is given to assess the potentially modifiable psychosocial stressors in hemodialysis patients.

Sleep disorders are highly prevalent in patients with renal impairment. The most frequent sleep disorders, such as restless legs syndrome, periodic leg movements in sleep, insomnia, and obstructive sleep apnea, are associated with significantly impaired HRQoL in patients with moderate renal failure not yet requiring RRTs as well as in patients on hemodialysis [17,32]

4. Assessment of health-related quality of life in patientsundergoing hemodialysis

Health-related QoL assessment, as a supplement to more objective clinical indicators, is becoming more topical in view of the increasing questioning of the effectiveness and appropriateness of many existing medical treatments and methods of organizing health services [2,4]. The US Centers for Disease Control and Prevention CDC (1993) suggested that: measuring health-related QoL can help determine the burden of preventable diseases, injuries, and disabilities, and it can provide valuable new insights into the relationships between health-related QoL and risk factors. Measuring health-related QoL will help monitor progress in achieving the notions' health objectives. Analysis of health-related QoL surveillance data can identify subgroups with relatively poor perceived health and help to guide interventions to improve their situations and avert more serious consequences [69].

In the field of nephrology, the evaluation of health-related QoL involves determining the efficiency and effectiveness of the different forms of renal replacement therapy (e.g. HD and peritoneal dialysis), evaluating the efficiency and effectiveness of the different types of other treatments applied to patients with ESRD (e.g., recombinant human erythropoietin therapy) and follow-up of the evolution of individual renal patients [43].

Different generic disease-specific instruments and domain-specific instruments have been used for assessing the QoL in patients undergoing hemodialysis (Germin-Petrovic et al. 2011).

4.1. Generic instruments

Measures which implicitly or explicitly aim to tap health-related QoL. They encompass the dimensions of physical, mental and social health [69]. These instruments are intended for general use, irrespective for the illness or condition of the patient. These generic questionnaires may often be applicable to healthy people, too [13]. The Sickness Impact Profile, the Medical Outcome Study 36-Item Short Form, and the Nottingham Health Profile are examples of the generic instruments.

4.1.2. Medical outcome study 36-item short Form (SF-36)

The SF-36 developed by Ware et al. in 1993 evaluates general health status, it is designed to provide assessments involving generic health concepts that are not specific to any age, disease or treatment groups. Emphasis is placed upon physical, social, and emotional functioning. It can be either self-assessed or administered by a trained interviewer. As the name implies, there are 36 questions addressing physical health and mental health [13].

4.1.3. The Nottingham Health Profile (NHP)

The Nottingham Health Profile (NHP) was developed to be used in epidemiological studies of health and disease [70]. It consists of two parts. Part I contains 38 yes/no items in 6 dimensions: pain, physical mobility, emotional reactions, energy, social isolation and sleep. Part II contains 7 general yes/no questions concerning daily living problems. The two parts may be used independently. Part I is scored using weighted values which give a range of possible scores from zero (no problems at all) to 100 (presence of all problems within a dimension).

4.1.4. Sickness impact profile

A 136-item self- or interviewer-administered, behaviorally-based, health status questionnaire. Everyday activities in 12 categories (sleep and rest, emotional behavior, body care and movement, home management, mobility, social interaction, ambulation, alertness behavior, communication, work, recreation and pastimes, and eating) are measured. Respondents endorse items that describe themselves and are related to their health. The SIP is scored according to the number and type of items endorsed. Scoring can be done at the level of categories and dimensions as well as at the total SIP level. It may be either interviewer- or self-administered [13].

4.1.5. Disease-specific instruments

4.1.5.1. Quality of life index-D (QLI-D)

The Quality of Life Index (QLI) was developed in the USA during the 1980s as a measure of morbidity for application in both normal and unwell populations [71]. The original instrument, with the addition of six dialysis-specific items, was developed and tested in patients receiving haemodialysis [71]; factor analysis confirmed instrument construction. The instrument comprises two sections assessing respondent satisfaction and relative importance of each domain, respectively. Each section has 32 items, with eight items per domain. Six-point ordinal response scales range from ‘very dissatisfied’ or ‘very unimportant’ (1), to ‘very satisfied’ or ‘very important’ (6). Scoring is complicated and the developers recommend a computer programme. In summary, importance scores are used to weight satisfaction scores; index or domain scores range from 0 to 30, where higher scores indicate better quality of life.

Regarding evidence in relation to kidney disease, reliability was supported for the QLI in a one month time interval for dialysis patients. High internal consistency was also reported

in a small study by [71]and reproduced in a further study with a larger sample of patients [71]. Additional items for haemodialysis patients relating to treatment were added to each section (Satisfaction with various domains and Importance of the domain to the individual) in Ferrans and Powers 1985). Items were endorsed by patients receiving haemodialysis. A transplant version is also available which included two items relating to the potential for a successful transplant. This is for patients receiving haemodialysis and on the transplant list.

A four factor structure was supported in Ferrans and Powers (1985) of Health and functioning, socioeconomic, psychological/spiritual and family. A high order factor was revealed representing Quality of Life. Moderate correlation of QLI-D scores with a life satisfaction questionnaire has been reported [71]. Further convergent validity is supported for each domain and life satisfaction, with higher correlations for the Psychological/spiritual domain. Moderate correlation was reported between scores from the QLI-D and other patient-reported measures of symptoms and psychological adjustment to disease. Moderate correlation of scores has been reported between QLI-D and symptoms.

A larger population was recruited in another study by the developers [13]. This included 349 patients from a haemodialysis unit and questionnaires mailed to patients. 20% of patients had missing values greater than 15% and overall computable responses were available from 46% of participants invited. A 46% response rate was obtained to postal administration of the questionnaire [13].

4.1.5.2. Kidney Disease Quality of Life Short Form (KDQOL-SF)

The KDQOL-SF includes both general measures and measures specific to patients with kidney disease. The general measures were based on questions from the 36-item Short-Form Health Survey (SF-36), developed by Ware and Sherbourne [73]. Previous data support the use of the SF-36 and the KDQOL-SF as research instruments to HRQoL [74]. The internal consistency and reliability are similar among translations of the SF-36 and the KDQOL-SF [9,68]. Patient responses to the SF-36 questions were used to determine scores for the mental component summary (MCS) and the physical component summary (PCS). The scales for MCS and PCS are derived from eight different subscales: physical functioning role (physical, bodily pain, general health, and vitality) and social functioning role (emotional, and mental health).

The KDQOL-SF includes questions that supplement the SF-36. These additional questions were designed to assess the particular health-related concerns of individuals with kidney diseases and ESRD patients treated by dialysis [74]. The kidney disease component summary (KDCS) score, which corresponds to the MCS and PCS of the SF-36, is derived from 11 subscales: symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, dialysis staff encouragement, and patient satisfaction.

The SF-36 and kidney disease–targeted portions of the questionnaire were scored according to the manual by Ware et al (1993) and the KDQOL scoring manual (Hays et al.1994) [74].

On all scales, the possible scores range from 0 to 100; higher scores indicate more or better functioning, or better quality of life. The summary scales have the same interpretation, but do not span the entire 0 to 100 range.

4.1.5.3. Kidney Disease Questionnaire (KDQ)

This 26 itemed questionnaire was developed in Canada with the involvement of patients receiving haemodialysis and empirically by factor analysis. Five domains included are: Physical symptoms (6 individualised symptoms identified by the patient); Fatigue: 6); Depression (5); Relationships (6); Frustration (3). Responses are scored in a 7 point Likert scale during the last 2 weeks. It is reported to take 10 to 15 minutes to complete.

Reproducibility is supported with ICCs above 0.80 for all domains. Construct validity is reported with moderate correlations with analogous domains using the SIP. Trial data [76], provide support for responsiveness with significant improvement in scores for patients receiving treatment for anaemia which was consistent with score changes on the SIP.

4.1.6. Renal Quality of Life Profile (RQLP)

The Renal Quality of Life profile (RQLP) is a 43 itemed questionnaire with a 5 point Likert scale for responses. Five dimensions include: Eating and drinking, Physical activities, Leisure time, Psychosocial activities and Impact of treatment. It was developed adopting a comprehensive methodology involving patients and clinicians in the UK [77].

Principal component factor analysis supported the five dimensions. A high response rate is reported in Barton et al., [78].The RQLP scores were responsive to change in a trial of pharmacy care compared to standard care for patients receiving HD. Effect sizes were moderate [78]. Moderate correlation is reported between the RQLP and SF-36 dimensions which were similar in construct.

4.1.7. CHOICE Health Experience Questionnaire (CHEQ)

The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study was designed to evaluate the effectiveness of alternative dialysis prescription. As part of the CHOICE study, the CHEQ as patient-reported HRQoL instrument was developed to specifically complement the SF-36; be sensitive to dialysis treatment modalities and regimes; and be useful for longitudinal evaluation. A comprehensive, patientcentred approach was used during development. Items were derived from interviews with patients; literature; and clinicians' expertise [79]. The questionnaire has 83 items addressing 21 domains: the 8 domains of the SF-36, 8 additional generic domains (cognitive functioning, sexual functioning, sleep, work, recreation, travel, finances, and general quality of life); and 5 ESRD-specific domains (diet, freedom, body image, dialysis access. The original study byWu and colleagues (2001) provided some evidence for the reliability and validity of the scales. Adequate internal consistency is reported for most domains in Wu et al. (2001) [79].

4.1.8. Renal dependantindividualised quality of life questionnaire

This instrument was developed out of an instrument used in relation to diabetes, the Audit of Diabetes Dependent Quality of Life (ADDQoL) diabetes-specific individualized quality of life questionnaire. From a small study with patients in eight U.K. renal clinics each of the 13 ADDQoL items were found relevant and important for renal patients. Additional items were also identified by patients including physical appearance, dependency, freedom, restrictions of fluid intake, and societal prejudice [80]. No psychometric data for the new instrument were reported. No further studies using the instrument were identified.

4.2. Domain-specific instruments

4.2.1. Barthel Index of disability (BI)

The BI was developed in 1965 (Barthel, 1965)and later modified by Granger and coworkers (1979) as a scoring technique that measures the patient's performance in 10 activities of daily life [81,82]. The BI is considered a reliable disability scale for stroke patients. The items can be divided into a group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and a group related to mobility (ambulation, transfers, and stair climbing). The maximal score is 100 if 5-point increments are used, indicating that the patient is fully independent in physical functioning. The lowest score is 0, representing a totally dependent bedridden state. The MRS measures independence rather than performance of specific tasks The BI examines the ability to perform normal or expected activities [13]. In this way, mental as well as physical adaptations to the neurological deficits are incorporated. The scale consists of 6 grades, from 0 to 5, with 0 corresponding to no symptoms and 5 corresponding to severe disability.

4.2.2. McGill Pain Questionnaire (MPQ)

The McGill Pain Questionnaire, also known as McGill pain index, is a scale of rating pain developed at McGill University by Melzack and Torgerson [83].

To use the questionnaire, circle the words that describe your pain but do not circle more than one word in a group. Then when you have that done, go back and circle the three words in groups 1-10 that most convey your pain response. Pick the two words in groups 11-15 that do the same thing. Then pick one word in group 16. Finally, pick 1 word in groups 17-20. At the end you should have seven words that you can take to your doctor that will help describe both the quality of your pain and the intensity of it [13].

5. Improving health-related quality of life in patientsundergoing hemodialysis

There is growing recognition of health-related QoL issues in ESRD patients undergoing hemodialysis. Considerable progress has been made in the treatment and health intervention

of chronic kidney disease, however, health-related QoL continues to be a significant problem for patients receiving hemodialysis [31,39]. Hemodialysis patients are subjected to multiple physiological and psychological stressors and may be threatened with many potential losses and life style changes as they experience problems with disease-specific symptoms. The combination of a decrease in energy, the unavoidable emergence of socioeconomic problems, and emotional reactions compounds the stress facing the patient [38, 45]. The initiation of long-term dialysis treatment increases survival, but health-related QoL remains impaired. Therefore, researchers and clinicians generally agree that health-related QoL, its determinants and treatment options that may preserve subjective well-being merit continued investigation [62,63].

Health care workers should understand the health-related QoL of patients undergoing hemodialysis. The rich information collected can help health professionals to determine which patients may be at risk for diminished health-related QoL. It has direct consequences for clinical decision-making, rehabilitation and management of individual patients [65,72]. Draper (1992) stated that health professionals, in their decisions and actions, can influence their patient's QoL [84]. Additionally, they will be interested in promoting these conditions, which enhance life's quality, and eliminating those that impair it. Health professionals working in hemodialysis units can direct resources to areas where improvement may be required. Patients can then have a greater chance of leading a fulfilling life. All these factors can positively influence the health-related QoL of patients, and directly benefit the family as well [62,63, 65]. This could be accomplished through health education and promotion of awareness about the disease, treatment options, complications and self-care activities. Counseling, on the other hand, is an important intervention that health professionals - with appropriate training - can provide. Referral of patients to the appropriate person according to their needs could be provided by an ordinary health professional who cares for the patient. Finally, health professionals can develop and implement rehabilitation programs for ESRD patients undergoing hemodialysis to assist them lead a productive life.

ESRD has a profound effect on HRQoL with the most prominent areas of difficulty being the physical domains. Hemodynamic instability is a major problem observed in hemodialysis patients and thus managed carefully. Anemia management in ESRD patients is a challenge for the health care team. The use of erythropoietin-stimulating agents (ESAs) has become a routine practice in hemodialysis patients in an effort to correct anemiaand improve HRQoL. Nonetheless, two simultaneously published trials [85,86] raised concerns regarding the optimal hemoglobin target levels. Druekeet al. (2006), the CREATE investigators, reported significant increment in HRQoL with higher hemoglobin levels whereas Singh et al. (2006), the CHOIR investigators, reported no difference in the HRQoL between the low and high hemoglobin arms after EPO therapy [86]. Additionally, normalization of hematocrit was shown to be associated with adverse cardiovascular outcomes in the CHOIR trial (2006). In consideration of the conflicting results of these publications, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) published revised guidelines for the management of anemia in CKD patients [87], which were further reviewed at the Kidney Disease: Improving Global Outcomes (KDIGO) international conference. Members voiced a

general consensus on maintaining target hemoglobin levels in the range of 11.0 to 12.0 g/dL (KDOQI 2007) and acknowledged the potential for harm associated with levels higher than 13.0 g/dL [87].

Considering the dramatically increasing prevalence of ESRD, the risk of progression of ESRD with hypertension and the significant impact of the disease on HRQoL, improving HRQoL is emerging as one of the therapeutic goals in hypertensive individuals. High blood pressure is managed by an appropriate choice of antihypertensive medications to have a target blood pressure of 125/75 mmHg. Cardiovascular risk factors are minimized as ESRD patients are at increased risk for coronary heart disease over the standard risk factors, prevention includes frequent monitoring of plasma lipid levels, diet control, and pharmacologic treatment of specific hyperlipidemias [87].

The increasing prevalence of ESRD in the older population and the poor prognosis and impaired HRQoL associated with frailty warrant early identification of high-risk patients. Suggested management strategies to prevent further deterioration include exercise training and correction of malnutrition, anemia, depression and hormonal imbalances. Growth hormone supplementation in elderly dialysis patients has been shown to improve muscle performance and HRQoL [88], but whether this approach would be helpful in patients with non-dialysis dependent CKD remains to be established.

Among the psychological stressors of ESRD patients undergoing HD, depression and anxiety are the most common problems encountered. The onset of ESRD and HD impacts significantly one's functional state and health-related QoL, it causes major alterations in the lifestyle of most patients, who may encounter frustration in all areas of life, this frustration causes depression which is known to be strongly associated to decreased health-related QoL. This is illustrated in Walters et al. (2002) study that assessed health-related QoL, depressive symptoms, anemia and malnutrition at HD initiation and found that HD patients who screened positive for depression (45% of the sample) scored lower on health-related QoL scale [38]. Anxiety, on the other hand, is detected in HD patients, and is caused by unstable health status leading to fears from worsening health condition, disturbed social relations, unemployment and consequent economic alterations, and even death. A study by White and Grenyer (1999) that aimed at investigating the impact of dialysis on both the patient and their partner found that dialysis patients had anxiety as they expressed uncertainty related to health instability within a progressively debilitating disease state and frequent interruptions of acute illness episodes [89].

Socioeconomic status is also altered in ESRD patients undergoing HD as chronic dialysis imposes a considerable burden on patients and families [17,38],the relationships of the patients with family members is altered as there is role reversal, with the assumption of added responsibilities by the spouse, resulting in a loss of authority for the patients [63]. Social isolation and decreased social interactions is observed in HD patients and this is caused by their health status and the treatment schedules. Another alteration of lifestyle includes the probable loss of financial security resulting from lower productivity and income, and possible unemployment. All the above factors are strongly related to health-related QoL of HD patients. Parkerson and Gutman, (2000) assessed health-related QoL of 103 ESRD patients on HD,

and found that patients living with family reported more social support and better health-related QoL, general health, emotional well-being, social health and quality of social interactions than other patients [89].

The development and evaluation of effective interventions to reduce psychological distress, improve QoL and enhance social intimacy are of clinical and scientific importance to HD patients, their family members and healthcare providers. Tsayand Lee, (2005) randomized patients with end-stage renal disease to a cognitive–behavioural coping skills and stress management training programme or standard care (primarily education) [91]. Cognitive–behavioural treatment reduced symptoms of stress and depression, and improved QoL, compared with a standard care condition. Chang et al. (2004) combined education, vocational rehabilitation and social support enhancement, and found significant QoL improvements in ESRD patients [92]. Gross et al. (2004) used a mindfulness-based stress reduction programme in ESRD patients to reduce depression and anxiety, although no QoL improvements were found. Quality of life therapy (QoLT) is the only cognitive–behavioural treatment that targets happiness and life satisfaction in multiple life domains (e.g. relationships, enjoyable activities, self-esteem, etc.) with a specific goal of improving overall QoL [93]. This is important because the World Health Organization has emphasized the importance of a patient's subjective perception of life in the context of his or her value systems, goals, expectations and standards.

6. Conclusion

Although advances in dialysis treatment have contributed to improved survival of patients with end-stage renal disease,such individuals particularly those treated by hemodialysis, health-related quality of life is much lower for those patients than for the general population. Impaired health-related QoL, dependence on others, and poor rehabilitation all contribute to physical and emotional disabilities that may persist even in well-dialyzed ESRD patients. Chronic HD patients are subjected to multiple physiological and psychological stressors and may be threatened by many potential losses and lifestyle changes. Analysis of health-related QoL surveillance data can identify subgroups with relatively poor perceived health and help to guide interventions to improve their situations and avert more serious consequences. Developments of HD technology, treatment of comorbidities, continuous patients' education, social and psychological support may improve the HRQoL in these patients.

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Chapter 38

Physiotherapy in the Patients on Hemodialysis

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Additional information is available at the end of the chapter

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1. Introduction

Today end-stage renal disease (ESRD) is still major health concern. ESRD, the deterioration of nephrons to an advanced stage resulting in the dysfunction of the kidneys for a long period, requires either dialysis treatment or transplantation in advance. ESRD results in a negative clinical status, which in turn results in both structural and functional changes in the muskuloskeletal system. Consequently, the patient is faced with a sedentary life, making the patient even further dependent. Low functional capacity, exhaustion / fatigue and under nutrition was found to be prevalent among incident dialysis patients.

Complications such as uremia, anemia, myopathy, and neuropathy decrease muscular strength, cardio-pulmonary fitness, and quality of life, which is why this population is seen more frequently in physiotherapy practice currently.

Dialysis regulates the patients' general condition and fluid-electrolytes balance, assures the disposal of accumulated toxic substances in the body, facilitates the patient' continued healthy life, and prepares the patient for the transplantation. During this stage of treatment, there are two considerations: to increase both the quality of life and the life expectancy. To improve and enhance the quality of life through dialysis or transplantation, a well-planned exercise program also must be included. As the exercise program entails a risk in itself, the implemented program must be carefully planned, coordinated, and supervised based on health related fitness in this population.

There are many exercise training studies in patients with end-stage renal disease on hemodialysis, but exercise type and planning are open to discussion in this population. But it is clear that, physiotherapists are responsible from suitable exercise programs in inpatient and outpatient renal clinics.

2. Chronic kidney disease and physical activity

Chronic kidney disease is the progressive deficiency of renal function for months and years. When renal function decreases, the disease reaches life threatening (ESRD) stage which requires urgency replacement, in other words, dialysis or transplantation. Mortality can be delayed by these approaches [1].

The effects of intradialytic exercise programs on quality of life of chronic kidney disease (CKD) patients have been analyzed for the last three decades [1]. Quality of life is a consequence; in fact physical inadequacy issues affecting quality of life should be investigated in detail. Results of "Health, Aging and Body Composition Study" [2,3] and "Cardiovascular Health Study" [4] revealed that physical impairment can be detected at early stages of chronic kidney diseases. "Dialysis Morbidity and Mortality Wave 2 Study" [5] showed that poor self-physical performance, exhaustion and fatigue, low physical activity and inadequate nutrition were high among dialysis patients. Low physical performance indicates hospitalization and high mortality risk among dialysis patients [5,6]. Physiotherapists should follow physical function to monitor disease progression and to evaluate exercise programs.

Decrease in physical function is known to increase when combined with dialysis time, metabolic changes accompanying the disease and catabolic effects of dialysis [5,7]. Invasive studies evaluated physical performance by "International Classification of Function, Disability and Health (ICF)" [8]. 6 Minute Walking Test [9] and Timed Sit- to- Stand Test [7,10] are other approaches measuring physical performance. Although Timed Sit- to- Stand Test is realized at different durations and repetitions when compared to 10 sec Timed Sit- to- Stand or times 5-10 sit to stand maneuvers on the elderly living in nursing home 30 sec Timed Sit- to-Stand is more valid. Human Activity Profile (HAP) [8] developed by Fix and Daugton is another tool to evaluate physical perofrmance in ESRD population. The HAP consists of 94 questions. The questions are graded according to oxygen consumption ratio of activities using metabolic equivalence. Thus, HAP involves various tasks from waking up to joggings. "have stopped doing this" response given to any HAP question is considered as a sign of inadequacy in terms of disease progression. Despite perfect validity and utility properties of all three tests, routinely at least two trials are recommended. A wide distribution can be observed between the real scores of individuals in the tests and repetitions can proximate to real score.

In addition to physical measurement of tests, it is also important to evaluate post invasive changes of individuals such as psychometric properties and reliability. Physiotherapists and clinicians should also be aware of the psychometric properties of the tests they will choose to monitor physical performance and capacity.

ESRD is characterized by anemia, decreased cardiac function, changes in skeleton muscle strength and decreased aerobic capacity which affect multiple organ system [8]. Therefore, in hemodialysis patients with ESRD with morphologic, electrophysiological and metabolic changes, weak muscles should be strengthened at early stage [11]. Apart from muscle weakness, low exercise tolerance is also a serious problem in ESRD patients which might result in

increased cardiovascular risk or even sudden death [12]. As a result of the above mentioned problems, physical activity and quality of life are low in these patients [13].

Small sampling size in studies on exercise and quality of life also made evaluations inadequate. Sampling size should be paid attention in study planning. However, in this population, planning of study is difficult as the patients' conditions are critical. Thus, available study results should be tried to derive clinical implications and to be adapted to practice.

Hemodialysis is a time consuming approach which is applied to ESRD patients as one of the basic renal replacement therapy with a frequency of 3-5 h /day and 2-3 times/week [13]. As a result, exercise programs in patients who received hemodialysis are structured as intradialytic and home exercise programs.

Exercise is reported to have a positive impact on anemia, functional capacity, cardiovascular risk factors, dyslipidemia and psychosocial problems in ESRD patients [14]. There is strong evidence that exercise is a part of medical treatment after renal transplantation [15]. It is suggested that similar to exercise, physical activity reduced renal cell cancer risk by decreasing body fat, blood pressure and growth factor concentration in circulation [16].

In patients who receive dialysis, muscle mass decreases as a response to mainly inflammation, physical inactivity and acidemia. Muscle mass can be protected by increasing dialysis frequency and giving nutritional support, regulation of acidemia and stimulation of physical activity [16].

Structural integration and functional continuity of postmitotic tissues such as mitochondrial biogenesis skeleton muscle [17]. Degradation of mitochondrial function is believed to cause decreases which play a role in changes (sarcopenia) in contractile functions appearing due to loss of skeleton muscle mass of DNA damage or age [1]. Muscle mass loss accompanied by mitochondrial dysfunction resembling sarcopenic changes due to age appears in chronic kidney disease [1,2,18]. Resistive exercise trainings are exercise modality reversing sarcopenia and increase mitochondrial function in aged muscle [11]. Yet, the effect of these exercises in increased mitochondrial biogenesis and cellular antioxidant protection were indicated [6].

It was argued that functional capacity, quality of life and survival increased in elder and hemodialysis patients with exercise training [19-21]. Despite the benefits of exercise, hemodialysis patients show low interest and participation to exercise. According to the results based on exercise barriers and facilitators, strategies to develop exercise participation were developed in patients receiving hemodialysis. In this context, Nonayama et al. [22]; evaluated applicability of combined hospital and home-based programs in elderly hemodialysis patients. Participation to hospital exercise programs in hemodialysis patients was found to be high (89%). High compliance was associated by the researchers with the fact that exercise program was formally included in dialysis program; the patient and their families were informed about the importance of exercise; exercise was supervised; exercise program was selected in accordance with the wish and preferences of the patient; a specially adapted equipment was provided for the patients who were unable to exercise in supine and prone position during hemodialysis and that exercise did not require extra time as it was per-

formed during dialysis [23,24]. The reasons for low participation of exercise at home programs were found to be lack of motivation of time constraint [23,25].

Although it is a rare complication, muscle infarction can develop in ESRD and diabetic patients. Since 1965 when reported for the first time, a total of 130 patients were reported. Of these patients, upper extremity involvement was the case of 2 patients. Muscle infarction whose pathogenesis is not exactly known is most common in femur; it appears with local edema, painful muscle mass and sudden pain. In upper extremity, edema and severe pain in posterior humeral lower half is determined. Shoulder and elbow joints are passively open [26]. It is a clinical process that prevents physiotherapy.

On the other hand, similar to low muscle mass, low bone mass is common in end stage renal disease patients, particularly in those who receive hemodialysis. As a result, fragility fracture incidence is high in ESRD patients with low bone mass [27].

Bone mass loss should be monitored in hemodialysis patients as it is asymptomatic and can be easily neglected. Since low bone density will increase fracture risk, if osteopenia is also present, the condition requires more attention. Detection of high risk patients which may develop fracture risk through regular bone mass density measurements can be considered as an effective healthy policy in decreasing mortality and medical spending. Approaches to optimize mineral metabolism, exercise trainings protective from falls and usage of hip protectors in risky patients are appropriate procedures [27,28]. A special attention should be shown to selection of appropriate exercises in patients with fracture risk.

Exercise is a non-pharmacological agent in preventing bone loss. Effective exercise that can load femoral neck was proved to increase bone mass in femur neck [29-31]. Huang et al. [27] emphasized that only regular exercise failed to prevent bone loss and that exercise type and duration that can be effective were also important factors. Exercise intensity is important in protecting involuntary bone loss particularly in ESRD patients. In this context, designing effective exercise programs in patients receiving ESRD and hemodialysis is also important [27]. Prospective studies evaluating the effects of exercise in hemodialysis patients on bone mass density are under way.

Fatigue is reported to be the most common symptom affected clinical status negatively in ESRD patients. Fatigue in patients receiving dialysis is a serious problem as it also indicates increased mortality risk. More importantly, since dialysis patients cannot find necessary energy in pursuing their daily life, increasing quality of life by exercise programs is given priority [32].

Causes of fatigue in dialysis patients can be listed as follows:

i. Physiologic fatigue (decreased aerobic capacity and muscle strength)

ii. Psychological and behavioral fatigue (anxiety, stress, depression, sleeping disorders)

iii. Dialysis-related (dialysis frequency, changes in life styles which also cause physical limitations)

iv. Socio-demographic issues (professional status, social support) [33].

Underlying cause of fatigue is mainly skeleton muscle weakness which is defined as a requirement for treatment by physiotherapy. Floyd et al, Lazaro and Kirshner and other researchers [34,35] explained progressive muscle weakness in ESRD patients who received hemodialysis as myopathy. Furthermore, sensorimotor neuropathy due to uremia and neuromuscular junction defects were also considered as potential outcomes of muscle weakness in this group of patients [36]. Recognition of the underlying mechanism of skeleton muscle weakness enables safe exercise application. Johanson et al. [37] observed no change in electrophysiological characteristics (CMAP) of skeleton muscle after a few exercise sessions in hemodialysis patients with ESRD accompanied by metabolic and electrophysiological changes [38].

Apart from muscle weakness, fatigue can be associated with inflammation, obesity, dialysis modalities, sleep, depression and cytokine levels. However, accurate understanding of these factors can help the clinician in terms of survival and quality of life of dialysis patients [32].

SF-36, which is a quality of life health survey to evaluate fatique in clinic, is practical. The SF-36 vitality scale has good psychometric properties and internal consistency reliability in people with ESRD [13]. A higher score reflects more vitality and less fatigue. Patients were also asked about the number of good waking hours they had (In the past 4 week, on an average day, how many good working hours did you have?).

Studies on patients with myopathic changes showed oxygen deficiency in the muscles and decrease in VO_2 max. Myopathy related to uremia inflictions and lessening of oxidative enzyme activities cause fibrillary atrophy and capillary density loss in muscles [39,40].

In addition to proximal muscle weakness, distal muscle involvement was also reported in ESRD patients receiving hemodialysis. On the other hand, McElrey et al. [41] reported varying muscles weaknesses in these patients. Therefore, physiotherapists should make a complete muscle evaluation in all proximal and distal muscles and should also evaluate muscle strengthening resistance exercise skills and tolerance in the patients due to interaction of ESRD and hemodialysis with multiple organ systems, cardiovascular and nutrition status and comorbid interactions. It should be remembered that weak skeleton muscles together with Vitamin D anomalies and inadequate glycotic mechanism.

A specific version of muscle loss in ESRD patients is termed as “protein energy wasting” (PEW). PEW is characterized by increased muscle protein catabolism related to protein synthesis. This condition is also related with metabolic disorder, hormonal anomalies and anomalies arising in time in muscle formation and has a strong mortality risk for ESRD patients [42]. For this reason, treatment of PEW or protection is important in maintenance of ESRD patients.

Exercise is one of protective approaches that reduce muscle protein loss or or muscle function muscle function. Exercise has a direct stimulating effect on synthesizing speed of muscle proteins ad also disturbs the balance between synthesis and destruction in favor of destruction [43-45]. Protective effects of regular physical activity or exercise have been determined in previous studies. Secondary gains of exercise include cardiovascular pro-

tection and improvement of some sudden cardiac death indicators in randomized controlled studies [46].

In ESRD patients treated with dialysis, peak oxygen uptake (VO_2 peak) is low. This decrease is affected from multiple factors including anemia, cardiac dysfunction (reduced contractility, increased anterior ad posterior load); vascular dysfunction (limited reach of cardiac output to skeleton muscle); skeleton muscle anomalies (decreased fiber type, capillary density, mitochondrial density and increased diffusion distance) and/or metabolic anomalies and autonomic dysfunction. The only study in the literature examining peak VO_2 in hemodialysis patients is Moore et al.'s study. Moore et al. [47] found that cardiac output at rest and a-VO_2 difference were similar; both values decreased in peak exercise which resulted in changed oxygen provision to working muscles. In chronic kidney patients who underwent renal replacement, transplantation improved oxygen consumption; this parameter remained unchanged with hemodialysis. VO_2 changes after transplantation develops in relation to cardiac output due to peak heart rate rather than central mechanisms (oxygen distribution) and peak stroke volume. Thus, in contrast to hemodialysis patients with limited peak heart rate and exercise capacity, cardiovascular fitness is improved following the transplantation [48]. In fact, aerobic exercises are required for the combination of exercise with routine treatment after kidney transplantation, strengthening exercises to minimize sarcopenia and osteoporosis, cardiovascular disease risks and to reduce body weight [15].

Future studies should analyze the effects of physical activity on graft in kidney donors in evidence-based manner (15).

When ESRD patients are evaluated by subjective feedbacks, peak oxygen consumption, physical performance and muscle strength tests, their physical performances are found to be limited. One third of hemodialysis patients are unable to perform their normal daily life activities without getting help. Physical functionality is the major determinant of quality of life. As a result, attempts to improve functionality in these patients also have potential to improve quality of life [14]. Physical function and quality of life in patients receiving hemodialysis can be evaluated by 2 MWT, KDQoL, PCS. In addition, IIRS should be used to monitor the effects of exercise on general life style. Evaluation of the relationship between IIRS scores and attendance to exercise can be guide in clinic [17].

Physical fitness, behavioral change and quality of life link with healthy were examined in a study [1]. Exercise program consisted of 12-week low-modarete intensity precondition exercises during dialysis for which exercise consultancy was provided; strengthening training and bisergo exercise before dialysis. Exercise was provided 2-3 times a week as 30 min training session within the first 2 hours of dialysis. Exercise intensity was personalized according to Borg Scale in patients. Motivational support was offered in addition to exercise consultancy to reduce dropout rate.

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Physical fitness components were achieved by exercise capacity (VO_2 peak), reaction time, manual dexterity and lower extremity muscle strength (sit-to-stand test). MOS Short-Form General Health Survey (RAND-36) was used to evaluate general health quality of life of patients. In conclusion, physical and psychological benefits of exercise program were indicated. Vitality, general health perception and health behavior change, which are three elements of quality of life and lower extremity muscle strength significantly changed within the scope of physical benefits. Particularly patients' belief that health behaviors can change was strengthened [1].

Due to strong connection between HRQoL results and morbidity and mortality in ESRD patients, it is important to understand mostly affected quality of life elements in ESRD patients and to personally monitor the patients. Brennen et al. [49] found that in ESRD patients, physical issues were affected the most and the underlying cause of these effects were found to be nutrition biomarkers and Hct levels.

3. Exercise approaches in the patients on hemodialysis

Johansen et al. [50] sought to comprehend whether hemodialysis patients differ from healthy sedentary persons. To ascertain whether or not they were as active, they researched physical activity levels and clinical status. It was determined that hemodialysis patients were less active than healthy sedentary persons. The difference between the two increased in paralel to age. It was indicated that anemia and muscular weakness were key factors in diminishing functional capacity.

Figure 1. Exercise apparatus for hemodialysis patients

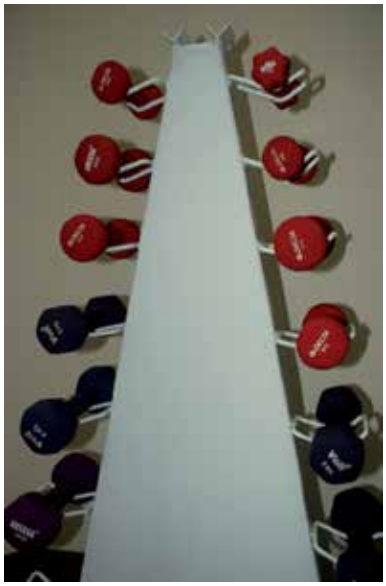

Figure 2. Dumbles sets for strengthening exercise

Figure 3. Dumbles for progressive resistance exercise

3.1. Intradialytic versus home based exercise training

Koh et al. examined the effects of supervised intradialytic exercise and non-supervised home-based exercise trainings on physical function and arterial stiffness. A total of 72 hemodialysis patients were randomized according to receiving intradialytic exercise training, home-based exercise training and standard treatment. In this controlled clinical study, hemodialysis patients were given bicycle ergometer while home-based exercise group was given walking program 3 days a week. As exercise intensity, the patients were expected to feel

fatigue corresponding to 12-13 intervals according to 6-20 Borg scale. Primary measurements were perceived as 6 MWD distance and aortic pulse wave (PWV) while secondary measurements consisted of augmentation index, peripheral and central blood pressures, physical activity and self- health evaluations. The evaluations were first conducted at 3. and 6. months.

"Active Australia Questionnaire" was used within the scope of physical activity and self-health evaluation [51,52]. Each patient was asked to give answers including any training they performed the week before. The survey evaluated frequency, intensity and duration of randomized and structured physical activity. Total duration for each activity was multiplied by 3.5 for light activity; by 4 for moderate level of activity and by 7 for intense activity as intensity value. Weekly physical activity of the participant was calculated as $MET.min^{-1}$ by this formula.

"Medical Outcome Short-Form 36 (SF 36) Health Survey was used for health self-evaluation. Home-based exercise program in hemodialysis patients was found to be cost effective considering intense dialysis units. This result can guide development of exercise guide books. Future studies can analyze the effects of exercise on arterial stiffness in patients with cardiovascular morbidity marker [51].

3.1.1. Low intensity intradialytic exercises

Moderate level strengthening exercises is known to improve physical performance, nutrition level and quality of life in chronic kidney patients and hemodialysis patients. On the other hand, there is no evidence of the effect of low level strengthening trainings.

Chen et al. [53] randomized 50 patients with a mean age of 69 ± 13 years who received long term dialysis (3.7 ± 4.2 years) and divided the patients into low intensity strengthening exercise and stretching exercises (control group) groups. The study aimed to evaluate physical performance using "Short Physical Performance Battery (SPPB) Score" if the patients were fit after 24 sessions. Another aim of the study was to evaluate body composition, lower body strength and quality of life. The measurements were repeated at 36. session (post) and 48.session (final) apart from 24.session (mid).

Exercise sessions took place twice weekly during the second hour of haemodialysis for a total of 48 exercise sessions. Supervised sessions began with a 5-min warm-up and ended with a 5-min cool-down. Participants in the strength training group exercised their lower body only using ankle weights progressively in half-pound increments from 0.5 to 20 lbs (TKO, Houston, TX). Exercises included seated right/left knee extension with dorsi/plantar flexion (quadriceps muscle), seated leg curl with both legs keeping the heels pressed firmly against a chair while rolling the legs in and out (hamstrings), semirecumbent right/left inner leg raises (hip adductors), and semirecumbent dorsi/plantar flexion with straight legs (tibialis anterior, gastrocnemius and soleus muscles). Participants did a seated pelvic tilt (abdominal and lower back muscles) without using free weights. Two sets of eight repetitions were performed for each exercise with a 1.5s concentric phase, a 0.5s pause in the lifted position and a 3-s eccentric phase; assuring 1–2 min rest between sets. Exercise intensity was assessed by

the rate of perceived exertion (RPE) modified OMNI Scale [54], with a target moderate intensity of 6 (somewhat hard) out of 10 (extremely hard), equivalent to 60% of a one-repetition maximum [55]. The first eight exercise sessions were done with none or little weight and progressed based on participants' ability to complete two sets of eight repetitions with proper form and a RPE rating of 2–4 (easy to somewhat easy).

Attention-control participants did stretching exercises with light resistance bands (TKO, Houston, TX), using right/left dorsi/plantar ankle flexion, right/left ankle rotation, right/left calf stretch, right/left hamstring stretch and right/left inner thigh stretch. These exercises were done in the semi recumbent position, held for 20–30 s and repeated twice. All participants were asked to continue their usual activities, including physical activity and diet, and to report any changes in health status or medications.

As a result, progressive low intensity strengthening training was found to be an effective and safe approach in maintenance of hemodialysis patients. Majority of the study participants were chronic patients and elderly and in fact physically inadequate. Physical inadequacy was indicated with low SPPB scores "meaning that chi score is lower than 7". It was found that there was a strong correlation between low SPPB scores and old age. SPPB score change in the study is directly associated with knee extension strength which is strongly recommended to be improved by strength trainings. It is understood from this study that intradialytic low intensity strengthening trainings might reverse functional losses, which are also known as physical inadequacy and disability of hemodialysis patients and might protect their acquisitions. Future studies might concentrate on generalizability of strengthening exercises on hemodialysis patients and routine programming of dialysis units.

Similarly, Johansen et al. [50] obtained a significant increase in knee extension strength. They found that fat mass significantly increased while there was no significant change in non-fat body mass analyzed by Dual-Energy X-ray Absorbsiometry (DEXA) and physical performance. The two studies differ in terms of exercise durations, comorbidity and presence of more disabled patients. In fact since low intensity exercise group consisting of patients in a worse condition can show higher change when compared to the beginning, they seem to have made benefitted from exercise at a higher extent.

3.2. Flexibility and strengthening exercises

Based on the definitions of Painter et al., Nonoyama et al. concentrated on flexibility and muscle strength with a 12-week exercise program and cardiovascular fitness and functional capacity [56]. Patients diagnosed with ESRD, who were receiving > 6 month and 3 times / week hemodialysis, above the age of 55 who were ambulated with or without help and did not recently receive a structure exercise program were selected. Exercise program was prescribed by a physiotherapist and was personalized according to the skills, exercise preferences and individual aims of the patients. The patients were given 5 training sessions [57].

In flexibility and strengthening exercises, exercise intensity was determined according to definition of the exercises by the patient as painless and "slightly difficult" according to rated perceived exertion (RPE). Upper and lower extremity strengthening exercises were com-

pleted using exercise bands and 0.5-2 lb dumbles in such a way not to exceed 6 different exercises at each session. Each exercise was started with 10 repetitions; one set was increased to 15 as the patient tolerated and then progressed to 2 or 3 sets with 15 repetitions. Resistance and dumbles was increased by 0.5- 2 lb when this frequency was reached.

To provide cardiovascular fitness by this program, exercise intensity was based on patients' level from "mild" to "slightly difficult" according to RPE during pedaling; patients ability to speak without difficulty during exercise; patients level at training heart rate according to heart rate reserve for very low exercise intensity; blood pressure values, presence of other symptoms and patient feedbacks [58,59]. Workload was increased by 1-5 watts if the patients managed adequate duration after 20-30 minutes aerobic exercise [57].

The patients were analyzed by ESRD-modified version of Charlson Index for Comorbidity [60]. Initial and 12.week Duke Activity Status Index (DASI) [61] was evaluated by 2 Min Walking Test (2 MWT) [62], Timed-Up-and-Go Test (TUG) [63], Illness Intrusiveness Ratings Scale (IRRS) [64] and The Kidney Disease Quality of Life Questionnaire (KDQoL) [65].

The study proved the applicability of exercise programs in hemodialysis patients with over the age of 55 with low functional level. Randomized studies with larger sampling should analyze exercise effectiveness during hemodialysis.

3.3. Resistance training

Balakrishan et al.[66]. analyzed aerobic effects of 12-week high intensity training in randomized controlled chronic kidney disease stage 3 and 4 patients with low protein diet (approximately 0.6 g/kg/day) to examine the effect of resistance training on mtDNA copy number and to identify combination with skeleton muscle phenotype (measurement of muscle mass and strength).

Resistance Exercise Training Group

Participants exercised three times per week under supervision. Each session lasted approximately 45 minutes and included the following: 5 minutes warm-up, 35 minutes resistance training on chest and leg press, M.latissimus pull-down, knee extension, and flexion pneumatic resistance training machines (Keiser Sports Health Equipment Inc., Fresno, CA), and 5 minutes cool-down. Participants performed three sets of eight repetitions on each machine per session. Training intensity was targeted at 80% of one repetition maximum (1RM) and progressively increased per participants' self-perceived level of exertion using a Rating of Perceived Exertion Scale [54]. Cool-down included five to eight upper and lower body-stretching and flexibility exercises.

Attention-Control Group

Participants met and performed the same stretching and flexibility exercises as those used during cool-down in the resistance exercise training group.

In conclusion it was found that oxidative metabolic capacity increased in uremic skeleton muscle. There was no relationship between mitochondrial content and insulin resistance.

The factors affecting anabolism such as energy intake and IGF^{-1} concentrations in circulation were found to be positively correlated with the changes in mtDNA copy number. Therefore, mechanisms of anabolic and genomic factors on mitochondrial functions should be analyzed and well understood [67].

3.3.1. Resistance exercise protocol example Jie Dong,et al. [68]

Subjects randomized to receive exercise (NS+EX) performed the prescribed resistance exercise, under supervision of study personnel, within 30 minutes prior to each dialysis session and ingestion of at least one can of Nepro®. A pneumatic leg press machine (Keiser®, Fresno, CA) was used, mainly focused at exercising the quadriceps, hamstring, and gluteus muscles. Subjects sat on the leg press machine with their feet placed on a platform, their legs at a 90 degree angle, and were instructed to push the platform forward, leaving their knees slightly bent. For the first month, exercise was set at approximately 70% of the subject's 1-RM established at the baseline control visits. An initial leg press weight approximately equal to the participant's body weight was used. Additional weight (~25-50 lb) was added at each repetition until the participant could no longer push the platform. Once the 1-RM was determined, 70% of this weight was used for participants in the NS+EX arm performing 3 sets of 12 repetitions prior to each dialysis session. At the month 3 and month 6 assessments, 1-RM was repeated in all subjects to evaluate progress and determine a new 1-RM for those in the NS+EX arm.

4. The effects of aerobic and resistance exercises on lipid profiles and inflammation level

In ESRD patients, exercise results in entrance of higher amounts of uremic toxins into vascular compartment by increasing muscle blood flow. Afshar et al. [14] investigated the effects of intradialytic aerobic exercise and resistance training on lipid profile and inflammation status in hemodialysis patients.

The training program consisted of a 5-min warm up, a 10–30min aerobic or resistance training and a 5 min cool down period during the first 2 h of each dialysis session in recumbent position, within 8 weeks. According to primary results of Baecke Questionnaire on physical activity which was filled for all participants at baseline, aerobic training participants should perform stationary cycling at an intensity of 12–16 out of 20 at the rate of perceived exertion of Borg scale so that intensity involved 65–85% of an individual's maximal capacity, a level at which cardiovascular health can be obtained.

Resistance exercise training of the lower extremities was performed in three sets and under the supervision of a physician by applying ankle weights for knee extension-flexion and hip abduction-flexion at an intensity of 15–17 out of 20 at the RPE scale. Starting weights were determined from a three-repetition maximum (3RM) using ankle weights that can be adjusted in 0.5^{-1} kg/week increments. A 3RM is the maximum weight that can be lifted three times

with a proper technique. Training started at approximately 60% of 3RM for two sets of eight repetitions and was increased to three sets as tolerated. When patients could perform three sets successfully, the weight was increased. Blood pressure and heart rate of the participants were monitored each 5 min during exercise. Fasting venous blood samples were obtained from patients before mid-week dialysis session in order to measure serum urea, creatinine, albumin, hemoglobin, lipid levels [low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride], and CRP (turbidometric technique with normal range below 10 mg/L), at baseline and 8 weeks.

In this study, 8-week aerobic and resistance training had a significant effect on chronic inflammation; hs-CRP levels increased by 83.4% or 67.9% by aerobic exercise when compared to resistance training. These two approaches are not effective on lipid profiles. Intradialytic aerobic exercise is accompanied by triglyceride decrease and HDL elevation; it improved lipid profile due to weight loss. However, 8 week is a short period in terms of lipid effect. Besides, secondary hyperparathyroidism which inhibits type, nutrition status and more complicately lipolytic activity should not be ignored. The fact that number of male patients in whom lipid change was observed was low affected the result.

5. Exercise as an anabolic intervention

Although the effectiveness of resistance training as an anabolic intervention have been shown in healthy and chronic patients, long term improvement results on muscle mass markers in chronic hemodialysis patient have not been shown. Follow-up studies showed that peak torque value increased in response of dominant leg extensions to exercise in type I and II muscle fiber hypertrophy and hemodialysis patients.

Johansen et al. [69] carried out a controlled study consisting of 12-week modarate intensity lower extremity resistance exercise training and found no change with DEXA; however they found that quadriceps muscle area measured by magnetic resonance imaging (MRI) have improved. This change accompanies increases in body weight and fat mass. In another controlled study, Cheema et al. [70] found no improvement in computerized tomograpgy (CT) scan in skeleton muscle amount with 12-week high intensity progressive resistance training routinely applied during hemodialysis. Similarly, the follow-up after 24 weeks found no additional benefit. Kopple et al. [71] examined the effects of different exercise training (strength, endurance and combination of both) in RNA levels in muscle genes. Although there was no significant difference in non-fat body mass (LBM) at the end of 6 month individual exercises, it was observed that exercise training in hemodialysis patients increased m RNA changes in skeleton muscle and muscle insulin-like growth factor-1 (IGF-I) protein. This factor is important as it accelerates protein anabolism.

On the other hand, although the effects of resistance exercise on muscle quantity and quality in hemodialysis patients have been shown, strength and physical function cannot be main-

tained in these patients. Although the causes are not clear, lack of nutritional support particularly during hemodialysis is held responsible.

6. Do muscle contraction types affect differently?

Koudi et al. [40] reported increase in proportion of type I fibers and muscle fiber hypertrophy following a 6-month low intensity resistance exercise program in ESRD patients receiving hemodialysis. Isometric contractions in contracted muscle position are more effective that dynamic training in maintenance of type II fibers [72,73]. However, this issue could not be customized in ESRD patients. Although eccentric muscle contractions have a protective effect on muscle with progressive weakness, the effects of eccentric contraction in muscle with myopathic changes could not be determined.

Reduced muscle mass and metabolic deficiencies of anaerobic metabolism require specific exercises. In this manner, we can discuss low intensity resistance exercises.

7. Assessment of isometric muscle strength

In the literature, grip strength studies are related mostly dominant or non-dominant hand strength in the healthy population [74]. For Yurdalan et al. study [75], the arm without fistula was considered dominant. In their study, they also measured the non-dominant arms at elbow flexion and extension. The results in elbow flexion were lower than those of extension. Though they didn't encounter a statistical difference, this result indicated that force distribution occurred from powerful muscles to weaken muscles. The arm with fistula was checked also against the values of the arm without fistula, and all cases were dramatically lower. This may be evidence of the nonuse of the arm with fistula in their daily living activities, which have been outlined in the literature.

8. Evaluation of functional capacity

Peak oxygen consumption (VO_2 peak) is the most commonly used parameter to evaluate functional capacity in ESRD patients. In addition, 6 MWT is one of clinical tools to determine functional capacity in almost all chronic diseases. This is a submaximal test, low-cost and easily applied. In addition, it is an alternative VO_2 peak determinant in patients who cannot tolerate ergometric tests.

In Yurdalan et al. study [75], the limited walking distance can be due to cardiopulmonary and musculoskeletal origins. The result exemplifies the lower functional capacity of the hemodialysis cases.

6 MWT was used to evaluate functional capacity in chronic kidney patients however was not adequately investigated as a mortality factor [76-78]. In the study of Kohl et al. [76]; walked distance was found as an independent predictor in ESRD patients in terms of mortality. Each 100 m walked was approximately 5.3% protective factor in relation to life expect-

ancy and it was at the same time found to be correlated with peak oxygen consumption. For this reason, 6MWT can be used as a strategy to define progression and aggravation of disease. In patients with terminal renal insufficiency it can be used to determine death risk. In other words, it is recommended to be used during treatment programs and follow-ups of hemodialysis patients.

Please visit http://cin2011.uninet.edu/es/trabajos/346.html. You will find ppt file titled " Evaluation of functional capacity in patients on hemodialysis,what is new?

9. Assessment of health related fitness: Using eurofit test battery

There are many exercise training studies in patients with end-stage renal disease on hemodialysis, but few, if any, health-related fitness assessment in the literature. For this reason, Yurdalan et al. hypothesize the suitability of Eurofit for adults in this group of patients and sought to evaluate the hemodialysis patients relevant to health-related physical fitness using Eurofit Test Battery, which tests all approved, valid, and reliable measures of these components for adults [79,80].

From the 25 end-stage renal disease patients in the maintenance hemodialysis program at the Renal Unit, 18 without exclusion criteria *(pre-dialysis potassium > 5.5 mmol l, Hb< 10 g/dL, unstable hypertension, congestive heart failure (grade > ıı according to NYHA),*cardiac arhythmias *(< ıı ıı according to Lown)*, recent myocardial infarction or unstable angina, persistent hyperkalemia before dialysis, peripheral vascular disease,arthritic or orthopedic problems limiting functional capacity) and 22 aged-matched healthy subjects volunteered to participate in the study.The hemodialysis patients had all been undergoing regular HD,three sessions a week, four hours each session.

Aerobic Fitness

A six-minute walking test (6MWT) was used in the determination of aerobic fitness in place of 2 km walking test, ergometer test, or multistage shuttle run test in original Eurofit Battery. Because 6MWT is more suitable for chronic patient groups, aerobic fitness was tested within this protocol according to American Thorasic Society (ATS) 6 MWT statement (81).Blood pressure (systolic/diastolic blood pressures (SBP/DBP) and heart rate (HR) were measured before and after test. The perception of exercise intensity was assessed by Original Borg Scale. At the end of test, the distance walked was recorded. The following formula was used determine VO_2 max($ml.min^{-1}.kg^{-1}$):

70.2xdistance(m)-0.191xage(year)-0.07xweight(kg)+0.09xheight(cm)0.26xrpp($x10^{-3}$)+2.45

Where RPP is the rate-pressure product (HRxSBP).

Musculoskeletal Fitness

The musculoskeletal fitnes of the patients was assessed by the components of muscle strength and endurance and flexibility of Eurofit Test Battery for Adults.

The grip strength for the hand muscle strength was performed with JAMAR dynamometer, once with each elbow in flexion,once with each elbow extension. Each measurement was repeated twice and the higher score was recorded.

The vertical jump test was used in order to measure the lower extremity muscle strength. The subject jumped as high as possible at a 20 cm distance from the wall and the distance he/she jumped was measured.

Side-bending test was used for evaluating the spinal flexibility. The patients stood upright against a wall on two paralel lines at right angles to the wall and 15 cm apart. The patients held their arms straight against the sides of their body. The position of the middle finger on each side was marked with a horizontal line on the lateral thigh.The subject was then asked to bend sideways as far as possible while maintaining contact between the back and the wall.The distance between the first and last position of the middle finger was recorded.

Motor Fitness

In the assessment of motor fitness, the single leg balance test was used with eyes open and closed. At the end of the test total time was recorded.

Anthropometry (Body Composition)

In order to assess body composition, height, body weight, body mass index, skinfold thickness, and percentage of body fat (PBF) were measured. Body mass index (BMI)was calculated as body weight in kg divided by square of height in meters (kg/m^2).

The skin fold thickness measurements were carried out in Holtain Calipers with 0.2 mm spaces, and the measurements have been applied on the right side of the body. Measurement sites were the biceps, triceps, subscapular, suprailiac, abdominal, and thigh. Four sites (biceps, triceps, subscapular, suprailiac)are measured to calculate the percentage of body fat.

In conclusion, two results were obtained from this research. First, it was seen that health-related physical fitness in hemodialysis patients resulted in a significant decrease in all aspects. Thus, limited health-related physical fitness should be taken into consideration during daily hemodialysis treatment, and must be improved regular fitness program. Second, the Eurofit Test Battery may be useful instrument to ascertain the spesific aspects related to hemodialysis cases in terms of health-related fitness; a well- planned exercise program that was tailored to hemodialysis patients' needs can be set through the Eurofit Test Battery. On the other hand, the Eurofit Test Battery was not employed in this group previously, and its novelty itself assured total originality in the process.

10. Accelerometric evaluation for physical activity

Accelerometer based technology is mainly used to measure physical activity. Accelerometer can objectively predict exercise frequency, duration and intensity; however its validity and reliability is controversial.

Although the study of Sloane et al. [82] did not include hemodialysis patients, it can be used to follow-up home-based exercise programs. Knowledge of energy consumption of modarate and high intensity activity can ensure more comprehensive evaluation of exercise program in terms of oxygen consumption.

11. Conclusion

The role of physiotherapist and physiotherapy and effectiveness of exercise programs is clear in hemodialysis patients. However, it is imperative to select correct patients and to re-evaluate their suitability to exercise at each session with a multidisciplinary team. Although patients with lower capacity make more benefit from due to the nature of exercise training, we should make sure that exercise is not contraindicated in patients with poor clinic. In fact exercise is an approach that is harmful for homeostasis; it might not create sequelae in healthy or other clinical patients. On the other hand, in renal patients with difficult clinical compensation internally it might cause irreversible damage.

Addition to above statement, positive impact of medical treatment on survival in hemodialysis patients helps long term maintenance of physiotherapy with the treatment and protection of physical gains. Follow up of patients during hemodialysis and through programs increasing clinical effectiveness by home-based programs can only be realized by patient follow-up record and electronic or face-to-face feedback from the patient and families the fact that the patients were young adults might require diversification or intensification of programs of the patients by the physiotherapist as much as clinical status allows in case they need more active life style in terms of work and social status.

The literature contains a growing number of studies analyzing different renal clinical problems. However, exercise evaluation and training protocols in hemodialysis patients could not be adequately defined. The research should give priority to physiotherapy approaches to address physical and functional improvement of hemodialysis patients to pursue their daily lives which can guide particularly clinicians. In addition, the fact that exercise approaches clarify effect mechanisms in parallel to pathophysiology will contribute to deciding on the need for exercise, preparing the content of exercise and clinical follow-up of patients doing exercise by the health professionals in nephrology particularly to physiotherapists.

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Edited by Hiromichi Suzuki

In this special issue, reviews of various aspects of HD therapy were submitted from both groups. In particular, various methods for vascular access were discussed by many contributors. From these reviews, the reader will gain precious hints and suggestions in every day practice. Previously, many textbooks on "Hemodialysis" have been published but they were written by only a couple of authors. However, in this special issue several authors discussed similar subjects, producing precious and fruitful suggestions. This will be very helpful for readers to understand and carry out HD practice. I hope this special issue will contain useful information for those who are involved in HD therapy.

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