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Diabetes Food Plan

Edited by Viduranga Waisundara

DIABETES FOOD PLAN

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http://dx.doi.org/10.5772/intechopen.68335
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Notice

First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Diabetes Food Plan
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p. cm.

Print ISBN 978-1-78923-274-5

Online ISBN 978-1-78923-275-2

eBook (PDF) ISBN 978-1-83881-307-9

Meet the editor

Dr. Viduranga Waisundara obtained her PhD degree in Food Science and Technology from the Department of Chemistry, National University of Singapore, in 2010. She was a lecturer at Temasek Polytechnic, Singapore, from July 2009 to March 2013. Following this, she relocated to her motherland Sri Lanka and spearheaded the Functional Food Product Development Project at the National Institute of Fundamental Studies from April 2013 to October 2016. She is currently a senior lecturer on a temporary basis, at the Department of Food Technology, Faculty of Technology, Rajarata University of Sri Lanka. Dr. Waisundara is a prolific writer with many research publications and articles in newspapers and magazines to her name. She is also the current Global Harmonization Initiative (GHI) Ambassador of Sri Lanka.

Contents

Preface

Diabetes is a disease that has caused immense economic burden across both the developed and developing countries as a whole. There is no permanent cure in sight, and the prevalence of the disease appears to be increasing beyond control. Novel means of control have been recommended from time to time, but the measures seem to fail with new forms and figures of the disease surfacing just as frequently. Dietary control appears to be the more effective means nevertheless, although a multitude of other factors have been highlighted through research as being the causes.

This book primarily focuses on three aspects: (1) dietary interventions for diabetes, (2) diabetes and oxidative stress, and (3) updates and novel approaches of combating diabetes. There have been many publications that have appeared recently on diabetes and dietary interventions. However, it is hoped that this book serves as an update in highlighting gaps and voids as well as providing insights into novel developments of the disease.

I would like to extend my most sincere gratitude to the authors who have kindly contributed chapters to this book, without whom this project would not have been a success. Also, my heartfelt thanks go to IntechOpen Publishing with whom I have been working for quite a number of book projects of similar nature. Last but not least, my appreciation goes to Ms. Kristina Kardum, the Publishing Process Manager assigned to this book, who has rendered her utmost support in putting the material together.

In conclusion, it is hoped that this book will be of value to both scientific and nonscientific communities in making informed choices about diabetes and possible dietary interventions in preventing its occurrence.

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Section 1

Dietary Interventions for Diabetes

Chapter 1

Introductory Chapter: The Need for Dietary Interventions for Diabetes

Viduranga Yashasvi Waisundara

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72897

1. Introduction

Noncommunicable diseases pose a significant challenge to most of the high-income and low-income countries, with growing numbers of people experiencing the health and economic burden of one or more chronic disease conditions. As such, the incidence of diabetes has been on the rise worldwide. The disease may be associated with the poor quality of life and the risk of developing long-term comorbidities and a higher standard rate of mortality. Health-care professionals are burdened with the task of motivating patients to follow appropriate dietary and exercise guidelines as well as to take insulin injections to improve the regulation of diabetes, and thereby prevent the occurrence of diabetic micro- and macrovascular complications. At present, various interventions are being discussed on an authoritative and regimental level, such as diet, exercise, and even environmental changes.

The more frequently discussed intervention of all is dietary change. Food habits have been shown to be related to the development and management of diabetes—both types 1 and 2, especially through means of influencing glycemic control and insulin resistance. Dietary patterns, rather than individual nutrients, such as the Mediterranean diet, Western diets, and traditional diets, have recently received a great deal of attention in assessing the association between diet and health. In general, to improve glycemic control, a diet rich in fiber and low in saturated fat, sugar, and salt is recommended. Based on considerable medical literature and clinical practice, it has actually been shown that the prognosis of individuals with type 2 diabetes, in particular, is improved with better diet and resulting weight loss. For instance, according to the systematic review by Aguiar et al. [1], it was found that interventions of multicomponent lifestyle involving diet, aerobic exercise, and resistant training were sufficient in inducing modest weight losses and imparting minor improvements in glycemic control, along with the improvements in aerobic fitness and dietary intake.

2. Dietary and behavioral changes

Medical nutrition therapy is an important intervention of diabetes care. This is also of significant when it comes to diabetes self-management, education, and training. When it comes to nutrition, the first priority for individuals requiring insulin therapy is to change their lifestyle so that an insulin regimen is incorporated into their preferred diet and exercise routines.

Despite its importance, there is relatively little evidence on how dietary behavior changes after diagnosis. On average, weight loss after diagnosis is fairly limited. At the same time, there is considerable heterogeneity in this aspect, with some individuals losing more weight and having better clinical outcomes than others. Also, since food products are consumed in combination and nutrients metabolized altogether, it might be more difficult to estimate the associations between individual foods or nutrients and disease incidence compared with the collective approach. Despite these shortcomings of associating diet and diabetes, there have been several aspects, which have been conversed among scientists in relation to prevent the incidence and propagation of the disease.

Lifestyle modifications are an integral part of diabetes management and are generally recommended interventions for most diabetic patients. In fact, it is strongly believed that the treatment of diabetes should start with nonpharmacological therapies such as lifestyle interventions. It is construed as a result of an individual motivation and knowledge, based on personal initiative and responsibility. This focus, however, tends to neglect the relevance of contextual factors. Additionally, for most systematic and scientific studies in this aspect, diabetes duration is an imprecise entity and some individuals participating in such evaluations may have a prolonged period of unrecognized hyperglycemia preceding a diagnosis. For instance, self-management involves complex interactions among people diagnosed with diabetes, involving networks and the broader community [2]. As such, it is recognized that health-promoting initiatives seldom reach those who need them the most.

Out of all diets recommended for diabetes, plant-based diets have received the greatest amount of attention for their use in a variety of diseases such as the management of cancer, cardiovascular disease, obesity, hypertension, and type 2 diabetes mellitus [3, 4]. A plant-based diet is specifically defined as "a regimen that encourages whole, plant-based foods and discourages meats, dairy products and eggs as well as all refined and processed foods" [5]. Inadequate consumption of fruits and vegetables in particular, is estimated to contribute to 5% of excess mortality globally [6]. A recent prospective study in the EPIC cohort indicated that consuming a higher number of different items within the fruit (0–58) and/or vegetable (0–59) food groups was associated with a reduced risk of type 2 diabetes [7]. There are various types of plant-based diets being followed throughout the world, out of which the Mediterranean diet has received much attention recently. This diet is discussed in detail in the next section.

3. The Mediterranean diet as a plausible intervention for preventing the incidence of diabetes

The Mediterranean diet is the most widely discussed and historically significant plant-based diets of all. The Mediterranean diet is a homogeneous and straightforward construct having

its roots in southern European eating patterns. The typical Mediterranean diet, which was first postulated by Ancel Keys in the 1960s [8], is characterized by high intakes of mono-unsaturated fatty acids, vegetables and fruits, plant proteins, whole grains, fish and low-fat dairy products, moderate alcohol (red wine) intake, and low red meat consumption [9]. Following this dietary consumption has demonstrated a reduced risk of mortality associated with mostly neurodegenerative diseases [9, 10]. According to the systematic review by Schwingshackl et al. [9], it was revealed that a significant association between adherence to dietary patterns exhibiting specific Mediterranean diet characteristics and decreased risk of type 2 diabetes. With respect to potential mechanisms of action, there appears to be a causal link between oxidative stress, inflammation, endothelial dysfunction, and diabetes when following this dietary pattern [11]. The Mediterranean diet has also shown a durable effect on circulating levels of C-reactive protein (CRP) and adiponectin in subjects with newly diagnosed type 2 diabetes [12]—an aspect, which is directly related to anti-inflammatory activities.

An observational study aimed to explore a possible relationship between the incidence of gestational diabetes mellitus and the Mediterranean diet pattern of eating was conducted by Karamanos et al. [13]. In this study, in 10 Mediterranean countries, 1076 consecutive pregnant women underwent a 75-g oral glucose tolerance test (OGTT) at 24–32 weeks of gestation, interpreted both by the American Diabetes Association (ADA) 2010 and the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) 2012 criteria. Adherence to a Mediterranean dietary pattern of eating was found to be associated with lower incidence of gestational diabetes and better degree of glucose tolerance, even in women without gestational diabetes.

4. Dietary diversity

Many national and international policies and authorities have recognized the importance of a healthy balanced diet, and numerous dietary guidelines have been issued to emphasize the critical role of the consumption of a diet widely varies to include different types of food products coming from different food groups [6, 14–18]. Although a greater intake of different food subtypes (collectively referred as minor food groups) from each major food group is crucial for nutritional adequacy, indices of diet quality rarely include a measure of dietary diversity and none address variety within food groups other than for fruits and vegetables [19–22].

More recently, analysis in a multiethnic cohort concluded that a higher number of different food items (between 0 and 120) consumed at least twice a week was not associated with incident type 2 diabetes [23]. It is possible that a diet comprising of all five major food groups could still depend on the consumption of a comparatively slender range of foods within each group [19]. In this sense, it would be best if a higher overall diversity is maintained at the major food group consumption level, but with less variation in terms of different subtypes of foods. It is suggested in the review by Conklin et al. [19], that despite common advice recommended to consume a varied diet [6, 15, 18], it was not obvious whether studies have investigated how the number of different food groups and different subtypes within each food group included in a diet are associated with the risk of contracting diabetes. Nevertheless, the findings by Conklin et al. [19] supported many of the current public health recommendations, which encourage the consumption of all major food groups and also other different types of

fruits, vegetables, and dairy products as part of a regular balanced diet. However, it has to be borne in mind that the additional costs of greater diversity require a comprehensive food pricing strategy as well [19].

5. The Paleolithic diet

The Paleolithic diet is another regimen, which has been recently discussed as a means of obtaining weight loss and control of glycemic levels. This diet, in particular, has been shown to be more satiating per calorie compared to the diabetes diet [24, 25].

General information provided on the diabetes diet aims at providing meals with even distributions of increased portions of vegetables, root vegetables, dietary fiber, wholegrain bread, and other whole grain cereal products, fruits and berries, and less total fat—in particular, unsaturated fats [25]. The salt intake was recommended to be kept below 6 g/day [26]. In this respect, the Paleolithic diet was described to be based on lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts, with reduced intakes of dairy products, cereal grains, beans, refined fats, sugar, candy, soft drinks, beer, and added salt [26]. The following items were recommended in limited amounts for the Paleolithic diet: eggs (≤2 per day), nuts (preferentially walnuts), dried fruit, potatoes (≤1 medium-sized per day), rapeseed or olive oil (≤1 tablespoon per day), and wine (≤1 glass per day) [26, 27]. The recommended intake of the other types of food products did not carry any restrictions and no advice was given with regard to the proportions of food categories [26, 27]. The evolutionary preference and rationale for the Paleolithic diet has been highlighted in Eaton et al. [27].

The Paleolithic diet is known to result in significantly lower fasting plasma leptin, nonsignificantly lower fasting plasma glucagon concentrations as well as gain weight loss, compared with a standard diabetes diet [28–30]. However, the small sample size in studies such as those by Eaton et al. [27] makes it impossible to perform adjusted multivariate analysis. Overall, long-term and adequately powered trials investigating the effects of Paleolithic diet are warranted.

6. Diet and the microbiota

The importance of microbiota in the incidence of diabetes has been a recently discussed development. The gut microbiota has been hypothesized to be a link between environmental factors and the development of autoimmunity and diabetes [31]. The first gut microbiota composition is mostly acquired at birth, while the delivery mode determines the type of microorganisms that will colonize the newborn gut. After delivery, the diet is one of the main factors affecting the composition of infant gut microbiota. The diet provides substrates and sources of bacterial contamination from breast and nipple skin to breastfed babies [31]. Diet also contributes indirectly toward the regulation of intestinal and pancreatic health.

In several studies, it was found that the age, dietary patterns, geography, traditions, and culture were the main determinants explaining the differences in gut microbiota composition

[31–33]. The modulation of the immune system by the gut microbiota essentially begins even before birth. It is obvious that the intrauterine environment of the fetus during pregnancy is not completely sterile. There is evidence that the placenta of a term pregnancy has many nonpathogenic commensal microbiota in low-abundance, similar to the oral microbiome of nonpregnant women [31]. Following birth, diet, and microbiota are the decisive factors that guide the proper maturation of the immune system [32].

Dietary antigens, especially those associated with type 1 diabetes, depend on early feeding regimens, the age of introduction of foods, especially wheat, to the infant's diet, and the current consumption of nutrients [34, 35]. Understanding and hypothesizing that the gut microbiota is an organ will make it possible to integrate its relationship with diabetes as a key for designing new therapies to prevent and/or improve the control and propagation of the disease. Dietary components provide different substrates, which may ultimately result in several products during the fermentation processes. Changes in the structure of the microbiota due to dietary modifications are because some of the bacterial communities are "genetically better equipped" to metabolize those substrates [31].

7. Conclusions

A multicomponent-based lifestyle enabling the prevention of diabetes, which includes diet and both aerobic and resistance exercise training, is generally regarded as the most effective in inducing weight loss and improving impaired fasting glucose, glucose tolerance, dietary, and exercise outcomes in at-risk and prediabetic adult populations. Several scientific studies support the current dietary and exercise guidelines for the inclusion of resistance training in type 2 diabetes prevention. However, when it comes to exercise and other physical workouts, there remains an urgent need for more rigorous studies, with long-term follow-up evaluating program efficacy, muscular fitness outcomes, diabetes incidence, and risk reduction.

Overall, a low-carbohydrate diet score has been significantly associated with a decreased risk of diabetes. This association is attenuated through adjustment of the glycemic load. The composition of the gut microbiota is also believed to be related to diabetes prevention especially since it can be modulated by diet. This modulation can promote the proper maturation of the immune system or result in gut dysbiosis and aberrant immune responses, which can eventually lead to autoimmunity and diabetes, especially in children.

People who live their lives with their diabetes are interconnected with their multilevel network and it has been observed that they adapt the illness to their life, not the opposite. In terms of the psychology of being contracted with this disease, to meet a sustainable network approach, thus involves wide encounters encompassing life factors at different levels. All social, political, and cultural factors are influential and interwoven in the dynamics, negotiations, and tensions of everyday life for people with diabetes. The impact of network on self-management of diabetes needs to be recognized and emphasized in clinical practice, as well as in the education of healthcare professionals, in research as well as in health policy to understand and respond to provide support and advice to the diabetic patients.

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Chapter 2

The Microbiome and the Epigenetics of Diabetes Mellitus

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http://dx.doi.org/10.5772/intechopen.76201

Abstract

Gut microbiota (GM) in the epigenetic mechanisms of diabetes mellitus and the reprogramming of the cells is a novel and emerging concept. The purpose of this chapter is to describe the modification of the GM and its relation with DM2. The increased risk of this disease is associated with changes in the amount of *Bacteroides*/*Clostridium* in the *Firmicutes*/*Bacteroidetes* ratio of people having DM. A dysbiosis state associated generates low-grade inflammation with similar characteristics that occur under metabolic syndrome, whose pattern is recognized by Toll-like receptor that recognizes important patterns of immunity. The synthesis of butyrate generated by intestinal microorganisms inhibits the metabolic pathway of histone deacetylase, promoting cellular differentiation, proliferation, and insulin resistance. On the other hand, the direct relationship between the neuroendocrine system and the GM has been demonstrated through the production of serotonin by enterochromaffin cells, whose action could influence the etiopathogenic factors of DM2.

Keywords: diabetic, epigenetics, diet, microbiome

1. Introduction

Diabetes *mellitus* type 2 (DM2) is a global pandemic; although genetic factors can predispose subjects to suffer from it, external factors such as socioeconomic changes and cultural and eating habit changes have more contributions to increasing world prevalence [1], where overweight and obesity are considered as the main mediators of the disease. The number of cases of DM2 according to the International Diabetes Federation is 415 million adults by 2015. The risk death of subjects with DM is significantly higher than those without the disease, doubling it when we refer to cardiovascular death reason [2]. It has been determined that the gut microbiota (GM) is altered in subjects with type 2 diabetes, so studying its role in the development of pathology is essential to determine new approaches to treatment; it permits the identification of those bacteria beneficial to humans, from the bacterial genome recognition. The so-called microbiome correspond to the entire GM genome; it exceeds the size of the human genome, having about 500 times more genes that complement our coding; this bacterial ecosystem has evolved in a symbiotic relationship with human [3]; GM exerts nutritional, metabolic, and immunological functions that affect the human being. During the last decade, several studies have been reported on the effect of the GM on glycemic control [4]. In this context, GM in the epigenetic mechanisms of diabetes mellitus and the reprogramming of the cells is a novel and emerging concept. It is known that products derived from diet along with intestinal bacteria can change the epigenome of the host with favorable metabolic effects [5]. These microorganisms are essential for the biosynthesis of vitamins and hormones, as well as for the degradation of nondigestible dietary fibers and mucin in simple sugars and short-chain fatty acids [6]. Changes in the composition and function of the predominant GM are associated with an increased risk of DM2 and are linked to an increase in the number of *Bacteroides* [7] and *Clostridium* [8]. Specifically, the increase of *Firmicutes*/*Bacteroidetes* ratio in the distal bowel, as well as the number of opportunistic pathogens, and in the production of endotoxins of Gram-negative bacteria is capable of modifying intestinal permeability. The metabolic syndrome is associated with changes in the framework of the GM that lead to low-grade inflammations, since the increased permeability of the intestinal membrane damaged by bacteria induces inflammation, through the epigenetic alteration of inflammatory molecules such as Toll-like receptors [9]. Mucus and glycocalyx layer mainly produced by *Bacteroides thetaiotaomicron*, *Akkermansia muciniphila*, and *Escherichia coli* cause chronic low-level inflammation, insulin resistance, and, lastly, DM2 [10]. Evidence demonstrates the link between diabetes and histone deacetylase (HDA), because the microorganisms producing butyrate, an HDA inhibitory molecule that promotes differentiation and cellular proliferation and insulin resistance [11], are decreased in diabetics [5]. On the other hand, it has been recognized that the microbiome has a direct effect on the immune and neuroendocrine system, constituting a new brain gut axis [12], in which the circadian rhythm plays a fundamental role [13]. The production of colonic serotonin [14, 15] by the microbiome, through the effect of short-chain fatty acids on enterochromaffin cells [13, 16, 17], would allow to relate this neurotransmitter to the metabolic processes as one of the possible etiopathogenic factors of DM2. The next challenges are focused on integrating the transcriptomic, epigenetic, proteomic, and metabolic information of the human genome and the microbiome into the nutritional treatment [2].

2. Microbiome, epigenetics, and diabetes interactions (metabolic pathways)

The human intestinal microbiota (HIM) is composed of a complex community of microorganisms; more than 1000 species have been identified, where only a few are cultivable [18]. The gut microbiome corresponds to a total set of genes present in the HIM (about 3 million genes), approximately 150-fold human genome [19]. This microorganism participates as a counterpart of gut enzymatic activities by a diverse metabolic repertoire becoming an important contributor to the metabolism of the host [20]. Exploratory studies have been shown that play an important role in the etiology and development of many diseases, being considered as markers of the course of the disease. Some chronic illnesses in which HIM has been regarded are the inflammatory bowel disease (IBD), the irritable bowel syndrome (IBS), diarrhea, obesity, diabetes, and inclusive cancer. The recent role attributed to the microbiome and health has promoted the research to study the microorganism characteristics and the design of strategies to restore damage microbiome to a normal "state" by using a microbe inoculation strategy or by using dietary modification to feed specific species and help their development or otherwise consume foods or other substances that induce the extinguishment of some species in the intestine. The abundance and diversity of the intestinal bacteria are located mainly in the large intestine where it exerts its principal metabolic role. Bacteria are capable of hydrolyzing carbohydrates, lipids, and proteins principally; *saccharolytic* bacterial fermentation produces generally beneficial metabolites such as short-chain fatty acids (SCFAs) and gases. The three most abundant SCFAs detected in feces are acetate, propionate, and butyrate, in molar ratios of 3:1:1 to 10:2:1 [21]. Butyrate is recognized as the most important SCFA for human health and is absorbed by the epithelial cell of the colon in the proximal colon via passive diffusion and by active transport mechanisms. Some properties have been attributed to butyrate, for instance, being able to be used by colonocytes as energy source, the potential anticancer activity inducing apoptosis of colon cancer cells, its ability to regulate gene expression in host by inhibiting histone deacetylases [22], and the beneficial effects in glucose regulation by activation of gluconeogenesis in the gut via cAMP-dependent manner [23].On the other hand, propionate exerts a dual action in intestine and liver regulation of gluconeogenesis and is considered an important molecule for satiety signaling because of an interaction with G protein-coupled receptors GPR 41, GPR 43 receptors, and fatty acid receptors FFAR2 and FFAR3. The net effect of the conversion of propionate to glucose is the decrease of gluconeogenesis in the liver; this generates a reduction in the production of adiposity [23]. Acetate is the most abundant SCFA and is considered as essential metabolite for bacteria growth. *Faecalibacterium prausnitzii* will not grow in pure culture in the absence of acetate [24]. Acetate participates in the cholesterol metabolism and lipogenesis in the host [25].

2.1. Microbiota metabolism

A cross-feeding effect has recently been described, for instance, *Bifidobacterium longum* growing in fructooligosaccharides (FOS) produces a conversion into lactate and promotes the growth of *Eubacterium hallii* that could not grow in the presence of FOS alone and converts it to butyrate [26]. Another example of cross feeding occurs when *Roseburia intestinalis* increases its growth in co-cultures with—the acetate contributor—*B. longum* [27, 28]. Two main routes of butyrate

production [29] and three pathways for propionate production have been identified in bacteria; noteworthy peptide and amino acid can be used to form propionate and butyrate from some species of *Bacteroidetes* and *Firmicutes*. The main sources of propionate are aspartate, alanine, threonine and methionine, instead glutamate, lysine, histidine, cysteine, serine and methionine for butyrate production [30]. Sequencing targeted gene instead of 16S rRNA genes indicates that most bacteria had the capability to produce exclusively propionate or butyrate but not both. Conversely, bacteria change their fermentation depending on growth conditions and produce different SCFAs. *Roseburia inulinivorans* produces butyrate normally, but it can change its gene expression pattern in the presence of fucose producing propionate and propanol [31]. *Ruminococcus obeum* produces acetate, formate, and lactate on glucose growth and also produces propionate in the presence of fucose. *Bacteroides thetaiotaomicron* in the presence of fucose also increases fucosylated glycan to be used in absence of nutrients; it has been described that it is also important in early colonization of the infant gut [32]. By decreasing the carbohydrate content of the diet significantly reduced both fecal butyrate concentrations and numbers of the *Roseburia/E. rectale* group [33]; wheat bran has >70% arabinoxylan oligosaccharides (AXOS) that increase the SCFA content [34]. Unfortunately, the increased SCFA content causes reduced transit time and thus a decreased colonic absorption of SCFA. Excluding those vegetables rich in short fermentable carbohydrates such as oligosaccharides, monosaccharides, and polyol (FODMAP diet) reduces bacterial fermentation, showing a decrease in the total numbers of bacteria, and the fecal concentration of different SCFAs is similar to the control diet [35].

2.2. Gas production and the microbiome

HIM generates hydrogen, carbon dioxide, and methane, all of them odorless gases; odoriferous gases constitute less than 1% of total flatus and include NH_3, hydrogen sulfide, indole, skatole, and volatile amines. There are many bacteria that do not produce gas [36] such as lactobacilli and bifidobacteria, so they can be used as probiotic able to reduce the gas content in colon. Gases can be excreted by flatus (several liters per day in a healthy human) [37]. Hydrogen is produced by *Bacteroides* and *Clostridium* [38] and produces a high energy yield, and it can be used by other bacteria from the gut to produce lactate, succinate, and ethanol and sulfate-reducing bacteria (SRB), where *Desulfovibrio* is the principal [39]. In the methanogenesis CO_2 is converted to CH_4, and in the acetogenesis dioxide and hydrogen are converted into acetate both use hydrogen [38]. Carbon dioxide is between 5 and 50% of the total flatus volume, and it is produced by acidification of bicarbonate in the upper gastrointestinal tract, and bacterial metabolism [40], *C. sporogenes*, *C. butyricum*, and *C. perfringens*, produces hydrogen and CO_2.

2.3. Proteins

HIM has an important role converting protein metabolism, enzymes, mucin in short peptides, fatty acids and gases (H_2, NH_4, CO_2 and H_2S), Clostridia, Streptococci, Staphylococci, *Bacillus* and species of *Bacteroides* and *Propionibacterium* as the predominant proteolytic characteristics in fecal samples [41]. A preference for amino acid fermentation at higher ranges of colonic pH and a reduction in quantity when fermentable carbohydrate was available are observed [42]. The proximal colon was predominantly saccharolytic by nature; whereas protein fermentation increased distally, the fermentation was associated with the presence of phenol, indole, ammonia, and branched-chain fatty acids [21]. Aromatic amino acids phenylalanine, tyrosine,

and tryptophan can be fermented to phenylpropanoid, phenylacetic acid, and 4-hydroxyphenyl-acetic acid by *Bacteroides*, *Eubacterium hallii*, *and Clostridium bartlettii* [43].

2.4. Vitamin synthesis and the microbiome

Gut microbiome can synthesize certain vitamins, such as vitamin K, biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine of B group [44]. For instance, subjects having low vitamin K diet showed an important decrease in plasma prothrombin when treated with broad-spectrum antibiotic [45]. Explored genomes in gut showed presence of eight vitamin B synthesis pathways. The most represented were riboflavin [46] and niacin with 162 genomes. *Bacteroidetes* is the phylum with larger B predicted vitamin generators. In the same line, bacteria can complement the biosynthesis of vitamins. In sum, GM can contribute with 25% of total dietary vitamin intake [47].

2.5. Bile acids and the microbiome

Gut microbiota can modify the structure of bile acid in the colon, because bile acids have antimicrobial activity causing membranes and DNA damage [48]. Deoxycholic acid produced by microorganisms is tenfold greater than cholic acid producing a feedback to control bacteria population [49]. Bile salt hydrolase enzyme has been recognized in *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Lactobacillus*, and *Listeria* [50]. It can deconjugate bile acids reducing its toxicity [51]. Microbial dehydroxylation by *Clostridium and Eubacterium* transforms chenodeoxycholic acid and cholic acid into lithocholic acid and deoxycholic acid, it can produce a cytotoxic effect on enterocytes, and it can be associated with colon cancer. On the other hand, bile acids are also a ligand for nuclear receptor farnesoid X receptor (FXR) and plasma membrane-bound GPR TGR [52] that regulates their synthesis and affects the lipid and glucose metabolism [53]. Bacteria deconjugate bile acids reducing the efficacy of lipid emulsification showing a downstream effect in metabolic processes.

2.6. Gut microbiota and diabetes type 2

Diet plays an important role in obesity. There are preliminary studies suggesting that the consumption of probiotic bacteria found in yogurt and other fermented milk products can beneficially alter the composition of the gut microbiome. Yogurt, a fermented dairy product containing a variety of probiotic bacteria, is found to be associated with a reduction in inflammation markers and weight loss [54]. Yogurt consumption is involved in energy balance and/or energy homeostasis, which in turn controls body weight and reduces the risk of the development of DM2 [55]. One of the causes of dysbiosis is diet, and studies have shown that diet may change the gut microbiota and contribute to obesity and diabetes [56]. Obesity and DM2 are characterized by an altered gut microbiota, inflammation, and gut barrier disruption [57]. Studies in germ-free animals have shown that shifts in the composition of the gut microbiome may play an important role in disease development, specifically obesity and diabetes [58]. There is evidence demonstrating that the composition of the gut microbiota also influences metabolism and can affect energy balance [59], gut permeability [60], and inflammation [61], all of which are associated with obesity and associated disorders, including DM2 [62]. The evidence for the role of the HIM in metabolism of dietary components and the impact on health has been obtained from

comparative studies in germ-free animals, by using conventional microbiome, or by animals with human microbiome-associated, and from *in vitro* studies using human fecal incubations. In this sense, gastric bypass surgery leads to a substantial shift in the gut microbiota, which may contribute to weight loss in part by HIM modifications [63]. One of the most important situations is that the immune system faces microbiome continuously and it affects the host immunity and inflammation control. In this line, GM can affect the immune system by metabolites like SCFAs [64] and toxin production, such as LPS [61], modifying the adipogenesis and influence in the insulin resistance. LPS induces generation of pro-inflammatory cytokines by the immune system and adipocytes. Acetate, butyrate, and propionate (SCFA) modulate the gene expression in host, modifying the infant microbiome and stimulating white blood cells [65]. Some studies suggested that infants born by cesarean section are at greater risk of developing obesity and/or diabetes than those born vaginally [66]. Other studies with preschool children showed overweight or obesity in children born by cesarean [67], while in other showed the opposite [68]. On the other hand, infant feeding is also important to develop GM because mother milk is not sterile and is the first bacteria to colonize the gut [69]. Breast milk is a source of probiotics and other bacteria [71] containing more than 700 species [70]. The median bacterial load is 10^6 bacterial cells/Ml [71]. *Streptococci* and *Staphylococci* are predominant bacterial genera in human milk [69]. *Weissella*, *Leuconostoc*, *Staphylococcus*, *Streptococcus*, and *Lactococcus* are predominant in colostrum and are thought to modify the lactation to increase *Veillonella*, *Leptotrichia*, and *Prevotella* for over 6 months [71]. In this line, milk from obese mothers contains less-diverse bacteria than normal-weight mothers and has pro-inflammatory properties [72, 73, 74]. Another import issue is the infection of virus or bacteria pathogens. For instance, *Clostridium difficile* patients and asymptomatic carriers with the use of 16S ribosomal RNA gene pyrosequencing found that both had reduced microbial richness, diversity, and dysbiosis state compared with healthy subjects [75]. Gut microbiota transplants can help to increase the richness and diversity of GM [76]. For example, clearance of hepatitis B virus infection requires the reestablishment of the gut microbiota. Drugs also affect the microbiome including the drugs used to treat DM2 [77]. But also in the opposite direction. Broad-spectrum antibiotics reduce bacterial diversity and provoke the augmentation of some species like opportunistic pathogens [78], predisposing to inflammatory bowel disease [79]. *Clindamycin* produces a prolonged effect of modifying the microbiome in infants [80]. Studies in both mice and humans have found that the use of antibiotics early in life could promote obesity later in life, mediated by the alteration of the gut microbiota [81]. In the same line, antibiotics can reduce body weight and increase insulin sensitivity [82]. *Berberine* is recognized for its antidiabetic effect by modulating the gut microbiota and diminishing glucose and insulin resistance [83]. Metformin increases the insulin sensitivity in fat cells and hepatocytes and also reduces the overproduction of glucose in hepatocytes. Recent studies showed that metformin alters the GM [84, 85]. In obese mice, metformin caused the increase of mucin-degrading *Akkermansia* [85]. In human GM, altered gut microbiota can be the cause of common metformin side effects and could have a role in drug efficacy. There is a link between high-calorie diets contributing to obesity and DM2 and GM [55]. Dietary changes can result in substantial and rapid changes in the GM [86]. High-fat diet reduces the α diversity in GM. For instance, *A. muciniphila* decreased in obese mice and DM2, and it can be normalized by prebiotic consumption [62]. Treatments with *A. muciniphila* reduced fat mass, inflammation, and insulin resistance induced/caused by high-fat diet [62]. An enterotype is a classification of living organisms based on their bacteriological ecosystem in the gut microbiome. Changes in GM enterotypes were strongly associated with long-term diets, *Bacteroides* with protein and animal fat, and

Prevotella with carbohydrates; gut microbiota composition depends on diseases and long-term dietary interventions. GM alterations can be observed within 24 h after high-fat and low-fiber or low-fat and high-fiber diet [87]. Type 1 is characterized by high levels of *Bacteroides*, type 2 has few *Bacteroides* but *Prevotella* are common, and type 3 has high levels of *Ruminococcus* [18].

3. Metagenomic, metatranscriptomic, metaproteomic, and metabolomic approaches to mimic the gut ecosystem

Metagenomics is used to study differences in microbiome composition having diseases and compared with healthy people. Recently a technique was developed (Ecemble; enzyme classification using ensemble approach) to predict enzymes from protein sequences in gut microbiome from metagenomic samples and study the role of GM in metabolism; 48 pathways having at least one bacteria-encoded enzyme were found [88]. The carbohydrate active enzymes are important due to their role in dietary fiber and non-absorbed carbohydrate metabolism; 81 families of glycoside hydrolases have been identified. On the other hand, single-cell genomics uses isolated colonies to shotgun sequencing and put in phylogenetic context to complement metagenomic analysis. Is important to note that the presence of a gene does not mean it amounts to their expression; in this sense, metatranscriptomics, metaproteomics, and metabonomics are needed. Metatranscriptomics involves the generation of cDNA by reverse transcription and permits to identify noncoding RNAs and small RNAs that control quorum sensing and stress response [89]. Metatranscriptomics of fecal microbiome analysis of the 16S rRNA transcripts showed *Firmicutes* (49%) and *Bacteroidetes* (31%) are the main source of RNA and smaller proportion of *Proteobacteria* (3.7%), *Actinobacteria* (0.4%), and *Lentisphaerae* (0.2%) and *Lachnospiraceae* and *Ruminococcaceae* are the major proportion of *Firmicutes*, whereas *Bacteroidaceae, Prevotellaceae,* and *Rikenellaceae* for *Bacteroidetes phylum* [90]. Other transcripts were compared with COG database to obtain a functional distribution. Results showed similar behavior for carbohydrate transport, energy production, and synthesis of cellular components. Nevertheless acid and lipid metabolism, motibily, and secondary metabolite biosynthesis were underregulated. Unfortunately, short half time of bacteria RNA makes the detection of all RNAs in fecal samples difficult. Metaproteomics permits to determine gene translation and post-transductional modifications and permits to classify microorganism to a specific catalytic function [91, 92]. Temporal stability of the fecal metaproteome was assessed, and it was determined that glutamate dehydrogenase showed high level of redundancy in *Lachnospiraceae*, *Bacteroidaceae*, *Ruminococcaceae*, and *Bifidobacteriaceae*. Ten percent of total proteome is involved to ABC sugar transport and glycolytic enzymes; the main functional categories were metabolism of carbohydrates, nucleotides, energy, amino acids, and cofactors and vitamins (especially B12 and folic acid) [87]. Finally, metabolomic approach allows to determine low-molecular-weight compounds in fecal sample and can be influenced by environmental inputs and metabolic interactions between host and environment. For example, SCFA content in the gut can be modified by diet; after that, absorption from the gut initiates the metabolism of the host and results in downstream metabolic perturbations and the generation of microbial-host co-metabolites [93]. For instance, intake of choline (meat and eggs) can form trimethylamine and dimethylamine by GM, trimethylamine is toxic and should be converted to trimethylamine-*N*-oxide (TMAO), and the latter is an electron acceptor for anaerobic metabolism *of E. coli* and is implicated in cardiovascular disease (CVD) [94–98]. Genomic

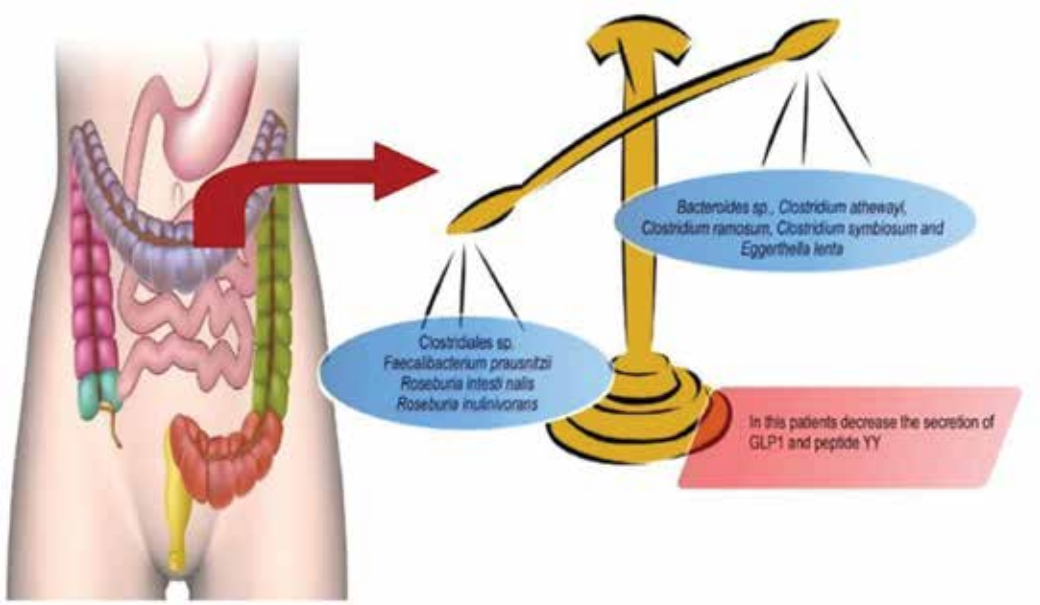

Figure 1. Changes in the composition of the gut microbiome are associated with an increased risk of DM2: In patients with DM2, the intestinal dysbiosis causes a decrease of short-chain fatty acid content, molecules that stimulate the secretion of peptide similar to glucagon type 1 (GLP1) and YY peptide by intestinal cells, proteins that control glucose homeostasis and regulate the intake of nutrients in intestinal cells.

analyses of the GM of subjects suffering from DM2 allowed to identify bacterial genes that are differentially expressed in those subjects; these changes in the gene expression of microbiome are related to the metabolic dysfunction and inflammation that these patients suffer from [99]. Bacterial genes including *Clostridiales* sp. SS3/4, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Roseburia inulinivorans* are decreased in patients with DM2, whereas genes corresponding to *Bacteroides* sp., *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, and *Eggerthella lenta*, are increased in these subjects [100]. Functional analyses suggest enriched genes in samples of DM2 patients are involved in plasmatic membrane sugar transport, branched-chain amino acids transport, methane metabolism, xenobiotic degradation and metabolism, biosynthesis of hydrogen sulfide, and oxidative stress. In contrast, decreased genes are related to functions such as chemotaxis, flagellum assembly, butyrate biosynthesis, and the metabolism of cofactors and vitamins [100]. The depletion of bacterial strains producing butyrate in patients with DM2 may be related to the ability of this fatty acid to increase secretion of peptide similar to glucagon type 1 (GLP1) and peptide YY, whose function is to promote intestinal gluconeogenesis, which leads to a better control of glucose homeostasis and cellular energy (**Figure 1**) [101, 102].

4. Nutrigenomics and the microbiome

In most chronic pathologies, environmental and genetic factors are involved because of a polygenic behavior. Recent research investigate the mechanisms involved in the dysfunction of a healthy phenotype to another with chronic dysfunction, explaining how gene expression

and dietary components regulate genetic information. Nutrigenomics involves understanding how diet components affect gene expression, meaning which genes are induced and which are repressed against a particular nutrient [103]. Chronic diseases, such as obesity, DM2, and cancer, are expressed from complex polygenic reactions with the environment. The most influential environmental interaction in the development of these diseases is given by the consumed nutrients. Evidence of gene-nutrient interaction is substantially demonstrated, estimating that a balanced healthy nutrition reduces the overall incidence of cancer by 35%. On the other hand, polymorphisms that predispose to certain diseases have been identified under unhealthy diet; this is the case of DM2, osteoporosis, vascular disease, and others, which can be prevented by modifying the diet [104]. The regulation of gene expression is performed through specific proteins that interact with DNA through posttranscriptional or posttranslational modifications. Regulation can occur at the level of mRNA during splicing; it would result from the interaction of certain molecules with specific nutrients, whose result could be potentially preventive [104]. The diet and the GM composition have also been associated with different characteristics of the metabolic syndrome (MS) (obesity, DM2, cardiovascular diseases, and nonalcoholic steatohepatitis). Increasing evidence suggests that the GM contributes to the onset of its characteristic low-grade inflammation, through mechanisms associated with intestinal barrier dysfunction [105]. The GM of an obese person in comparison with a normal-weight person presents a greater percentage of *Firmicutes* and smaller percentage of *Bacteroidetes*, causing dysbiosis in most of the obese and/or diabetic patients (**Figure 2**). Due to its physiological impact, GM is now recognized as an organ and can be transplanted from one individual to another [106]. Recent evidence suggests that the intestinal microbiome affects nutrient acquisition, energy storage, and metabolic pathways of the host [10]. *Bacteroidetes* have been shown to easily assimilate dietary carbohydrates. In a study in mice lacking Toll-like receptors (TLRs), which are receptors that recognize important patterns of inflammation and immunity, it is shown that these mice present hyperphagia and obesity and develop metabolic syndrome, when intestinal microbiome of these

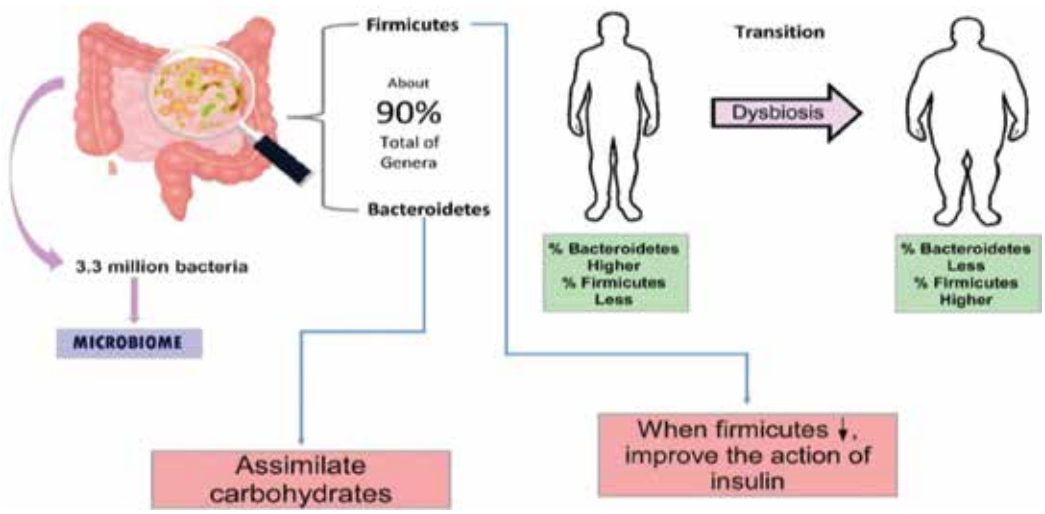

Figure 2. The GM of an obese person in comparison with a normal-weight person presents a greater percentage of *Firmicutes* and smaller percentage of *Bacteroidetes*, causing dysbiosis in most of the obese and/or diabetic patients.

mice is transplanted to germ-free mice with the TLR5 gene intact; they also developed the *Bifidobacterium* strain similar to the metabolic syndrome, suggesting that the GM was the determinant factor of this disease phenotype [107]. Another study showed that mice deficient in TLR2 presented greater amount of *Firmicutes* and *Actinobacteria* and smaller amount of the genus *Bifidobacterium* [10, 107]. Administration of an antibiotic cocktail eliminated many of the *Firmicutes* and resulted in improved insulin action and increased glucose tolerance [107].

5. New brain gut axis, serotonin production, and its relationship with DM

Some studies have shown the clear connection between immune system and neuroendocrine system highlighting the effect of the GM, which allows a new focus for research on the so-called brain gut axis [12]. The mechanisms of enteric neuroprotection were recently been described; enteric neurons have one of their own signaling molecules to this propose. In the adult intestine, serotonin acts like a paracrine signal hormone and neurotransmitter [108]. However, it is also a neuronal growth factor during development and a major promoter of mucosal epithelium growth by stimulating submucosal cholinergic neurons [109]. This neurotransmitter may even stimulate neurogenesis in the growing enteric nervous system, and in adults, this hormone promotes neurogenesis and neuroprotection through the activation of 5-HT4 receptors. It is interesting to mention that mucosal serotonin is not a direct neuroprotective agent to enteric neurons. Mucosal serotonin behaves as a pro-inflammatory factor, and this ability constitutes a threat to neuronal survival [110]. According to these facts, this hormone has received the name of "sword and shield" of the intestine. Mucosal serotonin is the pro-inflammatory "sword," while neuronal serotonin is the anti-inflammatory "shield" [111]. It has been demonstrate that DM1 is related with an excess of pro-inflammatory cytokines close to B pancreatic cells, while DM2 is caused due to an excess of pro-inflammatory cytokines in systemic circulation, which could be related to intestinal serotonin secretion. Gershon et al. have established that neurodegenerative/neuroprotective actions of 5-HT4 receptor complex may be vital for the normal enteric nervous system's maintenance [12]. Bianco et al. show the mechanisms through the 5-HT4 agonist participate in protection of enteric neurons against oxidation [112]. This sentence is relevant because the enteric neurons lost during inflammation strongly depend on the released forces throughout oxidative stress (**Figure 3**) [113, 114]. Bhattarai et al. suggest that the "sword" function is manipulated by the microbiome [115]. The intestine has a variety of regulatory mechanisms that contrast the actions of 5-HT for transport maintenance; conversely, Chang and Rao incorporate the GM as a homeostasis influence factor evading the alteration of 5-HT during diarrhea and intestine inflammatory diseases. Recently, observations have been made about the possible mechanisms by which dysbiosis of the microbiome alters the function of 5-HT [14]. The HIM plays a key role in enhancing the serotonin biosynthesis in enterochromaffin cells. This increased serotonin content stimulates the intrinsic projections of the primary afferent neurons and in turn activates interneurons, which activate the peristaltic reflex promoting intestinal motility and besides accelerate the gastric emptying, which is augmented when 5-HT receptor is antagonized [111]. The intestinal speedup promotes the production of several gastrointestinal hormone secretions that mediate glucose metabolism, unleashing

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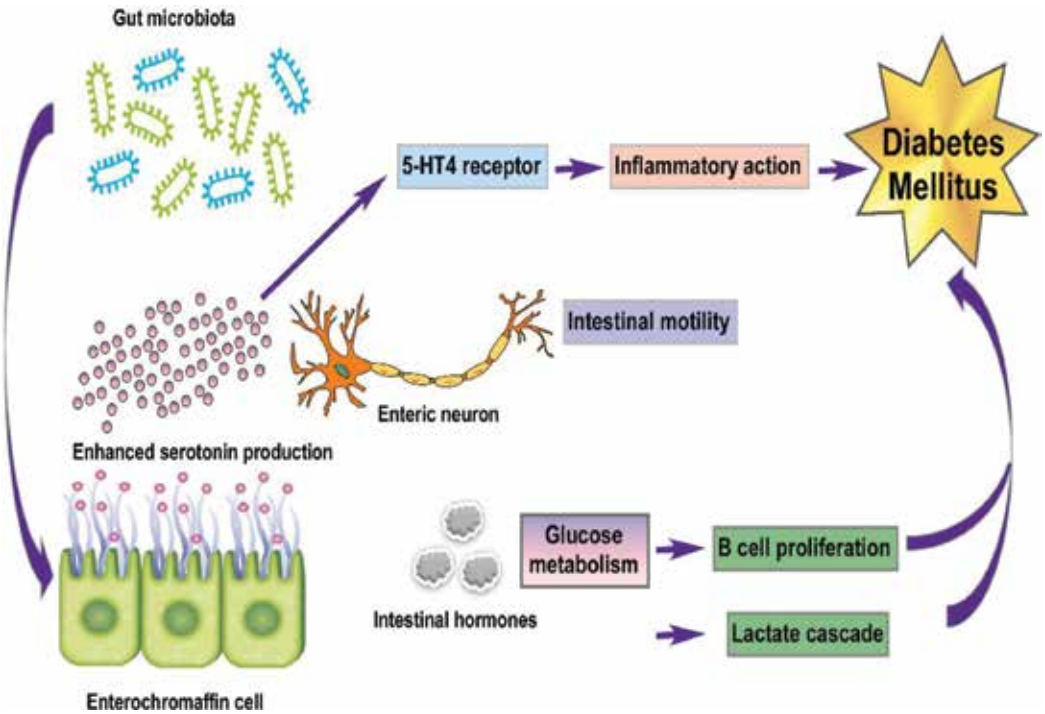

Figure 3. The hypothesis of the alteration of the GM by serotonin and the metabolic pathway that generates insulin resistance it could be considered as one of the possible etiopathogenic factors of DM2.

insulin synthesis such as β-cell proliferation or glucagon release [116]. On the other hand, it has been shown that serotonin participates during lactate signaling cascade to stimulate β-cell proliferation [117]. Under this premise, there is a hypothesis of a possible relation between the alteration of the GM by serotonin and the metabolic pathway that generates insulin resistance, and it could be considered as one of the possible etiopathogenic factors of DM2.

6. Conclusions

The interaction of the diet in the modification of HIM, in addition to its potential effect on the microbiome and the development of DM, has been positively affected by the evolution of nutrigenomics as a science discipline. Diets rich in carbohydrates and fats, favor the development of bacteria capable of causing intestinal dysbiosis of low degree of inflammation; affecting the permeability of the intestinal mucosa. It has been shown that intestinal production of serotonin by enterochromaffin cells participates in the cascade of stimulation of the proliferation of pancreatic β cells, via the lactate pathway, suggesting the hypothesis of a possible link between serotonin, insulin resistance, and DM2. Finally, the advances reflected in this chapter demonstrate a small part of the future projection around nutrigenomics and its effect on the composition of the

microbiome in diabetic subjects; it would be interesting to carry out more specific studies of this area, associating it with the effect of satiety and the alteration of the microbiome in patients with obesity and/or metabolic syndrome, as an integral part in the prevention of DM2.

Acknowledgements

This work team is composed of Carrera de Nutrición y Dietética, Universidad Andres Bello, Concepción, Chile; Centro de Investigaciones Endocrino - Metabólicas. Facultad de Medicina, Universidad del Zulia. Maracaibo - Venezuela. Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia. Facultad de Ciencias para el Cuidado de la Salud, Escuela de Nutrición y Dietética, Universidad San Sebastián, Santiago, Chile; Departamento de Salud Pública, Universidad Católica de la Santísima Concepción, Concepción, Chile; and Hospital 12 de Octubre, Madrid, España.

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Chapter 3

Dietary Recommendations for Patients with Cardiovascular Disease and Diabetes

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71391

Abstract

Cardiovascular disease remains the main cause of death and disability among patients suffering from diabetes mellitus. All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific macrovascular disease affecting the coronary arteries that supply the heart. Healthy diet plays an important role in the prevention and management of cardiovascular diseases and diabetes. The information in this chapter is divided into the following sections: mechanisms by which diabetes increases cardiovascular disease, the relationship between diet and disease, the potential of foods in preventing cardiovascular disease and diabetes, and dietary items and patterns.

Keywords: cardiovascular disease, type 2 diabetes mellitus, healthy diet, dietary patterns, nutrients

1. Introduction

Atherosclerotic cardiovascular disease (CVD) remains the main cause of disability and death among patients with diabetes mellitus, especially those with type 2 diabetes mellitus (T2DM). On average, CVD typically occurs 14.6 years earlier in patients with T2DM being characterized by greater severity than in individuals without diabetes mellitus [1, 2]. It is estimated that 90% of atherosclerotic CVD is preventable [3]. The dramatic increase of T2DM has developed into a major public health concern worldwide [4]. Several clinical studies have demonstrated that preventive strategies reduce significantly the risk of developing T2DM [4]. Understanding the mechanisms, strategies, and challenges as well as the potential cardiovascular risks and benefits of glucose-lowering diets are important in managing CVD in T2DM.

2. Mechanisms by which diabetes increases cardiovascular disease

All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific macrovascular disease affecting the coronary arteries. Large prospective clinical studies show a strong correlation between hyperglycemia, insulin resistance and diabetic macrovascular complications in both type 1 and type 2 diabetes mellitus [5]. Five major molecular mechanisms have been implicated in hyperglycemia-induced tissue damage [6]: (1) increased polyol pathway flux, (2) increased advanced glycation end products (AGEs), (3) activation of protein kinase C (PKC), (4) increased hexosamine pathway flux, and (5) activation of the 12/15-lipoxygenase (12/15-LO) pathway [5]. Hyperglycemia-induced overproduction of superoxide is the causal link between high glucose concentration and the pathways responsible for hyperglycemic damage [5] (**Figure 1**).

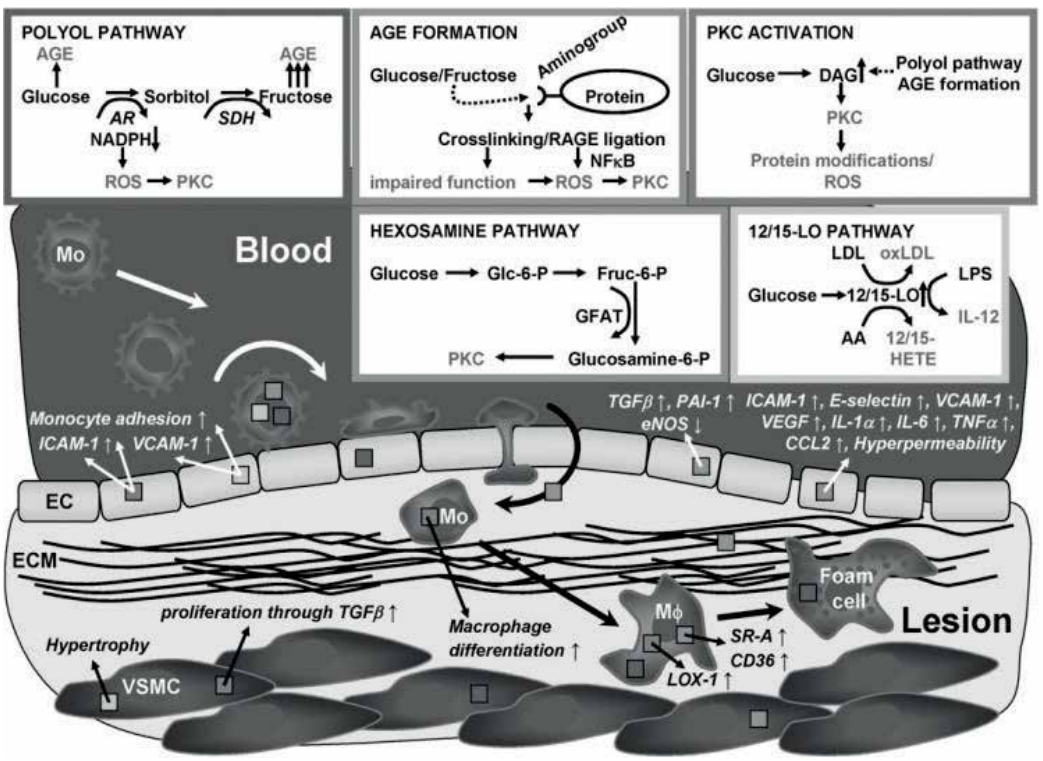

Figure 1. Pro-atherogenic mechanisms of diabetes associated with hyperglycemia. Four hyperglycemia-related mechanisms may promote diabetic atherosclerosis: (1) the polyol pathway, (2) formation of advanced glycation end products (AGEs), (3) activation of protein kinase C (PKC) isoforms, (4) the 12/15-lipoxyenase pathway, and (5) the hexosamine pathway. All four mechanisms result in increased formation of reactive oxygen species (ROS) and promote diabetic atherosclerosis by various mechanisms as depicted in the figure. Boxes in arrows, cells and ECM indicate relevant pathway. 12/15-LO = 12-/15-lipoxygenase, AR = aldose reductase, EC = endothelial cell, ECM = extracellular matrix, Fruc = fructose, GFAT = glutamine-fructose-6-phopshate amidotransferase, Glc = glucose, Mo = monocyte, Mϕ = macrophage, RAGE = receptor for advanced glycation end products, SDH = sorbitol dehydrogenase, VSMC = vascular smooth muscle cell, other abbreviations are explained in the text. Reprinted with permission from [5].

2.1. Increased polyol pathway flux

Aldose reductase (alditol:NADP+ 1-oxidoreductase) is a cytosolic NADPH-dependent oxidoreductase that catalyzes the reduction of glucose to sorbitol, which is further processed to fructose [7]. Aldose reductase (AR) has a low affinity (high *K*m) for glucose and, under euglycemic conditions, this pathway plays a minor role in glucose metabolism [6]. Excess glucose is also channeled into the accessory polyol pathway, where it is reduced to polyalcohol sorbitol by AR, an NADPH-dependent enzyme [8]. In the polyol pathway, sorbitol is oxidized to fructose by sorbitol dehydrogenase, with NAD+ reduced to NADH. Under hyperglycemia, this pathway can account for 25–30% of total glucose metabolism [9]. Overexpression of human AR in low-density lipoprotein (LDL) receptor (LDLR) deficient mice resulted in increased atherosclerotic lesion size if mice became diabetic by administration of streptozotocin (STZ) [5, 10]. Atherosclerotic lesions in normoglycemic LDLR−/− did not differ significantly between AR-overexpressing mice and mice with normal AR expression [11]. Long-term polyol pathway activation also increased intimal thickening in dog coronary arteries, an effect that could be blunted by AR inhibition [12]. Polyol pathway activation also triggered abnormalities in endothelium-dependent relaxation in aortas from STZ-diabetic rats and decreased nitric oxide (NO) release and functionality [13, 14].

2.2. Increased intracellular formation of advanced glycation end products (AGEs)

One of the important mechanisms responsible for accelerated atherosclerosis in diabetes is the Maillard reaction—a type of non-enzymic browning which involves the reaction of carbonyl compounds, especially reducing sugars, with compounds which possess a free amino group, such as amino acids, amines, and proteins [15]. This reaction is subdivided into three main stages. In an early stage, the protein glycation process starts with a nucleophilic addition between free ε-amino or NH_2-terminal groups of proteins and the carbonyl group of reducing sugars (normally glucose or glyceraldehyde) to form a reversible Schiff base [16]. By structural irreversible rearrangements, more Amadori products—stable keto-amines—are formed (i.e., hemoglobin A1c (Hb A1c) [17]. In an intermediate stage, breakdown of Amadori products results in a variety of reactive dicarbonyl compounds such as glyoxal, methylglyoxal, and deoxyglucosones. In the late stage of glycation due to oxidation, dehydration, and cyclization reactions, irreversible compounds called AGEs are formed [18]. AGEs act either by modifying substrates, or by interacting with specific receptors [16]. AGEs-induced damage can occur to the vasculature, vascular cells, and cells implicated in vascular homeostasis via at least the following 4 mechanisms [19, 20]: (1) AGEs modify intracellular proteins, including those involved in the regulation of gene transcription; (2) precursors of AGEs leave the cells via diffusion and modify nearby extracellular matrix molecules, subsequently altering the signaling between matrix and cells and ultimately causing cellular dysfunction; (3) AGEs and their precursors modify circulating proteins in the bloodstream, thereby altering their function; (4) circulating proteins modified by AGEs bind to and activate AGE receptors, thereby altering the production of inflammatory cytokines and growth factors and causing tissue damage [19, 20].

The deleterious effects of AGEs on the vasculature can also be classified either as follow:

2.2.1. Receptor-independent effects of AGEs

Collagen in the blood vessel wall has a relatively long biological half-life, and with time undergoes significant non-enzymatic glycation, which may have a considerable bearing on atherosclerosis [21]. Soluble plasma proteins, such as low-density lipoprotein cholesterol (LDL-C) and immunoglobulin G (IgG), are also entrapped and covalently cross-linked by AGEs on collagen [20, 22]. Glycation of LDL-C decreases recognition of LDL-C particles by the LDL-receptor and enhances the uptake of LDL-C by a low-affinity high-capacity receptor pathway on macrophages. Decreased LDLR affinity of glycated LDL-C may result in increased oxidation of particles and may sufficiently alter their structure to render them immunogenic [23]. Glycated LDL-C is more susceptible to oxidative modification than non-glycated LDL-C. Being immunogenic, glycated LDL-C accumulates in plasma and may enhance cholesterol ester accumulation in macrophages and thus may increase the risk of atherogenic complications [23]. Glycation of apolipoprotein A1 (Apo-AI), the major protein of the protective HDL-C (high-density lipoprotein cholesterol) complex is increased in T2DM and has been shown to induce conformational changes and decreased stability of the lipid-protein interaction, as well as a reduction in the ability of the lipoprotein to self-associate [24, 25]. HDL-C glycated in vitro and Apo-AI isolated from diabetic subjects show decreased ability to activate lecithin-cholesterol acyltransferase, which drives reverse cholesterol transport by esterifying the cellular cholesterol removed by HDL-C [26, 27]. In human aortic endothelial cells, glycated and glycoxidized HDL-C induces H_2O_2 formation, dampens the expression of endothelial nitric oxide synthases (eNOS) decreases NO production, promotes apoptosis associated with increased caspase 3 expression, attenuates caspase 3 inhibition, and increases release of cytochrome c into the cytosol [28, 29].

2.2.2. Receptor-dependent effects of AGEs

AGEs initiate diabetic micro- and macrovascular complications through the structural modification and functional alteration of the extracellular matrix proteins [30]. The receptor for AGEs (RAGE) is a multiligand receptor of the immunoglobulin superfamily of cell surface molecules, acting as a counter-receptor for these diverse molecules [31]. AGE/RAGE signaling elicits activation of multiple intracellular signal pathways involving NADPH oxidase, PKC, and mitogen-activated protein kinases (MAPKs), resulting in nuclear factor NF-kappaB activity [31]. In human diabetic atherosclerotic plaques, RAGE was demonstrated to be upregulated and its expression colocalized with inflammatory markers such as cyclooxygenase 2 and matrix metalloproteinases, particularly in macrophages at the vulnerable regions of atherosclerotic plaques [32, 33]. Administration of the soluble form of RAGE (sRAGE) could work as a decoy receptor for AGEs and might inhibit the binding of AGEs to RAGE, preventing the development and progression of atherosclerosis in animal subjects [34]. The augmented response to arterial injury in diabetes was shown to be associated with RAGE, because administration of sRAGE caused decreased neointimal expansion in hyperglycemic fatty Zucker rats [35].

2.3. Activation of protein kinase C

Protein kinase C (PKC), a multifunctional serine/threonine-specific protein kinase, plays a crucial role in many cellular functions and affects many signal transduction pathways. The AGC

group is named after the protein kinase A, G, and C families that are closely related to the cAMP-dependent protein kinase [36]. Twelve PKC isoforms have thus far been identified, which differ in terms of structure and substrate requirements [37]. Eight isoforms are activated by diacylglycerol (DAG) [6, 38]. Hyperglycemia can contribute to the direct and indirect production of ROS via the activation of the DAG-PKC pathway [6, 38]. Indirect PKC activation may be due to RAGE engagement or polyol pathway activation or activation of the12/15-lipoxygenase (12/15-LO) pathway [39]. Increased PKC levels associated with diabetes are found in several tissues including the aorta and the heart [40, 41]. Higher PKC activation triggers hyperglycemia-induced cardiometabolic perturbations such as changes in blood flow, basement membrane thickening, vascular permeability, angiogenesis, cell growth, and enzymatic activity alterations [42, 43]. PKC activation directly increases the permeability of albumin and other macromolecules through barriers formed by endothelial cells [44]. PKCβ_1 and PKCβ_2 are two of the classical isoforms (α, β, and γ) of PKC [45]. Of the two isoforms, PKCβ_2 overexpression and activation facilitates the development of cardiac hypertrophy and fibrosis, which eventually leads to left ventricular dysfunction suggesting that PKCβ may play a central role in the development of diabetic cardiomyopathy (DCM) [46, 47]. PKCβ_2 activation has been implicated in diabetes-associated abnormalities via inhibition of Akt (protein kinase B)-dependent endothelial nitric eNOS activity [48]. Restoration of Akt-eNOS-NO signaling has been shown to attenuate DCM and myocardial dysfunction [49]. Quantitative immunoblotting revealed a significant increase in membrane fraction expression of PKC-β1 and -β2 in failed human hearts [50]. Among the processes induced by hyperglycemia, activation of PKC may contribute to DCM by inhibiting the metabolic actions of insulin [51]. The PKC-β inhibitor ruboxistaurin (LY333531) is a class of bisindolylmaleimide [52]. In vivo LY333531 treatment prevents excessive PKCβ_2 activation and attenuates cardiac diastolic dysfunction in rats with STZ-induced diabetes. LY333531 suppresses the decreased expression of myocardial NO and phosphate endothelial eNOS [53]. Peroxisome proliferator-activated receptors gamma (PPARs-γ), could directly affect vascular function because of their expression in endothelial cells and smooth vascular muscle cells [54, 55].

2.4. Increased glucose flux through the hexosamine pathway

The hexosamine biosynthesis pathway (HBP) is another side branch of glycolysis [56]. The reaction in which glucose 6-phosphate is changed to fructose 6-phosphate is catalyzed by glutamine fructose-6-phosphate amidotransferase (GFAT) [57]. The major product of HBP is UDP-N-acetylglucosamine (UDP-GlcNAc) [57]. UDP-GlcNAc regulates flux through HBP by regulating GFAT activity and is the obligatory substrate of O-GlcNAc transferase [57, 58]. Hyperglycemia stimulates the expression of PAI-1 in smooth vascular muscle cells and aortic endothelial cells. This effect is thought to be an important factor in the development of vascular disease in diabetes [59, 60]. Sp1 (a protein that in humans is encoded by the SP1 gene) was the first transcription factor identified as an O-GlcNAc modified protein [60]. It has multiple O-GlcNAc modification sites, and its phosphorylation on serine–threonine is inversely proportional to its O-GlcNAc modification [57, 61]. The glycosylated form of Sp1 seems to be more transcriptionally active than the deglycosylated form [62]. The major mechanism of glucose toxicity is the increased mitochondrial superoxide production; this event can account for the diverse manifestations in vascular cells, i.e., increased polyol pathway flux, increased AGE products, activation of PKC, and increased HBP [6, 63]. Inhibition of the rate-limiting

enzyme in the conversion of glucose to GFAT blocks hyperglycemia-induced increases in the transcription of TGF-b1 and plasminogen activator inhibitor-1 [64, 65]. This pathway also plays an important role in hyperglycemia-induced and fat-induced insulin resistance [66, 67]. A prospective study examined the effect of strict blood glucose control through intravenous insulin aimed at euglycemia on the concentration of UDP-GlcNAc and UDP-GalNAc in the muscles of severely insulin resistant, uncontrolled, obese, T2DM patients [67, 68].

2.5. 12/15-lipoxygenase (12/15-LO) pathway

12/15-LOs are enzymes that insert molecular oxygen into polyunsaturated fatty acids, such as arachidonic acids, leading to formation of 12(S)- and 15(S)-hydroxyeicosatetraeonic acid [69]. 12/15-LO enzymes and their products, namely HETEs (hydroxyeicosatetraeonic acid) and hydroxyoctadecadienoic acids, have been implicated in the pathogenesis of atherosclerosis [70]. Several studies have shown that the 12/15-LO pathway is also able to mediate oxidative modification of LDL-C [71, 72]. 12/15-LO seems to be involved in hyperglycemia, as well as minimally modified LDL-mediated adhesion of monocytes to the endothelium and promotes smooth vascular muscle cell hypertrophy [73]. Also 12(S)- HETE promotes monocyte adhesion to endothelial cells, probably in part by inducing the fibronectin splice variant CS-1 (C-terminal fragment of the connecting segment 1) and VCAM-1 on endothelial cells [73]. Some metabolites of the 12/15-LO system, i.e., 13-hydroxyoctadecadieonic acid (13-HODE) reduces platelet adhesion to endothelial cells and binds to PPARγ thereby reducing macrophage expression of matrix metallopeptidase 9 and proinflammatory cytokines [74].

3. The potential of diet in preventing cardiovascular disease and diabetes

The 2016 American Diabetes Association (ADA) Lifestyle Guidelines support the idea of a healthy diet to improve overall health, in light of achieving body weight, individualized glycemic, blood pressure, and lipid goals [75]. The 2016 European Guidelines on CVD prevention in clinical practice acknowledge that the Mediterranean diet is the most studied specific dietary pattern, which comprises many of the foods and nutrients that have been recommended previously, such as high intake of fruits, vegetables, whole grain products, fish, and unsaturated fatty acids [76]. The PREDIMED study (Prevention with Mediterranean Diet) demonstrated that Mediterranean diet reached a statistically significant reduction in the rate of the composite cardiovascular primary end-point of myocardial infarction (MI), stroke, or cardiovascular death [77]. The Mediterranean diet protects the heart, improves lipid profile, reduces blood pressure, and improves glucose tolerance [78]. Current evidence indicates that the Mediterranean diet is effective in improving glycemic control and reducing cardiovascular risk factors in people with T2DM and should therefore be considered in the overall strategy for the management of people with diabetes [79]. In the most extensive study assessing the effects of the Mediterranean diet on patients with newly diagnosed T2DM, the follow-up results over 8.1 years show that compared to a traditional low-fat diet, the rate of regression in the intima-media thickness of the carotid artery was higher by 49%, and the rate of progression lower by 25% in the Mediterranean diet group [80, 81].

4. Using food to meet dietary guidelines

Evidence-based nutrition practice guidelines are devised to guide clinicians in assisting dietitians and patients/clients in taking appropriate decisions regarding nutrition care for specific disease, or conditions in typical settings [82, 83]. The 2015–2020 US Dietary Guidelines are a critical tool for professionals to help Americans make healthy choices in their daily lives to help prevent chronic disease. It serves as the evidence-based foundation for nutrition education materials that are developed by the US Federal Government for the public [77]. Strong evidence reflects a large, high-quality, and/or consistent body of evidence. Moderate evidence reflects sufficient evidence to draw conclusions. Limited evidence reflects a small number of studies, studies of weak design or with inconsistent results, and/or limitations on the generalizability of the findings [77, 84]. The ADA uses the Create Your Plate system, which divides a plate into three sections: non-starchy vegetables (the largest section), starchy foods, and meat or meat substitutes [85]. The Harvard School of Public Health uses the Healthy Eating Pyramid, which is split into nine sections, including a base of daily exercise and weight control [86]. The LiveWell for LIFE project uses National Plates to show the ideal composition of diets in various European Union countries which are both healthy, environmentally sustainable and affordable [87]. Prospective Urban Rural Epidemiology (PURE study) is an epidemiological study carried out in 18 countries, examining associations between diet and total mortality, CVD mortality, CVD events, and non-CVD mortality. [88] The PURE study carried out between 2003 and 2009 on 153,996 adults, aged 35–70 from urban and rural communities in low, middle, and high-income households, found that elevated carbohydrate diets (74.4–80.7% of daily calories from carbs) had a mortality hazard ratio 1.28 (1.12–1.46) times greater the median follow-up period of 7.4 years [88]. Total fat and individual types of fat were associated with lower risk of total mortality, but were not significantly associated with risk of CVD mortality [89]. Reducing saturated fatty acid intake and replacing it with carbohydrate have an adverse effect on blood lipids [88]. Global dietary guidelines should be reconsidered in light of these findings.

5. Dietary items

5.1. Dietary fiber

Dietary fiber can be classified in different ways: soluble versus insoluble based on water solubility; fermentable versus non-fermentable based on whether or not it can be fermented by the microbiota in the large intestine; and viscous versus non-viscous related to its viscosity [90]. Fruit, vegetables, and cereals are the major sources of dietary fiber. The analysis of 67 clinical trials on diets high in soluble fibers suggested that these fibers lower total cholesterol and LDL-C [91]. Water insoluble fibers remain unchanged during digestion and have no effect unless they displace foods supplying saturated fats and cholesterol [92]. Most of the available epidemiologic studies suggest that dietary fiber is inversely related to coronary artery disease [93]. Diet rich in dietary fiber is beneficial for the treatment of T2DM [94], as dietary fiber ameliorates postprandial hyperglycemia by delaying digestion and absorption of carbohydrates [95]. A recent systematic review of the literature reported that moderate

amounts of fiber supplements (4–19 g/day) achieved little improvement in glycemic control or CVD risk factors [96]. It has been reported that increased intake of dietary fiber and low GI diet with legumes reduced blood pressure compared with wheat fiber diet in T2DM patients [95]. A cross-sectional study in adults men and women indicated that the highest total dietary fiber and insoluble dietary fiber intakes were associated with a significantly lower risk of overweight, high blood pressure, plasma apolipoprotein (apo) B, apo B, apo A–I, cholesterol, triacylglycerols, and homocysteine [97]. The fiber intake should, ideally, be 40 g/day (or 20 g/1000 kcal/day) or more and about half should be of the water-soluble type. People with T2DM are encouraged to choose ≥5 servings of fiber-rich vegetables or fruit and ≥4 servings of legumes per week to achieve the fiber intake goals set for the general population [98].

5.2. Polyphenols

A number of antioxidants showed beneficial effect in experimental models of atherosclerosis and CVD [99, 100]. The main polyphenol dietary sources are fruit and beverages (fruit juice, wine, tea, coffee, chocolate, and beer), dry legumes, and cereals [101]. Dietary polyphenols have been shown to possess cardioprotective effects. Oleuropein inhibits the oxidation of LDL-C in vitro [102]. Dietary quercetin decreases lipid peroxidation and upregulates the expression of serum HDL-associated paraoxonase-1 (PON-1) in the liver [101]. PON-1 may mediate anti-atherogenic properties by protecting LDL-C from oxidation. Several studies have indicated that red wine polyphenolic compounds (RWPCs) were able to inhibit proliferation and migration of vascular cells. RWPCs induced NO-mediated endothelium-dependent relaxations in isolated arteries. The activation of eNOS led to an increase in $[Ca^{2+}]_i$ and phosphorylation of eNOS by the PI3-kinase/Akt pathway [103]. RWPCs also increased endothelial prostacyclin release and inhibited the synthesis and the effects of endothelin-1 in endothelial cells [101].

5.3. Lycopene

Lycopene is a natural carotenoid found in tomatoes, which has biochemical functions as an antioxidant scavenger, hypolipidemic agent, and inhibitor of pro-inflammatory and prothrombotic factors [104]. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots, and pink guavas, contain lycopene. Processed tomato products are good dietary sources of lycopene [105]. Two major hypotheses have been proposed to explain the anti-atherogenic activities of lycopene. The non-oxidative action of lycopene results in an increase of gap-junction communication between cells and modulation of immune function [106] .The oxidative hypothesis supports the prevention of the oxidization of LDL-C as the initial step leading to its uptake by the macrophages inside the arterial wall and the formation of foam cells and atherosclerotic plaque [105]. A possible mechanism for the protective role of lycopene in CVD is via the inhibition of cellular 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis [107]. Results from the Harvard Medical School's Women's Health Study showed that women with the highest intake of tomato-based foods rich in lycopene had a reduced risk for CVD compared to women with a low intake of these foods [108]. The European multicenter case-control study on antioxidants,

myocardial infarction, and breast cancer (EURAMIC) study found that the risk of MI was 60% lower for the highest quintile of adipose lycopene concentration compared to the lowest quintile, after adjustment for age, family history of CVD and cigarette smoking [109]. In a cross-sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates from CVD, lower blood lycopene levels were found to be associated with increased risk and mortality from CVD [110]. Many studies show that high consumption of tomato products can improve resistance to oxidation in people with T2DM [111]. Eating a lycopene-rich Mediterranean diet increases lycopene levels and can reduce the levels of hemoglobin A1c from 7.1 to 6.8% [112]. In a case-control study on serum β-carotene and the risk of T2DM, participants in the highest tertile of serum β-carotene levels had a 55% lower risk of developing T2DM [113]. In a quasi-experimental study, 32 T2DM patients received 200 g raw tomato daily for 8 weeks. There were significant decreases in systolic and diastolic blood pressure and also a significant increase in apoA-I compared with initial values, which suggests the beneficial role of tomato consumption in reducing cardiovascular risk associated with T2DM [114, 115].

5.4. Fatty acids

N−3 fatty acids including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have a significant role in the prevention of CVD [116]. The evidence supports a dietary recommendation of ≈500 mg/day of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) for CVD risk reduction [117]. A meta-analysis suggests that ALA consumption may also confer cardiovascular benefits, and each 1 g/d increment in ALA intake was associated with a 10% lower risk of CVD death [118]. Dietary sources of ALA include flaxseeds and flaxseed oil, walnuts and walnut oil, soybeans and soybean oil, pumpkin seeds, rapeseed oil, and olive oil [119]. In the GISSI Prevention Study, treatment with n-3 PUFA significantly lowered the risk of the primary endpoint (death, non-fatal MI, and stroke) [120]. Several mechanisms explaining the cardioprotective effect of the n-3 PUFA have been suggested including antiarrhythmic and antithrombotic roles [119].

5.5. Ethanol and non-ethanolic components of wine

Several groups are now beginning to use animal models of myocardial ischemia and reperfusion to explore whether certain nutrients, including ethanol and non-ethanolic components of wine, may have a specific protective effect on the myocardium, independently from the classical risk factors for coronary disease involved in vascular atherosclerosis and thrombosis [121]. Most epidemiological studies have suggested an inverse association between regular light to moderate drinking and the risks of CVD [122]. Researchers have wondered whether moderate alcohol consumption mediates some of its cardioprotective effects by stimulating NO, and conversely, whether binge drinking diminishes NO availability [123]. In a swine model of chronic ischemia, alcohol administration promoted angiogenesis, increased capillary and arteriolar density in non-ischemic myocardium [122]. Numerous studies indicate that moderate red wine consumption is associated with a protective effect on the cardiovascular system, which has largely been attributed to the rich content of phenolic compounds [124, 125]. Polyphenolic antioxidants scavenge the free radicals, inhibit lipid peroxidation (lipoproteins,

membranes), attenuate platelet aggregation, produce coronary vasorelaxation, and protect from cellular injury [126]. Sudden death was examined in US males who participated in the Physicians' Health Study over 12 years of follow-up. Men who consumed light to moderate amounts of alcohol (2–6 drinks/week) had a significantly reduced risk of CVD compared to those who never or rarely consumed alcohol [127]. Daily intake of red wine decreased plasma malondialdehyde and oxidized LDL-C, indicating the antioxidant activity of wine polyphenols [128]. The NO-mediated vasorelaxant effects of red wine phenolic extracts acted mainly through activating endothelial NO synthase [129]. Mild to moderate beer drinking (12.5–25 g/day) provides cardiac protection, improves endothelial function by inhibiting vascular oxidative damage and modulating the Akt/eNOS pathway, which should be attributed to the non-alcohol components in beer [130]. PPARγ plays an important role in glucose and lipid metabolism [131]. Ellagic acid and epicatechin gallate, active components of wine, were reported to have similar affinity to PPARγ of rosiglitazone, which is a standard drug for the treatment of T2DM [132]. Xanthohumol is a flavonoid which was reported to exist in hops and beer could decrease the activity of alpha glucosidase in a non-competitive and reversible way via directly binding to the enzyme and triggering conformational alterations [131].

6. Dietary patterns

6.1. Low-fat diets

Low-fat diets may improve quality of life and extend life expectancy in healthy people, as well as in patients with overweight issues, diabetes, and CVD [77]. Due to the high risk of CVD in individuals diagnosed with T2DM, the goal in dietary fat intake (amount and type) is similar to that of patients with CVD without diabetes [77]. Certain saturated fatty acids (SFA), trans fatty acids (TFA), conjugated linoleic acids (CLA), and cholesterol adversely affect blood lipid levels, whereas viscous fiber, unsaturated MUFA and PUFA, plant sterols/stanols, and to a certain extent, polyphenols have favorable effects [113]. Diet recommendations include obtaining 25 to 35% of daily calories from fats, and restricting saturated fats to less than 7% of total calories, TFA less than 1%, and cholesterol to less than 200 mg/day [133]. These levels can be achieved by eating more grain products, vegetables and fruits, low-fat dairy products, and fat-free milk, and by reducing food containing TFA [134]. A randomized controlled trial found that diets containing ≥7% SFA and ≥200 mg/day cholesterol led to a reduction of the LDL-C level by 9–12% compared to baseline values or to a more standard Western-type diet [135].

6.2. Low-carbohydrate diets

Low-carbohydrate diets are preferable to a low-fat diet in reducing triglycerides (TG) levels and for increasing HDL-C blood levels [77]. A low-carbohydrate diet is defined as consumption of 30–130 g of carbohydrates per day or up to 45% of total calories [136]. There is no justification for the recommendation of very low carbohydrate diets in T2DM. Carbohydrate quantities, sources, and distribution should be selected to facilitate near-normal long-term

glycemic control [137]. A two-year international Dietary Intervention Randomized Controlled (DIRECT) study found that compared to the other diets, the low-carbohydrate diet was most effective for weight loss, and changes in biomarkers (TG, HDL-C, glucose, and insulin) [138].

6.3. A Mediterranean diet

A Mediterranean diet characterized by a relatively high fat intake (40–50% of total daily calories), of which SFA comprises ≤8%, and MUFA 5–25% of calories is associated with a higher life expectancy in healthy people, as well as with lower rates of stroke, coronary heart disease, and diabetes [77]. Mediterranean-style diets are preferable to a low-fat diet in reducing cardiovascular events, increasing blood HDL-C levels, decreasing plasma TG levels, and improving insulin sensitivity [77]. This diet is characterized by abundant legumes, unrefined cereals, vegetables, fresh fruit, olive oil as the principal source of fat, moderate to high consumption of fish, dairy products (mostly as cheese and yogurt), wine consumed in low to moderate amounts, and red meat consumed in low amounts [139]. The Mediterranean-style eating pattern has been observed to improve cardiovascular risk factors in individuals with diabetes [140]. Interventional studies demonstrate the beneficial role of the Mediterranean diet in T2DM management, greater improvements in glycemic control, and reduction of CVD risk factors [141]. The Mediterranean diet is associated with a lower incidence of all-cause mortality [142].

6.4. The dietary approach to stop hypertension (DASH) diet

The dietary approach to stop hypertension (DASH) diet is a dietary pattern to prevent and control hypertension. Its main target is to lower blood pressure, and therefore CVD incidence, by dietary means [77]. The DASH diet includes a relatively high daily content of fruit, vegetables, and grain; moderate amounts of low-fat dairy products, fats, and oils; a decreased content of meat, regular-fat dairy products, snacks, and sweets. All meals have similar sodium content (approximately 3000 mg/day) [77, 143]. Several observational studies in adults have shown that adherence to a DASH-like diet has positive effects on cardiovascular health, including reduced risk of hypertension, T2DM, heart failure, coronary heart disease, stroke [144]. The PREMIER trial reported that standard dietary treatment of hypertensive patients often showed unfavorable control of lipid profile and other cardiovascular risk factors [145]. In the Diabetes Control and Complications Trial, intensive glucose control significantly reduced total cholesterol and LDL-C and TG. The DASH-sodium results indicate that low sodium levels are correlated with the largest reductions in blood pressure for participants at both pre-hypertensive and hypertensive levels [146].

7. Conclusions

To maintain a healthy weight, diet should include a variety of foods, increased intake of fruits and vegetables, whole grains, olive oil, and nuts. Moderate intake of fish, poultry, and red wine is recommended. Consumption of foods high in sodium and sugar should be minimized. The Mediterranean diet has been shown to reduce the incidence of major cardiovascular events

among patients with T2DM. Low-fat dietary patterns have been shown to reduce the risk of CVD in both primary and secondary prevention. The healthy DASH diet plan was developed to lower blood pressure and is associated with a lower risk for developing T2DM. Low-carbohydrate diets may help prevent obesity, T2DM, and atherosclerosis.

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Chapter 4

Antidiabetic and Safety Properties of Ethanolic Leaf Extract of *Corchorus olitorius* in Alloxan-Induced Diabetic Rats

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71529

Abstract

Diabetes is a major metabolic disease of global concern. Ethanolic extract of *Corchorus olitorius* leaf was investigated for antidiabetic activity in alloxan-induced diabetic rats. A total of thirty-six albino rats (*Rattus norvegicus*) with body weight 150.50 ± 10.50 g were randomly selected into six groups (A–F). Group A animals were non-diabetic and received 0.5 mL distilled water, groups B, C, D, E and F were made diabetic by administration of alloxan monohydrate (150 mg/kg, body weight i.p). Group B was diabetic untreated, group C was diabetic and treated with glibenclamide, while groups D, E and F received the ethanolic extract of *C. olitorius* leaf at a dose of 200 mg/kg, 400 mg/kg and 800 mg/kg body weight respectively. Phytochemical screening showed the presence of flavonoids, tannins, saponins, phlobatannin anthraquinones, phenol and cardiac glycoside and saponin. The blood glucose of the alloxanized rats after 72 hours which ranged from 17.30–25.33 mmol/L were significantly ($p < 0.05$) and progressively reduced in treated groups which compared favorably with the standard drug group. The significantly ($p < 0.05$) elevated levels of serum and liver bilirubin (direct and total), transaminases (AST and ALT), alkaline phosphatase, urea, creatinine, total cholesterol, triglyceride, LDL-C, as well as reduced levels of total protein, globulin, albumin and HDL-C in the diabetic untreated rats were normalized upon treatment with ethanolic extract of *C. olitorius* leaf. These results suggest that the ethanolic extract of *C. olitorius* leaf possesses antihyperglycemic property with no major side effect hence it could be considered safe for the management of diabetes.

Keywords: antioxidants, *Corchorus olitorius*, blood glucose, diabetes

1. Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar, or glucose), or when the body cannot effectively use the insulin it produces. Diabetes mellitus (DM) presents enormous and increasingly important public health issues as it is listed among the commonest non-communicable diseases (NCDs) globally, the prevalence of which increased in adults from 4.7% in 1980 to 8.5% in 2014. Diabetes mellitus led to about 1.5 million deaths in 2012. Elevated blood glucose resulted into an additional 2.2 million deaths through complications arising from heart related diseases. Over 43% of these deaths were recorded before the seventh decade of life [1, 2]. Prevalence of DM in Africa is approximately 1% in rural areas and up to 7% in urban sub-Sahara Africa [3]. In Nigeria, DM is estimated to be between 0.9–15% [4].

The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries. The disease is characterized by high blood glucose levels and abnormal metabolism of carbohydrates, proteins, and fat associated with a relative or absolute insufficiency of insulin secretion and with various degrees of insulin resistance. Such alterations result in increased blood glucose causing a chronic state of high blood glucose level (hyperglycemia) that results from an absolute or relative insulin deficiency and is associated with long-term complications affecting the eyes, kidneys, heart and nerves [5].

Cellular stress as a result of reactive oxygen species such as peroxyl (ROO), nitrogen dioxide (NO_2^-), superoxide ($O_2.-$), nitric oxide (NO.), hydroxyl (OH^-) and non-free hydrogen peroxide and singlet oxygen radicals play a significant role in the pathogenesis of several disease conditions such as DNA damage, cellular degeneration and oxidation of lipids and proteins. These have been implicated in the development of these diseased conditions associated with diabetes [6–9].

The pathogenesis of diabetes mellitus is managed by insulin and oral administration of hypoglycemic drugs such as sulfonylureas and biguanides which are not without a number of side effects. Moreover, none of the oral synthetic hypoglycemic agents has been successful in diabetes management and controlling long-term microvascular and macrovascular complications [10]. The toxicity of oral antidiabetic agents differs widely in clinical manifestations, severity, and treatment [11].

Optional therapies such as herbal preparations have been used for the management of diabetes. The benefits of these herbal medications are their efficacy, endogenous relativity, cost effectiveness and tolerability [12]. Various parts of medicinal trees have been employed in the third world traditional medicinal system and most have demonstrated pre-clinical or clinical normoglycemic activity [13]. Furthermore, World Health Organization has also recommended the evaluation of traditional plant treatments for diabetes [14].

Corchorus olitorius is a plant from the Tiliaceae family from the Mediterranean region, its leaves have been found to be rich in antioxidants, such as vitamin C, vitamin E, β-carotene, α-tocopherol, glutathione and phenols [15]. The leaves also contain fatty acids, minerals, other vitamins and

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Figure 1. *Corchorus olitorus.*

mucilaginous polysaccharides, and have been used as traditional folkmedicine. Yokoyama et al [16] reported *C. olitorius* leaves to ameliorate atopic dermatitis in NC/Nga mice [16]. It is called 'ewedu' in Yoruba Language and is a common source of vegetable among Yoruba tribe in Nigeria. This study therefore investigated the anti diabetic and safety potentials of ethanolic leaf extract of *Corchorus olitorius* in alloxan-induced diabetes in rats (**Figure 1**).

2. Materials and methods

Alloxan monohydrate obtained is a product of Sigma Chemical Company, St. Louis, Mo, USA. Kit for the estimation of AST, ALT, urea, creatinine and bilirubin, were produced by Randox Laboratories Ltd., Antrim, UK. All other chemicals were of analytical grades and prepared in all-glass apparatus using distilled water (BDH, UK).

2.1. Plant extract preparation

The fresh leaves of *Corchorus olitorius* were obtained from a vegetable farm in Ilorin West Local government, Ilorin, Kwara State, Nigeria. It was taxonomically authenticated at the Department of Plant Biology, University of Ilorin, Ilorin Kwara state, Nigeria where a voucher specimen number 064 was deposited. Fresh leaves of *C. olitorius* was collected and air-dried for 21 days until constant weight was obtained. They were pulverized using an electric blender machine and sieved to obtain a fine powder. Forty grams (400 g) was macerated in 2500 ml of 80% ethanol, shaken at regular intervals to achieve maximum extraction. The solution was filtered using Whatman No.1 filter paper and the filtrate concentrated in water bath at 40°C. The dried extract was later weighed and reconstituted in distilled water to the required dosage for administration.

2.2. Experimental animals

A total of thirty-six (36) Albino rats (*Rattus norvegicus*) weighing 150.50 ± 10.50 g were obtained from the Animal Holding Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Kwara State, Nigeria. Animals were maintained under standard environmental conditions i.e. ambient temperature of (27 ± 2°C) and at 45–55% relative humidity for 12 hours,

each of dark and light cycle. The rats were allowed free access to standard laboratory food and water ad libitum throughout the experiment.

2.3. Induction of diabetes

The animals were fasted overnight and diabetes was induced by a single intraperitoneal injection of freshly prepared 150 mg/kg b.w alloxan monohydrate dissolved in (5%) sterile saline. Two days after alloxan injection, rats with blood glucose level of >12 mmol/L were separated and considered diabetic and were used for the study. Blood glucose levels were measured using blood glucose test strips with fine test glucometer (infopia Co. limited Korea). The treatment started 48 hours after alloxan injection and this was considered the first day of treatment. The treatment continued for 14 days.

2.4. Animal grouping and extract administration

Animals were divided into six groups, and for each group, six animals were treated orally once a day for 14 days as follows:

Group A: Control rats received distilled water only.

Group B: Diabetic control.

Group C: Diabetic rats received Glibenclamide at a dose of 5 mg/kg.

Group D: Diabetic rats received 200 mg/kg body weight extract.

Group E: Diabetic rats received 400 mg/kg body weight extract.

Group F: Diabetic rats received 800 mg/kg body weight extract.

2.5. Samples preparation

At the end of the experimental period, food was withdrawn from the rats and they were fasted overnight while the animals had free access to water. They were then euthanized under diethyl ether vapor and sacrificed. Venous blood was collected from the experimental animals and serum was prepared by centrifuging the blood samples at 3000 rpm for 5 minutes and serum collected by pipetting. The animals were quickly dissected and internal organs including liver and kidney were collected, blotted using filter paper to remove traces of blood and then weighed with an analytical balance. The pancreas, liver and kidney were suspended in ice-cold 0.25 M sucrose solution (1:5 m/v) and homogenized as described by Akanji and Yakubu [17].

2.6. Statistical analysis

Comparisons were made using Duncan's multiple range test, and values were considered to be significant at $p < 0.05$.

3. Results

3.1. Phytochemical constituents of ethanolic extract of *Corchorus olitorius* leaf

Table 1 shows the results of the preliminary phytochemical analysis of the leaf extract. Analysis revealed the presence of alkaloids, flavonoids, tannins, saponins, phlobatannin anthraquinones, phenol, cardiac glycoside and saponin while Terpenoids, Steroids, Triterpenes were not detected.

3.2. Glycemic effect of ethanolic extract of *Corchorus olitorius* leaf of alloxan-induced diabetic rats

Table 2 presents the glycemic effects of ethanolic extract of *Corchorus olitorius* leaf in alloxan induced diabetic rats. Single dose of alloxan monohydrate (150 mg/kg) continuously increased the fasting blood glucose from the first day of treatment till the third, while upon oral administration of ethanolic extract of *Corchorus olitorius* and standard drug (Glibenclamide) for 14 days, a significant decrease ($P < 0.05$) in fasting blood glucose was observed particularly at the highest dose of 800 mg/kg of the plant extract.

3.3. Effect of ethanolic leaf extract of *Corchorus olitorius* on body weight of alloxan-induced diabetic rats

In diabetic rats, continuous reduction in body weight was observed as shown in **Table 3**. Glibenclamide (5 mg/kg) as well as the extract treatment groups at the dose of 400 and 800 mg/kg b.w showed improvement ($P < 0.05$) improvement in body weight of diabetic rats.

Phytochemicals	Crude extracts
Anthraquinones	+
Tannins	+
Phenolics	+
Saponins	+
Terpenoids	−
Alkaloids	+
Steroids	−
Cardiac glycoside	+
Flavonoids	+
Triterpenes	−

Where: (+) indicates present; (−) indicates not present

Table 1. Phytochemical composition of the crude extract of *Corchorus olitorus*.

Treatment groups	Fasting blood glucose level after diabetes induction			
	Day 0	Day 5	Day 10	Day 14
Control	5.13 ± 0.60^{a}	4.00 ± 0.70^{a}	4.38 ± 0.20^{a}	4.13 ± 0.29^{a}
Diabetic rats + distilled water	17.03 ± 1.70^{b}	19.18 ± 1.11^{b}	18.83 ± 1.25^{b}	20.41 ± 1.07^{b}
Diabetic rats + Gliblenclamide	21.68 ± 1.93^{b}	16.05 ± 0.72^{b}	12.10 ± 0.29^{ab}	5.80 ± 0.35^{a}
Diabetic rats +200 mg/kg body weight of the extract	18.43 ± 1.04^{b}	14.58 ± 0.55^{b}	13.08 ± 0.44^{ab}	9.43 ± 0.26^{ab}
Diabetic rats +400 mg/kg body weight of the extract	20.80 ± 2.46^{b}	13.63 ± 0.21^{b}	12.30 ± 0.81^{ab}	7.88 ± 0.63^{ab}
Diabetic rats +800 mg/kg body weight of the extract	25.33 ± 1.91^{b}	22.95 ± 1.41^{b}	13.43 ± 1.10^{ab}	6.05 ± 0.66^{a}

Values are expressed as mean of six replicates ±SD and those with different superscripts down the column are statistically different ($p < 0.05$)

Table 2. Effect of ethanolic extract of *Corchorus olitorus* leaf on fasting blood glucose level (mmol/L) of alloxan-induced diabetic rats.

Treatment groups	Initial body weight (g)	Final body weight (g)
Control	136.25 ± 10.33^{a}	180.07 ± 13.07^{b}
Diabetic rats + distilled water	172.67 ± 5.10^{b}	134.01 ± 13.17^{a}
Diabetic rats + Gliblenclamide	153.33 ± 1.55^{ab}	184.22 ± 8.46^{b}
Diabetic rats +200 mg/kg body weight of the extract	157.25 ± 3.07^{ab}	164.08 ± 10.56^{ab}
Diabetic rats +400 mg/kg body weight of the extract	175.67 ± 14.06^{b}	183.19 ± 14.79^{b}
Diabetic rats +800 mg/kg body weight of the extract	141.42 ± 4.47^{ab}	172.69 ± 10.70^{b}

Values are expressed as mean of six replicates ± SD and those with different superscripts down the column are statistically different ($p < 0.05$)

Table 3. Effect of *Corchorus olitorus* leaf extract on total body weight of alloxan-induced diabetic rats.

3.4. Effect of ethanolic leaf extract of *Corchorus olitorius* on liver function enzymes of alloxan-induced diabetic rats

The effect of ethanolic leaf extract of *Corchorus olitorius* on liver function enzymes is represented in **Figure 2**. ALT, AST and ALP levels were significantly elevated in alloxan induced diabetes. The rats treated with ethanolic leaf extract of *Corchorus olitorius* showed significant ($P < 0.05$) reduction in the activity of liver and serum ALT, AST and ALP in the groups administered 800 mg/kg b.w and standard drug (Gilblenclamide) when compared with the control while there was no significant difference ($P > 0.05$) in other treatment groups.

3.5. Effect of ethanolic leaf extract of *Corchorus olitorius* on some biochemical parameters of alloxan-induced diabetic rats

Figures 3 and **4** show the effect of administration of ethanolic leaf extract of *Corchorus olitorius* on total bilirubin, conjugated bilirubin, total protein, albumin and globulin in alloxan induced diabetic rats. The concentration of both total bilirubin and conjugated bilirubin level in serum and liver was

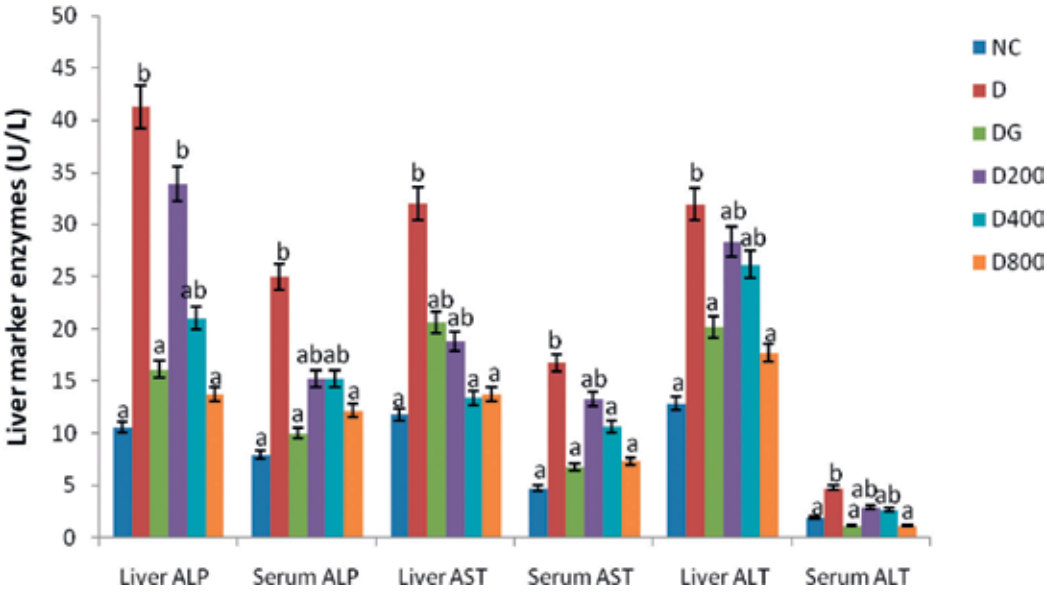

Figure 2. Effect of ethanolic leaf extract of *Corchorus olitorus* on liver function marker enzymes of alloxan-induced diabetic rats.Values are given as mean ± SD from six rats in each group. Bars not sharing a common superscript differ significantly at $p < 0.05$.

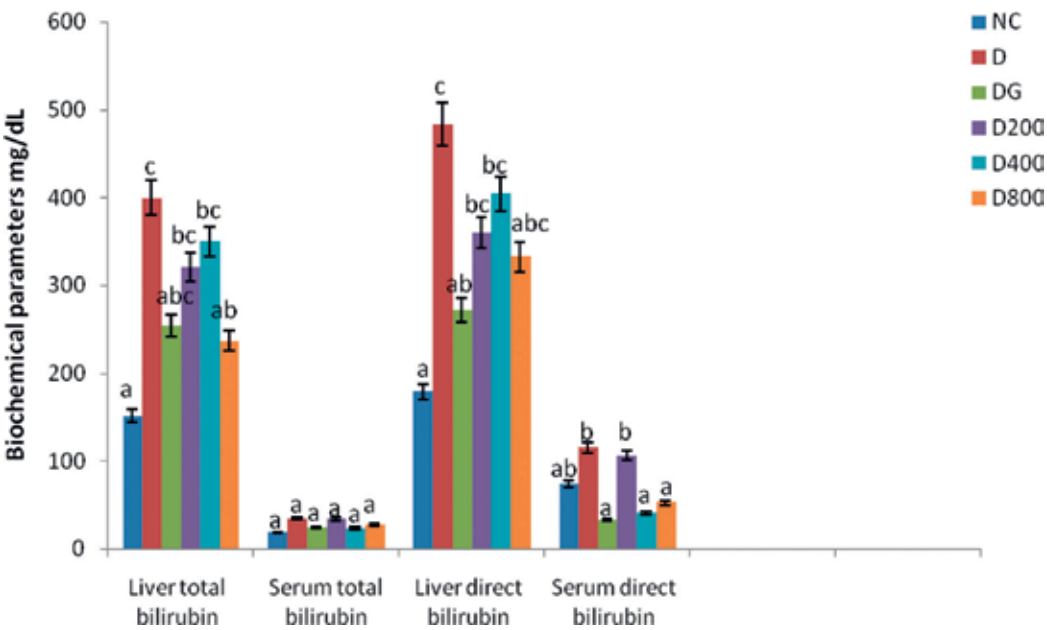

Figure 3. Effect of ethanolic leaf extract of *Corchorus olitorus* on some biochemical parameters of alloxan-induced diabetic rats.Values are given as mean ± SD from six rats in each group. Bars not sharing a common superscript differ significantly at $p < 0.05$.

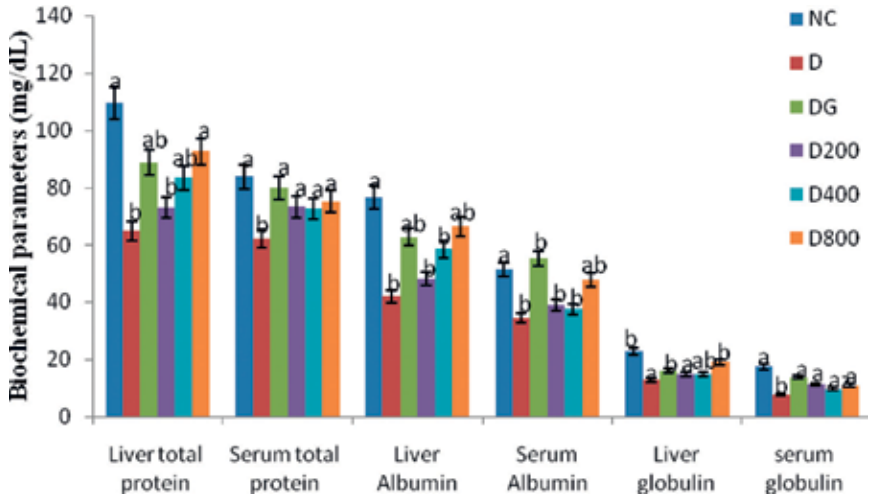

Figure 4. Effect of ethanolic leaf extract of *Corchorus olitorus* on serum and liver protein of alloxan-induced diabetic rats. Values are given as mean ± SD from six rats in each group. Bars not sharing a common superscript differ significantly at $p < 0.05$.

increased significantly ($P < 0.05$) in diabetic untreated group compared to the control but was reduced upon administration of ethanolic leaf extract of *Corchorus olitorius* for 14 days.

The diabetic untreated rats group had decreased levels of serum and liver total protein, albumin and globulin when compared with normal control rats. After treatment for 14 days, liver and serum total protein, albumin and globulin levels were restored to normalcy especially in the groups treated with 800 mg/kg body weight of the extract and reference drug (gliblenclamide).

3.6. Effect ethanolic leaf extract of *Corchorus olitorius* on kidney function indices of alloxan-induced diabetic rats

The influence of administration of ethanolic leaf extract of *Corchorus olitorius* on kidney function indices is shown in **Figure 5**. In this study, urea and creatinine levels showed significant ($p < 0.05$) increase in diabetic rats group when compared with the control but showed no significant ($p > 0.05$) difference at all doses of treatment when compared with the control.

3.7. Effect of administration of ethanolic leaf extract of *Corchorus olitorius* on liver lipid profile of alloxan-induced diabetic rats

The effect of oral administration of ethanolic leaf extract of *Corchorus olitorius* on the levels of total TC, TG, HDL, LDL-C, and VLDL-C in the serum and liver of diabetic rats are shown in **Figures 6** and **7**. In alloxan-induced diabetic rats, TC, TG, LDL, and VLDL levels were increased and HDL level was decreased significantly ($p < 0.05$) when compared with normal control rats. In diabetic rats group, administration of ethanolic leaf extract of *Corchorus olitorius* at 800 mg/kg body weight dose particularly, showed significant ($p < 0.05$) reduction in elevated TC, TG, LDL and VLDL levels while at doses 200 and 400 mg/kg body weight of the extract no significant ($p > 0.05$) difference was observed when compared to diabetic rats group. Also, a

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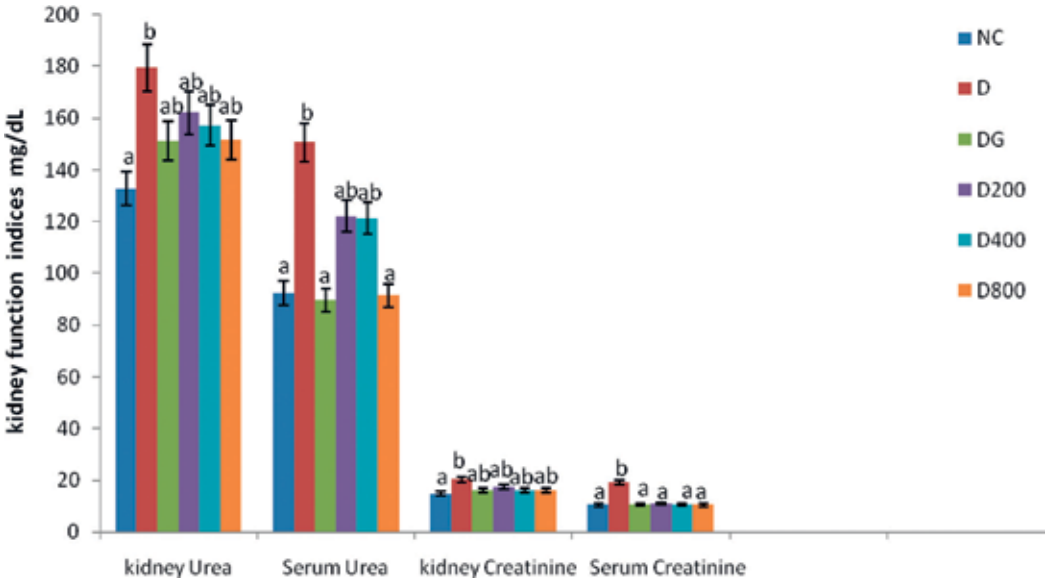

Figure 5. Effect of ethanolic leaf extract of *Corchorus olitorus* on kidney function indices of alloxan-induced diabetic rats. Values are given as mean ± SD from six rats in each group. Bars not sharing a common superscript differ significantly at $p < 0.05$.

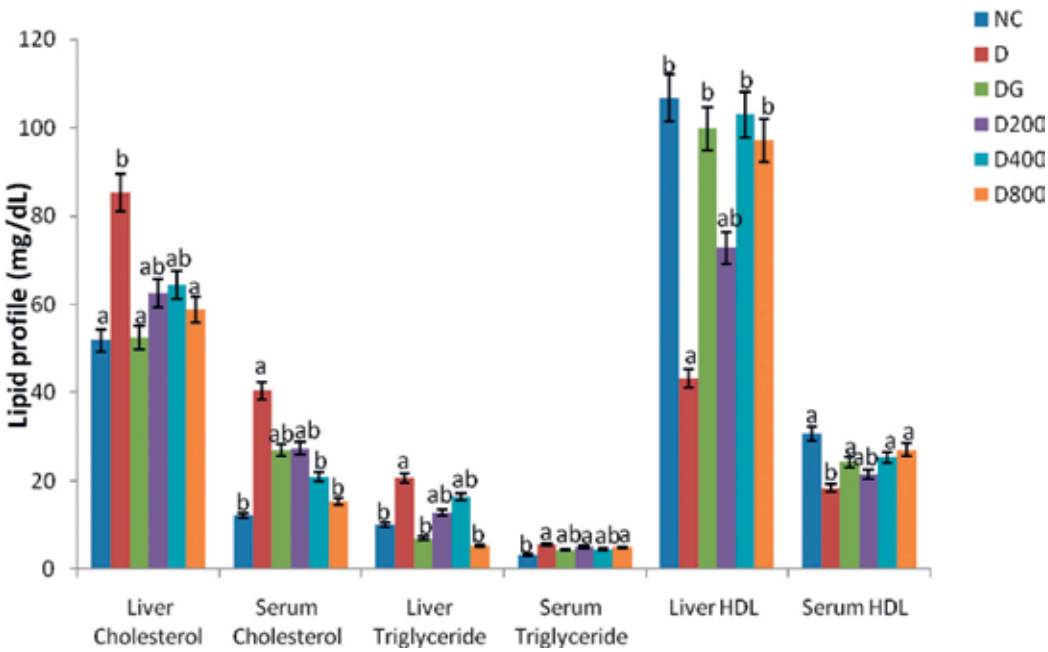

Figure 6. Effect of ethanolic leaf extract of *Corchorus olitorus* on lipid profile of alloxan-induced diabetic rats.Values are given as mean ± SD from six rats in each group. Bars not sharing a common superscript differ significantly at $p < 0.05$ (Duncan's multiple range test).

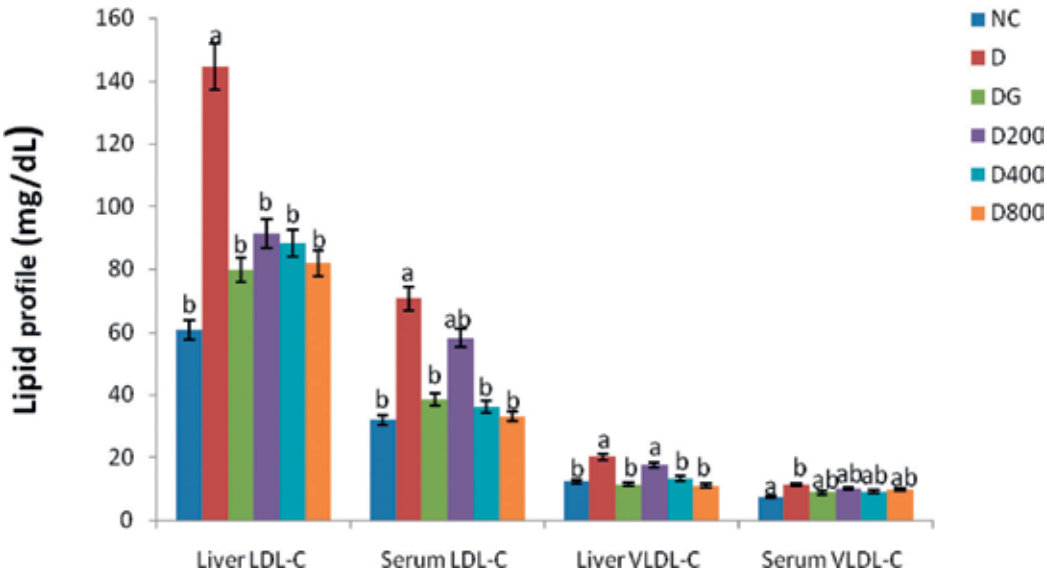

Figure 7. Effect of ethanolic leaf extract of *Corchorus olitorus* on liver and serum LDL-C and VLDL-C.Values are given as mean ± SD from six rats in each group. Values not sharing a common superscript differ significantly at $p < 0.05$ (Duncan's Multiple Range Test).

significantly ($p < 0.05$) increased level of HDL was observed in diabetic rats treated with the plant extract at doses 400 mg/kg body weight and 800 mg/kg body weight and glibenclamide compared to diabetic control rats.

4. Discussion

The therapeutic cure for diabetes mellitus has remained elusive despite the discovery of an array of medications that can ameliorate the symtopms of the disease [18]. Phytotherapies have remained a veritable source for drug discovery the world over [19], and for some decades have played an important role in the management of diabetes especially in resource poor countries.

Alloxan acts as diabetogenic by the destruction of β-cells of the islets of langerhans and causes massive reduction in insulin release, thereby inducing hyperglycaemia [20]. Insulin deficiency leads to various metabolic alterations in the animals viz. increased blood glucosel, increased levels of alkaline phosphate and transaminases etc. [21].

Phytochemical investigation of ethanolic leaf extract of *Corchorus olitorius* as shown in **Table 1** reveals the presences of alkaloids, flavonoids, tannins, saponins, phlobatannin anthraquinones, phenol and cardiac glycoside and saponin. These secondary principles are known to be bioactive for the management of diabetes. It is well known that certain flavonoids exhibit hypoglycemic activity and pancreas beta cell regeneration ability. Thus, the significant antidiabetic effect of ethanolic leaf extract of *Corchorus olitorius* may be due to the presence of more than one antihyperglycemic principle and their synergistic properties [22].

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Single dose intra-peritoneal (i.p) treatment of rats with alloxan monohydrate (150 mg/kg) caused an increase in the blood glucose. Ethanolic leaf extract of *Corchorus olitorius* and glibenclamide were found to reduce the elevated glucose level significantly in alloxan induced diabetes animals during the 14 days treatment. This suggests the hypoglycaemic effect of the plant. As suggested by Ekpenyong et al [23] that normal protein level reflects normal synthesis while high level is common in high protein diet.

The concentration of total protein globulin, albumin and bilirubin may indicate the state of the liver and type of damage. Protein molecules that are regularly employed to assess the state of health of the liver are albumins and globulins (Total Proteins). The blood circulated albumin is the main carrier protein produced in the liver. The larger globulins are responsible for immunogenic activities [24]. Decreased serum albumin and globulin concentrations in the untreated diabetic rats suggests reduced synthetic function of the hepatic cells. Oral administration of ethanolic leaf extract of *Corchorus olitorius,* however, normalized the serum albumin and globulin concentration. This is a further proof of the protective potential of ethanolic leaf extract of *Corchorus olitorius* on the liver of diabetic rats.

Bilirubin is a useful index of the excretory function of the liver. It is an important breakdown product of blood with biological and diagnostic values [25] Elevated bilirubin is an indication of liver cell impairment. The gradual increase in the serum levels of unconjugated (total and conjugated) bilirubin in diabetic rats when compared with the normal control may be an indication that the rats had liver function impairment, resulting in diminished ability of hepatocytes to conjugate bilirubin. The insignificant decrease in total and conjugated bilirubin of both the serum and liver in all the treated animals suggest the ability of the plant extract to ameliorate liver impairment caused by diabetes induction.

Liver enzymes e.g. alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alanine phosphatise level (ALP) were increased in diabetic rats which is responsible for the liver damage. The elevated serum level of these enzymes was significantly reduced by ethanolic leaf extract of *Corchorus olitorius* treatment particularly at the dose of 800 mg/kg bw, suggesting the protective effect of the plant extract against diabetes- induced hepatocellular damage especially at high dose. The diabetic complications such as increased gluconeogenesis and ketogenesis may be due to elevated enzymes [26]. The restoration of transaminases to their normal levels also treatment also indicates revival of insulin secretion.

The kidney removes metabolic wastes such as urea and creatinine, the concentration of which are usually required to assess the normal functioning of different parts of the nephrons [27]. The serum creatinine and urea concentrations are widely interpreted as measures of the glomerular filtration rate (GFR) and are used as indices of renal function in clinical practice. The concentration of these metabolites increase in blood during renal damage associated with uncontrollable diabetes mellitus. On the contrary those treated with ethanolic leaf extract of *Corchorus olitorius* effected decrease in creatinine and urea levels, indicating ameliorative effect of the plant extract on kidney functions in diabetic rats. This may suggest that the damage caused on renal function indices by the disease had been restored by the plant extract, thus the proper function of the nephrons at the tubular and glomerular level.

Inbalances in serum lipid levels are usual occurrences in a diabetic state [28]. Since changes in lipoproteins concentrations is an inherent property of diabetes mellitus, such changes are usually triggered by diabetes induced obesity and renal complications [29]. As observed in this study, administration of ethanolic leaf extract of *Corchorus olitorius* led to a reduction in cholesterol, triglycerides and low density lipoprotein (LDL) concentrations while it led to the normalization of high density lipoprotein (HDL) concentration in diabetic rats when compared to the untreated diabetic group. The serum concentration of cholesterol is usually elevated in diabetes, and such an increase is a risk factor for cardiovascular diseases. The observed high concentration of serum cholesterol during diabetes is mainly attributable to pronounced mobilization of free fatty acids from the peripheral depots, because the hormone-sensitive lipase is usually inhibited by insulin [30]. Administration of ethanolic leaf extract of *Corchorus olitorius* to diabetic rats significantly decreased the plasma cholesterol level to near normalcy and therefore reduces the risk of cardiovascular disease [31]. An increase in the concentrations of LDL- cholesterol and reduced HDL-cholesterol as observed during diabetes are associated with raised risk of myocardial infarction [32]. Administration of ethanolic leaf extract of *Corchorus olitorius* led to an increased concentration of HDL-cholesterol and depleted VLD-cholesterol levels which are characteristic of reduced risk of myocardial infarction. Convincing evidence from laboratory, clinical and epidemiologic data have confirmed that increased serum concentration of triglyceride is a standalone risk factor for cardiovascular complications. Hyper triglyceridemia is a characteristic condition observed in diabetics, in this study, treatment with ethanolic leaf extract of *Corchorus olitorius* has prevented the elevation of triglycerides, signifying that myocardial memebrane is intact and not damaged.

5. Conclusion

The present study showed that the ethanolic extract of *Corchorus olitorius* leaf exhibited antihyperglycemic and anti-dyslipidemic effects and there was no significant changes in the toxicological parameters and marker enzymes evaluated hence it could be considered safe for use as an antidiabetic recipe.

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Chapter 5

Low-Carbohydrate High-Fat (LCHF) Diet: Evidence of Its Benefits

Parijat De and Sagnik Mukhopadhyay

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73138

Abstract

Current dietary recommendations state that there is insufficient evidence to prescribe an exact percentage of calories from carbohydrate, protein and fat for people with diabetes from the choice of a variety of popular diets currently available. Over the years, many a research has focused on the relative importance of the right proportion of carbohydrates and fat combination in a balanced diabetic diet. Jury is still out regarding the relative merits and demerits of a diabetic diet – low carbohydrate, high fat or low fat, high carbohydrate diet. Evidence from various studies suggest that low carbohydrate diets improve cardiovascular (CVD) risk through lowering HbA1c levels, improving blood pressure and body weight. There is also a positive effect on lipid profile and reversal of non-alcoholic fatty liver disease (NAFLD). Whilst there are some significant metabolic benefits of LCHF diet, it is accepted that there needs to be more long-term studies before it can be used in daily clinical practice.This chapter focuses on basic physiology and metabolism of carbohydrate and fat content in normal and diabetic patients and a review of the literature on these two diet combinations with current thoughts and evidence on this core issue affecting insulin utilization and metabolic profile.

Keywords: carbohydrate, fat, diabetes, metabolic syndrome, insulin, insulin resistance, weight gain, lipids, NAFLD, cardiovascular disease

1. Introduction

Diet in diabetes has always been an area of much discussion. This is even more so now as there has been a lot of interest and research focusing on the relative contributions of carbohydrate and fat in diabetic diet affecting the overall metabolic profile. An area of confusion in diabetes diet is carbohydrates—Should one eat carbohydrates and to what extent or avoid

them? Another area that has traditionally always been important, although poorly understood, is the amount and type of fat that needs to be consumed; a lot of research is currently focussed on this matter.

It is currently unclear as to the exact percentage of calories that is required from carbohydrate, protein and fat in the diet for the diabetes patient—this should be based on metabolic needs and targets for the preferred individual. There are a variety of popular diets (low carb, intermittent fasting, low fat, ketogenic, mediterranean, vegetarian, DASH, very low calorie, Adkins, 5:2 and commercial food points) for patients to choose from in order to make informed decisions about their diet.

Over the years, many researches have focused on the relative importance of the right proportion of carbohydrates and fat combination in a balanced diabetic diet with some recent research challenging traditional viewpoint of the importance of one over the other. Jury is still out regarding the relative merits and demerits of a diabetic diet—low-carbohydrate high-fat or low-fat high-carbohydrate diet.

Low-carbohydrate high-fat (LCHF) diets are an upcoming although a debatable topic in current nutrition. Since the publication of Dr. Atkins' Diet Revolution in 1972 [1], LCHF diets have divided the opinion of medical fraternity significantly. Some believe that these diets effectively treat type 2 diabetes mellitus (T2DM), obesity and metabolic syndrome [2, 3], while others consider them too non-conventional and in conflict with current globally accepted dietary guidelines that advocate low-fat high-carbohydrate (LFHC) diets to reduce the risk of cardiovascular disease [4, 5]. Given such conflicting opinions, the medical profession may be unsure how to advise on the right diet for the individual patient with diabetes.

This chapter focuses on the basic physiology and metabolism of carbohydrate and fat in patients with diabetes and reviews the literature on these two diet combinations with current thoughts and evidence on this core issue affecting insulin utilisation in the individual with diabetes.

The aim of this chapter is to provide current thinking and evidence behind LCHF diets and in the process and to provide clinicians with additional evidence to inform their clinical decision-making and understanding the potential benefits of these eating plans for at least some patients.

2. Glycaemic index (GI) and diabetes

Carbohydrates have a direct influence on blood sugar levels—diabetes diet therefore tends to focus either on carbohydrate portion size or the speed at which carbohydrates are absorbed by the body. Patients with diabetes are generally advised to follow a low GI diet rather than a low-carb diet.

The glycaemic index [6] categorises food dependant on the rate at which the body breaks it down to form glucose. High GI foods (white bread, potatoes and biscuits) are those that are quickly broken down into glucose. Low GI foods (whole grain bread, milk, leafy vegetables) are typically those that are broken down more slowly by the body. A low glycaemic index diet is beneficial for people with diabetes in keeping their glycaemic control more stable since they are less likely to cause rapid surges in blood glucose levels compared to high GI foods. Low GI food keeps one more satisfied and makes one feel less hungry before the next meal. Other advantages of lower GI foods include a higher nutritional value, a varied diet and reduced immediate demand for insulin following eating.

3. Carbohydrate controlled diets

A carbohydrate controlled diet is a diet in which carbohydrate intake is either limited or set at a particular value, to help stabilise blood glucose levels in patients with diabetes. Examples of such diets are low-carbohydrate diets, Atkins diet, ketogenic diets, low-carb high-fat diet (LCHF), South beach diet and the Zone diet.

3.1. Fixed carbohydrate diet

This is a diet where intake of carbohydrate is pre-set, thereby offering less flexibility in terms of meals through the day. It is simple to follow and offer consistency and is especially useful for those on fixed-dose insulin regimens. People with type 1 diabetes do need to have competence in carbohydrate counting.

3.2. Restricted carbohydrate diets

Low-carbohydrate diets are a form of restricted carbohydrate diet. Restricted carbohydrate diets set a limit on how much carbohydrate can be consumed over the course of a day or for each meal. This can help reduce hunger and prevent wide swings in blood glucose levels responsible for causing hunger.

If carbohydrate and calorie intake is kept low enough, this form of dieting can not only help maintain good glucose control but also help promote regular ketosis and aid weight loss. It is important to maintain a healthy balance of nutrients including fruit and vegetables.

3.3. Low-carbohydrate diet

Many people with diabetes, both type 1 and type 2, are following a low-carb diet because of its benefits in improving diabetes control, weight loss, flexibility and simplicity. Carbohydrates, like proteins and fats, provide energy to help fuel the body. Carbohydrate is the nutrient which has the greatest effect on blood sugar levels and requires insulin to be produced by the

body. Lowering sugar levels reduces need for insulin and this can also help reduce insulin resistance and improve metabolic profile.

Insulin is also being the fat storage (anabolic) hormone in the body; thus, reducing insulin in the body with a low-carb diet can help with losing weight. People also generally reduce their calorie intake. This together with the satiating influence of fat helps with further weight loss. However, people on medications, such as insulin, sulphonylurea or glinides, should be careful about hypoglycaemia.

Low-carbohydrate diets have been said to provide diabetes patients with more energy levels through the day. There is less craving for sugary and snack foods. As a result of lower glucose results and improved HbA1c, there is clearer thinking process and less 'brain fog'. People have also found that low-carb diets can improve cholesterol and triglyceride levels.

There are various ways of following a low-carbohydrate diet—one will need to cut down on common foods like bread, pasta, rice, potatoes and sweet processed foods. There are a number of other ways to replace starchy foods—such as using swede or celeriac instead of potato and using cauliflower instead of rice. A healthy low-carb diet should also have a strong vegetable intake and moderate protein (unprocessed meat) and fat intake from natural sources (to provide a balance of monounsaturated, polyunsaturated and saturated fat).

In 2015, Diabetes UK launched the Low Carb Program [7], which has helped thousands of people with type 2 diabetes to improve their diabetes control and reduce their dependency on diabetes medication.

The counterargument against low-carb diets for people with diabetes is that there is not enough evidence to support the effectiveness and safety of low-carbohydrate diets in the medium to long term. However, more and more research and evidence seems to be favouring low-carb diets in general.

Diabetes UK has put together a position statement [8] to explain how low-carb diets might be used to help manage diabetes using the best level of evidence from systematic reviews, meta-analyses and randomised controlled trials.

Diabetes UK suggests that low-carb diets can be safe and effective for people with type 2 diabetes. They can help with weight loss and glucose management and reduce the risk of cardiovascular disease. So, they recommend a low-carb diet for some people with type 2 diabetes. But there is no consistent evidence that a low-carb diet is any more effective than other approaches in the long term, so it shouldn't be seen as the diet for everyone. Currently, there is no strong evidence to say that a low-carb diet is safe or effective for people with type 1 diabetes. Because of this, Diabetes UK does not recommend low-carb diets to people with type 1 diabetes.

Evidence for low-carb diets in children reports adverse effects such as poor growth, a greater risk of cardiovascular disease and psychological problems. So, low-carb diets are not recommended for children with diabetes.

http://dx.doi.org/10.5772/intechopen.73138

4. The controversy about high fat intake

Consuming fats have very little direct effect on blood glucose levels, and as a result does not lead to an increase in insulin levels. The principle of LCHF diet is to replace carbohydrate intake with fat, thus reducing insulin levels and increase the body's ability to utilise its own fat stores for energy.

Metabolic syndrome is a conglomeration of three or more risk factors (elevated waist circumference, elevated triglycerides, low HDL-c, high blood pressure and elevated glucose). Metabolic syndrome is a condition of insulin resistance and can lead to obesity, type 2 diabetes, fatty liver and many other conditions [9]. A LCHF dietary approach can be used to reduce insulin levels and therefore can also be an effective method for treating or preventing the metabolic syndrome [10].

With LCHF diets, there is an increased intake from fats and proteins, and concerns have been raised about the potential dangers of their increased intake. As has been shown a number of times in the past [11–15], a reduction in dietary carbohydrate intake does not necessarily cause a concomitant increase in total fat and protein intake. The absolute amounts of energy intake often remain very similar, as total energy intake decreases on LCHF diets (although proportional amounts of energy supplied from fat and protein increase). Nevertheless, it is this absolute or relative increase in fat intake that causes a lot of anxiety within the medical profession.

Current dietary guidelines do not define a specific limit in terms of fat intake [16, 17]. Moreover, a few articles in the lay and scientific literature suggest that the intake of total fat (mainly, saturated fats) may not need to be limited [2, 18, 19]. American Diabetes Association position statement for type 2 diabetes recommends that a total fat intake of 20–35% may be desirable for reducing the risk of obesity and suggests minimising carbohydrate intake, but it has refrained from specifying ideal amounts of macronutrients [16].

The diet heart hypothesis based largely on Ancel Keys' original Seven Countries Study [20] suggested that saturated fat intake is the direct cause of coronary atherosclerosis. This theory is now being questioned as it is not supported by current evidence [21–31], which finds no association between saturated fat intake and all-cause mortality or progression of coronary atherosclerosis [32]. Instead, higher fat intakes have been associated with lower rates of ischaemic stroke in men [33] as evidenced by a continued decline in coronary mortality in the Japanese with high blood cholesterol levels [34] and high fat intake [35]. To the contrary, it has been shown that LCHF diets sometimes show significant improvements in coronary risk factors [36–39] and the fear of adverse effects from the increased (saturated) fat intake on this diet would appear to be groundless.

Benefits of replacing saturated fats with dietary polyunsaturated fats may not be as strong [40–44] and even harmful [44, 45]. Again, there is no evidence to suggest that the intake of moderate amounts of red meat has detrimental effects on conventional coronary risk factors [46, 47].

5. Low-carbohydrate high-fat (LCHF) diet

Low-carb high-fat diets are gaining popularity in Europe, especially Scandinavia, having originated in Sweden. The LCHF diet has been popularised by Swedish GP Dr Annika Dahlqvist, who has been recommending a low-carb high-fat diet to her patients for some years now. As this was a somewhat revolutionary concept, she had her opposition. The story goes that she was investigated by the Swedish Health authorities for any wrong doing but investigations cleared her based on their findings that her methods were scientifically sound [48].

As the name suggests, the diet suggests eating high fat and low carbohydrate foods. The LCHF diet is different to the Atkins diet as there are no 'stages' to work through, so the diet can be followed indefinitely. People are encouraged to eat full fat versions of dairy food and fatty meats with fat on rather than removing it.

The diet, because of its low requirement for insulin, has been recognised by the Swedish government as being suitable for people with type 2 diabetes and as helpful to individuals looking to lose weight or maintain a healthy weight. Lower carbohydrate consumption will invoke lower insulin release and thus lower storage of fat and rise in blood sugar levels [49, 50]. However, as the major contributors to hyperglycaemia in type 2 diabetes include a combination of insulin resistance and an inability of pancreatic β-cells to secrete enough insulin [51], it is important to clarify the impact of LCHFD on these important aspects of metabolic regulation.

Studies have shown that insulin-stimulated glucose uptake into muscle and adipose tissue is significantly improved by weight loss on a LCFD diet [52, 53]. LCHFD diet has not necessarily been shown to result in weight reduction in animal studies, regardless of effects on body weight. To the contrary, it has been shown to cause an increased accumulation of lipids in the liver, which negatively affects insulin's ability to reduce hepatic glucose production [54–56]. Thus, from animal studies at least, the proposed benefits versus potential negative effects of an LCHFD on blood glucose control are not very clear. Moreover, whether LCHFDs will prove beneficial for improving glucose control in type 2 diabetes in the longer term will also depend on their impact on glucose-induced insulin secretion.

It is still not very clear that very low carbohydrate intake improves metabolic profile in every diabetes patients, and we need further scientific evidence for this [2, 36]. Although LCHFDs have been shown to reduce post-meal glucose excursions but without any improvement in β-cell function or mass [49, 50, 57], high-dietary fat has been shown, in multiple animal studies, to cause impairments in the ability of insulin to reduce blood glucose resulting in glucose intolerance [58, 59]. Thus, these results from animal studies do not support the recommendation of an LCHFD for use in prediabetes; rather, interventions aimed specifically at reducing obesity and improving insulin sensitivity need to be pursued.

6. What foods are encouraged in LCHF diet plan?

Reduced carbohydrate diets are those that have carbohydrate intakes below the Dietary Guidelines for Americans (DGA) recommendations (of 45–65% of total energy intake). 'Low'

carbohydrate is defined as less than 130 g per day, whereas 'very low' carbohydrate is less than 50 g per day [60]. Although individual responses vary, ketosis usually occurs in people who restrict their carbohydrate intake to below 20–50 g/day with some degree of protein restriction (nutritional ketosis).

Contrary to what many people think, most LCHF diets are not high in protein. In fact, for every 100 g of protein consumed, 56 g of glucose can be produced [61]; thus, having too much can affect blood glucose and undermine the principle of LCHF. Protein can also directly stimulate insulin resistance. Moderate protein consumption, 2–3 portions per day, is therefore usually recommended. Protein can also increase satiety, i.e. it can help you to feel fuller.

When carbohydrate is restricted, it is important to increase the levels of fat consumed—a low carbohydrate AND low fat diet inevitably lead to hunger. Fat should be consumed to satiety. Healthy natural sources of fat include olive oil, butter, grass-fed meats, eggs and dairy products. There is no need to be afraid of fats, including saturated fats and cholesterol, though trans-fats and hydrogenated or partly hydrogenated vegetable oils (often found in junk foods) should be avoided!

A LCHF diet should also include a lot of green leafy vegetables, although consumption of starchy vegetables (such as potatoes and other root vegetables) and fruit should be limited due to their higher carbohydrate content.

According to the Banting diet eating plan [62], foods that can be consumed liberally on the LCHF diet include dairy like natural yoghurt, cheese, cream, butter, along with meat, fish, eggs, vegetables and olive oil. Foods that can be consumed in moderate amounts are bean and lentils, nuts, almonds and sunflower seeds, fruits (not dried fruit), chocolate with a high cocoa quantity (65–90%), sausages and moderate amounts of alcohol. Foods to be avoided are potato; rice; bread; flour and corn-based products; cereal-based products, such as pasta, pastry, biscuits and breakfast cereals; sweets and cakes; sugary drinks; margarines and omega-6 based oils such as corn, sunflower, safflower, soybean and peanut oil. More information about the LCHF diet can be found in the book, 'Diabetes, No thanks' [63]—description of one man's journey from his diagnosis of diabetes to controlling his diabetes with the diet alone.

7. Mechanisms for weight loss on the LCHF eating plan

Increased satiety, allowing a lower energy intake without hunger and a specific metabolic advantage have been proposed to explain how LCHF diets produce weight loss, despite an increased consumption of energy-dense 'fatty' foods.

A recent systematic review compared weight loss between participants on 'LCHF diets' and 'low fat balanced diets' [64] but excluded all trials that were not isoenergetic. Although the original study did not find any differences in weight loss between the different diets, a reanalysis [64] of the same data found a small but significantly great weight loss on the lower carbohydrate diet.

Greater satiety on LCHF diets in persons responding to the diet may result from a number of mechanisms, including increased protein intake, which promotes satiety [65]; ketogenesis, which suppresses appetite [66] and fewer instances of rebound hypoglycaemia.

Although still controversial, it has been suggested that LCHF diets may provide a metabolic 'advantage' favouring greater weight loss, despite the ingestion of an equal number of calories. This metabolic advantage could be related to thermogenic effects of protein intake, greater protein turnover for gluconeogenesis and loss of energy through excretion of ketones in sweat or urine [67, 68]. This state of increased lipolysis with reduced lipogenesis contributes to a metabolic milieu theoretically favouring fat loss. This effect is dependent on reduced blood insulin concentrations, uniquely produced by the LCHF diet.

8. LCHF diets in the management of T2DM

Any diet that reduces carbohydrate load and insulin concentrations will have a beneficial effect on diabetes. Therefore, LCHF diets are currently being discussed as a potential first-line treatment for T2DM [69, 70].

Three hundred and sixty-three patients, who were overweight and obese, were given either a ketogenic LCHF diet or a 'low calorie, high nutritional value' diet in a 6-month trial [71]. Those with T2DM (102 patients) had significantly lower HbA1c and fasting glucose levels and also lost more weight (−12.0% vs. −7.0%) with the LCHF diet.

Thirty-four prediabetic or T2DM patients were randomised to a calorie-restricted diet according to American Diabetes Association (ADA) guidelines or a very LCHF diet in another 3-month trial [72]. HbA1c did not alter in the ADA group, whereas in the very LCHF group, there was a significant reduction (6.6–6.0%) in HbA1c, decrease in the use of anti-diabetic medications and weight loss (−5.5 vs. −2.6 kg).

Westman et al. [73], in their 24-week trial comparing a very LCHF diet with a low GI diet, similarly showed greater decreases in HbA1c (−1.5% vs. −0.5%, $p = 0.03$) with the very LCHF diet, despite more patients reducing or stopping their diabetes medications.

In another study, 115 obese adults with T2DM were randomised to either LCHF or LFHC diet for 1 year [74]. Both diets showed significant weight loss and HbA1c reduction. LCHF diet, however, resulted in better blood glucose stability, greater reductions in diabetes medication requirements and significant improvements in all aspects of lipid concentrations.

Although it could be assumed that all the above positive metabolic changes with an LCHF diet is attributable to its associated weight loss, it is also well established that carbohydrate restriction in diabetes patients per se improves glycaemic control even in the absence of weight loss [75, 76].

http://dx.doi.org/10.5772/intechopen.73138

9. LCHF diets and cardiovascular risk factors

An understandable concern with any increased dietary fat intake on the LCHF diet is the increased risk of future cardiovascular disease. This is largely based on the Ancel Keys' original seven countries study [20], which led to the development of traditional LFHC dietary guidance. However, there is good evidence emerging now that LCHF diets significantly alter cardiovascular risk more so than LFHC diets, especially in those with T2DM and metabolic syndrome.

Many RCTs show that LCHF diets lower blood triglyceride [77] and blood apoprotein B concentrations significantly more than do LFHC diets [3, 78–81]. Furthermore, no other diet increases HDL-C concentrations as effectively as do LCHF diets, which outperform LFHC [79, 82, 83] low glycaemic index [84] and many other diets.

Tay et al. [79] compared a very LCHF with an LFHC diet over a 1-year period—despite similar weight loss, there was significantly more lowering of blood TG concentrations (−0.58 vs. −0.22 mmol/L) and greater increase in HDL-C concentrations (+0.30 vs. +0.07 mmol/L) with the LCHF diet. This has huge connotations for reducing coronary artery disease and would be especially beneficial for those with insulin resistance.

A contentious issue regarding the LCHF diet is the variable LDL-C response to the increase in dietary fat intake. Some trials show a decrease or non-significant change in LDL-C concentrations [38, 85], whereas others report a more marked increase in LDL-C levels [86]. Tay et al. [79], in their study, have demonstrated that both LDL-C (+0.6 vs. +0.1 mmol/L) and total cholesterol (+0.7 vs. +0.1 mmol/L) concentrations increased significantly more in those following the LCHF diet.

Many other systematic reviews [87] and trials [88] have confirmed similar positive effects on overall lipid profile. However, one needs to remember that LDL-C concentrations predicted by the Friedewald equation becoming increasingly inaccurate at low blood TG concentrations [89] as seen with the LCHF diet. It has been shown that LCHF diets consistently reduce the proportion of small, dense LDL particles while increasing the number of large, buoyant LDL particles [3, 81, 85, 90–92].

Additionally, LCHF diets have been associated with improvements in flow-mediated arteriolar dilation [80], decreased inflammatory biomarkers [14], lower systolic and diastolic blood pressures [3], improved glycaemic control with reduced HbA1c, plasma glucose and insulin concentrations [87] and preferential reduction in visceral and liver fat—changes in these surrogate markers would be expected to reduce cardiovascular risk significantly [3, 93].

10. LCHF and non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is characterised by elevated TG and low HDL-C concentrations with overproduction of VLDL and impaired clearance of TG-rich lipoproteins

[94, 95]. It is also recognised that cardiovascular disease is the leading cause of death in NAFLD [96]. It has been shown that NAFLD with insulin resistance is the cause of atherosclerotic disease characterised by many of these features [97]. Since NAFLD is caused by excessive carbohydrate, especially fructose intake [98–100], it is postulated that a carbohydrate-restricted LCHF diet can reverse NAFLD.

Thus, LCHF diet is likely to benefit patients with high TG to HDL-C ratios and NAFLD, all of which are common in the insulin-resistant individual. A recent lifestyle intervention trial reduced the prevalence of metabolic syndrome from 58 to 19% among obese and overweight patients treated with LCHF for 3–8 months, showing how quickly carbohydrate restriction can improve health in those with metabolic syndrome [37].

11. What are the drawbacks of LCHF diet?

As with any dietary approach, there are some caveats to following a LCHF approach. The concept of LCHF is relatively new and not everyone is fully familiar with it. The following are some of the common concerns.

11.1. Hunger

Some people experience increased hunger on a LCHF diet. However, if they eat fat to true fullness, hunger should not be an issue. Lowering insulin levels and reducing insulin resistance can reduce hunger, and also protein and high-fibre green leafy vegetables can reduce this sense of hunger [101].

11.2. Lack of variety

It is assumed that eating the same thing all the time following a LCHF diet will reduce variety and enjoyment. This can be circumvented as there are a wide variety of meals and foods in the LCHF diet to choose from.

11.3. Nutritional deficiencies

It has also been suggested that following a LCHF approach can lead to deficiencies of certain vitamins and minerals. However, there is no evidence of this from trials [60]. An LCHF diet based on meat, seeds/nuts and dairy should provide a diet rich in all the essential nutrients. An online survey found that most people using LCHF diet substituted carbohydrates like bread, rice and pasta with green leafy vegetables, thus reducing likelihood of nutritional deficiencies [102].

11.4. 'Low carb flu': headache, fatigue and muscle cramping

These are potential side effects of LCHF diets at the start of dieting. This is simply because the body is used to using glucose as a primary fuel source and needs some time to adapt to

using fats. However, these symptoms may be especially prevalent only in the period of adaptation to the diet, after which most subside. Some suggest additional sodium (especially for cramping) and fluid intake to minimise side effects, since excretion of water and sodium are increased on these diets as a result of reduction in insulin levels with LCHF diet [103].

11.5. Weight loss on LCHF diets is due to increased water loss

Some have suggested that weight loss on LCHF diets is the result mainly of water loss. This increased diuresis may be true in the first weeks of carbohydrate restriction [104]. However, body composition by DEXA analysis indicates that long-term weight loss on the LCHF diet is predominantly the result of the loss of fat mass with some loss of fat-free mass [3].

11.6. Sustainability

Trials show that adherence to LCHF and LFHC diets are similar [13, 72, 105]. On the other hand, a recent systematic review found a higher attrition rate from LFHC than from LCHF diets [106]. Therefore, sticking to a LCHF diet is perhaps as convenient as any other dietary plan and thus may be more sustainable as it tends to reduce hunger without need for specific calorie restriction. In fact, studies of long-term adherence of up to a year [38, 39] on the LCHF have not identified any evidence of harm.

12. Summary

From the current evidence and above reviews of lower carbohydrate diets, it can be postulated that LCHF diets reduce insulin resistance, improves glycaemic regulation and has positive effects on reducing cardiovascular risk factors, including reducing serum triglyceride, increasing HDL cholesterol, increasing LDL particle size and reducing blood pressure. A substantial proportion of individuals have also been shown to discontinue one or more diabetes medication.

Low-carbohydrate high-fat (LCHF) diet has been shown to be as effective as other diets for weight reduction, through increased satiety and reduction in calorie intake. LCHF diet also helps improve glycaemic control in type 2 diabetes mellitus and in otherwise healthy patients with insulin resistance.

Some of the benefits of the LCHF diet results from the often large weight loss typically produced by this diet. Therefore, at least some of the beneficial changes from LCHF diet would also be experienced by patients prepared to adhere to any calorie-restricted diet. LCHF diets control energy balance through increased satiety and reduced ad libitum energy intake while encouraging the ingestion of a nutrient-dense diet by replacing refined foods with natural foods.

LCHF diets have beneficial effects on cardiovascular risk factors through their effect on blood lipid concentrations. They decrease triglycerides, apoprotein B and saturated fat levels in

blood, together with reduction in small dense LDL particles and increase in HDL-C concentrations. Their effect on LDL-C concentration seems to be variable.

LCHF diet, thus far, has proven to be a safe and efficacious strategy for weight loss and improved health outcomes especially for those with metabolic syndrome and NAFLD. Thus, LCHF diets may be the ideal choice for patients who have struggled to lose weight on traditional diets, especially T2DM with or without cardiovascular risk factors. A life-long completely carbohydrate-free diet is unlikely to be achievable but a LCHF, through reducing post-meal glucose excursions, could potentially have some benefit for improving glucose control in diabetes. However, from animal models, it has been shown that there are no longer term benefits for β-cell function or glucose metabolism.

Notably, most diets are effective at inducing at least short-term weight loss, usually followed by some weight regain as adherence diminishes. However, it can be argued that LCHF diets perform at least as well as do any other dietary approaches. In practice, beneficial responses to any diet is entirely dependent on the degree of patients' adherence, so a LCHF diet is only likely to benefit patients motivated to comply.

A growing understanding that obesity/hypertension/T2DM/non-alcoholic fatty liver disease/atherogenic dyslipidaemia and metabolic syndrome may all be substantially influenced by a high-carbohydrate diet, acting on a single metabolic state, insulin resistance—could revolutionise the dietary management of these conditions over the next few years. It can therefore be argued that the LCHF eating plan should form an integral part of medical management for all these conditions.

LCHF diet may not be an answer for everyone as every individual metabolic profile is different. However, it may present a sensible dietary option for weight loss and health improvement in certain group of patients. Despite its numerous benefits, individual LDL-C responses need to be monitored and continued emphasis should be placed on nutrient-rich choices, avoiding ultra-processed foods. We need more well-designed comparative studies to confirm whether the metabolic changes from LCHF diet will be sustained long term.

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Section 2

Diabetes and Oxidative Stress

Chapter 6

Trace Elements Modulates Oxidative Stress in Type 2 Diabetes

Ines Gouaref and Elhadj-Ahmed Koceir

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71172

Abstract

The relationship between antioxidant trace elements (ATE) and metabolic disease is subtle and complex due to overproduction of reactive oxygen species (ROS). In type 2 diabetes (T2D), the relationship between ATE and insulin-like trace elements is very complex during oxidative stress (OS), being mediated by hyperglycemia, dyslipidemia and inflammation. The important role assigned to ATE (zinc, selenium, copper, manganese and chromium) by their involvement at different levels: Hemodynamic homeostasis (endothelial function and protein glycation), energy metabolism (carbohydrate and lipid tolerance) and enzymatic antioxidant protection [superoxide dismutase (SOD), glutathione peroxidase (GPx)]. The ROS-mediated cellular signaling process is crucial. Manganese and selenium levels abnormalities might to be useful indicators of oxidative damage. Two major factors were suggested: lack of Mn bioavailability leading to the decrease of mitochondrial SOD activity (cytosolic SOD remains active), and low blood selenium level implying a decrease in GPx activity. In T2D pathophysiology, it appears that antioxidant defense is preserved in the cytosol (Cu/Zn-SOD) in T2D, whereas it is impaired in mitochondria (Mn-SOD) in the three pathologies, which make this cell organelle a true ATE therapeutic target. Future challenges require the in-depth investigations of mitochondrial mechanisms, involved the antioxidant trace elements signaling pathways in T2D pathophysiology.

Keywords: type 2 diabetes, oxidative stress, antioxidant trace elements (zinc, selenium, copper, manganese, and chromium)

1. Introduction

Type 2 diabetes (T2D) is a major risk factor for cardiovascular diseases and acute oxidative stress (OS) by high production of reactive oxygen species (ROS) related to the lipotoxicity and glucotoxicity processes [1]. The mechanisms underlying OS disorders modulated by antioxidant trace

elements (ATE) such as selenium (Se), manganese (Mn), zinc (Zn), copper (Cu) and chromium (Cr) status are not completely clear [2]. The role of ATE as an essential micronutrient has been identified for a long time as a potential candidate for improving metabolic disorders, like glucose homeostasis in prediabetes state [3]. Antioxidant enzymatic system (AES) such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase plays an important protective role in the emergency of glucose intolerance, insulin resistance and dyslipidemia. T2D is characterized by elevated glycated hemoglobin (HbA1c) and insulin resistance maintains the toxic hyperglycemia and dyslipidemia effects, leads to disturb ATE status. This situation amplifies OS and aggravates the diabetes vascular complications [4].

The ROS neutralization is conducted primarily by AES through ATE integrated as AES cofactors. Cu and Zn are incorporated both into the Cu-Zn-SOD to reduce the cytotoxic ROS effects in cytosolic compartment cells [5]. Mn is incorporated into the Mn-SOD to remove the ROS effects in mitochondrial compartment cells [6]. Se is incorporated into the GPx1 to remove the ROS effects in cytosolic and mitochondrial compartment cells [7]. The present review updates our actual state of knowledge about highlight role of ATE in OS damage in T2D pathogenesis, and that consider their therapeutic potential.

Several studies have reported that pathogenesis of type 2 diabetes (T2D) is related to the imbalance of some antioxidant trace elements such as zinc, selenium, copper, manganese and chromium might adversely affect pancreatic islet and cause development of diabetes [8]. Type 2 diabetes is clearly associated with ROS production and insulin signaling depends on the balance of ROS production and antioxidant defense. Excessive ROS are involved in the multifactorial etiology of insulin resistance and the subsequent development of T2D [9]. Oxidative stress alters the insulin receptor and the insulin receptor substrate (IRS) signaling pathway via kinase activity (serine/threonine), leading to multi-site phosphorylation [10]. These events increase serine IRS phosphorylation and decrease thyrosine, leading to insulin resistance [11]. The ATE trace elements shows a profile disturbance in T2D is associated with increased proinflammatory cytokines (TNF-α, IL-6) may contribute to development of diabetic complications [12, 13] and increased glycated hemoglobin formation [4].

2. Zinc in T2D pathogenesis

Zinc (Zn) is a necessary micronutrient which has an essential role in insulin metabolism [14, 15]. In pancreatic beta cells, Zn is required for the synthesis, storage and insulin secretion [79]. It has been described in diabetic subjects pancreas is zinc deficiency compared to normal subject. These data confirmed that zinc is involved in insulin signaling pathways [16]. Zn may stimulate energy consumption in skeletal muscle and brown adipose tissue and may increase the pancreatic insulin content and improve the glucose tolerance test [17]. Zn is found largely in cereals, animal protein and seafood [18]. Zn absorption can be inhibited by iron. Zn is transported across cell membranes via ZnT family's transporters [19].

In diabetes diseases (insulin resistance, metabolic syndrome), Zn is considered important mainly because: (i) it plays a major role in the stabilization of insulin hexamers and the hormone pancreatic storage [20] and (ii) it is an efficient antioxidant [21]. Zinc deficiency in

type 2 diabetes is mainly due to a significant urinary zinc loss [22], nevertheless, this Zinc deficiency is not very significant versus healthy subject [23]. Lower Zn plasma concentrations were found in T2D to relate of cardiovascular risk metabolic syndrome factors [24], and reduced Zn levels in diabetics appear to be related to increased risk for coronary artery disease [25]. It has been described that zinc effects mimic the insulin action mainly via the glycogen synthesis/degradation enzymes signaling pathways [26]. Other mechanisms include Cu/Zn-superoxide dismutase regulation via the post receptor proteins Akt and PI3-kinase via NF_B [27]. On the other hand, some particular forms of Zn have been discovered in ob/ob mice, such Zn-α 2-glycoprotein is an adipokine which stimulates energy expenditure in skeletal muscle and brown adipose tissue, resulting in reductions in glycaemia, triglycerides and Free Fatty Acids. Their level is lower in obese human subcutaneous and visceral adipose tissue and liver, but interestingly does not appear to be related to insulin resistance [28].

3. Selenium in T2D pathogenesis

Early studies indicated that inorganic Se acted as an insulin mimic [29] and epidemiologic investigations showed correlations between abnormal glucose or lipid metabolism and decreased plasma Se concentrations or glutathione peroxidase activity in diabetic subjects [30–32]. Indeed, intraperitoneal injection or oral administration of sodium selenate improved glucose homeostasis in type 1 and type 2 diabetic animals [33]. Similarly, previous studies have shown that the insulin-like and antidiabetic effects of sodium selenite and selenomethionine were also observed in diabetic animals [34]. Several selenium supplementation studies were undertaken in diabetic subject with vascular complications, unfortunately the beneficial antioxidant effects were not obtained [35, 36].

Se is a key component of GPx, an enzyme that prevents the cells oxidation. Compared with liver, islets contain only 2% GPx [37]. Accordingly, β cells are considered to be low in antioxidant defenses and susceptible to oxidative stress. In diabetic subjects, β-cell apoptosis seems to be more of a deciding factor than replication in controlling the cell mass compared with control subjects [38]. Selenoprotein (SelP), a secretory protein primarily produced by the liver and regulated similar to that of the gluconeogenic enzyme glucose 6-phosphatase [39], by concerted action of peroxisome proliferator-activated receptor co activator 1α (PPAR-1α) and the transcription hepatocyte nuclear factor-4α [40]. It has been shown a positive correlation between hepatic SelP mRNA levels and insulin resistance in humans, a long with a positive correlation between serum SelP levels and both fasting plasma glucose and hemoglobin A1C (HbA1c) levels. The metabolic selenium effects are mediated by selenoproteins (SeP) via the adenosine monophosphate-activated protein kinase (AMPK) inactivation [41]. Probably, SePs insulin-sensitizing effect like to glutathione peroxidase (GPx). However, SelP does not seem to act upon insulin synthesis or a trophic effect on pancreatic beta mass cells [42].

On the other hand, some studies have shown that Tanis (in humans encoded by the SelP gene) was regulated by glucose and altered in the diabetic state [43]. It has been reported that Tanis protein overexpression in H4IIE cells acts at different points: (i) glucose transport; (ii) basal insulin secretion; (iii) glycogen synthesis and storage; (iv) attenuates the phosphoenol pyruvate

carboxykinase gene expression [44]. These data confirm that Tanis protein is involved in glycemic homeostasis and hepatic insulin resistance. Furthermore, emerging evidence suggests that elevation of SelP [45] mRNA and protein expression was observed in T2D patients. Otherwise, it has been described that Selenium modulates vascular inflammatory syndrome by reducing p38 MAP kinase and NF-κB signaling pathway [46]. Besides, selenium is able to inhibit atherosclerotic processes by endothelial adhesion molecules expression [47].

4. Copper in T2D pathogenesis

Plasma Cu concentrations have been reported in some studies to be altered in diabetic humans compared to non-diabetics [4], particularly in diabetic patients with microvascular disease complications [48] and proteinuria [49]. Similarly, serum ceruloplasmin has been noted to be higher in T2D subjects compared to non-diabetics in numerous studies [50]. Alterations in Cu metabolism coupled with an increase in glycated proteins [4] may contribute to the progression of diabetes-related pathologies. Several lines of evidence support a role of Cu in diabetes-induced oxidative stress. Several previous studies have showed that ceruloplasmin can be fragmented following non-enzymatic glycosylation [51]. Secondly, glycation of CuZn-SOD in humans with diabetes leads to a site-specific fragmentation resulting in its inactivation [52] as well as the release of Cu, which can further exacerbate oxidative stress. Glycation of CuZn-SOD increases the formation of DNA damage in vitro, which suggests that the release of Cu^{2+} from glycated SOD can participate in cleavage of nuclear DNA [53]. As CuZn-SOD accounts for 90% of the total SOD activity of the mouse lens [54], the excessively high concentrations of glycated CuZn-SOD in diabetic rat lenses are postulated to be involved in lens pathology [55]. Cu can increase the rate advanced glycated end (AGE) products formation, which is associated with the pathogenesis of secondary complications in diabetes [56]. Agents used to prevent or reduce AGE formation typically have potent Cu chelating [57].

5. Manganese in T2D pathogenesis

The manganese status in T2D is still unclear and the few studies that have addressed this issue in humans are controversial. However, Mn acts as a cofactor in several metalloenzymes including those involved in glucose homeostasis (*Pyruvate carboxylase, GTP oxaloacetate carboxylase, Isocitrate dehydrogenase, Malate dehydrogenase, Phosphoenolpyruvate carboxykinase*). These enzymes play a critical role in the blood glucose regulation via glycolysis, gluconeogenesis, Krebs cycle [58]. Mn is required for insulin synthesis [59], and to regulate of glucose utilization and lipogenesis in adipose tissue [60]. Previous studies have shown that blood manganese levels are unchanged in plasma, not significantly (approx. 15%) reduced in whole blood [61], or decreased in erythrocytes [62], from diabetic patients as compared to controls. In healthy subjects, manganese is very present in tissues rich in mitochondria (12–16 mg), in particular skeletal muscle, liver, pancreas and kidney. Mn is necessary for the synthesis, secretion and action of insulin. Mn is also indispensable for the maturation of bones and cartilage. Mn plasma levels are essentially regulated via the bile excretion pathway. Mn also

participates in vitamins E and B1 synthesis [63]. Mn is found mainly in quinoa, rye, whole rice, soybeans, avocado, egg yolk, green beans, spinach, walnuts, olive oil, oysters, green tea and provence herbs [64].

Our recently diabetes investigation [65], we found Mn blood concentrations are significantly increased (23%) in diabetic patients compared to controls. The correlation is positive with hyperglycemia and HbA1C. Our data suggest that Mn play a crucial role in antioxidant capacity and we hypothesize that antioxidant defense is preserved in the cytosol (superoxide dismutase Cu/Zn-SOD), whereas it is impaired in mitochondria (Mn-SOD), which makes this cell organelle a true therapeutic target in diabetes. In our recent study, we showed the competitive effect between the manganese and iron in T2D. However, when the iron was in the free form and reduced, it was constantly a pro-oxidant, whereas Mn was an anti-oxidant. Several studies suggesting that transferrin (Tf)/Tf receptor (TfR) transport system is the major transport of manganese and iron in plasma. The Mn bioavailability is reduced due to altered Tf/TfR transport system [66–69]. Consequently, the Mn (III) forms a more stable with Tf than the Mn (II) form [70]. The more complex questions related to the regulation of each by Mn and Fe might affect the insulin secretion and glucose homeostasis. Probably the increased Mn levels would affect the availability or concentration of both various transporters and finally bêta cell Mn distribution [71]. The interactions of Mn, Fe and ferritin are closely related in the following manner; and can lead to hyperglycemia associated to mitochondrial Fe, Mn, copper, and zinc levels [72], demonstrating the interrelationship with glycemia homeostasis. Probably, that the heightened β-cell oxidative stress may result from occurring Tf/Tf receptor system, and elevated manganese is produced via an extracellular Tf-manganese redox mechanism, rather than simply the presence of elevated tissue manganese per se. In this context, the plasma manganese accumulation was associated to iron plasma depletion and ferritin increased, suggesting that mitochondrial iron accumulation resulting in generation of ROS by Fenton chemistry [73]. The Mn is confined to the cytosol where it is associated with decreased mitochondrial SOD-Mn due the lack of mitochondrial manganese. The finding that DT2 pathogenesis are able to regulate manganese transport into, and/or export from, mitochondria and maintain a normal pool of mitochondrial manganese, despite the presence of a two-fold increase in cytosolic manganese content. Among possible explanations for this result, the upregulation of mitochondrial manganese transporters in situations of large changes in metal availability, or a heretofore undescribed function for the transferrin in regulation of mitochondrial metal accumulation. At last, in diabetes vascular complications, Mn is involved in Arginine production, precursor to nitric oxide (NO) formation as endothelial vasodilator [74].

6. Chromium in T2D pathogenesis

Chromium (Cr) that is mineral trace deserves special attention in diabetes pathophysiology, as has been reported during the 50th anniversary of this trace element and they termed it glucose tolerance factor (GTF) [75]. The Cr recommended nutritional requirements are estimated between 50 and 200 mg, but this requirement is estimated at 30 mg/day. Barley is the most important Cr food source [76]. Cr plays a crucial role in glycaemia homeostasis and Cr deficiency leads to a glucose tolerance disorder, moderate fasting hyperglycemia and occasionally

dyslipidemia. This observation has been observed both in human clinical and experimental models [77, 78]. Cr plasma concentrations can be explained by its mobilization from its storage site (liver, kidneys) to the blood by chromodulin binding (intracellular transport protein) [79]. However, Cr bioavailability depends on the nutrients with which it is associated: Cr/phenylalanine, Cr/cysteine, Cr/biotin and Cr/vitamin E or Cr/vitamin C complexes have been described [80–83]. Cr acts as carbohydrate tolerance factor, increases insulin sensitivity, particularly in the skeletal muscle. Indeed, trivalent chromium is an insulin pathway signaling. Cr increases insulin receptors number, insulin internalization and an activation of the GLUT4 and GLUT1 glucose carriers translocation [84]. The insulin binding to the α-subunit receptor is induced by a phosphorylation reactions cascade catalyzed by tyrosine kinase that is activated by Cr; however, phosphotyrosine phosphatase which inactivates the insulin receptor is inhibited by Cr [85]. In type 2 diabetes and obesity, the Cr deficiency can be observed in subjects consuming excessively rapid absorption carbohydrates that increase the urinary elimination of chromium. Cr Supplementation during 6 months may be prescribed in a forms variety: Cr-chloride, Cr-nicotinate, Cr-propionate, Cr-histidinate or Cr-picolinate leads to a significant decrease HbA1c and AGE [86, 87]. Cr supplementation effects appear to be mediated by AMP kinase activation and p38 MAP kinase signaling pathway [88]. Cr controls body fat and body weight by satiety mechanisms (food intake control) and thermogenesis [89]. The Cr effects are observed via the resistin and *uncoupling protein* (UCP) decoupling proteins signaling pathway [84, 90]. Otherwise, experimental animal studies have shown that Cr modulates the inflammatory state during diabetes by decreasing proinflammatory cytokines production such as *tumor necrosis factor* (TNF-α), and interleukin IL-6 [91].

7. Conclusions

Glycemic homeostasis is not only dependent on hormonal control, especially insulin; but also the micronutrients such as Chromium, Zinc, Selenium, Manganese and Copper. These Antioxidant Trace Elements act as cofactors of antioxidant enzymes (SOD, GPx) which protect the glucose-dependent tissues from the deleterious effects of reactive oxygen species following oxidation of glucose.

Acknowledgements

The research was supported by the General Division for Algerian Scientific Research and Technological Development (DG-RSDT). www: www.dgrsdt.dz.

Conflict of interests

The authors declare that there is no conflict of interests regarding this paper.

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Chapter 7

Savior of Diabetes: Antioxidants

Zar Chi Thent and Azian Abd Latiff

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71748

Abstract

Introduction: The exposure of humans to antioxidants regulating the process and progress of diabetes mellitus (DM) is of major interest. Several phytoactive compounds such as flavonoids, lignans, prophenylphenols, etc. possess antioxidant property. Antioxidants exert free radical scavenging activity, improve the insulin sensitivity and pancreatic β cell activity, stimulate insulin secretion, and reduce the carbohydrate absorption. Antioxidants also combat complications like diabetic wound healing by increasing the collagen deposition, improving the fibroblasts level, and decreasing the 11-β hydroxydehydrogenase level. They revert the cardiovascular changes of DM by reducing the lipid profile level. Antioxidants also exert their regulatory effect on diabetic nephropathy and peripheral vascular diseases. Body-research methods: The terms "diabetes" or "diabetes mellitus" or type 1 diabetes mellitus" or "type 2 diabetes mellitus" or "hyperglycaemia" or "antioxidant" or "antioxidant" combined with "diabetic complication" were searched in following databases such as PubMed, Web of Science Scopus, and Google Scholar. Conclusion: Understanding the effects of antioxidants against DM is beneficial for disease progress assessment and development of prophylaxis regimens. Although several researches are carried out on antioxidants, current population has still less confidence on them. Hence, more detailed analysis and clinical studies investigating on the underlying mechanisms of antioxidants towards DM are mandatory.

Keywords: diabetes mellitus, antioxidant, prophylaxis, natural products, supplementation

1. Introduction

Diabetes mellitus (DM) is one of the most common noncommunicable diseases worldwide including Malaysia. Increasing prevalence of the disease both in developed and developing countries is of major concern. Based on the previous global statistical analysis, DM is

expected to increase more than 400 million in the year 2030, which leads the disease to be the seventh leading cause of death worldwide [1]. DM is characterized as chronic hyperglycemia resulting due to insulin deficiency (type 1) or resistance (type 2). Both types of diabetes mellitus eventually develop various problems such as microvascular and macrovascular complications.

Chronic hyperglycemia is a multifaceted, progressive oxidative stress disorder results from imbalance between free radical formation and the antioxidant defense activity [2]. Several complications arise from diabetes mellitus (**Figure 1**). According to statistic, the high mortality rate among diabetic patients is due to the cardiovascular complications [3]. Numerous clinical and in vivo studies showed that diabetic state itself is responsible for developing

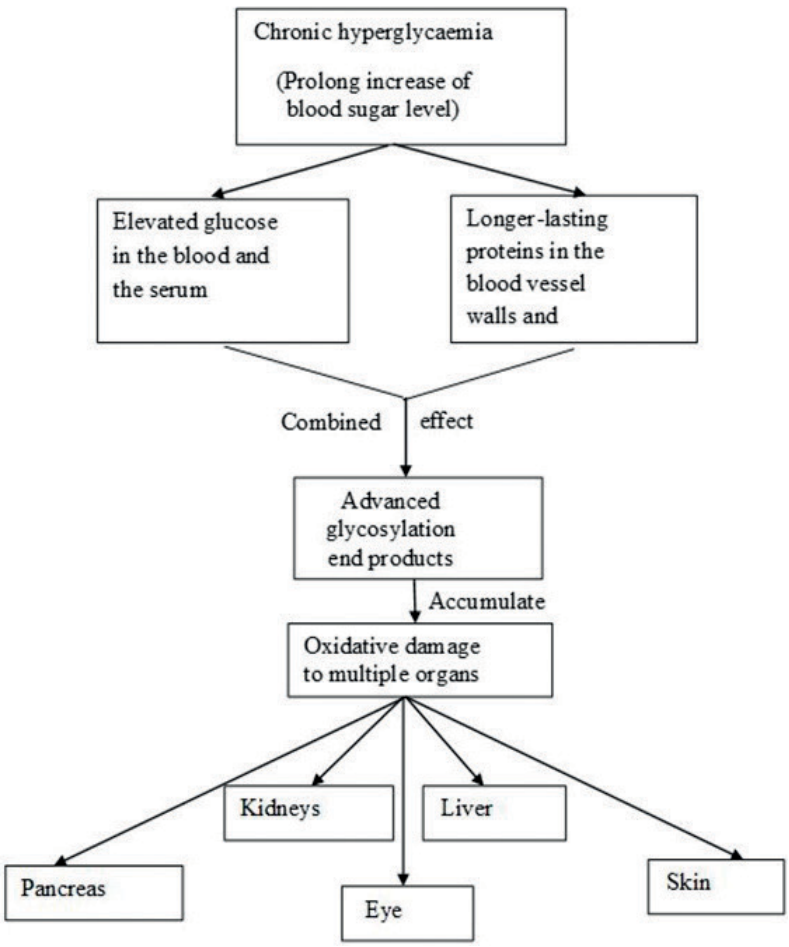

Figure 1. Flow chart shows the process of DM and its complications.

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cardiac dysfunction and atherosclerosis [4]. In addition, it also causes foot ulcers, impaired wound healing in association with peripheral neuropathy and autonomic dysfunction, and later results in limb amputation [5]. Amputation in diabetic patients is believed as global health burden in the current society [6].

In diabetic state, glucose combines with longer lasting proteins in blood-vessel walls and in the interstitial tissues. Following the event, the returning irreversible products called advanced glycosylation end-products (AGEs) are formed. DM is associated with increased formation of free radicals such as superoxide and reactive oxygen species (ROS) [7]. Therefore, the disturbance in oxidant and antioxidant activities, the increased formation of free radicals, and accumulation of AGEs lead to cause oxidative damage to multiple organs and systems of human body (**Figure 2**).

Over the years, the oxidative stress served as a common pathway for the pathogenesis of DM. Long-term DM leads to damages of the multiple organs like pancreas, liver, kidney, eyes, heart, and great vessels especially aorta and skin. Diabetic cardiomyopathy or cardiac dysfunction, microangiopathy, diabetic nephropathy, neuropathy, cataract, pancreatic β cell destruction, nonalcoholic liver cirrhosis, poor wound healing, and erectile dysfunctions are the common complications that diabetic patients encountered to date [8]. Therefore, the stability and capacity of antioxidant status during the phase of DM seriously influence the outcome oxidative stress disorders like DM. Moreover, life-long treatment with high-cost modern drugs (biguanides, sulphonylurea, etc.) for DM is considered as a universal burden as well as believed to have several side effects [9]. Depending on the incidences of DM and its complications, it is important to explore the alternative source of antidiabetic supplement,

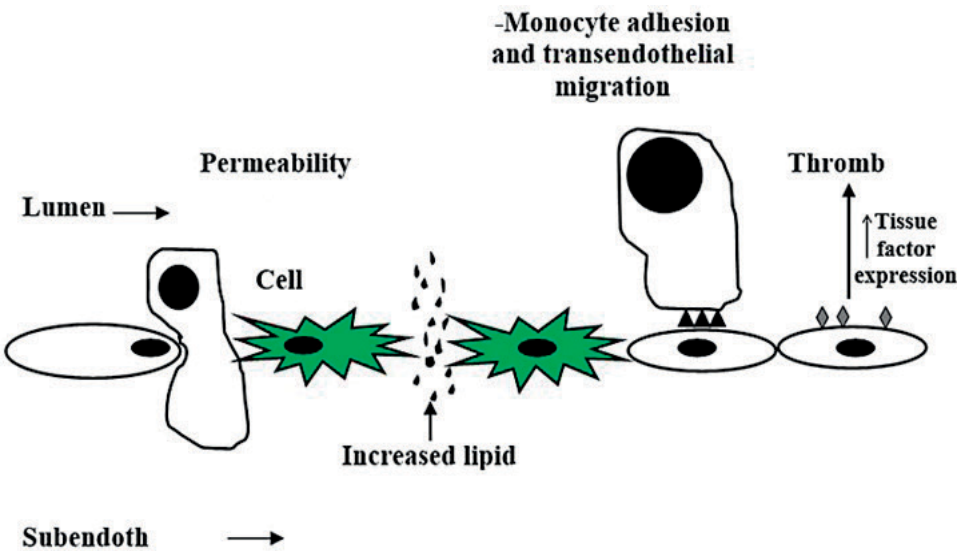

Figure 2. Diagram showing mechanism by which AGEs induce cardiovascular changes in DM [3].

which is enriched with antioxidant properties. We agreed the fact that there are plenty of natural products which have antioxidant property; however, only a few are highlighted in this chapter. Herein with, we present some common herbs and active compounds that are enriched with antioxidant activity.

2. Antioxidants

The decreased antioxidant level is found in the diabetic patient. In a previous study, the total antioxidant capacity in the plasma of type 1 DM was shown to be 16% lower than that of normal subjects. Antioxidants counter the action of free radicals via several mechanisms such as degradation of free radicals, regulating the metals that stimulate the production free radicals, and scavenging the free radical. Lately, researchers found out the beneficial use of antioxidants from natural resources to replace synthetic ones.

Among the natural resources, data from laboratory studies showed that plants contain a large amount of antioxidant properties. Antioxidants occur in all parts of any higher plants (wood, bark, stems, pods, leaves, fruit, roots, flowers, pollen, and seeds). Plants with high levels of antioxidant have a significant role in improving oxidative stress disorders like DM. A number of findings showed the protective effect of the antioxidant ingredients against DM and achieved good results [10]. Hence, classical antioxidant could regulate the process and progress of DM and its complications. The good impact antioxidant activity toward DM and its associated complications has highly gained attention in the recent therapeutic society. Plenty of plants are rich in antioxidant property. To name it few, the plant or natural herbs such as *Piper sarmentosum* [11], *Momordica charantia* (bitter gourd) [12], and *Piper betel* [6], the common herbs used in improving the diabetic status enriched with antioxidant compounds. Noticeable active compounds like naringenin and quercetin are also important in managing hyperglycemic condition as well as regulating the oxidative stress–induced complication in DM. Vitamin C and E are well-known antioxidant agents for DM [13]. The antioxidant-enriched herbs not only increase the antioxidant level but also reduce the serum glucose level as well as improve the deteriorative changes in DM.

2.1. *Piper sarmentosum*

Piper sarmentosum (P.s), locally referred to as "daun kadok," is a member of the Piperaceae family which closely resembled the features of a betel leaf (**Figure 3**). Its leaves and roots are commonly used for experimental purposes [15]. P.s possesses high antioxidant compounds such as naringenin (75.7%), hesperetin (91.7%), taxifolin/dihydroquercetin (90.9%), and quercetin (98.1%) from its leaves [15].

During the past few years, our research group observed that type 1 diabetic rat treated with P.s groups showed a significant decrease ($P < 0.05$) in fasting blood glucose level, urine glucose level [11], and blood pressure level [14] compared to untreated diabetic group in experimental Sprague-Dawley rats. The decrease in fasting blood and urine glucose level following P.s administration (0.125 g/kg) is probably due to the underlying action of the antioxidant

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Figure 3. Photograph of *Piper sarmentosum* leaves [14].

compounds that are present in the leaves of P.s. Quercetin present in P.s has a positive role in reducing blood sugar levels, promoting the regeneration of the pancreatic islets and increasing insulin release with high superoxide scavenging activity [16].

Moreover, antioxidant compounds present in P.s prevent the morphological changes of diabetic cardiac and aortic tissues following 28 days of treatment (**Figure 4**). The antioxidant activity of quercetin controls the glucose uptake and increased levels of mitochondrial reactive oxygen species (ROS) linked to hyperglycemia [16]. This would protect the excess collagen deposition in cardiac tissues by inhibiting the metabolic disturbances of DM. Another antioxidant compound, naringenin, also improves endothelial function that reduces the risk of developing coronary heart disease [15]. The authors suggested that P.s could modify the cellular deteriorations in hyperglycemic condition. It was presumed that the mechanism by which P.s exerts its cardio-protective and vascular-protective effects might be due to the presence of antioxidant compounds [11].

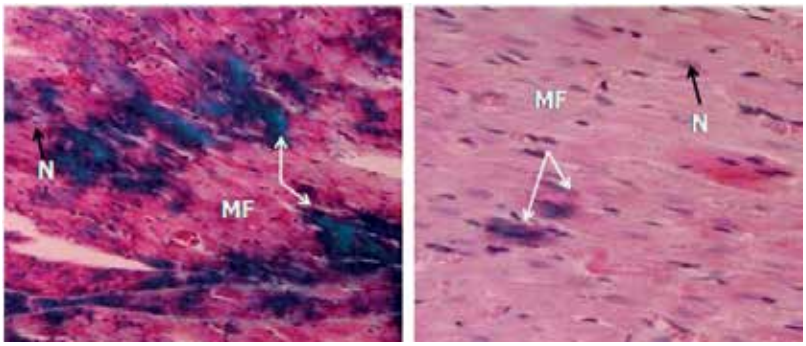

Figure 4. Photomicrograph showing the longitudinal section of cardiac tissues of untreated diabetic group (Left) diabetic group treated with 0.125 g/kg *Piper sarmentosum* (Right). Note: N: nuclei of cardiomyocytes, MF: myofibers, white arrows: connective tissue under Masson's Trichome stain (LM ×400) [17].

2.2. *Momordica charantia*

Momordica charantia (MC) belongs to the family of *Cucurbitaceae* (**Figure 5**) and is commonly known as bitter gourd or bitter melon [18]. The immature fruits of MC are a good source of Vitamin C and A. Several active compounds such as momorcharins, momordin, charantin, and goyasaponins are found in MC extract [19]. These are reported to present in all parts of the plant.

The leaf and fruit extract of MC are enriched with carbohydrate and protein. The supplementation with MC extract is a source of energy and nutrients for the body metabolic activities [20]. MC stimulates the number of pancreatic beta cells and promotes the insulin secretion.

Figure 5. Fruits of *Momordica charantia*.

Charantins from MC increase the glucose transporter (GLUT4), thus increases glucose utilization in the liver and muscle [18]. Increasing body weight that was observed in MC-treated experimental rats was due to the increase in glucose metabolism as compared to DM group [21]. Moreover, it was found out that the active compound present in MC fruit extract, leptin, lowered the blood pressure in diabetes. In the rural African communities, leptin is used in the management and control of DM-associated hypertension. Leptin reduces blood pressure by increasing the anti-oxidant and nitric oxide efficiency [22]. Our previous findings also showed significant decrease in systolic, diastolic, and mean blood pressure in experimental diabetic rats treated with MC [23].

In the diabetic state, there is a decrease in the activities of superoxide dismutase (SOD), glutathione, and catalase due to the increase production of ROS. Supplementation with MC extract restores anti-oxidant levels of SOD, glutathione, and catalase by regulating the deleterious effects of free radicals in diabetic state due to the presence of charantosides [24]. Moreover, supplementation with MC fruit extract also reverted the histological deteriorations of aortic tissue in diabetic rats (**Figure 6**). Apart from this, antioxidant compounds, luteolin, in the MC extract is observed to improve diabetic cardiac tissue morphology in experimental animals [12]. Previous study showed that MC fruit extract exerts positive effect on plasma MDA level in alloxan-induced diabetic. MC regulates membrane lipid peroxidation and reduces the thickness of diabetic aortic tissue with the presence of antioxidant effect [23].

2.3. *Piper betel*

Betel vine or scientifically known as *Piper betel* (PB), which belongs to *Piperaceae* family, is commonly found in South East Asia. PB is commonly found in South East Asian

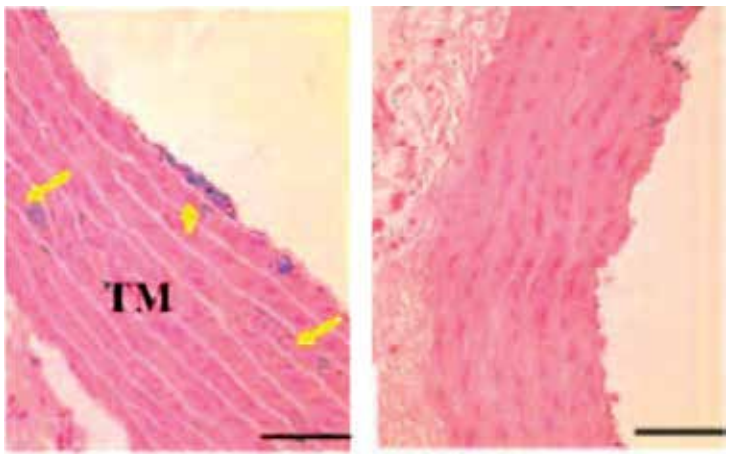

Figure 6. Photomicrograph showing transverse sections of the thoracic aorta under Alcian blue staining. Untreated diabetic group (Left) diabetic group treated with *Momordica charantia* fruit extract (Right). Note: TM = Tunica Media, LM ×200) [23].

countries [25]. It was observed that PB is enriched with antioxidant activity by investigating on DPPH scavenging assay [25, 26]. Researchers found the potent antioxidant property of PB suspension (75 mg/kg) in streptozotocin-induced diabetic animals. Eventually, it was believed that the antioxidant property of PB leaves plays a protective role in diabetes [27]. The topical application of PB 50 mg/kg for 10 days enhanced wound healing in diabetic rats [28].

Delayed wound healing is one of the critical complications in diabetes mellitus. Increased production of ROS and imbalance between oxidant and antioxidant enzymes contribute to impair healing process. In hyperglycemic condition, there is decreased superoxide dismutase (SOD) and increased malondialdehyde (MDA), a marker of lipid peroxidation and 11β hydroxysteriod dehydrogenase-1 (11β HSD-1) enzyme, involving in the interconversion of cortisone and cortisol [29]. Increasing level of 11β HSD-1 enzyme has a negative influence on the fibroblasts proliferation. Less-responsive fibroblasts to growth factors in DM results in poor-wound tensile strength and decreased-wound closure rate [30]. Following 5 days of topical PB application to the diabetic wounds showed the fast wound closure rate (**Figure 7**) [7] as well as reduced 11β HSD-1 enzyme expression in wound tissue (**Figure 8**) [8]. This might be due to the presence of potent active compounds in PB extract, which act as a free radical scavenger increase the anti-oxidant activity [32].

2.4. Common active antioxidant compounds for diabetes

Each compound contains its own efficacy. Naringenin (4′,5,7-trihydroxyflavanone) is a highly potent natural antioxidant with high superoxide scavenging activity (**Figure 9**). Quercetin, an example of flavonoids, is also reported to improve the endothelial dysfunction by enhancing nitric oxide (NO) synthesis in human umbilical vein endothelial cells [16]. Tannins, the active potent anti-oxidant compounds, could increase the secretion of insulin and reduce hyperglycemia in experimental DM rats [34]. The mechanism of enhancing insulin secretion was clearly explained that the compounds contain an enzyme: a benzoic acid related molecules inhibited insulinase. This enzyme enhances the effect of insulin by inhibiting insulin degradation [34].

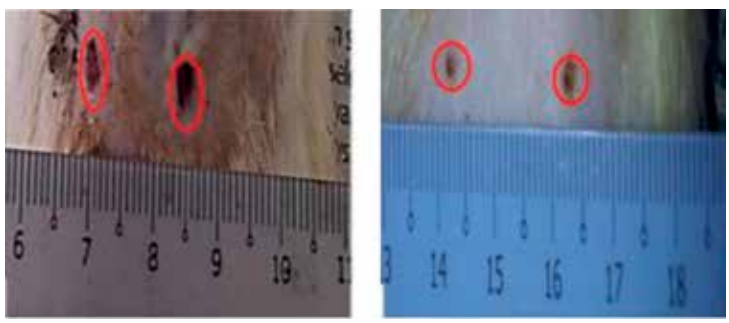

Figure 7. Increase in wound healing following topical *piper betel* application for 5 days. Untreated diabetic group (Left) diabetic group treated with PB extract (Right). Red circle = wounded area [31].

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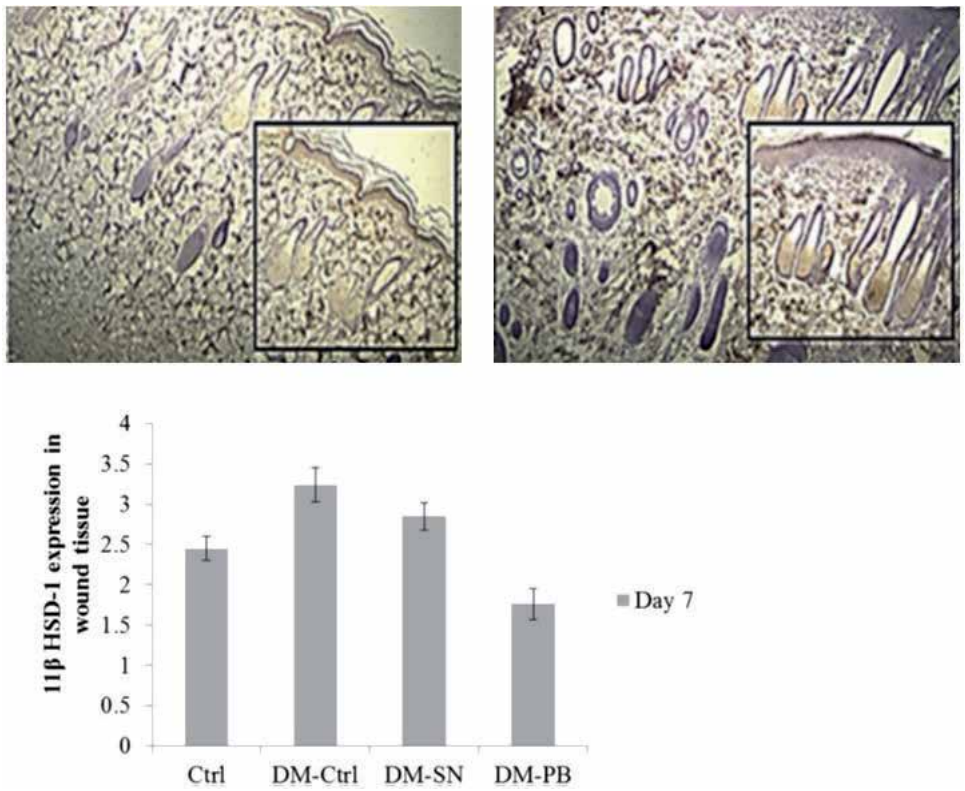

Figure 8. Expression of 11bHSD-1 by immunohistochemistry in wounded skin of diabetic rat model. Untreated diabetic group (Left) diabetic group treated with PB extract (Right). Decreased in expression was observed in the epidermal layer of the wounded skin of diabetic PB group compared to DM-Control (DM-Ctrl) and diabetic silver nitrate treated (DM-SN) groups [6].

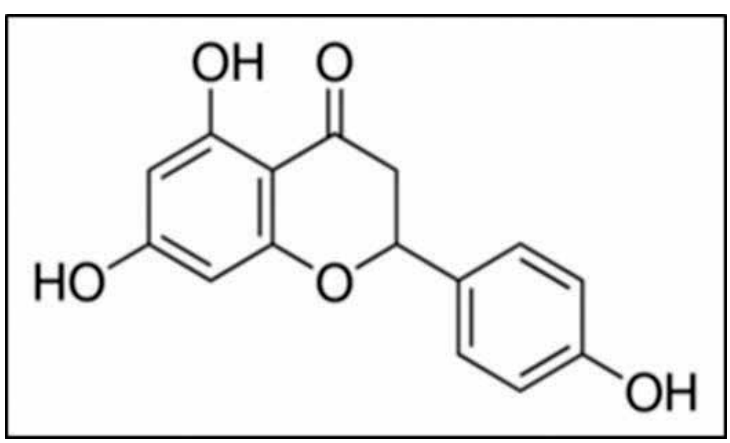

Figure 9. Chemical structure of Naringenin [33].

3. Conclusion

In conclusion, supplementation with antioxidant has been underestimated in modern society. However, studies have shown the positive findings of antioxidants against diabetes mellitus such as reducing the blood glucose level, regulating the disease complications such as cardiovascular complications, peripheral vascular disease like poor wound healing effect. Although natural sources of antioxidants are easily available worldwide, little attention is paid on its therapeutic usage. Detailed knowledge on the beneficial effects of antioxidants on oxidative stress disorder like diabetes mellitus is required. Understanding the underlying mechanism of antioxidant will be beneficial for disease progress assessment and development of prophylaxis regimens. It is believed that in future, supplements with antioxidant might serve as a savior of diabetes for general population.

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Section 3

Updates and Novel Approaches of Combating Diabetes

Chapter 8

Influence of Glycaemic Control on Cognitive Function in Diabetic Children and Adolescents

Estefanía Diéguez Castillo, Ana Nieto-Ruíz, Mireia Escudero-Marín and Cristina Campoy

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75562

Abstract

According to the World Health Organisation (WHO), the number of people with diabetes has risen to 422 million in 2014. Poorly managed diabetes leads to chronic hyper and/or hypoglycaemia, which are associated with neurological complications in type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. Therefore, the primary target of diabetic treatment is to achieve a good glycaemic control (GC). In this chapter, we reviewed studies published up to September 2017 about GC and cognitive development in diabetic children and adolescents, as well as the nutritional approaches used for the management of diabetes in childhood, focusing on low glycaemic index (GI) diets. According to different studies, low GI diets effectively improve GC, which may reduce the risk of diabetes-related complications, such as cognitive dysfunction; however, the evidence is not sufficiently robust and the results are inconclusive. Despite the fact that, low GI diets are consistent with healthy eating recommendations and should be encouraged in the prevention and nutritional management of diabetes. Further research is needed in diabetic children and adolescents at risk, especially well-designed long-term randomised controlled trials, with larger sample size, to determine the true value of low GI diets on long-term GC and diabetes prevention and management.

Keywords: diabetes, glycaemic index, blood glucose, neurodevelopment, cognitive performance, brain

1. Introduction

Diabetes mellitus (DM) is a complex, chronic endocrine disorder of carbohydrate metabolism resulting from a defect in insulin secretion, insulin action, or both and characterised by high

plasma glucose levels. Currently, it is a major contributor to morbidity and mortality and is becoming an epidemic together with obesity worldwide. In fact, according to the WHO, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014; furthermore, WHO projects that diabetes will be the seventh leading cause of death in 2030. However, the most worrying fact is that the number of people who suffer diabetes will reach over half a billion by 2030, becoming a major public health issue [1–5].

Diabetes is classified into four clinical categories, T1DM, T2DM, gestational diabetes mellitus (GDM) and other specific types of diabetes due to other causes, such as genetic defects in β-cell function, genetic defects in insulin action or diseases of the exocrine pancreas, among others [6]. The two primary forms of diabetes are T1DM and T2DM. T1DM or insulin-dependent DM is an autoimmune disorder characterised by insulin deficiency (an absolute or near total loss of insulin secretion) caused by the destruction of the insulin-producing pancreatic β-cells; the onset occurs typically during childhood or early adulthood, between the ages of 8 and 12, although it could happen at early ages. This form of diabetes is fatal in the absence of insulin replacement therapy. T1DM represents approximately 5–10% of all diagnosed cases of diabetes [1, 3, 7–9], whereas T2DM or non-insulin-dependent diabetes, that accounts for 90–95% of all diagnosed cases. T2DM is characterised by decreased insulin sensitivity or insulin resistance in peripheral tissues and relative insulin deficiency; this pathology is commonly associated with other metabolic disturbances like obesity, hypercholesterolemia, hypertension and other features of the metabolic syndrome. The prevalence of this disturbance is increasing and is been diagnosed at increasingly younger ages [1–3, 7, 8, 10].

Cognitive dysfunction is a well-established consequence of diabetes. There is extensive literature which has demonstrated that diabetes, its microvascular complications (nephropathy, neuropathy and retinopathy), and its management with insulin and other drugs can induce mild to moderately severe neurocognitive dysfunction as a consequence of structural and functional changes in the central nervous system (CNS), and it will be especially harmful in infancy and childhood when it is under development. It is known that glycaemic extremes (hyper and hypoglycaemia) affect brain development. The subjects who develop diabetes early in life (6–7 years old) have an elevated risk of mild to moderately severe dysfunction that affects virtually all cognitive domains, including learning and memory. However, if the onset of the diabetes is after this critical period, the neurocognitive dysfunction will be less severe and more restricted. But, although "later onset" subjects show lower scores compared with their healthy siblings on tests of intelligence, sustained attention, visuospatial skills, psychomotor speed and executive functions, they show essentially normal learning and memory skills [9, 11]. Despite the fact that, poorly managed diabetes is associated with neurological complications [4, 12, 13].

Therefore, the primary target of diabetic treatment is to achieve a good GC measured by the glycated haemoglobin A1c (HbA1c). HbA1c reflects average glycaemia during the last 3 months and has strong predictive value for diabetes-related complications. It has to be measured every 3 months in order to determine if patients´ glycaemic targets have been reached and maintained (HbA1c < 7.5% is recommended among all paediatric age-groups according to the American Diabetes Association; a lower goal <7% is recommended if it can be achieved

without excessive risk of hypoglycaemia) [4, 12, 13]. The optimal diet and macronutrient composition for diabetic children or adolescents remain controversial [14]. Initial reports support the use of the GI in diabetic management; GI is defined as *'the incremental area under the blood glucose response curve elicited by a 50 g available carbohydrate of a test food expressed as a percentage of the response elicited by 50 g glucose in the same subject'* [15]. Recent criticisms of the GI focus on its validity, claiming that GI values are inaccurate and imprecise. Although, there are controversial results in this matter and some research groups claim that there is insufficient evidence for the beneficial effects of GI diets, several studies have demonstrated that diets promoting low GI patterns effectively improved GC by reducing the occurrence of glycaemic extremes in subjects with diabetes [2, 4, 10, 14–20].

In this chapter, we reviewed the studies published up to September 2017 about GC and cognitive development in diabetic children and adolescents. Furthermore, it has been performed a review of the nutritional approaches (*Mediterranean diet, low GI diet, high-cereal fibre diet, carbohydrate exchange or low carbohydrate diets, low fat diet or diets rich in antioxidants*) used for the management of diabetes, focused on low GI diets.

2. Early programming of diabetes

Recent studies highlight the importance of the intrauterine environment in women with preexisting diabetes and obesity on the long-term health of the offspring. Thus, an intrauterine environment that exposes the foetus to excess of glucose, lipids, inflammation, growth factors, and cytokines may promote adipogenesis, alter appetite regulation, adversely affect pancreas development, and modify mitochondrial function, resulting in long-term metabolic risk to the offspring. The metabolic intrauterine environment is considered a critical risk factor for the development of adult diabetes and cardiovascular diseases [21]. As a consequence, any harm during critical developmental windows induces permanent adaptive programming in key organs, leading to persistent alterations in gene expression through epigenetic mechanisms. Nutrition constitutes the most significant environmental factor, being both a risk factor and the key in the prevention and protection against different metabolic disorders later in life [22].

In utero programming seems to create a *'metabolic memory'*, considering that physiological anomalies during the gestational period are responsible for the onset of T2DM and obesity associated with metabolic syndrome in the offspring at adulthood [23]. The periconceptional period has also been found as a critical period for nutritional effects on the ability of the foetus to respond to acute and chronic stressors, and for postnatal and adult metabolic health outcomes. It has been suggested that this period constitutes a critical time for nutritional effects on gene expression, with a potential preventive effect of postnatal risks related to prenatal maternal overconsumption and/or overweight, and DM or metabolic syndrome during pregnancy [22].

The association between poor psychosocial health, the risk of obesity and T2DM is well established. DynaHEALTH EU project hypothesises that factors determining glucose metabolism and insulin sensitivity on one hand, and the neuroendocrine response resulting from exposure to psychosocial stress on the other, should be incorporated as a single health indicator,

named *'gluco-psychosocial axis'* (GPA) [24]. It is proposed that long-term GPA status could be established during developmental windows throughout early stages of life, via programming. The metabolic and psychosocial environments in early stages of life play an important role in the structural and functional development of the GPA components. Several studies have demonstrated the importance of the prenatal environment in determining long-term health and the ageing process [24].

Epidemiological evidence suggests impaired glucose metabolism begins much earlier in life [24]. According to clinical studies pre-pregnancy diabetes or GDM, together with maternal obesity, have been associated with higher risk in the offspring of developing obesity, insulin resistance and T2DM later in life [25]. Complications in the offspring might appear even with gestational glucose levels below the thresholds of GDM; even borderline high blood glucose levels increase the risk of infants of being large for gestational age, early adiposity rebound and higher prevalence of metabolic syndrome, especially if they become obese [22]. Infants born from mothers who developed DM before pregnancy had higher risk to develop obesity, higher blood glucose and HbA1c levels, as well as lower HDL cholesterol concentrations and were more prone to DM during childhood, compared to those infants born from mothers who developed DM after pregnancy [25]. Furthermore, different studies have demonstrated that both, GDM or pre-gestational diabetes are related to delayed brain maturation, deficiencies in fine/gross motor development, cognitive deficiencies, and higher risk to develop Attention Deficit Hyperactivity Disease (ADHD) in the offspring, especially when there was a bad control of the maternal illness (HbA1c > 7.5%) during pregnancy [26–28].

T2DM burden is currently increasing in young people; higher maternal body mass index (BMI) during pregnancy is associated with higher all-cause mortality, higher cardiovascular morbidity and mortality, and increased risk of T2DM among offspring [24]. Data from PREOBE project have demonstrated that infants born from obese mothers had significantly higher birth weight and waist circumference, and those born from mothers with GDM had higher waist/height index compared to the healthy controls [29]. Maftei et al. reported that maternal pre-pregnancy BMI is related to offspring's insulin resistance at 9–10 years old, independently of GDM, and gestational weight gain does not appear to affect insulin resistance in children [30]. Other studies, showed that both foetal hyperglycaemia and hyperinsulinaemia in GDM increase the obesity and diabetes rates in the offspring, independently of maternal genetic influence [31]. Additionally, Westermeier et al., found that maternal obesity and neonatal insulin resistance are associated with long-term development of obesity, DM, and increased global cardiovascular risk in the offspring, involving deleterious mechanisms of intrauterine programming [32].

The DynaHEALTH EU project is testing how offspring's diseases later in life and their own GPA status is established in early life in response to metabolic and stress factors and partly related to maternal GPA status in pregnancy [24].

Nevertheless, developmental programming in humans is not limited to the *in utero* environment, the nutritional status during post-natal period has a considerable impact on later life health. As well, gender differences in developmental programming have been largely ignored and it has been suggested that offspring responses to the early metabolic environment are highly

http://dx.doi.org/10.5772/intechopen.75562

sexually driven. This could be due to inherent gender differences in hypothalamic development, or gender specificity of the adaptive response to environmental challenges. In fact, there is higher risk of T2DM in women who were exposed to high maternal BMI during foetal life. Thus, in the future it will be vital to take into account sex differences for the establishment of recommendations, health guidelines and in the design of new therapeutic interventions [24, 33].

Either pre-existing diabetes (T1DM/T2DM) or GDM are associated with macrosomia in the offspring. Alterations in macrosomic infants persist postnatally, leading to insulin resistance, obesity, diabetes and metabolic syndrome at adulthood [23]. Maternal programming creates a vicious cycle by which maternal diet, weight or glycaemic status can increase offspring susceptibility to metabolic disease. These offspring during their pregnancies will have their own children; also exposed to an adverse *in utero* environment, perpetuating the burden of such conditions to future generations (**Figure 1**) [25, 33].

The molecular mechanisms involved in foetal programming in diabetic women are far from understood [31]. It is essential that all diabetic women receive a proper management, including preconception counselling about weight management and weight loss (if they are overweight),

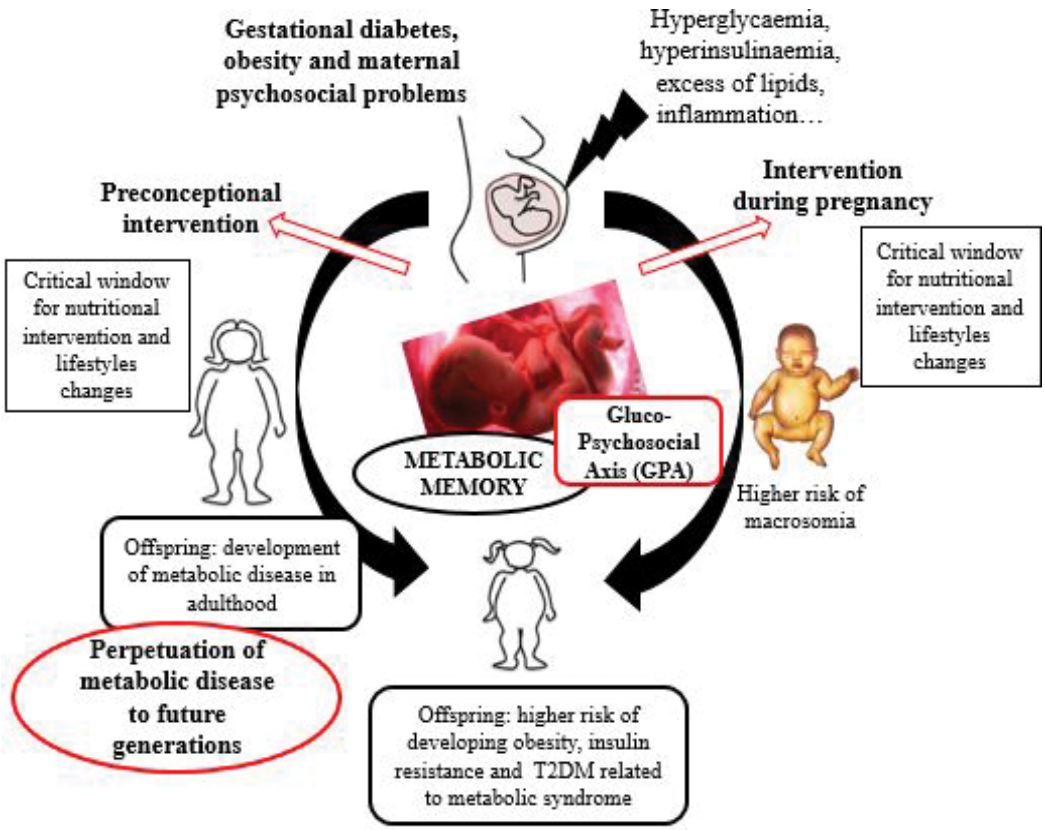

Figure 1. Vicious cycle of metabolic disease perpetuation to future generations and critical windows for intervention. Adapted from Dearden and Ozanne [33].

proper weight gain during pregnancy, the critical importance of optimising GC (HbA1c < 6.5), by self-monitoring blood glucose levels, medication (if needed), medical nutrition therapy (eating a healthy diet) and optimal individualised exercise [21, 31]. Therefore, prevention of foetal programming by tight GC will be essential in order to break the vicious cycle of obesity, diabetes and related-complications in future generations [31]. In order to develop effective intervention strategies, it is important to understand the programming effects of maternal nutrition during pregnancy and the post-natal period both separately and combined, as well as to define clearly the critical developmental periods in order to establish an appropriate time intervention [33].

3. Cognitive dysfunction related to diabetes

The negative effects of DM on retinal, renal, cardiovascular, and peripheral nervous systems are widely acknowledged, but less attention has received its effects on cognitive function and neurodevelopment. T1DM and T2DM are associated with reduced performance on numerous domains of cognitive function. The exact pathophysiology of cognitive dysfunction in diabetic patients is not well understood; nonetheless, vascular disease, hyper or hypoglycaemia, and insulin resistance seem to play significant roles [34].

Subjects with T1DM and T2DM can develop several microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (coronary heart disease, peripheral arterial disease, cerebrovascular disease) complications that will contribute to cognitive dysfunction in adults; however, the major cause of mortality and morbidity in children with T1DM is the diabetic ketoacidosis, which cause cerebral injury along with haemorrhage or cerebral infarction in some cases, leading to cerebral edema (**Table 1**) [7, 8, 35].

Cognitive dysfunction in T1DM and T2DM share many similarities, but important differences do exist [7], specifically in the degree of cognitive dysfunction and in the manifestation of cognitive abnormalities [1]. Poorly managed diabetes due to chronic hyper and hypoglycaemia or elevated postprandial glucose may be common aetiological causes of the neurological complications of T1DM and T2DM or cognitive dysfunction [12, 36].

3.1. Type 1 diabetes

Different studies assessing cognition in children and adolescents with an early onset of diabetes (EOD) (6–7 years) have shown higher risk of developing more severe cognitive deficits, especially impairments in *memory, learning, intelligence* and *verbal fluency/language* [36, 37], as well as in *attention, executive function* [38], *psychomotor speed* [9], *slowing of information processing, problem solving, visuoconstruction, visual perception* and *mental flexibility* [7].

Patients with T1DM often perform within normal cognitive range; however, they may perform more poorly on some cognitive tasks compared to non-diabetic control subjects, such as *executive functions, short-term memory, psychomotor efficiency* and measure of *mental efficiency*, which predispose for more rapid deterioration of cognitive function later in life [1]. Kodl and

Metabolic factors	• Chronic exposure to hyperglycaemia [1] • Acute exposure to hypoglycaemia [11] • Recurrent exposure to hypoglycaemia [1] • Increased plasmatic concentration of AGEs [34]
CV factors	• Microvascular complications (*nephropathy, neuropathy, retinopathy*) [8] • Macrovascular complications (*coronary heart, peripheral arterial and cerebrovascular diseases*) [8] • Endothelial dysfunction [17] • Increased inflammatory markers (*C-reactive protein, α-1-antichymotrypsin, interleukin-6 and intercellular adhesion molecule 1*) [34] • Changes in blood–brain barrier permeability • Reduced fibrinolysis [14] • Dyslipidemia (*increased total cholesterol, LDL-c and triglycerides, and reduced HDL-c*) [14] Hypertension [1]
Endocrine factors	• Insulin resistance [34] • Hyperinsulinaemia • Impaired HPA axis activity [12] • Absence of C-Peptide [34] • Increased antidiuretic hormone Hyperleptinaemia
CNS factors	• Genetic predisposition (*Absence of Apoε4 Allele*) [34] • Amyloid disposition • Increased oxidative stress [11] • Changes in neuronal calcium homeostasis • Depression and anxiety [2, 12] • Disrupted myelination [11] • Increased apoptosis in oligodendrocyte precursor cells [11] • Dysfunctional synaptic plasticity [1]
Disease onset	• Early onset diabetes (6–7 years old) [9]

Advanced glycation end products, AGEs; cardiovascular, CV; central nervous system, CNS; high density lipoprotein cholesterol, HDL-c; hypothalamic-pituitary-adrenal, HPA; low density lipoprotein cholesterol, LDL-c. Adapted from McCrimmon RJ, Ryan CM, Frier BM. Lancet, 2012 [7].

Table 1. Factors that contribute to the development of cognitive dysfunction in diabetic patients.

Seaquist found different cognitive domains negatively affected in T1DM, specifically *information processing*, psychomotor efficiency*, attention*, memory, learning, problem solving, motor speed, vocabulary, general intelligence, visuoconstruction*, visual perception, somatosensory examination, motor strength, mental flexibility** and *executive function*. According to the authors the domains marked by asterisks have strong supporting data [34].

Neuroimaging studies have found morphological abnormalities, cortical atrophy, lower grey matter volume and density in left temporal-occipital junction, white matter hyper-intensities and reduced white matter densities, concretely white matter microstructural deficits, as well as neuroanatomical changes in the hippocampal region. However, other studies did not find volumetric changes in the hippocampus [12, 36, 37]. In fact, Ho et al., have reported that measuring subfields of the hippocampus with high resolution magnetic resonance imaging may provide a way to specifically target the neurogenic regions of the hippocampus and may show different effects of diabetes on different parts of the hippocampus. It should be noted that studies carried out in rodents with T1DM have shown reductions in hippocampal cell proliferation and survival, leading to learning and memory deficits compared to control rodents (**Figure 2**) [3].

Additionally, glycaemic extremes (hyper and hypoglycaemia) affect brain development. Severe hypoglycaemia during a lifetime exposure decreases lateral temporal–parietal-occipital grey matter volume, whereas after 2 years with T1DM showed a greater reduction in the regional white matter volume in the precuneus/cuneus region [11]. Furthermore, severe

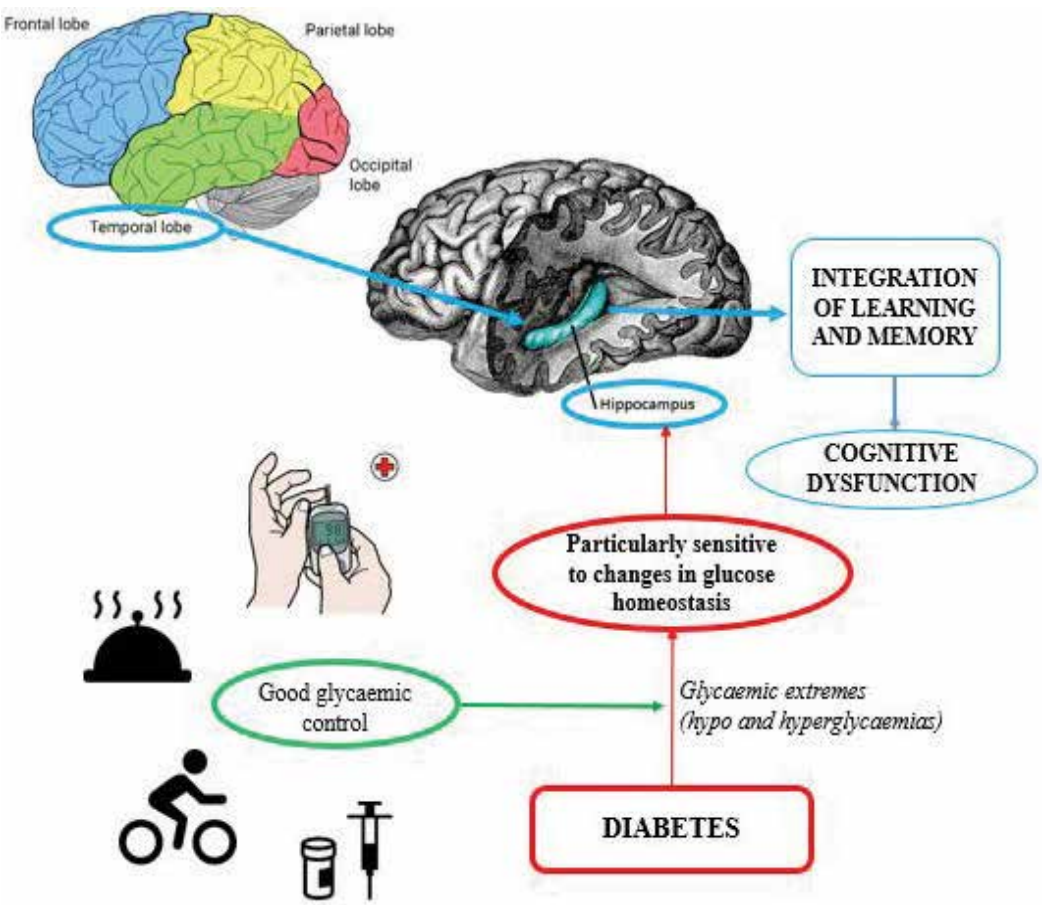

Figure 2. Effect of glycaemic extremes on the development of congestive dysfunction.

hypoglycaemia harms neurons in cerebral cortex, medial temporal region, including hippocampus, basal ganglia and brain stem with unknown individual consequences [36]. Hypoglycaemic episodes in T1DM children lead to significant declines in *verbal abilities*, *memory skills* and *ability to organise* and *recall information*. Severe hypoglycaemia may result in persistent electroencephalography (EEG) changes, with 80% of EEG abnormalities observed in diabetic children with history of severe hypoglycaemia compared with 30% of abnormalities in diabetic subjects without severe hypoglycaemia and 24% in healthy control children [39]. In presence of severe hypoglycaemia in T1DM, children show mildly reduced intelligence quotient (IQ), as well as adverse effects in general, verbal and performance IQ [40].

Children and adults with T1DM have worse performance in executive function, full IQ and motor speed; in presence of hyperglycaemia negative effects on memory function were observed in children. Moreover, higher HbA1c levels were associated with worse *motor speed* and *psychomotor efficiency* [41]. Additionally, chronic hyperglycaemia has been associated with reductions in grey matter volume and multiple posterior brain regions, including the cerebellum. Adolescents with three or more symptomatic hyperglycaemic episodes showed reductions in white matter integrity, specifically in superior parietal lobule, corpus callosum, posterior limb of the internal capsule, and grey matter integrity, concretely in thalamus and putamen, whereas children (4–10 years old) showed microstructural abnormalities in white matter with lower IQ scores [40]. A lifetime exposure to hyperglycaemia reduces occipital/parietal grey and matter volume; after 2 years with T1DM, a reduction in the whole brain grey matter has been observed [11]. Large effects have been observed in T1DM patients regarding *visuospatial ability, motor speed, writing, sustained attention* and *reading* [40, 42].

It is worth noting that a late onset of diabetes (LOD) entails several cognitive dysfunctions, although these impairments are less severe compared to those subjects with EOD. In subjects with a LOD, it has been found lower *overall cognition, intelligence, visual learning* and *memory, motor speed* and *visual motor integration, sustained attention* and *executive function* compared to their healthy siblings [9, 38].

Finally, several studies have shown that gender influences neurocognitive function in T1DM. In a study with children and adolescents (aged 7–16 years), boys presented decline in *verbal intelligence*, which was correlated with worse GC. This was not seen in girls of similar ages. It should be noted that most human studies do not distinguish between genders when describing results of neurocognitive testing [34].

3.2. Type 2 diabetes

The prevalence of childhood obesity has increased dramatically worldwide, leading to a variety of health problems, including T2DM, which previously was seen only in adults. The Centres for Disease Control (CDC) and Prevention foresee that the prevalence of T2DM in those under 20 years of age will quadruple in 40 years, assuming a 2.3% annual increase [6]. In the United States, up to 1 in 3 new cases of diabetes diagnosed in subjects younger than 18 years old is T2DM, occurring most commonly in children and adolescents between 10 and

19 years of age [43]. It is difficult to distinguish between T1DM and T2DM in children, given the current obesity epidemic worldwide. The rapid emergence of childhood T2DM means that health professionals have to treat a disease in children, which previously was encountered only in adults. This represents several challenges, because most of diabetes education materials are designed and directed to children with T1DM, but not to T2DM and probably obese patients. Another problem is that most medications used for T2DM have been tested for safety and efficacy in subjects older than 18 years old, because ethical reasons. Therefore, there is scarce scientific data for optimal management of children with T2DM [6, 43].

The comorbidities, such as obesity, hypertension and dyslipidaemia, may be present at the time of diagnosis in youth with T2DM, which contribute to the severity of the disease. The cause of diabetes-related cognitive dysfunction is difficult to establish, because of the prevalence of several comorbidities in the same individual, which might affect cognitive function [6, 7].

Lamport et al. [44], performed a systematic review in adults, concluding that T2DM is associated with cognitive impairments. In the present longitudinal review we found many studies relating an accelerated cognitive decline in adults with T2DM; however, it is difficult to conclude that these reported cognitive impairments are independently associated to abnormalities in glucose tolerance or due to the associated comorbidities present in these patients (cerebrovascular and cardiovascular diseases, obesity, hypertension and hypercholesterolemia) [44]. Some studies suggest that cognitive performance does not differ in T2DM subjects in relation to non-diabetic controls when it is taken into account the influence of age, premorbid IQ, BMI and depression [1]. Unlike the studies in T1DM patients, most studies suggest that T2DM subjects experience cognitive decline. T2DM most often is associated with deficits in cognitive domains, *declarative memory, attention* and *executive function*, alterations also seen in children and adolescents with Metabolic Syndrome or obesity and glycaemic disorders [45, 46]. The GC, the disease duration and cerebrovascular complications are considered risk factors that influence the magnitude of the cognitive decline [12]. *Learning* and *memory* deficits are the cognitive abnormalities that most clearly differentiate patients with T2DM from T1DM patients [7].

Kodl and Seaquist, established that the cognitive domains that are negatively affected in adults with T2DM are *memory* (verbal memory, visual retention, working memory, immediate recall, delayed recall), psychomotor speed*, executive function*, processing speed, complex motor function, verbal fluency, attention* and it seems to be related with the development of diabetes. According to the authors, the domains marked by asterisks have strong supporting data [34]. Additionally, Sweat et al., in a study carried out in 162 adolescents (aged 19.53 ± 1.53 years), found that obese adolescents showed slower *processing speed* maintaining equivalent *executive functioning* compared with their healthy siblings [46]. Whereas, a recent systematic review performed Barkin et al., showed a consistent inverse association between obesity and *executive function* in children and adolescents, emphasising that in future research is necessary to use a standardised method of *executive function* measurement in order to establish causality with obesity and develop new and more effective intervention strategies [47].

Neuroimaging studies have shown deficits in hippocampal-based cognitive performance, which may be attributed to changes in brain structure and volume, leading to deficits in *attention, learning* and *memory* [1]. T2DM subjects have similar morphological abnormalities than T1DM patients, such as cortical atrophy and white matter lesions. Moreover, it has been shown a reduction in the microstructural integrity of white matter and grey matter. The reductions in grey matter volumes have been observed in the prefrontal cortex, amygdala and hippocampus [12]. Additionally, greater cortical atrophy, more lesions in deep white matter and hippocampal (susceptible to acute metabolic changes, such as hypoglycaemia) atrophy, leading to impairments in *immediate memory*, have been observed (**Figure 2**) [7].

Hippocampal atrophy is one of the neuroanatomical characteristics that differs between people with T1DM and T2DM, both have reduced grey matter density and white matter lesions. Nevertheless, cortical atrophy is more pronounced in T2DM, possibly because the subjects are older on average. Moreover, the hippocampus is more affected in T2DM, is unclear why, because this area is susceptible to acute metabolic change, which is more prominent in T1DM. This suggests that age, sex, the associated comorbidities and the presence of macrovascular disease or insulin resistance might be important risk factors for hippocampal atrophy (**Figure 2**). T2DM subjects perform worse than healthy control on learning and memory tests, unlike those with T1DM, who rarely have deficits in these domains [7]. However, the results are inconclusive, because other studies have found deficits in *learning* and *memory* in T1DM patients, but Kodl and Seaquist confirmed that there is no strong evidence to suggest this [34].

4. Glycaemic index and dietetic management in diabetic children and adolescents

At present, nutritional interventions, physical activity and weight control remain the main pillars of effective diabetes management. Despite modern approaches to intensive insulin therapy and other drugs for the management of diabetes, dietary management remains as the main important action of diabetes treatment [48]. There is not an ideal nutritional intervention for the management of diabetes. A poor GC in subjects with T1DM and T2DM has been related with the onset of diabetes complications. Therefore, it is vital to develop new strategies in order to maintain a good GC. Current standards for diabetes management reflect the need to lower glucose as safely as possible, without increasing the risk or hypoglycaemic episodes. It should receive special consideration the risk of hypoglycaemia in young children (aged <6 years or EOD), because usually they are unable to recognise and/or manage the symptoms. This is called *'hypoglycaemia unawareness'* [6].

There are different dietetic approaches aimed at the improvement of the GC in children and adolescents with T1DM and T2DM, among them it is worth noting low GI diets, diets rich in antioxidants, carbohydrate exchange diets, high-cereal fibre diet, traditional Mediterranean-style dietary pattern, low carbohydrate Mediterranean style diet, low carbohydrate diets and low fat diets.

Although there are no long-term intervention studies looking at the effects of a low GI diet on diabetes prevention, there is a large body of evidence from animal models, clinical trials and epidemiologic studies that demonstrates the benefits of a low GI diet in the prevention and management of diabetes. Low GI diets in subjects with T1DM and T2DM improve blood glucose control to a similar extent as medications, improving GC and reducing the risk of hypoglycaemic events [14].

Derdemezis and Loveg [4], reported in by a systematic review that low GI diets effectively improve GC. They observed that subjects with T2DM presented significant beneficial effects after the consumption of low GI diets; however, in some cases, a low GI diet was associated with significant weight reduction, which makes difficult to establish firm conclusions, because it is not clear if the effect on the improvement of GC is for the low GI diet per se or derived from the weight loss itself. On the other hand, in subjects with T1DM there is insufficient evidence for the beneficial effects of GI control due to different confounding factors (differences in dietary fibre intake and the values used for calculation of dietary GI and weight loss), suggesting that total carbohydrate content adjusting pre-meal insulin infusion might be more important than GI in controlling postprandial glucose levels. However, low GI diets might be used as a treatment in T1DM in order to reduce the insulin infusions. The potential of a low GI diet in preventing diabetes has not been studied to date, but low GI diet may improve GC and reduce the risk of diabetes and its complications [4].

In another study, T1DM subjects (7–17 years old) were provided with four premade test meals, which were consumed at breakfast after a minimum 10 h overnight fast [16]. The low GI test meal had a GI of 48, meanwhile the one with high-GI test meal had a GI of 84. For the measurement of blood glucose, they used a continuous glucose monitoring system. The low GI meal produced significantly lower postprandial glucose excursion (PPGE) for 30–180 minutes, lower area under the blood glucose response curve (AUC), a smaller peak blood glucose excursion, and reduced time to reach baseline blood glucose levels compared with the high GI meal when preprandial ultra-short-acting insulin was administered. Nevertheless, the effect of GI on the postprandial glucose response requires further exploration in children receiving intensive insulin therapy [16].

A systematic review performed by Thomas and Elliott [2] in T1DM and T2DM children and adults, showed that GC in people with diabetes improved significantly with a low GI diet, by decreasing hypoglycaemic episodes, compared to those on higher GI diets or measured carbohydrate exchange diets. It was observed that a low GI diet produces a decrease of 0.5% HbA1c, clinically significant, similar to the reductions produce by the medications given to newly diagnosed T2DM subjects; as a result, it has been confirmed that a low GI diet is associated with a significant reduction in the risk of microvascular complications [2].

In 2010, these authors performed a meta-analysis with evidence that low GI diets significantly improve GC, by lowering HbA1c without any increase in the rate of hypoglycaemic episodes, when compared with a measured carbohydrate exchange diet and a high-cereal fibre diet. In other studies, low GI diet improved HbA1c levels in T1DM children; in contrast, T2DM low GI group presented a significant increase in insulin sensitivity compared to the high GI group.

The effect is sufficiently strong that may benefit diabetic patients by reducing or even avoiding their requirement for medication [10].

It is important to keep in mind that medications that improve blood glucose levels usually are associated with high risk of hypoglycaemia, which is the greatest barrier to achieve an optimal GC, particularly in T1DM. In people with T2DM a reduction in HbA1c levels after the consumption of low GI diets has been observed, whereas in children with T1DM, with both intensive multiple daily injection of insulin or insulin pump therapy, a reduction in postprandial glucose excursions, as well as improvements in insulin sensitivity after 3 to 4 weeks was demonstrated. However, a high GI diet worsens insulin resistance in individuals with and without diabetes and rises blood glucose levels and the need to medication in T2DM and the insulin requirements in T1DM. Therefore, the reduction of the risk of diabetes-related complications with low GI diets is similar to or greater than the diets including a high intake of fibre and whole grains [14].

A low GI diets favours slower and more gradual absorption of glucose from the gastrointestinal tract, avoiding hypoglycaemic episodes; moreover, it produces fewer stimuli for insulin release, reduces free fatty acids levels and oxidative stress, and increases insulin sensitivity [17].

According to the Canadian Diabetes Association, interventions replacing high GI carbohydrates with low GI carbohydrates in mixed meals have shown clinically significant improvements in GC over 2 weeks to 6 months in people with T1DM or T2DM; improvements were observed in cardiovascular risk factors, postprandial glycaemia and high sensitivity C-reactive protein over 1 year in people with T2DM, whereas adults and children with T1DM showed lower hypoglycaemic events over 24 to 52 weeks [20]. In addition, it has been shown that low GI diets sustain improved GC and HDL cholesterol compared with a high-cereal fibre diet over 6 months, and improved β-cell function in comparison with a low carbohydrate, high monounsaturated fat diet over 1 year in people with T2DM [20]. As it has been already mentioned, diets with lower GI result in improvements in HbA1c in the order of 0.5%. [19].

In contrast, a review carried out by Madsbad [49] in subjects with T1DM and T2DM showed different results. Dietary carbohydrate restriction as early therapy in T2DM, and as an adjunct to therapy in T1DM, effectively reduces blood glucose levels. However, longer-term studies (≥6 months) have variable results regarding the relative efficacy of low carbohydrate diets compared to low in fat or low GI diets on weight and HbA1c reductions. While recent meta-analyses suggest that low carbohydrate diets may be no more effective over the longer term than low fat or Low GI diets, in terms of weight and HbA1c changes [49].

It has been observed a reduction in the risk of diabetes with the consumption of low GI diet, whereas high dietary GI and/or glycaemic load increase the risk of T2DM [18]. Observational data suggest that replacing high GI with low GI carbohydrate reduces the risk of metabolic disturbances and T2DM. Nevertheless, some studies show inconclusive results that may be due to methodological differences and confounding parameters that can dramatically modify the post-meal metabolic response, such as the type of carbohydrate and its digestibility, quantity of carbohydrates as compared with other macronutrients, lipids, proteins and fibres [18].

Recent criticisms of the GI claim that GI methodology is not valid, and GI values are inaccurate and imprecise, and GI does not predict what foods are healthy and that whole grain and fibre are better markers of carbohydrate quality than GI. Eating a food as part of a mixed meal affects the glycaemic response, but does not alter the food's GI, because is an intrinsic characteristic of food. However, the glycaemic response of a food or a meal is altered in the presence of other foods depending on the amount and source (GI) of carbohydrate and the amounts and types of fat and protein added. Moreover, it is important to take into account that the relative glycaemic response of a meal is determined by its calculated meal GI and the amounts of available carbohydrates, fat and protein. Therefore, GI is a valid marker of carbohydrate quality because GI methodology is accurate and precise and GI is a property of the food, and is biologically meaningful and influences outcomes in health and disease, especially in the nutritional management of diabetes. Despite the fact that the results are inconclusive, there is no evidence to suggest any negative effect of following low GI diets, which are consistent with healthy eating recommendations aimed at weight control and reducing the risk of diabetes-related complications by improving the GC in people with diabetes (**Table 2**) [14, 15, 17, 49].

It should be noted that a traditional Mediterranean-style dietary pattern improves GC and cardiovascular risk factors, including systolic blood pressure, total cholesterol, HDL cholesterol, the total cholesterol/HDL cholesterol ratio and triglycerides in T2DM. On the other hand, a low carbohydrate Mediterranean-style diet has shown reductions in HbA1c and delays on the need for antihyperglycaemic drug therapy at 4 years of diagnosis, compared with low fat diet in overweight individuals with newly diagnosed T2DM. To sum up, traditional and low carbohydrate Mediterranean-style diets are shown to reduce HbA1c and triglycerides, whereas only the low carbohydrate Mediterranean-style diet improves LDL cholesterol and HDL cholesterol at 1 year of diagnosis in overweight subjects with T2DM [14, 20].

It has been shown that a disrupted balance between oxidative stress and antioxidant cascades contributes to neuroplasticity deficits in experimental models of diabetes; therefore, antioxidants treatments may provide excellent adjunct treatments to traditional approaches to reduce the neurological complications of diabetes. In a review carried out by Reagan, the neuroplasticity deficits were attenuated or eliminated by antioxidants, including melatonin and vitamin E, lycopene, resveratrol, dehydroepiandrosterone (DHEA) and essential fatty acids. T2DM patients supplemented with vitamin E and with increasing serum lycopene levels showed reductions in oxidative stress parameters, whereas DHEA administration showed reductions in plasma oxidative stress measures and lipid peroxidation products and increased antioxidants in T2DM subjects [12].

It is essential to take into account that the nutritional management in children and adolescents is more complex than in adults, because they do not have autonomy or the necessary knowledge to maintain a good GC. In a recent study carried out in 282 T1DM children and adolescents, a greater nutrition knowledge of parents and patients, measured by a type 1 diabetes Nutrition Knowledge Survey (NKS), was associated with both better GC and higher diet quality in their children. Therefore, it is vital an early nutritional education and the role of parents in order to achieve good nutritional management and GC during childhood [48].

	References	Low GI diet
T1DM	Rahelić, et al. [17]	• Lower fasting glucose • Reduction of oxidative stress
	Ryan, et al. [16]	• Lower PPGE • Lower AUC • Lower peak blood glucose excursion • Reduced time to reach baseline blood glucose levels
	Thomas, et al. [2, 10]	Acceptable/ Improved HbA1c levels
	Derdemezis, et al [4]; Dworatzek et al. [20]	Improved glycaemic control
	Thomas, et al. [2]; Marsh et al. [14]; Dworatzek et al. [20]	Lower hypoglycaemic events
	Marsh et al. [14]; Blaak et al. [18]	Reduced postprandial hyperglycaemia
		High GI diet
	Marsh et al. [14]	• Rapid rise in blood glucose and insulin levels • Increased insulin requirements • Increased postprandial glycaemia • Higher hypoglycaemic episodes
	References	**Low GI diet**
T2DM	Rahelić et al. [17]	Lower fasting glucose Reduction of oxidative stress
	Thomas et al. [2]; IDF* [19]	Decrease of 0.5% in HbA1c levels
	Thomas, et al. [10]; Marsh et al. [14]	Increased insulin sensitivity
	Thomas, et al. [10]	• Reduction or avoidance of diabetic medication • Significant reduction in BMI, total fat mass and body mass
	Thomas, et al. [2]; Derdemezis, et al. [2]; Dworatzek et al. [20]	Improved glycaemic control
	Thomas, et al. [10]; Marsh et al. [14]; Dworatzek et al. [20]	Improvement in lipid profiles *(total cholesterol, LDL-c and HDL-c levels)* and C-reactive protein
	Dworatzek et al. [20]	• Improvement in CV risk factors • Improved postprandial glycaemia
	Marsh et al. [14]	Reduced postprandial hyperglycaemia
	Derdemezis, et al. [4]; Thomas, et al. [10]	Significant weight loss in overweight/obese people

References	Low GI diet
	High GI diet
Marsh et al. [14]	• Rapid rise in blood glucose and insulin levels • Increased postprandial glycaemia • Higher need to medication • Fasting hypertriglyceridaemia • Lower HDL-c levels • Reduced fibrinolysis
Marsh et al. [14]; Rahelić et al. [17]	Increased insulin resistance
Marsh et al. [14]; Rahelić et al. [17]; Blaak et al. [18]	Increased risk of T2DM up to 40%

Area under the blood glucose response curve, AUC; body mass index, BMI; cardiovascular, CV; glycated haemoglobin A1c, HbA1c; high density lipoprotein cholesterol, HDL-c; low density lipoprotein cholesterol, LDL-c; postprandial glucose excursion, PPGE; type 1 diabetes mellitus, T1DM; type 2 diabetes mellitus, T2DM*International Diabetes Federation.

Table 2. Main effects of low and high glycaemic index diets on the nutritional management of diabetes in children and adolescents.

The previous nutritional recommendations are aimed to achieve a good GC and nutritional management in the long-term; nonetheless, it is necessary to address the acute dietary complications, meaning the management of hypoglycaemia, because it is the most common acute complication of the treatment of T1DM. In case of hypoglycaemia (<60–70 mg/dl) it is necessary an immediate oral, rapidly absorbed, simple carbohydrate to raise blood glucose up to 100 mg/dl [39].

Finally, the exercise is indispensable in the management of diabetes, especially in T2DM children and adolescents, due to this pathology is commonly associated with obesity. The American Academy of Paediatrics recommends that health care professionals encourage children and adolescents with T2DM to practice moderate to vigorous exercise for at least 60 minutes daily and to limit non-academic '*screen time*', such as watching television or playing computer games, to less than 2 hours per day for the reduction of BMI and the improvement of GC. Physical activity is an integral part of weight management for the prevention and treatment of T2DM. Although there is scarce available data from children and adolescents with T2DM, several well-controlled studies performed in obese children and adolescents at risk of metabolic syndrome and T2DM provide guidelines for physical activity [43].

5. Future prospects

Although, the optimal diet and macronutrient composition in diabetes remain controversial and the evidence is not sufficiently robust to recommend a low GI diet as the primary dietary

strategy for GC, low GI diets are high in fibre and whole-grain products, rich in legumes, fruits and vegetables with balanced fat profile, low saturated fats and high monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). Therefore, this nutritional intervention may have beneficial effects in diabetics and populations at risk, such as children with T1DM [4, 14]. Antioxidant treatments or diets rich in antioxidants may reduce the diabetes-related neurological complications, when they are used together with traditional treatments [12]. Given that there is no optimal diet for the management of GC in subjects with T1DM and T2DM, it would be interesting to study the effects of a low GI diet based in a traditional Mediterranean-diet pattern (rich in vegetables and fruits, high content in antioxidants and fibre), that had demonstrated to improve the GC in these subjects, to evaluate the power for preventing cognitive dysfunctions and to optimise the neurodevelopment in children and youth.

It is vital to perform more long-term studies in children and adolescents, especially in those with T2DM, due to the increased prevalence in this population, considering the scarce evidence for optimal management of children with T2DM [43]. On the other hand, it is essential to develop lifestyle interventions in population at risk during childhood and adolescence (individualised nutritional and exercise programmes), focused on investigating how to prevent the development of glucose tolerance impairment, and diabetes. These interventions could protect against cognitive decline, because they help to achieve GC, reducing hypo and hyperglycaemic episodes [44].

Furthermore, the clinical follow-up of T1DM children must include also a survey of neuropsychological and brain development to prevent long-lasting consequences.

6. Conclusions

Further research is needed in diabetic children and adolescents, especially well-designed long-term randomised controlled trials with larger sample size to determine the true value of low GI diets on overall quality of life, long-term GC and the prevention or management of diabetes-related complications. The results obtained up to the present moment are inconclusive due to discrepancies between the methods of analysis and the diversity in the methodology employed. Therefore, it is difficult to generalise results. It is necessary the use of validated questionnaires for the dietary assessment and standardised the GI databases in order to make the data comparable between different studies. One limitation of all observational studies published to date is that none of the food frequency questionnaires have been specifically designed to assess the GI and until recently, few were validated against another method of dietary assessment, such as 24 h recalls or diet records. Therefore, these questionnaires have poor ability to estimate carbohydrate intake, calling into question the accuracy of any GI or glycaemic load estimation [14]. On the other hand, the studies use different cognitive tests to assess cognitive domains. Therefore, it is difficult to compare results between studies. Brain imaging is becoming essential to clarify the effects of diabetes on brain development, and it will offer us new perspectives for the prevention of neurological disorders and mental health.

Covariates that could affect neurocognitive testing and should be taken into account are, age, education, sex, history of other chronic illnesses, psychiatric and neurological disorders, absence from school, socioeconomic status, and hypo/hyperglycaemia during testing. Most of the studies control for at least some of these covariates, but most fail to control all of them [34].

There is wide criticism and controversies about low GI diet. Some authors state that is easy to follow and effective, whereas other authors think GI is highly variable, not physiological and difficult to learn and follow. Despite this, GI concept is accepted by many diabetes associations around the world as an integral part of the dietary treatment of diabetes. Despite the controversy, there is substantial evidence that a low GI diet can improve the GC in subjects with diabetes. It is vital to carry out further research of the role of GI in the prevention and treatment of diabetes and its complications together with beneficial effects of a low GI diet [17]. One of the major controversies about GI is that different studies state that the GI of food change in the presence of other macronutrients, but the reality is that GI is an intrinsic characteristic of food. Therefore, the GI of food does not change in the presence of other macronutrients, such as lipids, proteins and fibre, is just the glycaemic response. It has been shown that proteins induce greater insulin secretion, while fats reduce gastric emptying and slow down the absorption of carbohydrate. It is essential to study the effects of protein, fat and fibre on the glycaemic response to a carbohydrate meal [15], especially in children and adolescents.

On the other hand, nutritional education and physical activity are essential in order to achieve a good GC of the disease. The main goal of diabetes management is to prevent long-term complications, not only cognitive dysfunction, also micro and macrovascular complications. More studies in cognitive function in diabetic children and adolescents with severe hypoglycaemia are needed, because preventing hypoglycaemia could reduce cognitive dysfunction [36], and improve healthy ageing in the diabetic patients. Long-term interventions will help also to know the impact of disease duration on cognition. More intensive diabetes medical regimes will be associated with less neurocognitive deficits, especially in patients with an EOD because they are more expose through time to glycaemic extremes (hypo and hyperglycaemias). It is vital to identify the factors that are involved in the aetiology and progression of the neurological complications, because currently the pathophysiology of cognitive dysfunction in diabetes is not well understood [1]. Therefore, it is important to understand the pathogenesis of cognitive dysfunction secondary to diabetes in order to establish more efficient treatments and prevent or reverse these cognitive alterations [34]. Thus, further well designed human studies are needed to elucidate the pathophysiology and the mechanisms of action of cognitive dysfunction through neuroimaging [3].

In conclusion, it is necessary to carry out well designed long-term intervention randomised control trials with larger sample size, detailed cognitive assessment combined with neuroimaging [7] and adequate dietetic management. Furthermore, it is essential an early dietetic intervention in order to prevent or reduce diabetes-related complications, especially in children and adolescents with an EOD, because they are exposed through time to glycaemic extremes and are more vulnerable than adults, because their CNS is developing and any damage could be irreversible. Finally, it is important to identify population at risk during early life and childhood in order to develop clear recommendations, prevent the development of diabetes and promote healthy ageing.

Acknowledgements

The authors of this chapter are participating in the DynaHEALTH project *'Understanding the dynamic determinants of glucose homeostasis and social capability to promote healthy and active aging'. European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No 633595*.

Abbreviations

ADHD	attention deficit hyperactivity disease
AGEs	advanced glycation end products
AUC	area under the blood glucose response curve
BMI	body mass index
CDC	Centres for Disease Control
CNS	central nervous system
DHEA	dehydroepiandrosterone
DM	diabetes mellitus
EEG	electroencephalography
EOD	early onset of diabetes
GC	glycaemic control
GDM	gestational diabetes mellitus
GI	glycaemic index
GPA	gluco-psychosocial axis
HbA1c	glycated haemoglobin A1c
HDL-c	high density lipoprotein cholesterol
HPA	hypothalamic-pituitary-adrenal
IQ	intelligence quotient
LDL-c	low density lipoprotein cholesterol
LOD	late onset of diabetes
MUFAs	monounsaturated fatty acids
NKS	Nutrition Knowledge Survey
PPGE	postprandial glucose excursion
PUFAs	polyunsaturated fatty acids
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WHO	World Health Organisation

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Chapter 9

Medical Nutrition Therapy for Special Groups with Diabetes Mellitus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70815

Abstract

The prevalence of diabetes mellitus (DM) is increasing worldwide. Medical nutrition therapy increases the success of diabetes treatment and provides an appropriate glycemic control that decreases diabetes complications. The requirement of energy and nutritional elements may differ according to specific conditions including age, the presence of pregnancy, or comorbidities. Therefore, these specific conditions should be taken into account in the planning of medical nutrition therapy. Ensuring continuity of children and young growth and development, providing requirements based on comorbidities and physiological alterations in older adults, and protection of fetal development and maternal glycemic and nutrient balance in pregnancy should be aimed in the determination of energy and nutritional elements requirements. Here, we will discuss the medical nutrition therapy in special groups with diabetes mellitus.

Keywords: diabetes mellitus, pregnancy, youth, elderly, nutrition

1. Diet in patients with gestational diabetes

1.1. Introduction

Gestational diabetes mellitus (GDM) is described as any degree of carbohydrate intolerance first recognized during pregnancy [1]. GDM affects 4–8% of pregnant women in developed countries [2]. GDM is associated with an increased risk of adverse maternal and fetal outcomes, hence providing good glycemic control to substantially improve outcome [3].

Alterations in the secretion of growth hormone and cortisol and increase in human placental lactogen and insulinase levels are the mechanisms of insulin resistance during pregnancy.

Additionally, increased estrogen and progesterone make a contribution to the impaired glucose tolerance. The increase in adipose tissue, less exercise, and increased caloric intake during pregnancy are also other contributors [4].

1.2. Diagnosis

Diabetes diagnosed during the first trimester of pregnancy should be described as type 2 diabetes mellitus. GDM is diabetes diagnosed after the first trimester of pregnancy that is not clearly either type 1 or type 2 DM [5].

There are two strategies in diagnosing of GDM [5].

"One step" approach:

A 2-h 75-g oral glucose tolerance test (OGTT) is performed at 24–28 weeks of gestation in women without an overt diabetes diagnosis. Glucose concentrations after fasting and 1 and 2 h after glucose administration <92 mg/dL (5.1 mmol/L), <180 mg/dL (10.0 mmol/L), and <153 mg/dL (8.5 mmol/L), respectively, were accepted as normal; if the glucose concentration is over than the normal at any point, the patient is diagnosed with GDM.

"Two-step" approach:

Step 1: Perform a 50-gr OGTT (nonfasting), measure plasma glucose at 1 h, at 24–28 weeks of gestation in women without an overt diabetes diagnosis. If the plasma glucose concentration is higher than 140 mg/dL (7.8 mmol/L) at 1 h after the load, proceed to a 100-gr OGTT.

Step 2: Perform a 100-g OGTT when the patient is fasting. If the glucose concentration is more than the normal at least two of the following four plasma glucose levels, the patient diagnosed with GDM.

Carpenter/Coustan	or National Diabetes Data Group (NDDG)
Fasting 95 mg/dL (5.3 mmol/L)	105 mg/dL (5.8 mmol/L)
1 h 180 mg/dL (10.0 mmol/L)	190 mg/dL (10.6 mmol/L)
2 h 155 mg/dL (8.6 mmol/L)	165 mg/dL (9.2 mmol/L)
3 h 140 mg/dL (7.8 mmol/L)	145 mg/dL (8.0 mmol/L)

Although one-way strategy was shown to be cost-effective [6] and may be the preferred approach, data comparing population-wide outcomes with two strategies are contradictory [7, 8]. Longer term outcome studies are currently on the way.

1.3. Metabolic changes during pregnancy

Women with GDM do not have an essential β-cell reserve to produce adequate insulin to overcome the insülin resistance of pregnancy, and all women with GDM have a degree of impaired function of β-cell [9]. Basal glucose and insulin levels are similar to nongravid

http://dx.doi.org/10.5772/intechopen.70815

values in early pregnancy [10]. Basal hepatic glucose production is also similar to the 12–14th week of pregnancy. Postprandial glucose concentrations are significantly elevated, and the glucose peak is prolonged. Basal glucose levels decrease by 10–15 mg/dL (0.56–0.83 mmol/L), insulin levels increased by two fold, and peak of glucose is prolonged at the third trimester [11]. Increased glucose production is seen by the increase in maternal body weight; however, glucose production per kilogram body weight remains unchanged during gestation [12].

Plasma triacylglycerol, fatty acid, cholesterol, and phospholipid levels are altered as a result of changes in hepatic and adipose metabolism [13]. Their levels decrease at the early weeks of pregnancy; however, these levels steadily increase during pregnancy. The increase in estrogen levels and insulin resistance are potential mechanisms of hypertriglyceridemia in pregnancy [14]. Placenta uses cholesterol for steroid synthesis and fatty acids for placental oxidation and membrane formation [15]. Hepatic lipoprotein lipase decreases postprandially; however, it increases during fasting, which increases production of fatty acids and ketones for the fetus to compensate low glucose supply [14]. GDM induces a state of dyslipidemia consistent with insulin resistance. During pregnancy, women with GDM do have higher serum triacylglycerol concentrations, but lower LDL-cholesterol concentrations decrease during pregnancy; however, total cholesterol, HDL cholesterol, and apolipoprotein concentrations are not changed [14, 16].

1.4. Management of Diabetes in pregnancy

Diagnosing women with GDM is extremely significant for close follow-up of the fetus throughout gestation and to identify women with risk of type 2 diabetes occurrence [17]. The main target of the medical treatment in GDM is to provide a good glycemic control, particularly for postprandial concentrations [2]. Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve the woman's health related [18]. Serious perinatal morbidity is decreased, and maternal health-related quality of life is improved by the treatment of GDM. Although glucose goals throughout gestation are very strict, hypoglycemia should be avoided. Preconceptional target for HbA1c is <6.5% to decrease congenital anomalies [19].

American Diabetes Association recommendation for glucose concentration goals in women with GDM:

- Fasting ≤95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

Glucose concentration goals in pregnant women with pre-existing type 1 or type 2 diabetes, if it can be achieved without excessive hypoglycemia:

- Premeal, bedtime, and overnight glucose 60–99 mg/dL (3.3–5.4 mmol/L)
- Peak postprandial glucose 100–129 mg/dL (5.4–7.1 mmol/L)
- A1C <6.0% [20]

GDM patients should have at least four blood glucose measurement daily (fasting and 1 h after the first bite of each meal) to monitor hyperglycemia that is known to increase the risk of adverse maternal and fetal outcomes. One-hour postprandial glucose monitoring provides a better glycemic control and fewer cases of large-for-gestational age infants compared to fasting glucose monitoring [21]. Postprandial monitoring provides a better glycemic control and lower risk of preeclampsia [22, 23].

GDM is associated with higher macrosomia risk and birth complications and an increased risk of maternal type 2 diabetes postpartum [3]. Diet, exercise, and lifestyle changes may decrease the risk of GDM [24, 25]. Lifestyle modification alone is sufficient in most of the patients to control GDM [26, 27]. However, early initiation of pharmacologic therapy might be needed when lifestyle modifications are insufficient for glycemic control.

Insulin is the recommended first-line agent in the treatment of GDM. Although randomized controlled trials demonstrated the efficacy and short-term safety of metformin [28, 29] and glyburide [30], long-term safety trials are still lacking for any oral drugs [31].

1.5. Medical nutritional therapy

Prevention of diabetes, providing good glycemic control in existing diabetes, and decreasing the rate of development of diabetic complications are the primary goals of medical nutrition therapy (MNT). All diabetic patients should have an individualized MNT, ideally prepared by a registered dietitian who is knowledgeable and experienced in the management of GDM [32].

Prenatal MNT should provide a meal plan to optimize blood glucose management. Woman's food and eating habits and plasma glucose responses should drive the energy distribution and carbohydrate intake throughout gestation. Since glucose goes through fetus from the mother, the times of food and regular meals and snacks taken are vital to prevent hypoglycemia. Monitoring of plasma glucose and daily food records maintains important information for insulin dosing and meal plan modifications. Sufficient maternal and fetal nutrition, energy taking for adequate weight gain, and all essential vitamin and mineral supplements are primary components of the MNT [26, 32].

The composition of a diabetic diet should be consistent with that for nonpregnant diabetic women and include all the necessary macronutrients and micronutrients in appropriate amounts for growth and development of the fetus.

MNT for GDM should maintain maternal and fetal health with sufficient energy levels providing adequate gestational weight gain, obtainment, continuity of normoglycemia, and lack of ketones. Carbohydrate intake should be divided into three small- to moderate-sized meals and two to four snacks. An evening snack might be recommended in avoiding accelerated ketosis night long [32]. Strict calorie restriction may lead to ketosis as a result of accelerated fat catabolism which is associated with altered psychomotor development [33].

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1.6. Energy

Most of the patients with GDM are obese, and additional weight increase during pregnancy leads to adverse pregnancy outcome and long-term risk for development of T2DM. The recommendation of minimal weight gain in obese GDM patients has not been confirmed yet. Weight gain in pregnancy should represent pregestational weight [9].

Although significant caloric restriction in obese GDM patients may cause ketosis, moderate caloric restriction (decrease by 30% of estimated energy requirements) in these patients may provide a good glycemic control without ketonemia and decrease maternal weight gain. The data regarding how such diets have impact on fetal outcomes are lacking [34]. Recommendations for weight gain during pregnancy were shown in **Table 1**.

Adequate energy intake is recommended for proper weight gain. Moderate energy and carbohydrate limitation are recommended, instead of weight loss, for overweight, and obese GDM patients. The primary goals of MNT for GDM are proper weight gain, normoglycemia, and absence of ketosis [34]. The requirement for energy does not rise in the first trimester of gestation. An additional 300 kcal/day is recommended to compensate the increase in maternal blood flow, breast, uterus, adipose tissue, placental growth, fetal growth, and amniotic fluids after the first trimester. Nevertheless, a safe pregnancy is possible with lower energy intake [36]. Quality nutritional intake is required. A number of calories should be calculated according to ideal body weight. The recommendations for daily calorie intake were shown in **Table 2**.

Calorie recommendations may provide normoglycemia in 75–80% of GDM [4]. Reduction in caloric intake by 30–33% would help blood glucose management without increasing ketosis risk in obese women with GDM. Nevertheless, the caloric intake should not be less than 1600–1800 kcal/ day. In cases of calorie reduction, urine should be monitored for ketones. Catabolic metabolism and malnutrition of fetus must be prevented.

The recommended overall dietary ratio: Carbohydrates: 40–50%, protein: 20–25%, and fat: 30–35%. Although restriction of carbohydrate intake to 40–45% of daily energy decreases postprandial glucose, the ratio of carbohydrates should not be lower than 40% [37].

Prepregnancy BMI	**Mothers of singletons**	
	Total weight gain (lb)	**Rate of weight gain in the second and third trimesters (lb/wk)**
Low (BMI < 19.8 kg/m^2)	28–40	~ 1.0 (0.5 kg/wk)
Normal (19.8–26.0 kg/m^2)	25–35	1.0 (0.4 kg/wk)
High (>26.0–29.0 kg/m^2)	15–25	0.66 (0.3 kg/wk)
Obese (≥29.0 kg/m^2)	≥ 15	Not specified

Table 1. Recommendations for weight gain and rate of weight gain during pregnancy [35].

	BMI	Daily calorie intake
Underweight	< 18.5	35–40 kcal/kg
Normal	18.5–24.9	30–34 kcal/kg
Overweight	25.0–29.9	25–29 kcal/kg
Obese	>30	24 kcal/kg

Table 2. The recommendations for daily calorie intake per kg of body weight are.

1.7. Carbohydrate

A specific glucose transporter carries glucose through placenta by a glucose level dependent process. GDM leads to upregulation of these transporters. Glucose transfer is highest during the postprandial period, and decreasing postprandial glucose has a bigger effect on reducing increased fetal growth. Therefore, MNT for GDM should be a focus on decreasing postprandial glucose [9].

The amount and ratio of carbohydrate should be calculated according to clinical outcome measures such as hunger, plasma glucose levels, weight gain, and ketone levels; however, daily carbohydrate should not be less than 175 gr. Total calculated carbohydrate should be divided into three small- to moderate-sized meals and two to four snacks. An evening snack might be added to avoid night long ketosis. Carbohydrate is generally better tolerated at other meals when compared to breakfast [34]. Hence, breakfast cereals with high glycemic index should be switched with more slowly absorbed carbohydrates [9]. A total of 15–30 g of carbohydrates are suggested for breakfast [37]. Small frequent meals with slowly absorbed carbohydrates are very helpful in reducing fasting ketosis which is known to have a negative impact on fetal cognitive development [9].

The glycemic index is a relative measure of a food's carbohydrate content by its impact on postprandial glucose levels. The combination of carbohydrates with high glycemic index and low-cereal-fiber diet could lead to 2.15 fold increase in GDM risk when compared to the reciprocal diet [38]. Decreasing the rate of carbohydrate digestion and absorption and consumption of low glycemic index (LGI) containing foods reduce postprandial blood glucose levels as well as fasting blood glucose [2, 33]. Carbohydrate ratio of >45% in the total energy has a negative impact on glycemic control; however, up to 60% carbohydrate ratio with low-glycemic-index carbohydrates do not have a detrimental effect on glucose tolerance in pregnancy [9]. A diet which is high in carbohydrates of LGI have a positive impact on postprandial glycemic control in nondiabetic pregnants, GDM patients, nonpregnant type 1, and type 2 diabetics. This diet also decreases the required insulin dose in GDM patients [39]. Although an LGI diet has favorable impact on gestational weight gain and maternal glycemic control, it does not decrease the incidence of large for gestational age infants with high risk for fetal macrosomia [40].

High dietary fiber has a positive effect on glycemic control in pregnant women with diabetes, and at least 24-g daily fiber is recommended for all women. Although fructose provides more favorable postprandial glucose when it switches sucrose or starch in the diet, it has a negative

effect on plasma lipid levels. Nevertheless, no studies support the avoidance of consuming fructose found in fruits, vegetables, and other foods [41].

Consuming Food and Drug Administration (FDA) or the European Food Safety Agency (EFSA) verified acceptable daily intake of sugar alcohols and noncaloric sweeteners are considered safe according to limited human studies. Aspartame (with the exception of women suffering from phenylketonuria), acesulfame potassium, sucralose, neotame, advantage, steviol glycosides, and extracts from monk fruit are all FDA-approved noncaloric sweeteners for use during pregnancy. Cyclamates and its salts are currently forbidden in the USA; however, data related to consuming these agents in patients with GDM are lacking [42].

1.8. Protein

Protein intake is very important during pregnancy to compensate the increase in protein synthesis, maintaining maternal tissues and fetal growth, and especially during the third trimester. Low protein intake may have negative effects on weight and length at birth; however, high intake may worsen fetal development [43]. A diet with appropriate protein (0.75 g/kg/day plus an additional 10 g/day) is also necessary for pregnant women. The necessity of nutrient composition during gestation and lactation is not different in women with and without diabetes [36]. Proteins and amino acids in the diet are significant regulators of glucose homeostasis, and a high-protein diet contributes to insulin resistance and increases gluconeogenesis [44]. The amount of protein in the diet should be about 20–25% of the total energy intake, with a minimum of 60–80 g/day according to the German Diabetes Association and German Association for Gynaecology and Obstetrics (DDG-DGGG) [42].

1.9. Fat

Limitation of carbohydrate intake often leads to higher fat intake as protein intake should remain constant at 15–20%. High-fat diet causes an increase in free fatty acid levels which contribute to insulin resistance. Studies in nonhuman primates and human demonstrated that high-fat diet leads to fetal fat accumulation and increase in fetal adipose tissue and contributes to hepatosteatosis, increase in inflammation and oxidative stress, and impairment of glucose uptake in muscles [39].

Limitation of carbohydrate intake increases the ratio of total calories provided from protein and fat to ensure overall energy requirements; however, the data about how the type of dietary fats and carbohydrates affects glycemic control GDM patients are insufficient. Low versus high glycemic foods and monounsaturated fat (MUFAs) versus polyunsaturated fatty acids in the diet have a better impact on glycemic control in nonpregnant patients with T2DM. Gunderson et al. demonstrated that addition of saturated fatty acids to the diet resulted in lower postprandial glucose and insülin response compared to the addition of MUFAs [45]. A recent meta-analysis evaluating the effects of a diet with high MUFAs in T2DM patients found a reduction in fasting blood glucose, postprandial glucose, and whole-day blood glucose and insulin concentrations [46].

2. Medical nutrition therapy in youth diabetics

2.1. Introduction

Type 1 diabetes mellitus (T1DM), the most commonly encountered endocrine disease of childhood, is defined as a decrease and later an absence of pancreatic ß-cell function causing chronic insulin deficiency. Type 1 diabetic youth needs to use insulin to metabolize glucose [47]. The prevalence of T2DM in adolescents increase is accompanied by an increase in T2DM complications such as hypertension, hyperlipidemia, nephropathy, and retinopathy [48].

Involving of adults in the diabetes care of adolescents by professionals is a very important key point. Young children, including school-aged children, are not able to manage their diabetes care, and middle school and high school students need help in managing their diabetes care. Therefore, the education about how all family can be involved in the diabetes care of a diabetic child and adolescent should be ensured [49]. MNT is an essential part of diabetes care in the modern era. MNT is defined as a period of personal guidance to train patients and families related to healthy eating practices to provide a good glycemic control and to prevent or manage comorbidities including overweight, hyperlipidemia, and hypertension. Therefore, MNT is an important component of self-diabetes care [47].

2.2. Diagnosis

The diagnosis of T1DM in children is usually not difficult and needs little or no specialized testing. The most common symptoms and findings of T1DM in children and adolescents are the several-week histories of polyuria, polydipsia, polyphagia, and weight loss with hyperglycemia, glycosuria, ketonemia, and ketonuria. Approximately 30% of children with the T1DM present with diabetic ketoacidosis (DKA). A second confirmatory test should be performed in the asymptomatic child or adolescent who is screened for diabetes in case of a fasting plasma glucose (FPG) ≥126 mg/dL or a 2-h plasma glucose or random glucose ≥200 mg/dL; however, no further testing is required if specific signs and symptoms of diabetes are present [49]. Type 2 diabetic adolescents have approximately 50% lower insulin sensitivity and 75% lower first-phase insulin secretion when compared to nondiabetic adolescent [50]. Plasma glucose goals for youth diabetics were shown in **Table 3**.

	Adolescents/young adults (13–19 years)	**School age (6–12 years)**	**Toddlers and preschoolers (0–6 years)**
Fasting glucose (mg/dL)	90–130	90–180	100–180
Bedtime/overnight glucose (mg/dL)	90–150	100–180	110–200
HbA1c	<7.5%*	<8%**	<8.5%***

*A lower target (<7.0%) is amenable if excessive hypoglycemia can be prevented.

**If excessive hypoglycemia can be avoided, a lower goal (7.5%) is reasonable.

***If excessive hypoglycemia can be avoided, a lower goal (8%) is reasonable.

Table 3. Targets for plasma glucose [20].

http://dx.doi.org/10.5772/intechopen.70815

2.3. Dietary management

Nutritional suggestions for children and adolescents with T1DM should focus on a good glycemic control that provides normal growth and development and avoid hypoglycemia [36]. One of the main components of diabetes care and education is the nutritional management. Dietary habits vary according to the culture and socioeconomic status. Cultural, ethnic, and family traditions and the psychosocial requirements should be taken into account in providing nutritional recommendations for children. The entire family should be involved in making the food plan to provide healthy eating habits [51]. MNT is one of the cornerstones of the management of type 1 diabetes in children; however, it is generally one of the most difficult parts of the treatment. Food preferences, cultural influences, physical activity patterns, and family eating habits and schedules should be considered in making an individualized meal plan. Consultation with a registered dietitian to develop a personalized nutrition plan is recommended.

Premeal insulin dosages should be calculated according to the amount of carbohydrate intake that should be consistent. Most of type 1 diabetic children present with weight loss that has to be restored with appropriate management including insulin therapy, hydration, and sufficient energy intake. A nutrition plan updated every year is recommended, since the energy required changes with age, physical activity patterns, and growth rate [49].

Management of type 2 diabetic youth should focus on avoiding sugar-containing beverages and high-fat/high-energy containing foods and providing a regular meal schedule and portion control [50].

Goals of MNT are

1. Sufficient energy intake to provide normal growth and development and integration of insulin dosages with general eating and physical activity habits in type 1 diabetic youth
2. Modify eating and physical activity habits to decrease insulin resistance and enhance metabolic condition in type 2 diabetic youth [36]

Goals of MNT in childhood according to expert consensus:

- Adequate and appropriate intake of energy and nutrients to provide normal growth and development and good health
- Promote healthy, lifelong eating habits to provide and maintain social, cultural, and psychological well-being with considering the patient's wishes and willingness to change
- Manage normoglycemia and avoid hypoglycemia provided by a balance between food intake, metabolic needs, energy expenditure, and insulin regimens
- Maintaining the appropriate BMI and waist circumference.
- Recommend regular physical activity to avoid and manage acute diabetic complications including hypoglycemia, hyperglycemic crises, illness, and exercise-related problems

- Decrease the risk for microvascular complications by providing normoglycemia
- Encourage appropriate nutrient intake and lifestyle to prevent and manage the chronic complications of diabetes, obesity, hyperlipidemia, cardiovascular disorders, hypertension, and nephropathy [52]

Goals for the distribution of total daily energy intake [52];

- Protein 10–15% (decrease by the aging)
- Fat 30–35%:
  - <10% saturated fat + trans fatty acids
  - <10% polyunsaturated fat
  - >10% monounsaturated fat (should be less than 20% of total energy)
  - n-3 fatty acids: 0.15 g/d
- Carbohydrate 50–55%:
- Mainly nonstarch polysaccharide (fiber) containing foods including whole-grain cereals, fruits and vegetables
- Sucrose intake should be less than 10% of total energy

LDL cholesterol and total cholesterol target for diabetic children and adolescents should be <110 mg/dL and <170 mg/dL, respectively [53].

Suggestions for Food Group/Nutrient:

- Fruits/vegetables: Daily 2 cups of fruit and 2.5 cups of vegetables (dark green, orange, legumes, starchy vegetables, and other vegetables) as an approximate total of 2.000 calorie intake is recommended.
- Dairy: Daily 2 cups of fat-free or low-fat milk or equivalent milk products are recommended for children with age between 2 and 8 years. Children ≥9 years old should take 3 cups/day.
- Whole grains: Grains product is frequently recommended, and whole grains should constitute at least half of the grains.
- Carbohydrates: Adequate amount of fiber with fruits, vegetables, and whole grains should be consumed. Excessive amounts of calories from carbohydrates should be prevented.
- Fat: The recommended amount of fat intake is 30–35% of calories for children 2–3 years of age and 25–35% for 4–18 years of age. Avoid excessive intake of fat high in saturated and/or trans fatty acids. Fat-containing more polyunsaturated and monounsaturated fatty acids should be consumed [54]. Carbohydrate counting is an effective way of improving glycemic control, while allowing flexibility in food choice of diabetic children [55].

Family education for choosing foods containing lower saturated and higher monounsaturated fat can ameliorate hyperlipidemia. Approximately 60–70% of total calories consisting of carbohydrate and monounsaturated fat are recommended for diabetic patients by current

http://dx.doi.org/10.5772/intechopen.70815

guidelines. Using glycemic index is an option in making a diabetic food plan; however, it is not the main suggested method for diabetic food plan in pediatric patients [56].

2.4. Diabetes education

Diabetes education is described as the condition of ensuring an individual with the knowledge and skills required to carry out diabetes self-care and control crises and performing lifestyle modifications to successfully manage the disease. Educational programs with specific aims and learning objectives should be involving diabetic patients, their carers, and families [57].

Appropriate diabetes education is compact and complicated and have the need for educators with a number of abilities such as good communication, compassion, sensitivity, humor, and a comprehensive knowledge of childhood diabetes. The age and developmental stage of the child is a cornerstone of the education such that it should be parents and primary caregivers oriented for a preschooler diabetic as well as patient oriented for most adolescent [49].

Diabetes education should have continuity and repeatability for its effectiveness [57]. Behavioral focus involving the whole family is the key point of a nutrition plan because parents substantially have an impact on eating habits of diabetic children by ensuring the food and promoting to develop food attitudes, preferences, and values.

3. Medical nutrition therapy in elderly diabetics

3.1. Introduction

Diabetes mellitus is a very common disease among elderly individuals, affecting approximately 20% of older adults aged 65–75 years and 40% of adults older than 80 years [58]. Fifty years and older men and women with diabetes live an average 7.5 and 8.2 years less than nondiabetic individuals [59]. Diabetic individuals are 2 to 4 times more likely to have coronary heart disease (CHD) than nondiabetics, and approximately 70–80% of diabetics are dying from CHD [60]. Elderly diabetics have increased the risk of premature death, functional disability, and comorbidities including hypertension, CHD, and stroke. Elderly diabetics also have a higher risk for various known geriatric disorders including depression, cognitive dysfunction, urinary incontinence, fall-related injuries, and persistent pain [61].

Worldwide lifestyle changes cause elevated prevalence of obesity and urbanization, accompanied with higher predicted prevalence of diabetes, particularly among persons 75 years and older [41]. According to national population estimates, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries between 2010 and 2030. Currently, the highest number of people with diabetes around the world is in the 40–59-year-old age-group; however, there will be slightly more people with diabetes in the 60–79-year-old age-group by 2030 [62]. Nutritional evaluation is suggested for all elderly diabetics at the diagnosis time and regularly thereafter, which provide the determination of patients with undernutrition [63].

3.2. Management of diabetes

The general goals of diabetes care in elderly diabetics are similar as in younger diabetic individuals and include control of hyperglycemia and related symptoms; prevention, assessment, and treatment of macrovascular and microvascular complications of diabetes; education for self-management; and maintenance or improvement of general health condition. However, goals are similar in older and younger persons, and the care in elderly diabetics is complicated as a result of their clinical and functional heterogeneity [61]. Hyperglycemia leads to dehydration and impairs vision and cognitive function, contributing to functional decrease and a higher risk of falls in elderly diabetics [64]. Most of the clinicians consider too strict glycemic control (HbA1c of 7%), when compared to poor control (HbA1c >9%), leads to increased risk of wide glucose excursions and hypoglycemia. Therefore, current guidelines recommend a target glycemic range of 7–8.5% in elderly diabetics after explaining their comorbidities.

3.3. Medical nutritional therapy

Food preferences of persons, eating habits, religion and culture, and physical and cognitive health condition should be taken into account while making a nutrition plan. Appropriate amounts of essential vitamins, minerals, protein, and fiber should be included in a meal plan [65].

Diet in an elderly diabetic individual [64]:

- All patients should have a balanced diet
- Generally, a diet not too tight can provide a better quality of life, with little or no effects on glycemic control.
- Elderly individuals carry a higher risk for both undernutrition and obesity.
- Excess weight loss leads to increase the risk of morbidity and mortality in elderly persons.
- Modification of eating habits in elderly persons could be difficult due to consolidated over many years.
- Cognitive impairment or depression may affect cognitive decline or depression

The American Geriatrics Society underlines the significance of MNT in elderly diabetics. Weight loss of 5–10% of body weight is recommended for obese persons. Nevertheless, an involuntary gain or loss of >10 lb. or 10% of body weight during 6 months period should be mentioned in the assessment of the MNT. Energy limitation and physical exercise are required to protect lean body mass. Exercise training attenuates decrease in maximal aerobic capacity, develops during aging, ameliorates atherosclerotic risk factors, protects lean body mass, reduces central obesity, and decreases insulin resistance in elderly diabetics [34].

The prevalence of undiagnosed diabetes in elderly living in the nursing home is not low; however, many of them do not need pharmacologic treatment. Elderly nursing home residents are prone to underweight rather than overweight. Low body weight may lead to higher risk of morbidity and mortality in elderly diabetics. Less restrictive diets are a preferable way of

residents to eat better, since specialized diabetic diets do not seem to be superior to standard diets in this population. Food plans without concentrated sweets or added sugar and liberal diabetic diet are not recommended anymore. Current diabetes nutritional suggestions are not fulfilled by these diets which redundantly limit sucrose intake [34].

3.4. Energy

European Society of Clinical nutrition and Metabolism recommends minimum daily intake of 1.0–1.2 g protein/kg and 20–30 kcal/kg of nonprotein energy for sick elderly patients. The target for nutritional support in malnourished elderly individuals should be a total daily energy intake of 30–40 kcal/kg and a daily protein intake of 1.2–1.5 g protein/kg, according to current geriatric guidelines; however, person-to-person variability for nutritional requirements and physiological and pathological status should be taken into consideration [66].

3.5. Carbohydrate

Carbohydrate intake from vegetables, fruits, whole grains, legumes, and dairy products should be preferred instead of other carbohydrate sources, particularly those that comprise added fats, sugars, or sodium for good health. Consuming LGI food instead of HGI food is better for ensuring good glycemic control and decreasing HbA1c levels [32].

3.6. Protein

Higher protein intake is associated with higher bone mass density, decrease in bone loss, and increase in muscle mass and strength [67–70]. An epidemiologic study reported that higher protein intake decreased health problems in older women [71]. The ADA suggests normal protein intake (15–20% of daily energy) in patients with normal renal function. The data about the safety of high-protein intake are scanty. However, a recent study reported that high-protein diet (approximately 30% of daily energy) provided less glucose-lowering medications after 1 year in elderly type 2 diabetic patients [72]. Kidney Disease Outcomes Quality Initiative of the American National Kidney Foundation (KDOQI) guidelines recommend a daily protein intake of 0.8 g/kg in diabetic patients with chronic kidney disease (CKD); however, there is little evidence related to adults older than 75 years. The results of 5-year prospective cohort study showed that higher daily protein intake (about 1.1 g/kg/day) did not decrease kidney function [73]. Low-protein intake might be associated with a decrease in muscle mass in CKD patients. Therefore, daily energy intake of 30 kcal/kg should be recommended to keep a neutral nitrogen balance [74].

3.7. Fat

A Mediterranean-style, MUFA-rich eating pattern could be recommended as an alternative to a lower fat, higher carbohydrate eating pattern to provide a good glycemic control and decrease the CVD risk factors in type 2 diabetics. The general public recommendation to eat fish (especially fatty fish) at minimum 2 times a week could be applied to diabetic individuals. Diabetic patients should follow nutritional recommendations similar to the general population

to CVD risk factors. These recommendations are decreasing in SFA to 10% of total calories, taking 300 mg daily cholesterol and restriction of trans fat as much as possible [32].

3.8. Fiber

Fiber-containing foods such as legumes, fiber-rich cereals (≥5 g fiber/serving), fruits, vegetables, and whole grain products are recommended for diabetic patients, since they ensure vitamins, minerals, and other substances important for a healthy life. U.S. Department of Agriculture (USDA) recommends 14 g (1000 kcal) daily dietary fiber and foods containing whole grains (one-half of grain intake) in persons with high risk for T2DM [34]. The insoluble dietary fiber in diet decreases cholesterol, glucose, and insulin levels. A fiber-rich meal promotes satiety, since it is processed more slowly in the gastrointestinal tract [75].

3.9. Vitamins

Elderly diabetics are more prone to risk for deficiency of trace elements, and magnesium and zinc supplementation results may worsen glycemic control. Uncontrolled diabetes leads to increase in oxidative stress. Small-size studies showed vitamins C and E (antioxidants) may positively affect glycemic control [76]. Decreased intake and unbalanced diet may lead to a deficiency of vitamins and minerals. Drugs may decrease absorption of vitamins by affecting hepatic metabolism. Older people cannot eliminate vitamin A that may lead to hypervitaminosis. Decreased dietary consumption and gastrointestinal and renal disease lead to vitamin D deficiency which is associated with osteomalacia, rickets, and myopathy. It also leads to decreased bone density, disability, and higher risk for falls. Vitamin deficiency is common in elderly persons. It may lead to macrocytic anemia, subacute combined degeneration of the spinal cord, neuropathies, ataxia, glossitis, and dementia. Vitamin B12 deficiency is also associated with higher levels of homocysteine that may increase the risk for cardiovascular disorders, decreased bone density, and increased fracture risk [77]. Since elderly persons are prone to deficiencies of vitamin B groups (B1, B2, B12, B6, and folate) that lead to cognitive dysfunction, adequate intake of vitamin and micronutrients is essential in elderly diabetics [78].

Conflict of interest

None.

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Chapter 10

Exercise and Diabetes Mellitus

Asmare Yitayeh Gelaw

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71392

Abstract

In the past 20 years, the magnitude of diabetes has increased dramatically in many parts of the world and the disease is now a worldwide community health problem. Diabetes mellitus is associated with numerous systemic complications that affect the retina, heart, brain, kidneys and nerves. Abnormal/reduced sensation, diminished reflexes, decreased proprioception and reduced muscle strength in lower limbs leads to balance and functional problems in patients with diabetic peripheral neuropathy. Evidences strongly support that physiotherapists play a significant role in the prevention, treatment and management of diabetes mellitus and its associated complications. Physiotherapy management techniques and rehabilitation interventions, including exercise prescription and education will help to facilitate patient participation in programs that improve and maintain physical well-being which has a significant impact on their activities of daily living and health-related quality of life (HRQOL).

Keywords: physical therapy, diabetes mellitus, physical rehabilitation, physical activity, ADL, QOL

1. Overall introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by an increase in the blood-glucose level resulting from a relative insulin deficiency or insulin resistance or both. It is a growing public health problem and is considered as one of the main threats to human health in the twenty-first century. It imposes a significant burden on patients and society [1–3]. It is one of the leading causes of complexity of the illness, an increased risk of medical comorbidities like fatigue, recent weight loss, severe restriction in mobility and strength and increased propensity to falls [4, 5].

According to the Centers for Disease Control, about 26 million children and adults are living with diabetes. In addition, almost 79 million people have "pre-diabetes". The overall magnitude of DM in adults older than 20 years was estimated as 171 million in the year 2000. The

prevalence will likely to be twice as much as the current prevalence by the year 2030. The type 2 diabetes mellitus is the most common type of diabetes and accounts for 90–95% of overall diabetes cases [5, 6]. The number of adults with DM in the world elevated from 108 million to 422 million between 1980 and 2014 [7].

As the diabetes epidemic grows in size and complexity, there is an increasing realization that physicians alone are unable to provide the care required by people with diabetes. To help them live life to the fullest, people with DM need to have an integrated and interdisciplinary rehabilitation team consisting a range of healthcare personnel, including physiotherapists, psychologists and eye specialists. Diet, medication, physical activity and education play a significant role for the prevention, rehabilitation and self-management of diabetes mellitus [5, 8, 9].

Most individuals with diabetes mellitus will visit a physical therapist in the multidisciplinary clinic where they receive care for their DM-related problems. Physical therapists are professionally allowed to exercise in several treatment settings including acute care, nursing home and inpatient and outpatient rehabilitation settings. Physical therapists also work in conjunction with the rehabilitation team to design components of community-based rehabilitation strategy so as to enhance physiological, anatomical and psychosocial outcomes [10] (**Figure 1**).

Physical therapy is a thus corner stone of prevention and treatment of diabetes mellitus. Physical therapy-directed movement and exercise programs are clinically effective in helping diabetic patients to produce the desired health-related quality of life (HRQOL) outcomes [11].

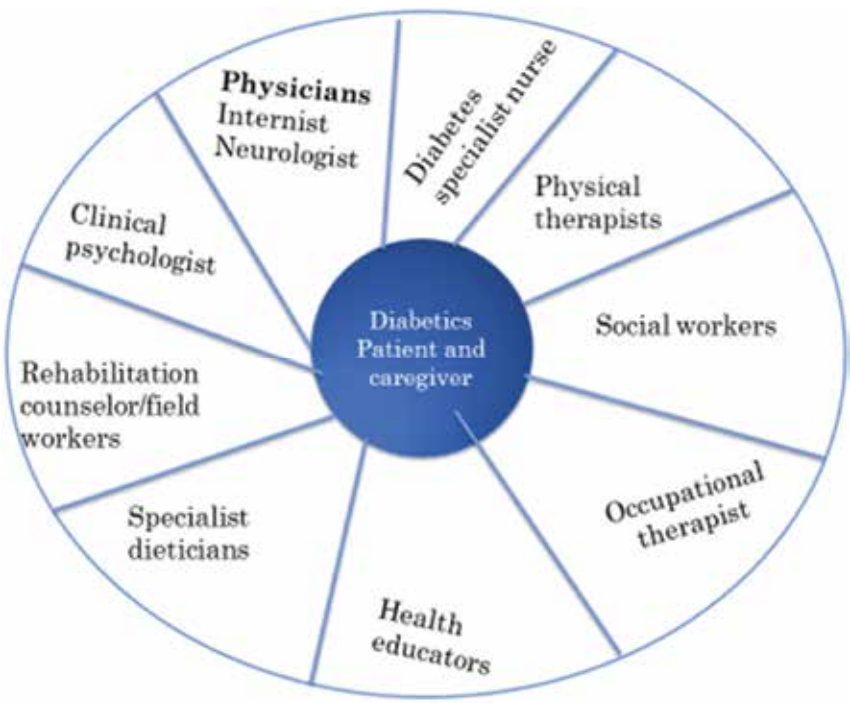

Figure 1. The multidisciplinary rehabilitation team approach centres on the patient and caregiver.

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Active and passive range of motion exercises, stretching techniques, strengthening and aerobic exercises are some of the physical therapy management techniques for the inpatients, outpatients and prediabetes. These physiotherapy treatments help patients to regain normal range of motion, muscle strength, endurance and physical functioning. It can also maximize the level of independence of DM patients during mobility and activities of daily living. Ultimately, physical therapy aims to improve the health-related quality of life of DM patients [12].

2. The diabetic care pathway and general concept of physical therapy

2.1. The diabetic care pathway

It is the right of people with diabetes mellitus to expect a timely, accessible and of uniformly high-quality care. However, diabetes care is complex and multidirectional due to their multifaceted needs [13–16]. It should be delivered in a wide range of clinical settings by healthcare professionals from diverse backgrounds and with diverse skills. The diabetic care pathway improves the delivery of effective care, facilitate critical evaluation of that care and strengthen multidisciplinary communication [17]. They promote a uniform standard of care delivery in a wide variety of clinical settings (**Figure 2**).

2.2. General concept of physical therapy

Physical therapists must undergo assessment based on the International Classification of Functioning, Disability and Health (ICF) model before, during and after physical therapy for each diabetic patient (**Figure 3**). ICF enables physical therapists to identify and analyze problems to provide diabetic patients with therapy. Diabetic patients have many problems caused by diabetes itself and its associated complications. Physical therapy assessment should include

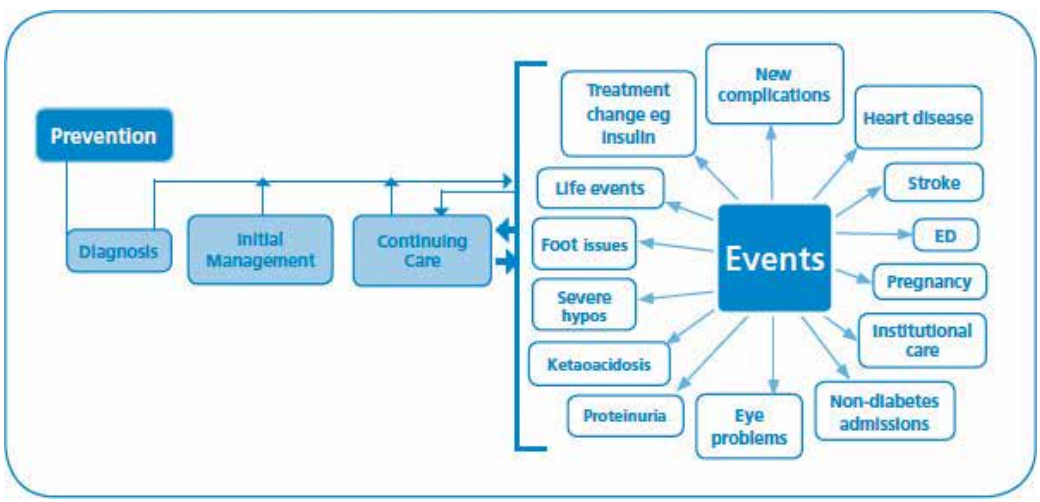

Figure 2. The integrated diabetes care pathway.

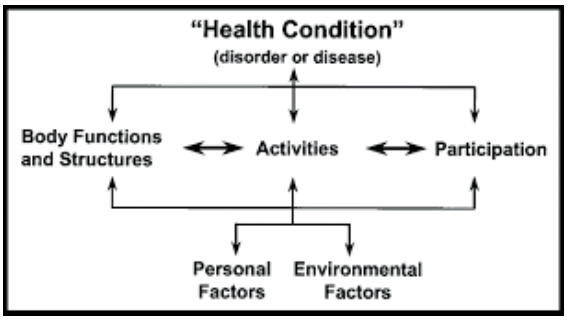

Figure 3. International Classification of Functioning, Disability, and Health.

sensory integration, motor control and manual muscle testing (MMT), range of motion (ROM), balance test, endurance test, ADL test and participation in social affairs.

Physical therapists should be aware that diabetic patients are exposed to various risks such as infections and bedsores.

The importance of different modes of exercises in patients with type 2 diabetes is emphasized by increasing uptake of glucose by muscles, improving utilization, altering lipid levels, increasing high density lipoprotein and decreasing triglyceride and total cholesterol. Thus exercise helps people to overcome disability by preventing, treating and rehabilitating neuromuscular complications like neuropathies, skin break down, foot ulcers, arthritis, other joint pains, frozen shoulder, back pain and osteoarthritis associated with DM [17–20]. Moderate to high levels of different modes of exercises like cardio respiratory fitness exercises, aerobic exercise and progressive resistance exercises are also associated with substantially lower morbidity and mortality in men and women with diabetes. [11, 12, 15].

2.2.1. Subjective assessment

An effective problem-solving approach exploits historical data and information gathered from a basic screening physical examination in a problem-oriented method to guide further investigation. Subjective assessment is an explanation which describes the patients self-report of their current status in terms of their function, disability, symptoms and history. Problem-oriented assessment forms should be used to record the relevant patient reported data, clinical investigation and physical examination results. Record-keeping is an essential component of patient management. It is used for follow-up and evaluation. Taking a full history of the present condition and its possible risk factors, such as smoking, hypertension, obesity, hyperlipidemia and family history is so imperious. Asking for the other symptoms of neuropathic complications such as numbness, joint pain and muscle weakness will also help to evaluate the biopsychosocial context, severity and nature of the patients' current DM state [21, 22].

2.2.2. Objective measurement

Objective assessment should be done routinely to test and objectify the patient identified problems by using appropriate equipments and outcome measurement tools. In physiotherapy,

physical assessment findings, or objective data of diabetes mellitus patients can be obtained through the use of three specific diagnostic techniques: Observation, palpation and physical examination. An assessor physiotherapist has to quantify levels of impairment, physical activity limitation and participation restrictions of DM patients. The active and passive range of motion, the sensory integrity, the muscle power, balance, walking pattern and other gross motor activities of diabetes mellitus patients should also be evaluated and objectified.

3. Physical rehabilitation in diabetes mellitus patients

3.1. Physical activity for persons at higher risk of developing type 2 diabetes mellitus

Different clinical practice guidelines and systematic reviews agreed that participation in lifestyle therapy that includes regular physical activity should be the first line of defense against T2D development from a state of pre diabetes [23–26]. *Both aerobic* and *anaerobic* forms of physical activity have also various beneficial effects on metabolism in a number of tissues and organs, including skeletal muscle, adipose, liver, pancreas and even brain. Exercise may increase body's response to intrinsic insulin, by multiple mechanisms including [27, 28].

The American Diabetes Association states that simple lifestyle measures have been shown to be effective in preventing or delaying the onset of type 2 diabetes. To help prevent type 2 diabetes and its complications, people should be physically active at least 30 minutes of regular, moderate-intensity activity on most days [16, 17, 29].

Several large-scale clinical trials have established that about 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity per week, such as brisk walking, with no more than 1 or 2 days off in a row, reduces the risk of developing type 2 diabetes regardless of the degree of adiposity [30–34].

People with prediabetes can be taught physical activities to use their body weight as resistance. They can also use mechanical devices like machines. Major muscle groups of both the upper and lower extremities such as the quadriceps, hamstrings, calves, abdominals, biceps, triceps and forearms should be trained to build their girth and strength. Physical activity guidelines vary on intensity and frequency of prescribing such exercises. The frequency and intensity of exercises should be designed based on an individual's observed capacity to continue the program [16, 35].

Resistance exercise can be performed 2 or 3 times per week for 30–60 min per session. It increases muscle mass, elevates resting metabolic rate, enhances muscular endurance, increases insulin sensitivity and attenuates muscle mass loss during caloric restriction and aging [31, 36].

A systematic review done on the effectiveness of combined diet and physical activity for the prevention of type 2 diabetes stated that combined diet and physical activity promotion programs are effective at decreasing diabetes incidence and improving cardio metabolic risk factors in persons at increased risk. It stated that the more the intensive programs are the more effective will be [37].

Safety should be a major consideration for both health-care professionals and patients before initiating a new program of physical activity.

Therefore physiotherapists should encourage patients who are at high risk of developing diabetes mellitus type 2 to do the following.

1. Increase their physical activities and reduce their sedentary time
2. Start a regular physical activity program: 3–4 days per week for 10–15 minutes per session.
3. Start with a preliminary resistance exercise: It can be done for 1–2 days per week, and for 15–30 minutes per session.
4. Practicing an aerobic exercise for a minimum of 30 minutes per session of 5 days per week.
5. Doing a regular resistance exercise for a minimum of 30 minutes per session of up to 2 or more days per week.

3.2. Physiotherapy management of physical impairments and associated complications with diabetes mellitus

3.2.1. Both aerobic and resistance exercises help to improve metabolic control

Clinical trials have provided strong evidence that a combination of both aerobic and resistance exercise has a significant effect in glycemic control than either aerobic exercise only or resistance exercise only [27, 37]. These two studies added that both aerobic exercise and resistance training have better outcomes in glycemic control than advice through phone call and maintaining present life style. Progressive resistance training was also found to be helpful in improving glycemic control [38, 39].

A RCT comparing aerobic exercise and resistance training found that both exercises have similar effects in reducing HbA1c. However, there is a chance of potential increase in late-onset hypoglycemia risk after aerobic exercise [40]. It is also been found that physical activities using Physio ball among type 2 diabetes has also its own result in improving glycemic control and blood pressure [41].

Generally, the major benefits of resistance training in individuals with diabetes are:

1. improved **blood cholesterol profiles**,
2. increased heart function,
3. decreased blood pressure,
4. improved insulin sensitivity and blood glucose control,

3.2.2. Both aerobic and resistance training helps to improve muscular strength

An evidence done on the comparison of muscle strength and short-term endurance in the different periods of type 2 diabetes suggested that patients suffering from diabetes mellitus

have less muscular strength than people without type 2 DM [42]. This further leads to reduced physical activity unless it is properly managed. However, physical activities in form of aerobic/resistance or combination of both resulted in increase in strength in persons with diabetes mellitus.

3.2.3. Exercises can improve gait and balance of patients with diabetes mellitus

Individuals with diabetic peripheral neuropathy (DPN) are 15 times more likely to experience fall compared to the healthy subjects. Falls are marked as a dangerous health issue in DPN especially in the geriatric population. Therefore, knowledge of the factors that influence falls such as postural control deficit and gait instability in DPN patients is essential. Tailored preventive programs including specific gait and balance exercises and cognitive training might be beneficial in reducing fall risk in older adults suffering from diabetes.

A growing number of studies have shown that exercises have some effect on gait and balance. Multisensory exercise and specific gait and balance training programs combined with functional orientated strengthening activities can improve gait speed and balance, and increase both muscle strength and joint mobility of diabetic patients [43, 44].

Task-oriented motor gait training for DPN patients can be used to enhance performance during walking, balance and foot mechanics during walking. Changes in the provided sensorimotor information and enhanced muscle abilities can be regarded as reliable contributions for gait responses in DPN patients [44].

As evidenced by a review on the effectiveness of balance training in the intervention of fall risk in elderly with DPN, Proprioception training, vestibular training, lower limb strength training and mixed sports training enhance balance and reduce its risk of falling in elderly with DPN [45]. When the therapist applies the balance training to elderly patients with DPN, they should focus on the features of different kinds of balance training.

Proprioceptive training can be applied to moderate to severe neuropathy in elderly patients due to the safety and its effectiveness. Vestibular training is more suitable for younger DPN patients. When we apply it to elderly patients, we should pay attention to their safety and should choose low-intensity training. Weight training could significantly improve the lower limbs of patients with DPN walking ability, and relatively more effective than non-weight training [44].

3.3. Physical therapy for diabetic peripheral neuropathy

Peripheral neuropathy is the most common complication of diabetes mellitus (DM) both in developed and developing countries. It is found in about 10% of diabetic patients at diagnosis and in the majority of patients 25 years later on. In diabetic peripheral neuropathy peripheral nerves are unable to function optimally as a result of high blood sugar levels. This condition affects almost half of patients with type 1 and type 2 DM. It involves the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after other possible causes have been excluded. Thus, decreasing blood glucose levels can help inhibit and possibly reverse some of the consequences of diabetic peripheral neuropathy.

In type 1 diabetes mellitus, distal lower extremity peripheral neuropathy typically becomes symptomatic after many years of chronic extended hyperglycemia. However, it will be usually obvious after only a few years of well-known poor glycemic control in patients with type 2 DM. Sometimes it may even be recognized at diagnosis. Clinical features of peripheral neuropathy can be categorized in three: sensory, motor and autonomic symptoms.

- Sensory: Sensory symptoms like burning pain, tingling sensation, numbness, pain and paresthesia appears symmetrically and commonly at the nerve endings of the longest nerves. It is prevalent in the lower extremities and feet. These symptoms usually develop before motor symptoms such as weakness.
- Motor: characterized by flaccid paralysis, diminished deep tendon reflex, muscle weakness and loss of balance and coordination.
- Autonomic: It is manifested by features of cardiovascular, gastrointestinal and genitourinary systems dysfunction.

Physical therapy can improve the overall quality of life of DM patients with peripheral neuropathy and alleviate them from the symptoms of diabetic neuropathy. It is also improve muscle strength, joint mobility, balance, coordination and physical function.

3.3.1. The goals of physiotherapy treatment

To maintain and improve functions by using a range of motion

- To improve and increase the muscle strength, endurance and power
- To improve balance and stability
- To prevent falls and fall related injury

Physical therapists can also recommend assistive devices such as braces and splints to enhance balance and posture. Splinting is often used in the treatment of compression mononeuropathies, such as carpal tunnel syndrome. Research has shown that strengthening exercises for peripheral neuropathy moderately improve muscle strength in people with DPN. In addition, exercises to help peripheral neuropathy, when done regularly, may reduce neuropathic pain and can help control blood sugar levels. A combination of aerobic and strength exercises are shown to be effective to improve both the strength and balance of individuals with diabetic peripheral neuropathy [45].

3.3.2. Aerobic exercise

It is suggested that increasing energy expenditure by **aerobic exercise** will decrease heart rate, blood pressure and increase **exercise** tolerance. For the majority of individuals, it will be noble to plan for a 30 minutes per day exercise for about 3–5 days a week. It is advisable that you can exercise for 5–10 minutes a day, and work up to more time each week if you have not been very active recently. They can also vary their activity for the . A 10-minute walk exercise after each meal is also marvelous.

Here are some useful aerobic exercises:

- Walking for 30–60 minutes, three times per week is a great and easy way to increase physical activity.
- Participating in a low-impact aerobics class is also very important
- Swimming helps to stretch and relax muscles
- Though it is not easily accessible for all diabetics individuals, stationary bicycling indoors is another useful form aerobics exercise

3.3.3. Strengthening exercises

There are different forms of strengthening exercises that can be done by diabetic patients. Resistance exercises are commonly applied in physical rehabilitation programs to improve muscular strength, power and endurance of diabetic's patients. Many newly recognized type 2 diabetics may not have exercised in years. Therefore, there should be an awareness rising program together with health promotion and disease prevention campaigns about the clinical advantages of exercises with weights or other forms of mechanical resistance [46]. Then it will be imperative if they check in with their doctor first. After asking if there are any contraindicated moves they should avoid, they can start learning the right way to do each strengthening exercise. However, strengthening exercises have different requirements depending upon the treatment goals or function [28, 47]. The strengthening exercise programs need to be personalized to each patient's chief complaint, functional problems and goals. The workout variables such as speed, the intensity, the frequency and the type of muscle contraction used or the amount of muscles recruited in each contraction all effect the outcome of the program. Physiotherapists are experts who can guide and supervise patients with DPN. In addition to muscle strength, which can involve power, endurance and speed of contraction, the timing and balance of muscle contractions is very important. There are many different benefits of strengthening exercises for people with diabetes. Some of the benefits of working out a strengthening exercise are:

- It helps them to respond better to insulin
- It Improves the way it uses blood sugar
- It helps to lose weight
- It helps to lower the risk for heart disease

In addition, the American College of Sports Medicine recommends that people with type 2 diabetes should start practicing a strength training program to reduce the risk of further injury, to improve muscle strength, to improve the quality and range of movement and overall quality of functional mobility [35].

Strengthening exercise programs will include a variety of exercises designed to target specific groups or individual muscles. These exercises will begin easier and progress as strength is developed. Some of the exercises may involve the following:

- Exercising against gravity
- Exercising against the resistance of water
- Exercising against a resistance band
- Exercising with weight
- Exercising using your own body weight as the load

3.3.4. Muscle tone and joint flexibility exercises

Muscle tone and joint flexibility exercises are also called stretching exercises. There are two main types of stretching exercises: therapeutic stretching and self-stretching. While the first is indicated for therapeutic purposes, the second is used in bodybuilding, athletic training, dance and certain ritual exercises. The therapeutic stretching can be implemented on the desired muscle groups *either* by the therapist *or* by the patient himself. It is believed that stretching stimulates the body-mind complex to resolve injury, stress and pain. Gradual therapeutic stretching helps to keep the joints flexible and reduce the chances of injury during other activities. Thus gentle stretching for 5–10 minutes helps our body warm up and get ready for aerobic activities such as walking or swimming. Diabetes patients and prediabetes can do the following flexibility exercises of major muscle groups of both upper and lower limbs bilaterally. These exercises can be done either individually or in groups.

- Calf stretching exercise
- Sitting hamstring stretch exercise
- Plantar fascia stretching exercise.
- Hip flexors and adductors stretch exercise
- Biceps and triceps stretching exercise

4. Guidelines for a sound exercise program

If the blood glucose level is less than 100 mg/dl or greater than 250 mg/dl, do not exercise.

It is recommended to exercise indoor instead of outdoor to minimize the risk of integumentary and musculoskeletal trauma. It is also helpful for the patient to have an immediate access to necessary things to address hypoglycemia, hyperglycemia or diabetic ketoacidosis.

When patients plan to come out of their house to go somewhere else, they are highly advised to wear the medical tag for diabetics.

During prolonged exercise duration, 10–15 g of carbohydrate snack is recommended for every 30 minutes.

They are recommended to have a carbohydrate snack such as a glass of orange juice or milk at every exercise session. Exercising in a comfortable temperature is worthwhile. Never exercise in extreme temperatures.

For type 1 (insulin-dependent) patients, it is not allowed to exercise during the peak times of insulin. Before a physiotherapist asks a patient to do exercise, he should coordinate with the referring physician or nurse in charge for the patient regarding the stability of the patient and the type of insulin administered.

Type 2 diabetics are advised to have an average of 30 minutes of exercise duration per session.

Always wear proper footwear and exercise in a safe environment.

Menstruating women should have to boost insulin during menses, especially if they are not active.

It is not reasonable to inject insulin close to the muscles to be exercised within 1 hour of exercise.

Patients ought to eat 2 hours before they go for exercise. If they plan to exercise after meal, they should have to wait 1 hour prior to start. They should always bring their own portable blood glucose monitor. They should keep an eye on their glucose levels before and after exercise.

It is also important to drink adequate amount of fluid before exercise. If blood glucose level is between 70 and 100 mg/dl, the physical therapist can be allowed to provide carbohydrate snack and then reassess the glucose level after 15 minutes.

Make sure exercise does not contribute an unnecessary stress to the patient. Stress increases insulin requirements. A gradual progression from aerobic and resistance exercises is the key.

Avoid exercising late at night. Thus, exercising five times a week as maintenance is preferred. Any known DM patient must not exercise alone as much as possible so as to call someone to help in unexpected situations.

5. Summary and conclusion

Majority of diabetes mellitus patients have physical impairments, activity limitations and associated complications. Physical therapy has an important role to improve physical function, activities of daily living and quality of life of diabetic patients. Persons who are at risk of developing diabetes mellitus should also be involved in appropriate levels of daily physical activity based on personal preference and anticipated physical limitations.

It is recommended that people with DM ought to have a regular aerobic exercise and strength training to reassure positive adaptations in the control of blood glucose concentration, insulin action, muscular strength and exercise tolerance. Blood glucose levels should be monitored before and after exercise to prevent hypoglycemia. A medical screening and evaluation is essential to distinguish diabetes-related complications affecting cardiovascular function, which may be aggravated by an exercise program.

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Chapter 11

New Insights into Alleviating Diabetes Mellitus: Role of Gut Microbiota and a Nutrigenomic Approach

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76202

Abstract

The scientific literature has shown that diet is able to modify the gut microbiota and contribute to obesity and diabetes development. This process—characterized by inflammation and gut barrier disruption—can affect the immune system and alter the adipogenesis and insulin resistance. This chapter describes the advances in nutrigenomics and Human Intestinal Microbiota (HIM) modification, and its relation with diabetes mellitus type two (DM2). In context where health and feeding are the main concerns of the human being, food innovation takes a special interest to people that look for a healthy diet or demand a functional aliments, such as nutraceutical. Some products derived from diet and interaction with HIM module the expression of many genes on the host, the so-called epigenome, with favorable effects. Novel functional fiber like low-glycemic oligosaccharides and sweeteners shows a potential prebiotic activity giving a new focus of nutritional guidelines for control and prevention of DM2. The use of prebiotics derived from functional fiber sources, such as fructo-oligosaccharides and beta-glucans as well as lignin and keffir, can contribute to the development of a healthy HIM by promoting the growth of specific bacteria, some of them associated with the prevention of obesity and diabetes.

Keywords: human intestinal, diet, fiber, prebiotic, carbohydrates, diabetes

1. Introduction

Diabetes mellitus type two (DM2) is a complex pathology, it depends of the interaction of genetic, epigenetic, environmental, and lifestyle factors [1]. This disease has generated an epidemiological worldwide impact, with a current report of 425 million adults having the disease according to the International Diabetes Federation (IDF). Currently, the last report of the year 2017, the epidemiological data showed an increment of 10 million cases diagnosed respect to 2015 [2]. According to the IDF, projection for 2045 is 650 million subjects with DM2. North America and the Caribbean have the highest prevalence of this disease (11%), where an increase of 62% is expected for the same period [3].

In the multidisciplinary treatment of this pathology, dietotherapy has been specifically considered as a critical control point in the international guidelines for DM2 [4, 5]. Recently, important advances in nutrition management have been developed associated to nutritional genomics, whose objective focuses on the interaction between the bioactive components of food and the human genome, this approach includes studies of nutrigenetics, nutrigenomics, and epigenetic modifications caused by nutrients [6].

Some investigations have used nutrigenomics to illustrate the modulation mechanism of specific fatty acids on gene expression, producing an impact on human metabolism [7, 8]. A common approach is the examination of individual levels of mRNA in relation to nutrient intake [9]. Tests with carbohydrates and dietary components such as fiber show a relationship between specific polymorphisms and the effect on insulin resistance [10]. In this sense, in a recent review, the effectiveness of the supply of fermentable carbohydrates on human metabolism is explained [11].

Furthermore, new advances in study of the composition of the human microbiota have shown an evident relationship between Human Intestinal Microbiota (HIM) and DM2 [12]. In this context, a significantly greater association of Firmicutes/Bacteroidetes in DM2 has been observed when is compared with normal weight and obese subjects [13].

New focus of nutritional treatment and its potential epigenetic effect constitute a panacea in the modification of the diabetic patient's microbiota [14]. The HIM is affected by the ingestion of bioactive compounds, showing prebiotic or probiotic effects, whose action can help to generate the growth of beneficial bacteria, such as *Bifidobacterium* and Bacteroidetes. The development of personalized nutritional methods considering the genomic information, use of prebiotics from novel sources of functional fibers (Fructo-oligosaccharides FOS, beta-glucans) [15], consumption of carbohydrates with low-glycemic index (GI), as well as the use of monosaccharide sweeteners with potential prebiotic activity, such as (tagatose) [16], would allow to generate a new therapeutic orientation for the control and prevention of this pathology. These dietary practices are important as part of the near future and will be analyzed in this chapter. Finally, a description in nutrigenomics advances and the effect of prebiotics consumption on modification of HIM are shown and its relationship with DM2 will be discussed.

http://dx.doi.org/10.5772/intechopen.76202

2. Nutritional treatment and new perspectives

2.1. Prebiotics derived from functional fiber sources

A prebiotic is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" [17]. Modification encouraged by prebiotics on the composition of HIM leads to the predominance of a few of the potentially health-promoting bacteria, especially, but not exclusively, *Lactobacilli* and *Bifidobacteria* [18]. Some prebiotics pass by the small intestine to the lower gut and become accessible for probiotic bacteria without being utilized by other intestinal bacteria [19]. Lactulose, galacto-oligosaccharides, fructo-oligosaccharides, inulin, and its hydrolysates, malto-oligosaccharides, and resistant starch are prebiotics normally used in the human diet [20, 21].

The definition used at present was given by the Food and Agriculture Organization of the United Nations World Health Organization, according to which probiotics are redefined as "live microorganisms which when are administered in adequate amounts confer a health benefit on the host." In relation to foods, the definition can be adjusted to beneficial effect exerted by microorganisms "when are consumed in adequate amounts as part of food" [17, 21].

2.1.1. Betaglucans

2.1.1.1. Cereal β-glucans

Functional properties of β-glucans have been particularly attributed to the fact that these create viscous solutions in aqueous solution, as occurs in the digestive tract [22, 23]. This viscosity causes β-glucans to delay gastric emptying and interfere with the contact between pancreatic enzymes and their substrates in the intestinal lumen, slowing the digestion and absorption processes of nutrients [24]. This property could explain the effect of β-glucans on the reduction of plasma cholesterol concentrations and the glycemic index [25, 26].

2.1.1.2. Yeasts and fungi β-glucans

Another pivotal property of fungi/yeasts β-glucans is the modulation of the immune system [27, 28]. This effect could be due to the ability of β-glucans to stimulate receptors of the innate immune system present in the membrane of enterocytes, M cells and dendritic cells, improving the phagocytic activity of macrophages and antimicrobial activity of mononuclear cells and neutrophils [29–31]. This type of β-glucans would also prevent the promotion and progression of certain types of cancer, acting synergistically with monoclonal antibodies and chemotherapy [32, 33]. This stimulation of immunity would be achieved by increasing the secretion of pro-inflammatory cytokines and chemokines [34]. The main receptor involved in the effect of B-glucans immunity is Dectin-1, even though there is also a role for the receptor 3 of the complement, TLR-2, TLR-6 and the "scavengers" receptors [35, 36]. Dectin-1, known in human beings as β-glucans receptor (βGR), is a member of the pattern recognition receptors (PRR)

which fulfill an essential role in the innate immune response against viruses, bacteria, yeasts, and fungi, contributing to the recognition and elimination of pathogens [34]. This receptor is highly expressed in immune cells such as dendritic cells, neutrophils, eosinophils, and monocytes as well as in some populations of T and B cells and, to a lesser extent, in macrophages and enterocytes [31, 34, 35]. Dectin-1 acts through signal transduction activating Syk and RAF-1 [14]. It can also act synergistically with TLR which mediates the production of pro-inflammatory cytokines, such as IL-12 and TNF-α [33, 35].

2.1.2. Fructo-oligosaccharides

Inulin is a non-digestible carbohydrate present in many vegetables, fruits, and cereals [36]. Currently, at the industrial level it is extracted from the chicory root *(Cichorium intybus*) and is widely used as an ingredient in functional foods. Inulin and its derivatives (oligofructose, fructo-oligosaccharides) are generally called fructans, basically composed of linear chains of fructose [37]. The maximum dose allowed to be added to food formulated with inulin is up to 20 g/day for a simple dose and up to 10 g/day for multiple doses. At higher doses it can cause intolerances after consumption, such as osmotic effects (diarrhea), intestinal noises and flatulence as a result of the fermentation process [38]. Oligofructose is obtained by the partial enzymatic hydrolysis of inulin, composed of linear chains of glucosyl-fructosil. GP ranges between 2 and 8, with an average value of approximately [37]. It is present in foods such as cereals, onions, garlic, banana, and corn [38, 39]. There are promising evidences of its performance in the regulation of lipid parameters, reduction of the risk of cancer, reinforcement of the immune response and protection against intestinal disorders [40]. In a wide variety of food products, inulin and its derivatives are used as: thickener, emulsifier, gelling agent, sugar and fat substitute, moisturizer, depressor of the freezing point [37, 39].

2.1.3. Lignin's: mucilage's (flaxseed)

2.1.3.1. Lignans

Plant lignans are phenolic compounds with a skeleton of 2,3-dibenzylbutane [40]. Flaxseed is the richest food source in the precursors of lignans, secoisolariciresinol diglucoside (SDG), and materesinol, which are phytoestrogens that by action of gastric acid and bacterial glucosidase (facultative aerobics of Clostridia class) of the digestive tract transform into enterolactone and enterodiol, respectively, known as lignans of mammals [41]. These have more antioxidant capacity than their predecessors. Other lignans, such as lariciresinol, hinoquinina, arctigenin, divanillyl tetrahydrofuran nordihydroguaiaretic acid, isolariciresinol, and pinoresinol, are also present in flaxseed but the most abundant is SDG [40]. The health benefits of flaxseed lignans rely in their antioxidant capacity as retainers of hydroxyl radicals, and as estrogenic and anti-estrogenic compounds due to their structural similarity to the 17-β-estradiol [37, 41]. The antioxidant activity of flaxseed lignan (SDG) is related to the suppression of the oxidizing conditions of oxygen reactive species [41]. Secoisolariciresinol diglucoside and its aglycone secoisolariciresinol show a high antioxidant capacity and protective effects to the damage of the DNA and liposomes, especially in the epithelial cells of the colon exposed to these

compounds, during the metabolism of the colon bacteria that transform them into lignans of mammals [42, 43].

2.1.3.2. Mucilage

Mucilage is water-soluble polysaccharide present in many seeds, capable of absorbing 60–100 times their weight in water forming gels. They are formed by ramified arabinoxylans chains [44]. The mucilage is similar to the gums, composed of galactose, mannose, xylose, and other sugars [45]. One of the best known mucilage is psyllium (psyllium) or also called plantain, coming from the seeds of Plantago genus [42, 44]. The mucilage extracted from algae contains sugars somewhat different from terrestrial vegetables, such as agarobiose in the agar and sulf-sugar in the carrageenan, used in food technology [44]. Flaxseed mucilage is a complex polydisperse hydrocolloid and the different rheological behaviors observed in cultivars are caused by the differences in the ratio between neutral and acid polymers and by the molecular weight and structural conformation of polysaccharides [45, 46].

2.1.3.3. Flaxseed

Even though flaxseed is much known, it is not widely used in the formulation of food [47]. This seed has significant amounts of bioactive compounds, such as alpha-linolenic acid, lignans and dietary fiber, with potential effects in the prevention of some chronic diseases such as reducing the risk of cardiovascular diseases, mitigating the effects of diabetes, renal pathologies, obesity, colon and rectum cancer, reducing serum cholesterol level, and promoting the intestinal evacuation [46, 47]. These characteristics make flaxseed an attractive source of ingredients to be used in the elaboration of different functional foods [48].

2.1.4. Kefirs

Different *in vitro* and *in vivo* studies have demonstrated the ability of kefir to promote health through the presence of bioactive peptides. Multiple bioactivities of this beverage such as antihypertensive, antimicrobial, immune-modulating, mineral-carrying, antithrombotic, opioid, and antioxidant have been the most reported [49]. These characteristics of kefir, along to the pre- and probiotic properties, hypocholesterolemic, the bioavailability of milk components with biological activity and the presence of metabolites such as organic acids and bacteriocins, situate it as functional food [50]. This is a food that beyond the nutritional contribution of its components has been proven to benefit one or more physiological functions of the organism, improving the health, well-being, and/or reducing the risk to suffer diseases [51–53]. Additionally, there are bioactivities that have been poorly studied as the mineral fixing properties and the antithrombotic activity. There are some studies about the substrate-microorganism-metabolite-bioactivity inter-relationships based on metagenome studies [54, 55]. It would be important to carry out more investigations to determine the different bioactivities more deeply and the effective dose by trying to reach the intestinal level in sufficient quantity to implant and colonize its surface [56].

2.2. Low-glycemic index of carbohydrates and inflammatory state intestinal mucose

2.2.1. Historic context glycemic index and glycemic load

One of the major dietary changes of the modern world has been the high consumption of processed foods rich in carbohydrates and low in fiber; highly related to the increasing rates of obesity and diabetes [49]. In this sense, pharmacological approaches focused on large clinical trials have been useful for improving glycemic control in patients with type 2 diabetes (DM2) [51]. Similarly, a positive effect in the control of diabetes has been associated with the consumption of diets low in GI [52], these indicator determines the effect of the available carbohydrates in food on the average concentration of glucose in blood, this value is defined as the relation between the area under the curve of 50 g of available carbohydrates in a food, with the area under the curve of same amount of carbohydrates of a reference food [53].

White bread and glucose, which has been assigned a GI of 100, are considered reference foods rather than a high value for this indicator [54]. Different entities worldwide, such as the American Diabetes Association (ADA) [55], the European Association for the Study of Diabetes [56], the Canadian Diabetes Association [57], and the UK Diabetes Nutrition Sub-Committee [58] have prioritized dietary treatment with a relevant approach to carbohydrate quality for the glycemic control, with special emphasis on reducing the digestion rate, absorption and metabolism of carbohydrates from foods [59].

Therefore, this indicator expresses the potential glycemia of a meal, representing the quality of foods with predominance of carbohydrates [60]. Foods with carbohydrates capable of digesting, absorbing and metabolizing quickly are considered food with high GI (GI ≥ 70 in the glucose scale). Those between GI = 55 and 70 are considered in an intermediate value, while those digested, absorbed and metabolized slowly are classified as foods with low GI (GI ≤ 55 in the glucose scale) [53, 60]. There are international tables with the published values of this indicator for a large number of products on the market. The first table was published in 1981 and was later updated in 1994 and 1995 [61, 62]. There is a marked controversy over the use of this indicator in the decade of the 80, due to an inadequate interpretation of the evidence for its determination [60, 63]. Criticism has focused on the methodological validity of the process to quantify it since a large number of factors had influenced the results [60, 64]. The position of the latest consensus of glycemic index experts in 925 held in Europe has determined that most of the current critics are not valid, and that these reflect a failure of the knowledge translation [60]. In this context, it is important to consider that important entities such as the International Diabetes Federation have recognized the relevance of post-prandial regulation of glucose in order to achieve the objectives of HBA1C by developing specific guidelines, whose management is related to the GI concept [64].

2.2.2. Glycemic load, glycemic index, and insulin response

The value of glycemia and the insulin response depends on the quantity and quality of carbohydrate and the mix of food ingested, the so-called glycemic load (GL). The GL represents a relationship between the quantity and quality of carbohydrate [54, 60], and is defined as the total carbohydrate content available in an amount of food (GL = GI × available carbohydrates/specific amount of food) [60], and is the result of multiplying the amount of carbohydrate

ingested in food by the value of its GI. The GL should be interpreted as a measure in the demand for insulin, this value is a good indicator of the levels of post-prandial glycemia, associated to the amount of calories in a particular portion of food or diet [65]. Thus, foods with high GL and high GI have a direct effect on the development of hyperinsulinemia [66], insulin resistance and risks to develop DM, which also have been linked to high-IG foods [67].

2.2.3. Insulin response and inflammation mucus and glycocalyx layer

Several studies have determined a clear link between the glycemic index and the glycemic load of food and the insulin response [52, 68, 69]. Studies suggest that carbohydrates can modify the microbiota, depending on their ability to increase glycemic and insulin response values according to glycemic and insulinemic index [70, 71]. In this sense, several studies in rodents have reported oligofructose as a recognized prebiotic, capable of modulating IM and improving insulin sensitivity [72, 73]. Similarly, inulin-type fructans have been tested to determine their ability to modulate lipid metabolism and carbohydrate in various animal models [73, 74]. It has been reported that oligofructose (OFS) decreases the intake of food, the development of fat mass and hepatic steatosis in normal and obese rodents. In addition, OFS exerts an antidiabetic effect in rats treated with streptozotocin and mice treated with high content of fat [72]. Chang et al. demonstrated that the addition of OFS also caused changes in the IM, specifically for *Bifidobacterium* and *Clostridium leptum* [75] content. These results suggest that OFS may be an effective therapeutic complement in the treatment of diabetes type 1 (DM1) by improving insulin sensitivity and beta cell function, leading to better glycemic control [76]. OFS reduced body weight, energy intake and fat mass in both phenotypes ($P < 0.05$) [76]. In another study carried out in two different groups of rodents, OFS did not modify ghrelin in plasma, but plasma levels of GIP were reduced and PYY were elevated ($P < 0.05$) [76] by OFS, reducing body weight and adiposity in prone obese phenotypes and in those insulin-resistant [76].

The changes induced by this saccharide in the profiles of IM of these animals, along with the changes of intestinal hormone levels probably contribute to lower body weights sustained [76, 77]. Milk prebiotic oligosaccharides have been reported to alter the IM and may influence the metabolism of the host. In a study performed in rats comparing diets with 15% of glucose, fructose, galactose, and methylcellulose content, daily intake of 15% galactose improved the sensitivity to hepatic insulin compared with glucose and fructose, producing an increase in the content of hepatic glycogen in the feeding state and a positive change in the IM populations; unlike the intake of galacto-oligosaccharides [78], which improved the IM profile without any effect on the insulin sensitivity. The GI of lactose, fructose and isomaltose is (=43), (=20), and (=2), respectively [62]. Further studies on these indicators are required in monosaccharides and their effect on the human microbiome.

3. New perspectives in biotechnology of foods, low-glycemic index and the microbiota

In context where health and feeding are the main concerns of the human being, food innovation takes a special interest to people that look for a healthy diet or demands a greater number

of functional products, such as nutraceutical, that often generates more contribution than nutrients, helping to improve the prevent of different diseases [79].

A functional food has been defined as a: (i) natural food, (ii) food which a component with some technology or biotechnology has been added or removed, (iii) food where the nature of one or more components has been varied, (iv) food which the bioavailability of one or more of its components has been modified, and/or (v) any combination of the above possibilities [80]. The world commercialization for functional foods and beverages have grown from $ 33 billion in 2000 to 67.7 billion pesos in 2013, that mean the 5% of the global food commercialization, and the growth of investment in food industry as a whole. Latin America is currently a potential producer and consumer of functional foods, because of its large natural resources, a wide biodiversity of flora and fauna having a variety of plants and edible fruits with potential and beneficial effects for health [78].

Bioactive molecules works mainly modifying cellular signaling and causing changes in expression of certain genes, for instance producing a defensive response to harmful processes like differentiation and cell proliferation, inflammation, it is the base of the understanding for most prevalent diseases. New technology applied for food and nutrition sciences are closely related to the biomedical area, researchers require strong training in molecular biology, genetics and nutritional biochemistry, among others disciplines [81]. The current "omics" technologies, such as genomics, transcriptomics, proteomics, metagenomics, metatranscriptomics and metabolomics, have introduced important strides in the fields of health, biotechnology, ecology, and food [81]. The increase of the importance of (I + D) from academy, where food and pharmaceutical industry have worked together to promote healthy feeding, functional foods and nutraceuticals developing, those products when are consumed in a regular way, contribute to the prevention and/or treatments of certain diseases [82]. Genetic engineering plays an important role in the improvement of functional foods, which involves biological and technological research and also normative and ethical communication [83]. New probiotic strains isolated from natural niches and other produced by genetically engineered organisms (GMOs) have broadened the spectrum of organisms with improved probiotic properties for incorporation into functional foods [84]. More than 500 probiotic food products have been introduced into the world stores over the last couple of decades [81]. The contribution of biotechnology to production of prebiotics is remarkable. Prebiotic such as inulin and fructose polymer are produced by extraction of natural products (mainly chicory for fructose polymer), other prebiotics are produced by bioprocesses involving microorganisms or enzymes specifically conditioned for efficient synthesis of non-digestible oligosaccharides. On the other hand, inulin is the most used prebiotic, although it is probably not the most effective, actually, in the formulation of functional foods, also providing textural and rheological properties to the food matrix [83]. Another example of innovation is the design and development of product with intestinal microbiota and/or GI control effects, such as powdered additive, that incorporates also beneficial bacteria to the food. This development, achieved by researchers from National Institute Food Technology in Chile and Conicet Argentina, incorporated as an additive to certain foods—cold or lukewarm liquids—enriches the digestive system, balances the intestinal microbiota with a positive impact on the immune system [85].

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3.1. Non-caloric sweeteners and gut microbiota

Non-caloric sweeteners (NCSs) are food additives widely used as sugar substitutes; these sweeteners enhance tastes and simultaneously reduce calories consumption. Some epidemiological studies have shown that artificial sweeteners are beneficial for weight loss, principally for subjects having glucose intolerance and type 2 diabetes [86]. Historically, the consumption of NCSs was restricted to people who have diseases such as diabetes; however, their consumption has increased in recent decades for general population. For their approval for human consumption, there are rigorous procedures required to consider them safe, however, today a controversy exist in its safety and it has been noted the possibility that the NCSs alter intestinal microbiota (IM). IM is involved in the metabolism of the host and plays a crucial role in food digestion and energy homeostasis. However, multiple environmental factors, such as diet, antibiotics and heavy metals, can disrupt the ecological balance of microbiota in the intestine [87]. A study in male Sprague-Dawley rats who were subjected to oral probe of 100, 300, 500, or 1000 mg/kg of Splenda for 12 weeks showed at the end of the treatment period, the number of total anaerobes, *Bifidobacteria*, *Lactobacilli*, *Bacteroides*, *Clostridia* and total aerobic bacteria decreased significantly. These changes occurred in Splenda doses containing sucralose at 1.1–11 mg/kg (FDA's acceptable daily intake for sucralose is 5 mg/kg) [88]. Other study realized in 8 weeks old C57B1 mice, two experiments were performed. Experiment 1, 4-week-old male mice were divided into three groups (n = 8 x group) and treated for 8 weeks as follows: mice in control group received distilled water; mice in the low dose sucralose group (LS) a sucralose solution of 1.5 mg/kg body weight per day were given; and mice in the high-dose sucralose group (HS) received a sucralose solution of 15 mg/kg body weight per day, which is equal to the maximum IDA. In Experiment 2, 4-week-old male mice were divided into two groups and treated for 8 weeks as follows: Mice in control group received distilled water (n = 8); and acesulfame-K mice were given an acesulfame-K solution of 15 mg/kg body weight per day, which is equal to the ADI (n = 9), resulting that consumption of sucralose, but not of acesulfame-K, reduced the relative amount of *Clostridium cluste*r XIVa in feces. Meanwhile, sucralose and acesulfame-K did not increase food intake [89]. Acesulfame k is genotoxic, and can inhibit the fermentation of glucose by intestinal bacteria [90]. A study in CD-1 mice (~8 weeks of age), were given a dose of 37.5 mg/kg body weight/day of acesulfame-K during 4 weeks, in males *Bacteroides* showed increased instead in females mice drastically decreased the relative abundance of multiple genres, including *Lactobacillus*, *Clostridium*, Ace-K disrupts the composition of the intestinal microbiome in a sex-dependent manner [90]. Another study in adult male C57B1/6 WT mice, gave two groups of mice a high in fat diet (60%) and commercial saccharin (equivalent to one human IDA) or glucose [91], resulting in an alteration in the glucose tolerance, the authors concluded that glucose intolerance was mediated by change in the microbiota (increase of *Bacteroidetes* and *Clostridium*). To corroborate the latter, a fecal transplantation to germ-free mice w performed, after 6 days an altered glucose tolerance was present in these mice. A similar study was carried out this time in seven humans (five men and two women), who were given 5 mg/kg/weight of saccharin (IDA equivalent) for 7 days, four of whom had altered glycemic responses. Other study, carried out in 31 humans that evaluated the consumption of aspartame and acesulfame k, showed that the consumers of these NCSs presented a different bacterial diversity to those who did not consume these

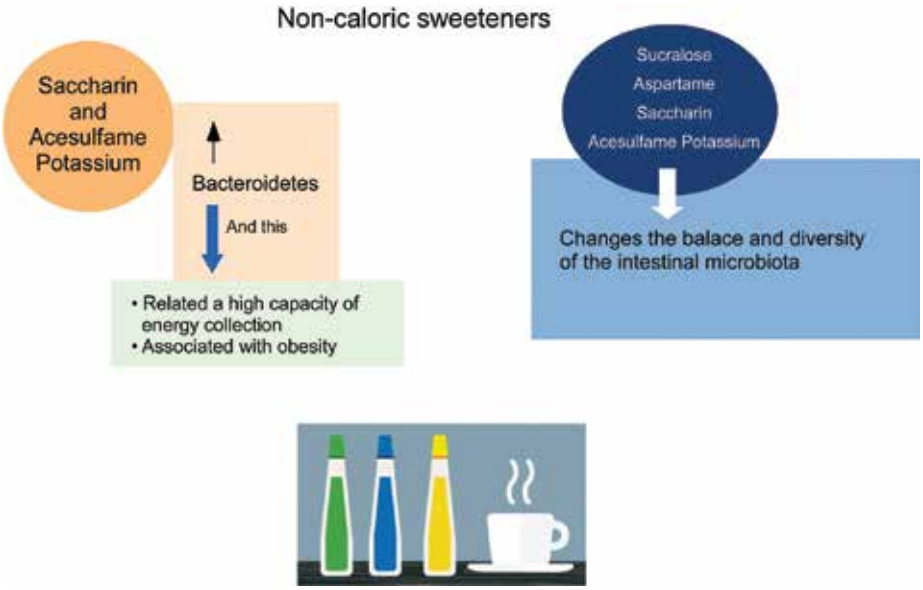

Figure 1. NCSs: sucralose, saccharin and acesulfame-K have been found to modify the balance of the HIM, either by decreasing or increasing the number of Bacteroidetes.

NCS [92]. This group also performed a smaller trial of seven healthy volunteers (five males, two females, and ages 28–36) who did not normally consume NCS and who received saccharin for 1 week at a dose of 5 mg/kg, IDA for these sweeteners. Most of these (4/7), known as "NCSs responders" developed lower glucose tolerance and altered IM compared to "non-responders of NCS" [92]. Microbiome of "NCS responders" showed changes in composition by 16S rRNA analysis. Due this control group was not included in the design, it is unclear whether some healthy individuals exposed to seven consecutive tests of oral glucose tolerance (daily intake of 75 g of glucose) would have developed changes in glucose metabolism in the absence of saccharin. Palmnas et al. [107], demonstrated that 8 weeks of exposure to aspartame (at an equal dose to subjects consuming approximately 2–3 sodas/day) disrupted the intestinal microbiota; aspartame + high fat diet vs. water + high fat diet increased total bacteria; *Enterobacteraceae*, *Clostridium leptum*, and *Roseburia* spp. reduced *Bifidobacterium* sp. On the contrary, when the diet was low fat + aspartame or low-fat + water, *Clostridium leptum* increased, resulting in elevated levels of fasting glucose and insufficiency tolerance to insulin in rats [51]. However, the mechanism by which aspartame disrupted the IM is unclear, as aspartame is metabolized before it reaches the colon by intestinal esterases and peptidases in amino acids and methanol (**Figure 1**) [49].

3.2. Tagatose and prebiotic potential activity

D-tagatose (D-tag) is an isomer of fructose approximately 90% sweeter than sucrose. Only 20% of the oral intake of tagatose is completely metabolized, mainly in the liver [49]. The mayor part of this molecule is not digested or absorbed and passes through colon where water is absorbed and D-tag is fermented by colonic bacteria. This natural sweetener can be artificially

http://dx.doi.org/10.5772/intechopen.76202

obtained from lactose. This sweetener with natural origin can be obtained artificially from lactose. Through food technology, glucose is separated and galactose is extracted, whose molecule is transformed into D-tagatose through an isomerization process [43].

D-tag would have an antihyperglycemic potential through its beneficial effects increasing postprandial serum glucose and hyperinsulinemia. Recent studies indicate that D-tag has a potent anti-diabetic effect and could be eventually associated with significant benefits for the treatment of obesity. The hypothesis regarding the mechanism of action proposed for this hypoglycemic effect would consider the interference with carbohydrates absorption by inhibition of intestinal disaccharidases and glucose transport, an also a mechanism of inhibition of hepatic glycogenolysis [37]. Another important characteristics of the D-tag is it low GI, considering white bread and glucose as reference foods, the D-tag GI is 3 and 4, respectively [63]. The potential applications of D-tag in the pharmaceutical industry and in food industry have reached a great boom [41]. However, the use of D-tag is limited by its high cost of production [36]. Another characteristic of D-tag is its potential prebiotic activity, and in order to preserve this effect the processing and storing of the food must ensure the maintenance of the chemical structure of the sweetener [35]. It has been determined that D-tag can be used for the formulation of diabetic beverages with minimal chance of degradation and very low loss of prebiotic activity [31, 33, 36], maintaining adequate thermal stability. Preliminary results suggest that D-tag would have an effect on the reduction of total cholesterol, VLDL, and LDL compared to sucrose in diabetic patients [53]; the contribution of D-tag to increase levels of HDL cholesterol has also been shown [54]. These clinical studies and wonderful advances in food technology make this molecule an ideal sweetener in functional products for patients with diabetes [62–64], with the ability to positively affect the intestinal microbiota of these patients, making its consumption more interesting and useful in a little explored area [85, 87]. On the other hand, the incorporation of novel functional sources of fiber, as well as oligosaccharides of potential prebiotic activity, has generated great scientific interest in the formulation of healthy foods aimed at diabetics. This new direction of science could be the anticipation of a new line of research that is beginning to emerge. Finally, future projection of personalized nutrigenomics foresees a great challenge toward the integration of different sciences as transcriptomics, epigenetics, proteomics, and metabolomics, with the purpose of positively modifying the microbiome, generating impact in the gene expression of the human organism, and avoiding manifestation of chronic diseases such as DM2.

4. Conclusions

The use of prebiotics obtained from functional fiber sources such as fructo-oligosaccharides and beta-glucans, as well as lignin and prebiotics such as keffir, can contribute to the development of a healthy HIM by promoting the growth of bacterial species that have been associated with obesity and diabetes prevention. On the other hand, it has been described that some low GI monosaccharides can positively modify the composition of the HIM in animal models, by regulating the mechanism of insulin sensitivity. More investigations are needed to evaluate the effect of saccharides, such as fructose, lactose and isomaltose in the human microbiome. Although, some NCS such as sucralose, saccharin, and acesulfame-K can modify the balance of HIM, mainly through the alteration in the number of *Bacteroidetes* species. Nevertheless, more studies in humans are required. In this sense, a new caloric sugar called D-tag has proposed

as possible hypoglycemic and probiotic effects. Finally, the new information presented in this chapter allows us to map out the near future where the integration of nutrigenomics and nutritional treatment focused on the microbiota modification will be plausible. Futhermore, the use of bioactive compounds that alter gene expression and/or affects immunity of pancreatic beta cells represent a projection toward the treatment and/or prevention of DM2.

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Edited by Viduranga Waisundara

Diabetes is a global pandemic where many remedies have been recommended as means of combating the prevalence of this disease. However, dietary control appears to be more effective than others. This book focuses on interventions concerning glycemic control, the oxidative stress-based occurrence of the disease and its prevention, as well as novel remedies. While many books have been published recently on this aspect, the book aims to serve as an update to the scientific community, as well as to those who have been adversely affected by the disease. There are many unexplored territories when it comes to diabetes, and it is hoped that this publication will open up new avenues of successfully curbing its occurrence.

Published in London, UK

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ISBN 978-1-83881-307-9