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Rheumatoid Arthritis

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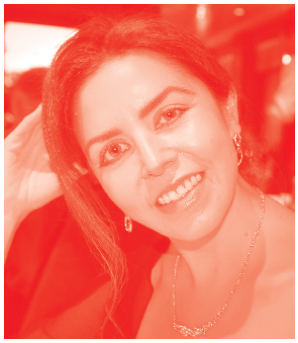

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Meet the editor

Professor Hechmi Toumi graduated from Blaise Pascal University in France. He is a research assistant at the University of Wisconsin in the USA and at Cardiff University and is an awarded professor at the University of Wales, UK. He has acted as dean of the Faculty of Sciences at the University of Orleans from 2013 to 2020. Currently, Professor Toumi is the scientific director of Translational Medical Research Platform, PRIMMO, at the Orleans Hospital in France and vice president of the Institute of Research, Treatment, and Prevention of Osteoporosis. He is currently filing for an international patent application for his invention on the use of algorithmic analyses to identify and quantify invisible detail in soft tissues using standard radiographs. Professor Toumi has lectured worldwide on the pathologies, treatment, and prevention of muscular-skeletal injuries.

Contents

Preface

Rheumatoid arthritis (RA) is a common long-term chronic disease causing joint inflammations, pain, and stiffness. RA affects women three times more than men. Hormones in both genders may play a role in either preventing or triggering the disease. There are four stages of osteoarthritis (OA): minor, mild, moderate, and severe. Most frequently, OA symptoms affect the fingers, feet, knees, hips, and spine and less commonly the elbows, wrists, shoulders, and ankles. Having RA can lead to several other conditions that may cause additional symptoms and can deteriorate living conditions. Currently, there is no rapid accurate cure. However, there are many operational treatments that prevent OA progression and help control the symptoms of joint pain and stiffness. Recent research confirmed that early intervention for RA is key because joint damage cannot be reversed. Clinically, a treat-to-target strategy management to control and prevent the disease and progression is recommended. Rheumatologists often complement this with low physical activity. Exercise, in general, seems to improve overall function in RA without any proven detrimental effects to disease activity, although more research is still required on the optimal dose and types of exercises. Note also, recently interest in traditional herbal medicines has increased considerably. In fact, herbal medicines are believed to be comparatively less toxic than synthetics. Currently, most of the tribal people still depend mostly on local medicinal plants for OA treatment.

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Section 1

Pathogenesis of Rheumatoid Arthritis

Chapter 1

Pathogenesis, Pathology and Genetics of Osteoarthritis

Ferhat Ege

Abstract

Osteoarthritis (OA) is a condition with high prevalence worldwide. OA affects not only the articular cartilage, but the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane and the periarticular muscles. Despite the fact that the risks associated with OA increase with age, it is not a part of the natural aging process. It typically involves the knee, hip, spine, hand and foot joints. Several factors play an important role in the pathogenesis of OA, including biomechanical factors, proinflammatory mediators and proteases. On the other hand, it was mostly the results of the studies conducted on the genetic, genomic and epigenetic aspects of OA, from among many of its underlying etiological factors, which shed light on the molecular processes involved in the etiopathogenesis of OA. As the mechanisms that cause joint tissue damage in OA come to light, the treatment of OA will go beyond just providing symptomatic relief. Consequentially, new treatments will emerge that will either slow or completely stop the progression of OA.

Keywords: Osteoarthritis, Genetics, Epigenetics, Etiopathogenesis, Pathology

1. Introduction

Osteoarthritis (OA) is a chronic disease that affects all structures of the joint as well as the periarticular tissues. In the past, OA was considered simply as a degenerative joint disease, yet the pathogenesis of OA is in fact much more complex than just wear and tear. Hence, the term "osteoarthritis" is indeed a pertinent term, as the suffix "itis" is indicative of an inflammatory process. It is estimated that approximately 50% of the world population over 65 years of age is affected by OA. The symptomatic treatment of this common disease provides regression of symptoms, nevertheless it often does not constitute an effective treatment option thus causing an increase in the OA-related health expenditures. The elucidation of the etiopathogenesis of OA and the molecular studies to be carried out in respect thereof are likely to allow early diagnosis of OA and also contribute to the development of new treatment options.

2. Pathology and pathogenesis of osteoarthritis

Articular cartilage degeneration, which develop as a result of the deterioration of the balance between the production and destruction of cartilage, new bone formation, sclerosis of subchondral bone, ligament and meniscus damage, periarticular muscle weakness, synovial inflammation and fibrosis are all involved in the

pathogenesis of OA [1]. Hence, the pathogenesis of OA would be better understood provided that the structure of the joint and the related histopathological features are reviewed.

2.1 Structure of the joint

Synovial joints consist of an articular cartilage that covers the ends of the opposing bones, the synovial fluid that nourishes and lubricates the tissues, the synovium that secretes the synovial fluid, the ligaments that hold the skeletal elements together, the tendons that connect the bones with the muscles, and the joint capsule surrounding the joint. In order to have normal joint functions, it is necessary that the opposing joint surfaces move over each other painlessly, that the load on the joint tissues is homogeneously distributed, and that the stability to that effect is sustained [2].

Articular cartilage is a connective tissue located at the bone ends and which has a thickness of 0.2 mm to 6 mm depending on the location. Articular cartilage provides a smooth and low-friction surface that primarily allows for normal gliding motion of the articular surfaces [3]. Cartilage consists of an extracellular matrix, 65–80% of which is water and 20–35% of which is solid matter, and of chondrocytes dispersed in this matrix. 5–6% of the tissue is composed of inorganic material consisting mostly of hydroxyapatite. The organic matter on the other hand is composed of fibrous proteins (collagen), hydrophilic sulfated proteoglycans (chondroitin sulfate, keratan sulfate I and II) and unsulfated proteins (hyaluronic acid). 90% of the collagen is type II collagen, whereas the remaining collagen consists of smaller amounts of type IX, XI, III, VI, XII and XIV collagen [4].

A proteoglycan consists of a protein and glycosaminoglycan chains attached to this protein. The most abundant type of proteoglycan is 'aggrecan' [5]. Type II collagen plays a role in maintaining the volume and shape of the content it is part of, whereas proteoglycans play a role in maintaining the hardness and elasticity [6].

Hyaluronic acid is the substance that maintains the viscosity in synovial fluid. Nonetheless, it requires the presence of a large mucinous protein, which is called lubrisin (proteoglycan-4), in order to maintain a low-friction environment and protect the surface of the joint [7].

Articular cartilage is a avascular heterogeneous structure with four different layers which has no nerve innervation and is fed by a bidirectional diffusion system. These layers are the superficial zone, transitional zone, deep zone and calcified zone. The calcified line between the deep zone and the calcified zone is called the Tide mark [8].

The extracellular matrix is synthesized by chondrocytes. Chondrocytes synthesize cartilage matrix molecules and the metalloproteinases which breakdown the matrix. The cartilage metabolism is based on the balance between the anabolic processes and the catabolic processes carried out by the matrix metalloproteinases (collagenase, gelatinase, stromelysin, cathepsin B and D) and the adamalysins [a disintegrin and metalloproteinase (ADAM), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), aggrecanase] [5]. This balance is regulated by anabolic cytokines such as transforming growth factor beta (TGF-β), insulin-like growth factor-1 (IGF-1) and bone morphogenetic proteins (BMPs) and catabolic cytokines such as interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [6].

The synovium, which produces the synovial fluid, consists of two layers as inner and outer layers. It is firmly attached to the joint capsule and prevents the synovial fluid from leaving the joint. The inner and outer layers of the synovium are composed of the synovial membrane and fibrous connective tissue, respectively. The

inner layer includes two types of cells. Type A synoviocytes have the characteristics of macrophages, whereas type B synoviocytes are cells with proliferative capacity and produce hyaluronic acid, collagen, lubricin and fibronectin [9].

The joint capsule is a tissue that contains vascular and nervous tissues and is rich in collagen fibers. It protects the whole joint both passively by restricting the movements of the joint and actively through the proprioceptive sensation triggered by the nerve endings.

2.2 Pathological changes that occur in connection with osteoarthritis

2.2.1 Changes that occur in the articular cartilage

Chondrocytes are active cells that maintain cartilage through normal anabolic/catabolic activities. The earliest pathological changes observed in association with OA are the fibrillations seen on the surface of the cartilage. Fibrillations are more common at parts of the cartilage exposed to higher loads. Loosening of the collagen network and loss of aggregate occurs in the cartilage at the onset of OA. This loosening of the collagen network allows the hydrophilic proteoglycans to attract water and expand.

The activity of chondrocytes, the only cell type found in cartilage, accelerates significantly as OA develops, that is, chondrocytes begin to proliferate moderately. Nevertheless, the reasons that trigger this premature aging and changes in the chondrocyte cycle such as inflammation, proteoglycan loss, collagen degeneration and chondrocyte failure, as well as the order of occurrence of these changes are still not fully known [10].

As OA progresses, extensive matrix breakdown and loss occur due to the continued production of the proteases driven by proinflammatory cytokines. Fragmented matrix proteins give rise to the further production of cytokine and protease by chondrocytes through autocrine and paracrine stimulations. Cartilage has limited regeneration capacity, hence once collagen is broken down and lost, regeneration does not occur at a measurable degree [11].

There are various histopathological staging-grading systems that are used to categorize the changes associated with OA according to their severity, extent or order of occurrence. These classification systems classically address the changes that occur in articular cartilage, since OA primarily targets the articular cartilage. One of these systems, the histological evaluation system proposed by **Osteoarthritis Research Society International (OARSI)** is a grading, staging and a scoring system. The grades used in the said OARSI system to classify the changes occur in articular cartilage, key features of these grades and the associated criteria in terms of tissue reactions are shown in **Table 1** [12].

2.2.2 Changes that occur in the bone

Thickening of the subchondral bone (bone sclerosis) occurs due to increased production of improperly mineralized collagen. Osteophytes occur at the margins of the joints, usually at the insertion sites of tendons or ligaments. Osteophytes seen in the distal interphalangeal joints of the hand are called "Heberden's nodes", whereas the osteophytes seen in the proximal interphalangeal joints are called "Bouchard's nodes". Bone cysts form in the advanced stages of the disease, but bone erosions are not typically seen. Erosive OA is commonly seen in the distal joints of the hands (distal interphalangeals and proximal interphalangeals) and central erosions are also seen as opposed to the marginal erosions seen in rheumatoid arthritis (RA) and gout [13].

Grade #	Key features	Associated criteria (tissue reaction)
Grade 0	Intact surface and cartilage morphology	Matrix: normal architecture
		Cells: intact with appropriate orientation
Grade 1	Intact surface	Matrix: intact superficial zone, oedema and/or superficial fibrillation (abrasion), focal superficial matrix condensation
		Cells: death, proliferation (clusters), hypertrophy, superficial zone reaction must be more than superficial fibrillation only
Grade 2	Surface discontinuity	As above CMatrix discontinuity at superficial zone (deep fibrillation) GCationic stain matrix depletion (Safranin O or Toluidine Blue) upper 1/3 of cartilage GFocal perichondronal increased stain (transitional zone) GDisorientation of chondron columns
		Cells: death, proliferation (clusters), hypertrophy
Grade 3	Vertical fissures	As above Matrix vertical fissures into transitional zone, branched fissures GCationic stain depletion (Safranin O or Toluidine Blue) into lower 2/3 of cartilage (deep zone) GNew collagen formation (polarized light microscopy, Picro Sirius Red stain)
		Cells: death, regeneration (clusters), hypertrophy, cartilage domains adjacent to fissures
Grade 4	Erosion	Cartilage matrix loss: delamination of superficial layer, transitional zone cyst formation
		Excavation: matrix loss superficial and transitional zones
Grade 5	Denudation	Surface: sclerotic bone or reparative tissue including fibrocartilage within denuded surface. Microfracture with repair limited to bone surface
Grade 6	Deformation	Bone remodeling (more than osteophyte formation only) including microfracture with fibrocartilaginous and osseous repair extending above the previous surface

Table 1.
A cartilage histopathology grading methodology.

2.2.3 Changes that occur in the synovium

Four patterns have been described in OA-related synovial pathology, which are hyperplastic, inflammatory, fibrotic and detritic patterns. Hyperplastic pattern is the most common manifestation in all stages of OA. Hyperplastic pattern is considered as an early OA finding in its isolated form. Inflammatory pattern is seen equally in both the early and late stages of OA. Inflammatory cell density in the inflammatory pattern is not as much as it is in rheumatoid arthritis. Fibrotic pattern is characterized by capsular fibrosis reflecting late-stage OA. Detrital pattern is characterized by macromolecular cartilages and debris within the synovium, and reflects late-stage OA [14].

2.2.4 Changes that occur in the meniscus

The changes that occur in the meniscus in connection with OA are first observed in the medial part of the meniscus. Meniscal tears are both a cause and effect of OA. Meniscal tears further increase the matrix degeneration through the inflammatory mediators which emerge as a result of the damage to the meniscus and may lead to the development of OA [15]. The regeneration capacity of the meniscus is limited. The red zone of the meniscus, which is peripherally located, is the area with the best blood supply and the best regeneration capacity, whereas the white zone of the

meniscus, which is more centrally located, is largely avascular and its regeneration is very slow and inadequate [16].

2.3 Etiopathogenesis of osteoarthritis

OA refers to a dynamic process, which is triggered by various biochemical and mechanical factors and in which destruction and regeneration both take place. In the past, OA was thought to be a degenerative joint disease that emerged with aging. Yet, it is known today that various factors such as biomechanical factors, proinflammatory mediators and proteases play a role in the pathogenesis of OA [17]. The release of biomarkers indicates that the findings that emerge in the earliest detectable stage of knee OA are bone and cartilage metabolisms that are impaired as a result inflammation [18].

2.3.1 Factors involved in the etiopathogenesis of osteoarthritis

2.3.1.1 Inflammation

The number of proinflammatory mediators included in the synovial fluid and tissue and which play a role in OA and is increasing by the day. Early studies on OA were focused on interleukin-1 (IL1), which stimulates cartilage catabolic activity. Nevertheless, the role of IL1 in OA has been questioned over the years, since the IL1 levels in OA joints are much lower than the levels that cause cartilage deterioration. It has been shown in the relevant clinical studies that the inhibition of IL1 in knee [19] and hand OA [20] have not improved the structure and symptoms of the disease.

Cytokines such as IL6, interferon-gamma inducible-protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) and monokine induced by gamma interferon (MIG) were found to be more abundant in OA synovial fluid than IL1 or TNF-α [21]. This finding suggests that these proinflammatory cytokines play a role in inflammation. It has been demonstrated in experimental animal models that there may be a relationship between IL-6 level and increased cartilage loss. The results of all these studies support the hypothesis that IL-6, as a regulatory cytokine, plays a role in the development of OA [22]. Other cytokines and chemokines involved in cartilage degeneration caused by inhibition of the anabolic process and induction of the catabolic process are IL-7, IL-15, IL-17, IL-18, oncostatin M (OSM), growth related oncogene-alpha (GRO-alpha), chemokine (C-C motif) ligand 19 (CCL19) and macrophage inflammatory protein-1beta (MIP-1beta) [23].

It was demonstrated in some studies that there is complement activity in OA joints. In one of these studies, which was conducted on mice, it was demonstrated that complement activation was inhibited by gene deletion or pharmacological modulation and that, as a result of this inhibition, the joint is protected from surgery-induced OA [24].

Adipokines secreted by adipose tissue cause cartilage damage by activating the inflammatory cytokines along with the matrix metalloproteinases (MMPs) triggered by the inflammatory cytokines. These adipokines include leptin, adiponectin, visfatin and resistin [25].

Prostaglandin E2 (PGE-2) has been shown to inhibit proteoglycan synthesis and increase matrix degradation. Additionally, it was shown that patients with OA have high levels of PGE-2 in cartilage [26]. Furthermore, leukotriene B4, a strong leukocyte chemotaxis, has been shown to stimulate proinflammatory cytokines in human synovial fluid samples [27].

2.3.1.2 Proteases

Proteases are mediators that play a primary role in the catabolic process of OA. There are several proteases that have a role in the pathogenesis of OA. These proteases are collagenase-containing matrix metalloproteinases, cathepsin K-containing proteases, and serine-containing proteases. As the proteases degrade collagen, the related catabolic process results in the progression of matrix loss, since the cartilage's response to damaged matrix repair is limited [28].

'Agreccan', the largest proteoglycan, provides cartilage elasticity. The ADAMTS family of enzymes, also called aggrecanases (ADAMTS-4-5), is involved in the early stage of OA degeneration and is responsible for aggrecan degradation [28].

Type-2 collagen, the most abundant type of collagen found in the cartilage tissue, provides cartilage tensile strength. It is broken down by collagenase-containing matrix metalloproteinases. MMP13 is considered to be the main collagenase responsible for cartilage destruction in OA [28].

Aggrecanase-2 (ADAMTS-5) and MMP-13 have an important place in the pathogenesis of OA. The development of specific inhibitors to these proteases in the context of the development of potential modifying treatments for OA has been of interest [29].

2.3.1.3 Molecular patterns associated with cartilage damage

Damage-associated molecular patterns (DAMPs) are molecules released from the chondrocytes in the damaged cartilage. DAMPs include extracellular matrix proteins, high mobility group box 1 protein (HMGB1), advanced glycation end products (AGEs) and receptor for advanced glycation endproducts (RAGEs), and alarmins [S100 calcium-binding protein A8 (S100A8) and S100 calcium-binding protein A9 (S100A9)].

It has been demonstrated that DAMPs have important roles in the pathogenesis of OA. DAMPs activate intercellular signaling pathways such as RAGE, toll-like receptors (TLR) and mitogen-activated protein kinases (MAPKs), thereby inducing the expression of catabolic proteases and inflammation-related genes [30]. DAMPs give rise to the increase in MMPs and activated macrophages which in turn lead to chondrocyte apoptosis and cause damage to the extracellular matrix (ECM) and cartilage [31, 32].

Fragmented matrix proteins such as cartilage oligomeric matrix protein (COMP), fibromodulin, proteoglycan, collagen, tenascin C, fibronectin, biglycan and aggregate are released from the damaged matrix. These fragmented matrix proteins stimulate the immune response. Consequentially, TLR and integrin are activated and the upregulation of the degenerative pathway is achieved [23, 33–35].

RAGE is a member of the immunoglobulin family. It is expressed in chondrocytes and macrophages. RAGE has been demonstrated to increase in OA joints. This increase causes the production of MMPs, which play a direct role in the pathogenesis of OA [36].

Alarmins are intracellular proteins secreted from bone cartilage or synovium in OA. It is an important member of DAMP family that has a role in the pathogenesis of OA [33].

HMGB1 is a nonhistone nuclear protein. Its release from the nucleus is associated with the apoptosis or necrosis or inflammatory stimulation of cells [37]. A significant increase occurs in the secretion of proinflammatory cytokines, chemokines and MMPs with the increase in HMGB1 secretion [38].

S100A8 and S100A9 are secreted from granulocytes, macrophages and monocytes. There is evidence that these proteins play a role in the cartilage damage and

OA progression [39]. In addition to their catabolic effect, S100A8 and S100A9 lead to the formation of bone/osteophyte [40].

It has been demonstrated in the literature that the basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals, from among the inorganic calcium crystals, accumulate in the synovial fluid [41]. Calcium-containing crystals trigger the inflammatory process by either directly stimulating the chondrocytes or indirectly stimulating the immune system [30]. Additionally, it has been reported in the literature that monosodium urate crystals also trigger inflammation and cause cartilage damage [42].

2.3.1.4 Free oxygen radicals

The amount of free oxygen radicals and the extent of the DNA damage they cause are higher in OA cartilages than in cartilages without OA. Free oxygen radicals have an important place in OA progression, since they increase the synovial inflammation and cartilage destruction [43].

2.3.1.5 Biomechanical factors

Abnormal mechanical loading has an important role in the onset and progression of OA [44]. Abnormal mechanical loading may be caused by various factors such as obesity, joint alignment disorders or joint instability. Abnormal mechanical loading leads to mechanical damage in the joint and result in an increase in the release of matrix-degrading enzymes. Cartilage destruction products trigger inflammation and damage to the joint cartilage occurs through cytokine activation.

2.4 Genetics of osteoarthritis

The molecular processes underlying OA, which have a complex etiology, have become clearer through genetic and epigenetic studies. OA has been categorized as early-onset OA and late-onset OA. Genetic factors are more prominent in the early-onset OA. Genetic studies on the early-onset OA will provide a better understanding of the etiopathogenesis of the disease.

Family and twin studies have been conducted to reveal the genetic factors in OA [45]. To give a few examples, in the family studies conducted by Kellgren in UK and US, it was determined that there is a genetic component of the hand and knee OA [46], whereas in the study conducted by Lanyon et al., it was shown that the risk of radiographic hip OA is higher in the siblings of the patients with advanced hip OA [47].

Studies, in which monozygotic (MZ) and dizygotic (DZ) twins were compared, have shown that genetic factors are effective in OA. In one of these studies, it was shown that genetic factors are 39–65% effective on hand and knee OA radiographs, independently of environmental and demographic factors [48]. In another study, knee OA progression was investigated in 114 MZ and 195 DZ female twin couples. Consequentially, a higher correlation was found in the MZ twins than in the DZ twins in terms of both osteophyte and joint space narrowing, and the heritability was calculated as 62% for osteophyte progression and 72% for joint space narrowing progression. Additionally, it has been reported that the genetic effect on knee OA progression is more prominent in the medial compartment [49]. Furthermore, it has also been reported that the genetic effect differs according to the affected area in OA. Accordingly, the heritability was reported as 40%, 60%, 65% and 70% in the knee, hip, hand and spine regions, respectively [48].

Candidate gene studies have focused on many gene groups such as cartilage structural genes [collagen type II alpha 1 (COL2A1), collagen type IX alpha 3 (COL9A3), collagen type XI alpha 1 (COL11A1)], genes associated with bone mineral density (BMD) [vitamin D receptor (VDR), estrogen receptor 1 (ESR1)], genes associated with chondrocyte cell signal transduction (bone morphogenetic protein 5 (BMP5), frizzled-related protein B (FRZB), interleukin-4 receptor alpha (IL-4Rα)], inflammatory cytokine genes (IL-1, IL-10, TGFβ1, IL-6, TNFα) [50].

The finding that VDR gene polymorphism is associated with BMD lead to the studies on the possible relationship of VDR gene polymorphism with OA [51]. In this context, it was shown in a study conducted on 543 women in Finland that VDR polymorphism plays a role in the etiology of symmetrical hand OA [52].

The prevalence of knee OA is significantly higher in women than in men. This difference was atrributed to the estrogen receptor α (ERα), which is encoded by ESR1. Several polymorphisms in ESR1 [PvuII (rs2234693) and BtgI (rs2228480)] have been confirmed as risk factors for OA [53].

FRZB is a glycoprotein and plays a role in chondrocyte maturation and bone development. In Rotterdam and Genetics, Osteoarthritis and Progression (GARP) studies, R324G single nucleotide polymorphism (SNP) of the FRZB gene was found to be associated with generalized OA, whereas rs7775 and rs2888326 SNPs were found to be associated with knee and hip OA [50]. BMPs are bone-derived factors that can induce new bone formation. In a study conducted by Sharma et al. on BMP5 gene, rs1470527 and rs9382564 polymorphisms were shown to be significantly associated with knee OA [54].

The hypothesis put forward in candidate gene studies is still being investigated in terms of the genetic variant. Researchers favor genome-wide association studies (GWAS), which is a hypothesis-free approach, in the event that they think that candidate gene studies do not contribute much to the etiopathogenesis of the disease. GWAS allows the identification of genetic loci and the discovery of new genetic variants. In this context, GWAS contributes to the discovery of prognostic biomarkers that can contribute to early diagnosis and the identification of new areas that can be targeted by medical treatments [55–58]. The number of OA genetic risk loci, most of which have small effect sizes, has increased to 90 in the GWAS studies carried out up till 2019 [59]. 56 new loci were identified in the two major OA analyzes published recently [59, 60]. First of these two studies, that is the deCODE (Decode Genetics, Iceland)-UKBB (UK Biobank, England) study, was conducted with more than 650,000 British and Icelandic citizens. 11.6 million genotype variants were examined within the scope of the said study, and 23 significant variants were detected in 22 loci [60]. Second of these studies, that is the Arthritis Research UK Osteoarthritis Genetics (arcOGEN)-UKBB study, was conducted with more than 455,000 British citizens. 17.5 million genotype variants were examined within the scope of the said study, and 65 significant variants were detected in 64 loci [61]. These studies, which were conducted via performing separate meta-analyses for the hip and knee OAs, are the largest OA GWAS studies published to date (**Figure 1**) [59].

Genetic variations are grouped into single nucleotide substitutions (mutations and single nucleotide polymorphisms (SNPs)], insertions and deletions, copy number variations or short tandem repeats [62]. Variations in the genome underlie the differences between the individuals. The most common of these variations are SNPs. SNPs are considered to be associated with susceptibility to diseases [63]. The majority of the common diseases that give rise to SNPs, including OA, are considered to affect the transcription of nearby genes by altering the transcription factor binding [59].

Epigenetics plays an important role in the regulation of gene expression and is associated with the pathogenesis of a number of human diseases. The term

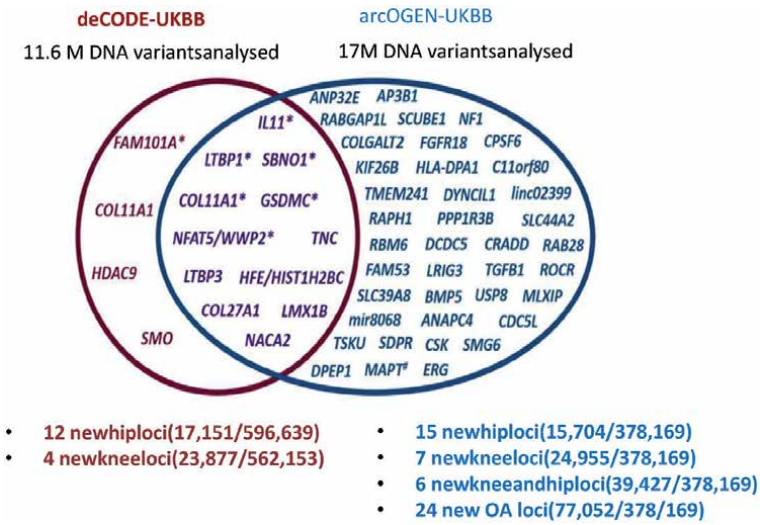

Figure 1.
The new OA risk loci identified in either or/both of the deCODE-UKBB and arcOGEN-UKBB studies.

epigenetics encompasses DNA and chromatin modifications and the functions related thereto, in addition to non-coding RNAs (ncRNAs). Epigenetic control of gene expression is necessary and essential for typical organism development and cell control [63]. Epigenetic changes are transmissible and reversible changes that do not change the nucleotide sequence but cause changes in gene expression [64]. Changes that occur within the gene itself cause structural changes in some synthesized proteins. These changes lead up to early onset-OA. Given the above considerations, epigenetics is a very important area in the diagnosis, prognosis and treatment of OA [63]. Three different epigenetic regulation are involved in the molecular pathogenesis of OA. These include DNA methylation, expression of non-coding RNAs [ncRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs)], histone modifications that regulate gene expression at transcriptional and/or post-transcriptional levels [65]. DNA methylation is the most studied epigenetic control mechanism. 5-methylcytosine is formed as a result of the addition of a methyl group to the 5′ position of cytosine in the CpG dinucleotide by DNA methyltransferase [DNA Mtase (DNMT)]. Methylation at gene promoter regions is associated with suppression of gene expression. On the other hand, methylation within the gene bodies is associated with increased gene expression [66, 67]. The candidate gene study conducted to examine DNA methylation of matrix-degrading proteases such as MMP3, MMP9, MMP13 and ADAMTS4 was the first study to describe the possible effect of DNA methylation in OA. In the said study, hypomethylation was demonstrated in the promoter regions of selected catabolic genes in OA chondrocytes, and it was found that this hypomethylation was associated with increased expression of the gene [68].

miRNAs are small ncRNAs, which consist of 19 to 25 nucleotides and function at the post-transcriptional level by binding and repressing the expression of specific mRNA targets. miRNAs are involved in different cellular pathways and play a role in OA and in maintaining cartilage homeostasis [69]. Despite the constantly increasing number of publications and miRs related to the pathogenesis of OA, there is still no miR biomarker, which has been validated for use in the early diagnosis of the disease. This has been atrributed in part to the fact that OA is a multifactorial heterogeneous disease [63].

lncRNAs are large RNA molecules comprising more than 200 nucleotides. Deregulated expression of lncRNAs plays an important role in inflammatory diseases. lncRNAs have been shown to be associated with OA progression and cartilage degeneration [70]. LncRNAs regulate gene expression at the post-transcriptional level via micro-RNAs and modulate transcriptional gene silencing through chromatin regulation [71].

2.5 New treatments and future in osteoarthritis

Since chronic low-severity inflammation is involved in OA, the development of drugs that act on pro-inflammatory cytokines has also become a new hope in the treatment of OA [72]. In a study, an intra-articular (IA) IL-1 receptor antagonist (IL-1Ra) was applied to the canine knee and it was reported that it reduced the number and size of osteophytes in the femoral condyle in the follow-ups [73]. However, in another study, anakinra, which is IL-1Ra, was applied IA to the knees of patients with OA. In this randomized controlled trial, they found no superior effect to placebo on pain and WOMAC scores [74].

It has been reported that the serum TNF levels of patients with OA are elevated. The positive results obtained with the use of TNF-α inhibitors especially in erosive hand osteoarthritis are promising. In the study of Magnano et al., 12 patients with erosive hand OA were treated with adalimumab (ADA) and reported a significant improvement in symptoms after 3 months [75].

Proteases are mediators that play a primary role in the catabolic process of OA. 'Agreccan', the largest proteoglycan, provides cartilage elasticity. The ADAMTS family of enzymes, also called aggrecanases (ADAMTS-4-5), is involved in the early stage of OA degeneration and is responsible for aggrecan degradation [28]. Preclinical studies of the molecule GSK2394002, which effectively inhibits ADAMTS 4 and 5, were discontinued because serious cardiovascular side effects were encountered in animal experiments with systemic use [76]. However, phase II studies on 114810, an IA administration molecule developed to reduce systemic side effects, are ongoing [77].

OA is a dynamic process triggered by various biochemical and mechanical factors, where destruction and repair are together. The fibroblast growth factor 3 (FGF-3) family, especially FGF 18, has an anabolic effect on human chondrocytes [78]. In a study including 549 patients with stage 2 and 3 knee OA, FGF-18 (sprifermin) IA was administered. An increase in tibiofemoral joint cartilage thickness has been reported up to 12 months. In the light of this information, it can be said that Sprifermin is currently one of the promising candidates for disease-modifying OA drug (DMOAD) [79].

The mechanism of action of platelet-rich plasma (PRP) is suggested to be that bioactive growth factors released from α granules in platelets stimulate tissue healing at high concentrations. In a meta-analysis of 16 studies, 1543 patients were examined; PRP and IA hyaluronic acid (HA) were compared. In terms of pain and functionality, it was found to be more effective than intra-articular HA injection [80]. However, the 2019 OARSI guidelines state that there is low-level evidence of the use of PRP in patients with knee, hip, and polyarticular OA and should not be used [81]. Larger randomized controlled studies with long-term follow-up are needed to elucidate its effects on tissue regeneration and delaying surgery.

In the light of these, the aim of OA treatment is to prevent disease formation or to provide regeneration of damaged tissue rather than eliminating the symptom. It would be more logical for DMOADs to be developed in the future to target the early stages of disease pathogenesis. For this reason, randomized double-blind controlled studies will contribute to the development of OA treatment.

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Chapter 2

Pathogenic Role of microRNA in Rheumatoid Arthritis

JiuJie Yang, Jerome P.L. Ng, Kaixi Zhang, Liang Liu and Vincent Kam Wai Wong

Abstract

Rheumatoid arthritis (RA) being a chronic inflammatory disease can be affected by both genetic and environmental factors. Abnormal functioning of immune response is the main underlying cause of RA. A growing number of studies on related diseases uncovered that microRNA (miRNA) may influence the pathogenesis of RA, such as the promotion of proliferation of fibroblast-like synoviocytes and secretion of cytokines by highly expressed miRNAs. A large number of studies have reported the aberrant expressions of miRNAs during the entire phase of RA, from the preclinical to terminal stages. These dynamic changes can be potentially developed as a bio-marker for predicting the risk, diagnosis and clinical management of RA. This chapter aims to summarize and discuss miRNAs' roles and mechanisms in the process of RA development, differential diagnosis from other diseases, clinical management and refractory RA. Therefore, miRNA demonstrates future perspectives of diagnosis and treatment of clinical RA under the support of newly discovered theoretical basis.

Keywords: Rheumatoid arthritis, microRNA, bio-marker, diagnosis, refractory rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease, which causes joint deformity and disability in patients. RA can occur at any age, particularly with a high incidence in women aged 30–50 [1]. It has been shown that the average lifespan of RA patients is 3 to 18 years shorter than that of healthy people [2]. Patients with RA have high mortality rate and extra-articular complications, such as cardiovascular diseases, becoming the greatest challenge [2]. Proliferation of synovial tissue, infiltration of inflammatory factors, imbalance of immunity system, and destructions of bone and cartilage are the main common pathological characteristics of RA [3]. However, the current understanding of RA etiology and pathology are far yet to be elucidated. Some opinions on RA etiology illustrated high risk factors including but not limited to gene background, gender difference, smoking, obesity and environment factors. During the last decade, a growing number of evidence has shown that the epigenetic mechanism of microRNA (miRNA) regulation contributes remarkably to RA pathogenesis.

MiRNAs belong to the non-coding RNA family, with about 22 nucleotides in length. The processes of miRNAs biogenesis and maturation take place in the nucleus.

The transcription of primary miRNAs (pri-miRNAs) from DNA molecule is the first step. After the recognition of these pri-miRNAs by an enzyme-protein complex, they are cleaved into precursor miRNAs (pre-miRNAs) with 70–100 nucleotides in length. Subsequently, the pre-miRNAs mature in the cytoplasm. Mature miRNAs finally regulate the post-transcriptional gene expression by binding to 3′-untranstaled region (3'UTR) of target mRNAs. Interestingly, the same gene can be modulated by multiple miRNAs, which collectively fine tune the expression of a certain gene. One-third of human genes of note is regulated by miRNA [4]. In addition, miRNAs participate the regulation of cell bio-behaviors, such as apoptosis, proliferation and invasion. Cytokine signaling is commonly known to regulate immune system, which is associated with the pathogenesis of RA. A large number of evidence showed that miRNAs participate in regulations of both innate and adaptive immunities by modulating cytokine signaling [5], such as the upregulations of miR-146 and miR-155 in LPS-mediated innate immune response. Besides, a high expression level of miR-155 during thymic differentiation can increase Treg sensitivity to IL-2 and growth factors [6]. Given their important roles in cell regulation mechanisms and immunity responses, miRNAs have been frequently studied as potential bio-markers in diagnosis, target treatment, activity monitoring and therapy for RA disease. For example, during the early stages of undifferentiated arthritis, a high expression level of miR-483 was only found in patients who finally developed RA. In this chapter, we aim to review the different roles of miRNAs in RA, from the pathogenesis to clinical impact.

2. The functions of miRNA in RA development

Studies showed that synovial hyperplasia is a main pathological feature of RA, but the pathogenesis of RA is not fully elucidated. Fibroblast-like synoviocyte (FLS) is a major cell type found in the structure of synovial intima [7]. The most important step in the development of RA is the transformation of FLS by over-activation to RAFLS [8]. This process makes RA to present a characteristic, aggressive, and active clinical phenotype. It has been reported that RAFLS can recruit inflammatory cells through autocrine and paracrine methods to maintain the inflammatory state [7]. At the same time, compared with FLS, RAFLS has the characteristics of anti-apoptosis, predominant cell proliferation, invasion and metastasis. It also secretes inflammatory factors and promotes erosion of bone matrix (e.g. matrix metalloproteinases, MMPs). These secreted cytokines form a complex network system that affects each other, leading to an imbalance between synovial cell proliferation and apoptosis. This process therefore plays an important role in the progression of RA disease. Controlling the local proliferation of synovial cells and inducing their apoptosis are the key towards improvement of RA prognosis. Recent results showed that the activated phenotype of RAFLS is underpinned by epigenetic mechanisms—DNA methylation, histone modifications, and miRNA activity [9]. Newly emerging evidence suggested that dysregulated miRNA expressions in RA synovial tissues, especially in RAFLS, may generally contribute to the molecular mechanism of disease. Comparing miRNAs expression in FLS between RA and osteoarthritis (OA) patients, miR-124a was only down-regulated in RAFLS [10]. Further experiments revealed that overexpression of miR-124a can to suppress RAFLS proliferation. In contrast to miR-124a, miR-203 was up-regulated in RAFLS compared with healthy FLS [11, 12]. Importantly, a high level of miR-203 can target NF-κB signaling pathway, promote IL-6 and MMPs secretions, and support RAFLS invasion and migration [12]. Besides, there are lots of miRNAs like miR-126 [13], miR-152 [14], miR-137 [15], miR-199a-3p [16] and miR-338-5p [17], controlling the development of RA via regulating RAFLS.

RA is a well-known autoimmune disease, and both innate and adaptive immunities are the crucial steps for RA development. The role of miRNAs in regulating immune response has been reported in the literature. Alternations of miRNAs level can control the differentiation and immunological functions of various immune cells (monocytes, macrophages, and T cells) [18]. Many changes of miRNAs in these cells in RA patients have been reported. Chronically activated T cells are considered to be the trigger and key to RA. They are also the crucial link in inducing and aggravating RA immunological inflammatory response. On the one hand, they can induce activation of synovial macrophages and RAFLS. On the other hand, they contribute to T-Treg imbalance, which is a predominant mechanism of RA. A great number of studies have confirmed that there are various miRNA expressions modulating T cells, such as miR-17 [19] and miR-146a [20]. Additionally, RA patients showed the increases of miR-16, miR-103a, and miR-222 in peripheral blood mononuclear cells (PBMCs) of RA patients, which promoted cytokine secretion and disturb T-Treg balance [20]. The main miRNAs changes in different cells of patients compared with healthy controls were summarized in **Table 1**.

miRNA	Regulation	Sample	Target	Effects	Ref.
miR-203	↑	RAFLS	NF-κB pathway	IL-6↑, MMPs↑	[12]
miR-126	↑	RAFLS	PI3K/AKT pathway	proliferation↑, apoptosis↓	[13]
miR-338-5p	↑	RAFLS	NFAT5	proliferation↑, invasion↑, migration↑	[17]
miR-155	↑	RAFLS	JAK2/ATST3	IL-6 mediated inflammation↓, invasion↓, proliferation↓, MMPs↓	[21, 22]
		Synovial tissue	FOXO3a	IL-1β↑, IL-6↑,TNF-α↑, RAFLS proliferation ↑	[23]
miR-125b	↑	Synovial tissue	NF-κB pathway	NF-κB mediated inflammation↑	[24]
miR-301a	↑	PBMCs	PIAS3	Th17 differentiation↑, cytokines↑	[25]
miR-124a	↓	RAFLS	CDK2,MCP1	proliferation ↑, chemotaxis↑	[10, 11]
miR-199a-3p	↓	RAFLS	RB1	proliferation↑, apoptosis↓	[16]
miR-152	↓	RAFLS	ADAM10	proliferation↑, apoptosis↓	[26]
miR-137	↓	RAFLS	CXCL12	proliferation↑, migration↑, pro-inflammatory cytokines↑	[27]
miR-22	↓	Synovial tissue	SIRT1	proliferation↑, proinflammatory cytokine↑	[28]
miR-192	↓	RAFLS	Caveolin 1	proliferation↑, apoptosis↓	[29]
miR-21	↓	PBMCs	STAT3	Th17↑, Treg↓	[30]
miR-548a	↓	PBMCs	TLR-4/NF-κB	NF-κB mediated inflammation↑	[31]

Table 1.
Changes in miRNA level in RA patients compared to healthy individuals.

Having a clear understanding of miRNAs in the regulation of RA pathogenesis provides a new direction and strategy for RA treatment. In some animal models, miRNA mimics or silencers were used to regulate miRNAs expressions, thereby reversing the inflammatory reaction or joint damage. One example is the amelioration of arthritis severity by reducing RAFLS's population via intra-articular injections of miR-124 and miR-140 mimics [32, 33]. Furthermore, intra-peritoneal injection of miR-223 silencer showed the same effect on relieving arthritis severity [34]. In a CIA mice model, intravenous administrations of miR-146a [35] and miR-708-5p [36] mimics were beneficial to prevent synovial hyperplasia and structural joint damage. Taken together, further investigations on the role of miRNAs in the pathogenesis of RA are of utmost importance for the treatment and delaying progression of RA, as well as developing novel targeted drugs.

3. MiRNA as a potential bio-marker in RA diagnosis

RA often begins insidiously with chronic developments of signs and symptoms, which may vary in intensity over many weeks. For most patients with new-onset RA, there is no obvious symptom in the early stage. Most of them show joint discomfort, which is difficult to distinguish RA from other diseases. In clinical practice, using rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibodies as diagnostic indicators are not sufficient [37]. Notably, the sensitivity and specificity of CCP antibodies in RA diagnosis were ~72% and ~92% respectively [38]. In some special cases, the CCP antibodies' titers cannot reach the diagnostic thresholds. Moreover, genetic and environmental risk factors, together with systemic immunization, affect the multi-stage development of RA. Identifying patients with RA and providing them a proper treatment can prevent 90% of patients in early-stage period from the progression of joint damage, and improve prognosis [39]. Therefore, there is an urgent need for identifying novel bio-markers to screen high-risk individuals and those with early stage of RA.

Single nucleotide polymorphism (SNP) variants residing within boundaries of genes encoding miRNAs is a common phenomenon, which may affect multiple major human disorders including RA [40]. The associations between miRNA-linked SNP and RA susceptibility have been studied extensively, such as rs11761231 in miR612, rs615672 in miR-541, rs2837960 in miR-509/602, rs6684865 in miR-181, rs9550642 in miR-1238 and rs6920220 in miR-519 [41]. Furthermore, the association of variations of miRNA target genes with RA was exemplified by the discovery of SNP rs3027898 variant in miR-146a target gene, IL-1 receptorassociated kinase (IRAK-1), in RA patients. Collectively, the alterations of miRNA gene and its target gene may increase the risk of developing RA.

The current understanding of the role of miRNAs in RA pathogenesis is limited, especially in the preclinical phase of RA. Some serum miRNA expression profiles from different people were evaluated to determine mechanisms underpinning the progression of RA onset in at-risk individuals. Among those miRNA expressions, only miR-103a-3p specifically increased in both RA patients and their seropositive first-degree relatives [42]. Patients who have symptoms of non-differential arthritis and a high serum miR-22 expression, finally developed RA [20]. Recently, a study examined circulatory miRNAs in RA patients, and further investigations illustrated that miR-221-3p, let-7d-5p, miR-431-3p, miR-130a-3p, miR-126-3p and miR-24-3p were significantly elevated in subjects "at risk" of developing RA [42]. Particularly, the elevated whole blood level of miR-103a-3p may become a powerful bio-marker for positive anti-citrullinated peptide antibodies (ACPA) individuals who have possibility to develop RA [42].

Early stage RA (ERA) is defined as a disease duration less than 12 months. Several clinical studies have shown that ERA is a "window of opportunity" for disease-modifying anti-rheumatic drug (DMARD) therapy. Most patients at this stage will get long-term remissions or even complete remissions after systematic treatments. There are no golden diagnostic criteria in ERA to date, although this stage is important in clinical practice. During the last decade, multiple studies have demonstrated miRNA as a powerful tool for identifying molecular bio-markers for diagnosis in ERA. One highlight example is the analysis of highly expressed miR-22 level for distinguishing ERA patients from healthy individuals. Besides, miR-16, miR-146a, miR-223 and miRNA-155 were significantly down-regulated in ERA, and even lowered in established RA and healthy controls [43–45]. Generally, these miRNAs possibly improve early diagnosis of RA, especially in sero-negative patients.

RA diagnosis not only distinguishes the different phases of RA, but also differentiates RA from other diseases, such as systemic lupus erythematousus (SLE), OA, multiple sclerosis (MS). Those diseases show similar symptoms to RA at the beginning. Several studies have established analyses of different expressions of miRNAs among those indistinguishable diseases. Compared with healthy people, miR-146a and miR-155 were up-regulated in PBMCs of RA cases, and conversely, they had low expressions in PBMCs of SLE patients. In addition, miRNA-516a-3p, miRNA-629 and miRNA-525-5p levels in PBMCs were significantly up-regulated in active SLE patients compared with those in healthy controls [46], but all these miRNAs have no specific expressions in RA patients. A recent study revealed that the expressions of miR-371b-5p and miR-5100 also increased notably in the serum of SLE compared with healthy control and RA [47]. Further results revealed that miRNA-346 in synovial tissues was only specifically elevated in RA [48]. Another seven miRNAs expressions in macrophages from patients with active RA and OA were also recently determined. MiR-99a, miR-100, miR-125b, miR-199-3p, miR-199-5p, miR-152 and miR-214 were down-regulated in macrophages in RA, while only miR-223 was up-regulated, compared with OA samples [49]. One more example is that the expression level of miR-34a-3p in RAFLS was generally lower than that in OAFLS [50].

Clearly, the observable changes in miRNAs and their molecular networks are of great values for determining new mechanisms related to the onset of RA, and also being used as bio-markers to predict the onset of preclinical RA and distinguish RA from other diseases.

4. The application values of miRNAs in RA clinical management

4.1 MiRNAs' functions in activity monitoring of RA

The clinical management strategy of RA is "treat-to-target" [51]. In other words, patients can achieve remission or at least low disease activity state within 6 months after effective treatment. If RA is insufficiently treated, extra-articular manifestations, such as the most frequently occurring rheumatoid nodules and even cardiovascular disease, may occur. Notably, this kind of cardiovascular disease is more closely associated with RA disease activity rather than traditional cardiovascular risk factors. Furthermore, either manifestation of RA or complication of RA therapies (e.g. MTX and leflunomide) may lead to interstitial lung disease (ILD). This affirms the importance of activity monitoring from different aspects. Hence, it is necessary to develop new treatment strategies to retard RA progression by quick identification of conditions of RA remission before irreversible damage in joint

[39]. Currently, clinical indicators for RA activity monitoring are mainly based on clinical, laboratory and physical examinations, including simplified disease activity index (SDAI), disease activity score 28 (DAS28), erythrocyte sedimentation rate (ESR), C reaction protein (CRP) [52]. These indicators can be affected by subjective and objective factors, such as OA, fibromyalgia, and assessor's experience. Both ESR and CRP are non-specific markers of inflammation, which are commonly affected by age, anemia, immunoglobulin and other factors. Therefore, these markers are not specific enough to RA patients. In view of the clinical demands, it is particularly important to develop effective, precise and accurate biological markers for the evaluation of RA disease activity. Recent studies demonstrated that miRNA, a potential bio-marker, can be aberrantly expressed in different stages of RA progression, and thus allowing to monitor disease activity.

The correlations of miRNA levels (miR-125b, miR-21, miR-155, miR-346, miR-223 and miR-146a) in PBMC of RA patients with clinical characteristics and inflammation markers in RA patients were reported [53]. The expression levels of miR-146a and miR-155 were positively related to ESR, DAS28-CPR and cytokines (IL-1β, IL-17α, IL-6 and TNF-α). On the contrary, miR-21 was negatively related to DAS28 and those cytokines. Another study found that miR-125b was inversely correlated with RA activity [54]. The studies on miR-24 in patients' serum with active RA disease uncovered that the miR-24 level increased with ESR and the DAS28 [55]. Besides, miR-5571-3p and miR-135b-5p levels were found to be positively correlated with the disease activity and the inflammation level of RA [56]. Notably, the upregulated expressions of hsa-miR-432-5p and especially hsa-miR-194-5p in serum were associated with relapse in RA patients [57]. Increasing serum level of miR-223 was also found in remission patients several days before RA relapse [20]. Moreover, blood samples from 76 RA patients illustrated that lowering the levels of miR-548a-3p can promote RA relapse or increase disease activity [31]. In some cases, RA patients without proper treatment were accompanied by extra-articular symptoms, together with changes in some miRNAs levels. Analyzing abnormal expressions of miRNAs can assist in diagnosis of RA-related diseases. For example, some researchers collected miRNAs (e.g. let-7c-5p, miR-30a-5p, miR-30e-5p, miR-125a-5p, miR-126-3p, miR-126-5p, miR-425-5p, miR-3168, and miR-4446-3p) in a panel to predict cardiovascular disease in patients with RA [58]. Other findings found that differences in circulating miR-200c levels can distinguish RA patients with and without ILD [59]. More examples of the relationship between miRNAs expression and RA activity were shown in **Table 2**.

4.2 MiRNAs as potential bio-markers of therapeutic effectiveness

Despite the great progress of management of RA over the past three decades, anti-rheumatoid drugs (DMARDs), including conventional synthetic DMARDs (csDMARDs) and specific targeted DMARDs (e.g. biologic DMARDs, b-DMARDs, and targeted synthetic DMARDs, tsDMARDs), are still the first-line drugs for RA patients; however, a certain number of patients does not benefit from the treatments with multiple DMARDs [65]. For those patients, biological treatments targeting inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (ILs), and B or T cells may give a better outcome [66–69]. Nevertheless, ~20–30% of patients fail to respond to these biological agents. Therefore, it is necessary to explore novel bio-markers for predicting the clinical responses of RA patients to DMARDs or other therapies. The current indicators for assessing the therapeutic effectiveness involve inflammatory factors, disease activity and patient response outcome (PRO) [70]. These evaluation indicators, however, are easily affected by many factors, resulting in certain deviations. Emerging research showed

miRNA	Correlation with RA activity	References
miR-146a	Positive	[60]
miR-155	Positive	[60]
miR-132	Positive	[60]
miR-21	Positive	[61]
miR-5571-3p	Positive	[56]
miR-135b-5p	Positive	[56]
miR-432-5p	Positive	[57]
miR-194-5p	Positive	[57]
miR-223	Positive	[62]
miR-206	Positive	[63]
miR-125b	Negative	[54]
miR-548a	Negative	[31]
miR-16	Negative	[62]
Let-7a	Negative	[64]

Table 2.
The relationship between miRNAs expression and RA activity.

that the prediction of RA treatment was possibly achieved by monitoring the alterations of miRNA levels. This encourages the development of novel therapeutic strategies for RA via identifying molecular mechanisms of miRNAs.

Several findings demonstrated that almost all miRNAs expressions were changed during therapy. Using MTX significantly decreased the expressions of miR-155 and miR-146a, but increased the expression of miR-34 in rat tibiotarsal tissues [71]. Clinical research proved that RA patients who responded to MTX had lower expressions of specific miRNAs, including not only hsa-miR-155-5p and hsa-miR-146a-5p, but also the newly reported hsa-miR-132-3p [60]. The circulating miR-10a in RA patients was markedly decreased, but was up-regulated when treated with MTX [72].

Although miR-223 and miR-16 were shown to be overexpressed in synovial tissues of RA patients, their expressions were decreased after treated with csDMARDs [62]. More importantly, disease severity was reduced when miR-223 was silenced in experimental arthritis [34]. Another finding demonstrated that miR-125b expression showed more alternations between patients in terms of good response and poor response [73]. Its expression was relatively low in patients with early RA, but increased markedly after 3 months of conventional therapy [54]. Thus, these miRNAs could become potential bio-markers in both csDMARD and bDMARD therapies.

Furthermore, some miRNAs were good candidates for predicting the treatment of RA with anti-TNF therapy. A placebo-controlled, double-blind and prospective study of patients with early RA showed that the highly expressed miR-886.3p in combination with lowly expressed miR-22 were associated with the probability of EULAR good response (~95%) [74]. This may indicate the responses of miR-22 and miR-886.3p to adalimumab treatment in RA. RA patients before TNF-α therapy showed a relatively higher miRNA-5196 expression than those treated with anti-TNF-α therapy and healthy controls [75]. Studies implied that an increase of miR-155 may result in the upregulation of membrane TNF expression on monocytes and the defect of monocyte capacity to differentiate into M2-like anti-inflammatory

macrophages, which were the clinical characteristics specific to RA. Notably, increased miR-155 could be partially reversed by monoclonal anti-TNF antibodies [76]. Besides, the expressions of miR-126, miR-148a, miR-29c, miR-30c, miR-17, miR-21, miR-223 and let-7b in neutrophil of RA patients were declined after treatment with anti-TNF-α drugs [77]. Obviously, these miRNAs could be the potential bio-markers for DMARDs therapy in RA.

Taken together, dynamic changes of miRNAs were not only associated with disease activity, but were also affected by therapeutic effects. This reflects the potential clinical values of miRNAs expression as novel prognostic markers for RA patients, in terms of RA management.

5. MiRNA in refractory rheumatoid arthritis

Most patients achieve remission or low disease activity state with effective therapies and treatment strategies. However, about 20–25% of the patients do not reach a state of low disease activity, and the causes of refractory rheumatoid arthritis (RRA) have not been identified. The RRA may attribute to the epigenetic changes accumulated by chronic RA. A large amount of evidence indicated that changes in miRNAs can occur either before or after treatment. Therefore, the alterations of miRNAs may affect the duration of RA or the therapeutic effect, leading to RRA. However, the mechanisms of miRNAs mediating RRA are still largely unknown. Up to date, the mechanism of miRNA on RRA has been known to be related to the regulation of drug efflux transporters, apoptosis and cell cycle modification. Notably, some somatic genes, such as p53, may also influence RA via miRNAs.

ATP-binding cassette (ABC) transporters are located in cell membrane responsible for transporting endogenous metabolites and xenobiotics across cell membranes in an ATP-dependent manner [78]. The high expression levels of ABC transporters were commonly found in cells from the inflammatory area of refractory RA patients [79]. These abnormal expressions in RA patients subsequently increased drug efflux and caused patients a lower response to treatment. The reduction of therapeutic effect of MTX by increased expression of ABCB1 in RA patients is a distinguishable example [80]. Importantly, the MTX-treated group showed the ABCC1 expression in synovial tissues higher than the untreated group [81]. These studies corroborated that the increasing MTX resistance in RA patients may result from the upregulations of ABC transporters. Hence, declining ABC transporter expression provides a potential solution for reversing drug resistance in RA chemotherapy. One of the reasons for miRNAs being as potential therapeutic targets for chemoresistant cancers is their regulations on the expression of ABC transporter. Research in ovarian cancer demonstrated that miR-522 inhibited ABCB5 in HT29 colon cancer cells to reverse drug resistance to doxorubicin [82]. ABCG2-mediated drug resistance to 5-FU in colon cancer side population cells was overcome by overexpressed miR-34a via suppressing DLL1 expression [83]. Similarly, ABCB1 (P-gp) expression was downregulated by miR-491-3p via directly bound to the 3'-UTR of ABCB1 [84]. MiR-214-3p also acts as a tumor suppressor to inhibit chemoresistance in retinoblastoma by targeting ABCB1 [85]. MiR-1268a regulated ABCC1-mediated drug resistance to temozolomide in glioblastoma [86].

Based on the important role of RAFLS in RA development, most drugs achieve the remission of RA by controlling RAFLS-related activities. MiRNA has been considered as a potential reason for refractory RA owing to its important role in regulating RAFLS mechanisms. On the one side, miRNA promoted the secretion of pro-inflammatory cytokines or MMPs; and increased RAFLS proliferation, invasiveness, survival and anti-apoptosis. On the other side, they can regulate various

intracellular pathways in RAFLS, which commonly include Wnt, NF-κB, JAK/STAT and TLRs signaling pathways. For example, reduced miR-20a expression in RASFs activated the JAK-STAT3-mediated inflammation, and promoted cell proliferation and apoptosis-resistance [87]. The regulation of PI3K/AKT pathway by targeting PIK3R2 with miR-126 promoted RA synovial fibroblasts proliferation and apoptosis-resistance [88]. In a separate study, miR-650 was down-regulated in RA patients compared with patients with joint trauma undergoing joint replacement surgery [89]. Further study confirmed that miR-650 targeted AKT2 to promote FLS proliferation and migration, and reduce apoptosis. In another example, down-regulated miR-375 in an AIA rat model aggravated the inflammation of FLS through Wnt signal pathway [90]. Interestingly, the expression level of the same miRNA varied in different tissues, along with different functions. One example is miR-21, which increased significantly in a rat model of collagen-induced RA with the promotion of FLS proliferation via NF-kB pathway [91]. In contrast, the miR-21 level in RA patients was declined due to the participation in the imbalance of Th17 and Treg cells [92].

Generally, p53 being as a tumor suppressor regulates many signaling pathways like apoptosis, cell cycle, DNA repair, and cellular stress responses by modulating the expressions of miRNAs [93]. Since p53 plays important roles in inflammation, apoptosis, and cell proliferation, the p53 function lost by gain-of-function (GOF) mutation or its low expression influences RA pathogenesis. Similarly, GOF mutation of p53 can confer tumor cell oncogenic properties such as chemoresistance and invasion. According to statistical investigations, the mutation rate of p53 gene in RA patients was about 50% [94]. In particular, a pro-apoptotic molecule, p53-regulated apoptosis-inducing protein 1 (p53AIP1) was suppressed by p53 mutation (from arginine to glutamine at site 248) in RAFLS, leading to an anti-apoptotic effect [95]. However, the mechanisms of p53-mediated apoptosis resistance are yet to elucidate.

Typically, wild-type p53 regulates miRNAs to work. For instance, p53 controlled cell apoptosis through regulating miRNAs expressions (e.g. miR-34a, miR15a, and miR16–1) [93]. In RA patients, miR-15a and miR16–1 initiated anti-apoptosis by inhibiting anti-apoptotic molecule B cell lymphoma 2 (Bcl2) [96]. In addition, miR-34a expression in RA-FLSs was positively related to X-linked inhibitor of apoptosis protein (XIAP) expression which induced RAFLS anti-apoptosis [97]. Since p53 activates all the above-mentioned miRNAs, functionally defective p53 (p53 mutation) may influence RAFLS apoptosis resistance.

Cyr61, which is a secreted and cysteine-rich extracellular matrix (ECM) protein produced by RAFLS, is stimulated by IL-17 for FLS proliferation [98]. Over-expressed Cyr61 is an important mediator in a malicious cycle, where a high level of Cyr61 promotes RAFLS proliferation and Th17 cell differentiation [99]. Generally, wild-type p53 from RA patients promoted expression of miR-22 targeting the 3-UTR of Cyr61, leading to a decrease of Cyr61 expression [100]. However, functional defect of mut-p53 in RA synovial tissue was unable to activate miR-22 expression, causing abnormally high Cyr61 expression and, in turn, promoted RAFLS proliferation and IL-6 production [100]. Thus, a reduced miR-22 level in RA synovial tissue and the resulting RRA attributes to somatic mutations of p53.

MiR-155 is also an important regulator in the pathogenesis of RA. Highly expressed miR-155 in PBMCs of RA patients was positively related to inflammatory cytokine (e.g. TNF-α and IL-1β), RA activity laboratory indicators (CRP, ESR) levels and DAS28 respectively [101]. Recent study indicated that mut-p53 increased miR-155 expression in breast cancer, which accelerated cell proliferation, epithelial-mesenchymal-transition (EMT) and invasion [102]. This implied that p53 mutations may affect the process of RA via miR-155 as similar to breast cancer.

Overall, miRNAs are not only an independent factor that affects the refractory of RA, but also are an intermediate link of certain gene mutations related to RRA. This may provide a new direction for treating refractory RA or reversing miRNA-related apoptosis resistance.

6. Conclusions

MiRNA, a non-coding RNA, widely exists in tissue cells and body fluids. It is worth mentioning that the studies on miRNA in RA are still limited, but the results verify its important role in immune response regulation and sustained inflammatory response to date. SNPs in specific miRNA genes, such as miR-541, are related to the high risk of RA development. Moreover, most miRNAs in synovial tissues can influence the process of RA by regulating RAFLS proliferation, invasion and apoptosis via targeting inflammatory or immune signaling pathways like NF-κB and Wnt pathways. Current efforts have confirmed that the expression level and mechanism of the same miRNA varies in different tissues or cells from RA. For example, miR-21 level in PBMCs was declined to regulate Th-Treg balance by targeting STAT3, STAT5 and Foxp3, but that in RAFLS was overexpressed to promote proliferation of RAFLS through NF-κB signaling pathway. For clinical management, the dynamic change of miRNAs can be a bio-marker for monitoring disease activity and therapeutic response, as exemplified by the association of high miR-223 level with high disease activity and RA relapse. In addition, some miRNAs may play a crucial role in regulating refractory RA or drug-resistance RA.

Finally, an increasing extent of data demonstrates the importance of miRNAs to the regulation of the RA process, along with its potential developments in biomarker discovery and special targets for treatment. Hence, understanding miRNA analysis can be served as a diagnostic and/or prognostic tool in an array of inflammatory disorders, especially RA.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 3

Role of LncRNA in Rheumatoid Arthritis

Ayse Kocak

Abstract

Long non-coding RNAs (lncRNAs) are a class of non-coding RNA (ncRNA) molecules that do not have protein coding. They are ubiquitous in the process of transcription and gene regulation. lncRNAs regulation is correlated with many diseases. Rheumatoid arthritis (RA) is a chronic inflammatory disorder and this disease can affect especially joints. Nevertheless, in some patients, RA and inflammation can damage body parts such as the eyes, lungs, skin, heart, and blood vessels. Lots of lncRNAs were confirmed to be correlated with rheumatoid arthritis (RA) pathogenesis. Particularly GAPLINC, ZFAS1, PTGS2, and HOTAIR lncRNAs play a role in RA. This chapter will be explained and summarized the relationship between lncRNAs and RA.

Keywords: lncRNA, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease. It is associated with progressive joint destruction complications and decreased life expectancy [1]. RA's main clinical features are typically symmetrical polyarthritis with swelling, redness, and pain in the distal joint, particularly the small joints of the hands and feet [2]. Advances in understanding the pathogenesis of the disease, RA treatment greatly improved with an emphasis in the early stage. To our best knowledge, lots of laboratory tests used for RA generally include rheumatoid factor (RF), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and anti-cyclic peptide containing citrulline (anti-CCP) antibodies [3]. Nevertheless, RA pathogenesis is still unclear, but it is most likely related to the physiological structure of the joint and anatomy [4].

Long non-coding RNAs' (lncRNAs) lengths are greater than >200 nucleotides, which are subclassified into five categories that include the natural antisense lncRNAs according to their positions relative to protein-coding genes, long intergenic ncRNAs (lincRNAs), intronic lncRNAs, bidirectional lncRNAs, sense-overlapping lncRNAs [5, 6]. Referring to the GENCODE database (version 31), 17,904 lncRNA genes were identified in the human genome. lncRNAs play a role as critical regulators of cellular processes and disease stage or progression. lncRNAs have been studied in cancer [7, 8], innate and adaptive immunity [9], and inflammation [10]. Recently, studies of the role of lncRNA in RA pathogenesis are increased. Sequencing or microarray analyses revealed the expression profiles of lncRNAs in RA. The lncRNA expression profile in RA is different in various immune cell types such as B cells, natural killer (NK) cells, and T cells, indicating immune cell-type specificity of lncRNA expression. Identification of aberrantly expressed lncRNAs in RA and investigation of the underlying molecular mechanisms.

Emerging evidence suggests that lncRNAs are involved in the development of RA. Although numerous aberrant-expressing lncRNAs (HOTAIR, MALAT1, GAPLINC, PVT-1, LERFS, GAS5, DILC, NEAT-1, Lnc-p21, THRIL, RMRP, NTT, MEG3, Lnc-IL7R, ZFAS1, UCA1, C5T1LncRNA) have been reported in RA [11, 12], only a few of them are functionally determined. In this chapter, we summarize here the current findings of lncRNAs that may be involved in the pathogenesis of RA, aiming to encourage future research on this topic.

2. Long non-coding RNAs in RA

2.1 Long non-coding RNAs

LncRNAs play epigenetic regulation, cell cycle regulation, and cell differentiation and genetic roles [13] such as physiological and pathological and regulator process; also, lncRNAs are Central regulators of the immune response, but they are poorly conserved in species [14]. LncRNAs regulate the coding genes directly various molecular mechanisms [15]. LncRNAs expressed differentially and effects on immune cells in autoimmune diseases. The regulatory mechanism of lncRNAs is complex and needs to be investigated by more functional and mechanistic experiments. A group of lncRNAs is associated with clinical indicators such as CRP, ESR, serum proinflammatory cytokines, and DAS28, suggesting that lncRNAs may serve as biomarkers to monitor RA activity.

2.1.1 LncRNA HOTAIR

In RA patients, the expression of HOX transcript antisense RNA (HOTAIR), HOTAIR is decreased in fibroblast-like synoviocytes (FLSs), also HOTAIR suppresses the activation of MMP-2 and MMP-13. lncRNA HOTAIR, miR-138, and NF-kB axis have also been established in chondrocytes in RA, LncRNA HOTAIR may target miR-138 and inhibit the activation of NF-kB pathway [16], and the expression of HOTAIR increases in peripheral blood mononuclear cell and blood exosomes using lncRNA array analysis [17].

2.1.2 LncRNA MALAT1

In RA FLSs, MALAT1 plays a role regulation of cell proliferation and inflammation [18]. MALAT1 binds to the beta-catenin promoter in the WNT signaling pathway [19]. One group study suggests that MALAT1 plays a role in apoptosis proteins [19]. MALAT1 silencing suppressed Bax, and Bcl-2, caspase-3, caspase-9 in RA FLSs [19].

2.1.3 LncRNA GAPLINC

LncRNA long intergenic non-coding RNA (GAPLINC) may play act as a molecular sponge of miR-382-5p and miR-575. There is a negative correlation observed between the expression of GAPLINC and the miRNAs [20]. Also, GAPLINC may be a new therapeutic target for RA [21].

2.1.4 LncRNA PVT-1

Knockdown of plasmacytoma variant translocation 1 (PVT-1) in RA's FLSs suppresses the TNF-α and IL-1β pro-inflammatory cytokines [22]. In the same study,

PVT1 regulates inflammation and apoptosis in RA-FLSs through the Sirt6 demethylation. Furthermore, PVT-1 increase at synovial tissue of RA patients and RA model and PVT-1 bound to miR-543 positively regulated the expression of signal peptide-CUB-EGF-like containing protein 2 (SCUBE2) by inhibiting the miR-543, guide to FLSs inhibition of apoptosis and IL-1β secretion. Inhibition of PVT1 may be a new idea for the treatment of RA [23].

2.1.5 LncRNA LERFS

Lowly expressed in rheumatoid fibroblast-like synoviocytes (lncRNA LERFS) negatively regulated the invasion, proliferation, and migration of joint synovium by interacting with heterogeneous nuclear ribonucleoprotein Q (hnRNP Q) but in RA FLSs, LERFS is low expressed in RA FLSs and the reduced LERFS led to the reduction of LERFS-hnRNP Q complex [24]. In this study, LERFS regulates the expression and activity of CDC42, Rac1, RhoA and, probably by binding to the hnRNP Q complex.

2.1.6 LncRNA GAS5

In RA FLSs, LncRNA growth arrest-specific transcript 5 (GAS5) overexpression organizes cell apoptosis by activating cleaved caspase-9 and caspase-3 and inhibits PI3K/AKT signaling pathway [25, 26]. Also, GAS5 plays a role in the inflammatory response in RA. In synovial tissue and FLSs, GAS5 expression is decreased and expression of homeodomain-interacting protein kinase 2 (HIPK2) increases significantly and GAS5 reduced the level of TNF-α and IL-6 [27]. Also, overexpression of LncRNA GAS5 affects IL-18 levels, and IL-18 is downregulated by LncRNA GAS5 [28].

2.1.7 LncRNA DILC

DILC of plasma RA patients was downregulated, while IL-6 was upregulated and DILC level is negatively correlated with RA. DILC overexpression promoted the inhibition of IL-6 expression and FLSs apoptosis and in RA [29].

2.1.8 LncRNA NEAT-1

NEAT-1 is significantly upregulated in th17 cells differentiated CD44 cells from RA patients. Also, upregulation of NEAT-1 plays a role differentiation of CD4+ T cells into Th17 cells by regulating its downstream molecule STAT3 [30].

2.1.9 LncRNA Lnc-p21

In RA, Lnc-p21 expression is so low and can be renovated by the methotrexate treatment [31]. This LncRNA-p21 suppresses inflammation and is downregulated [31].

2.1.10 LncRNA THRIL

According to the information obtained from RA, THRIL is on the upward path [32]. This LncRNA may use as a biomarker for RA. THRIL expression in the blood of RA patients was positively correlated with TNF-α and erythrocyte sedimentation rate. THRIL inhibition is reversed the regulatory effect of TNF-α, and significantly reduced the activity of p-AKT and phosphoinositide 3-kinase (PI3K) signaling

pathways. Also, expression of THRIL may promote the activating of the PI3K/AKT signaling pathway, and this leads to the result of inflammation and proliferation of FLSs [33, 34].

2.1.11 LncRNA RMRP

LncRNA RMRP expression is high in T cells from patients with RA [32]. Also, LncRNA RMRP has a positive correlation with RA progression [35]. This LncRNA may be a biomarker for RA.

2.1.12 LncRNA NTT

NTT expression is increased in a peripheral blood mononuclear cell (PBMC) from early patients with RA [36]. In the same study, the researchers found that in RA, lncRNA NTT/PBOV1 is capable of regulating monocyte differentiation.

2.1.13 LncRNA MEG3

The level of LncRNA maternally expressed gene 3 (MEG3) is significantly downregulated in FLSs of patients with RA [37]. Also, this study suggests that in lipopolysaccharide (LPS)-treated chondrocytes LncRNA MEG is downregulated. Overexpression of LncRNA MEG3 has an inhibitory effect on RA pathology can be achieved by increasing the rate of chondrocyte proliferation through negative regulation of miR-141 and AKT/mTOR signaling pathway [38–40]. In RA patients, low MEG3 expression correlated negatively with serum level of HIF-1α and vascular endothelial growth factor A (VEGF) and positively correlated with BAX. MEG3 gene rs941576(A/G) polymorphism has been confirmed to be associated with increased RA severity in the population [41]. We can say that LncRNA MEG3 promotes proliferation and it has an inhibitory effect.

2.1.14 LncRNA Lnc-IL7R

LncRNA long noncoding-interleukin-7 receptor (Lnc-IL7R) inhibits apoptosis and leads to proliferation [42]. Also, Lnc-IL7R interacts with the enhancer of zeste homolog 2 (EZH2) to assist the FLSs' growth and it is necessary for PRC2-mediated inhibition of the cyclin-dependent kinase inhibitors 1A and 2A [42].

2.1.15 LncRNA ZFAS1

Ye et al. found that LncRNA ZFAS1 has abnormal activity in RA FLSs. Also, the knockout of LncRNA ZFAS1 suppresses the migration and invasion of FLSs and it takes miR-27 s as a target and increased the expression of miR-27a [43].

2.1.16 LncRNA UCA1

LncRNA UCA1 expression is low in RA FLSs [44]. It reduces caspase-3 and cell apoptosis *via* Wnt-6 [44].

2.1.17 C5T1LncRNA

LncRNA C5T1LncRNA is a new LncRNA and it inhibits the mRNA of C5 protein, this protein plays a role in inflammation in RA [45, 46].

3. LncRNA as novel RA biomarkers

As with other pathological and chronic diseases, RA affects patients' life and status. Many pieces of evidence have confirmed the role of lncRNAs in the pathogenesis of RA [47]. Luo et al. found 5.045 irregular lncRNAs in PBMCs (2.635 downregulated and 2.410 upregulated) of RA patients compared to controls [48], 135 potential lncRNA-mRNA target pairs and RP11-498C9.15 targeted RA-related genes and pathways. Lots of LncRNAs such as PVT-1, MEG3, HOTAIR suggest that LncRNAs may serve as novel biomarkers to monitor RA pathogenesis.

4. Discussion

LncRNAs are of great importance in gene regulation and various RA biological processes. Expression profiles of lncRNAs vary in PBMCs, serum exosomes, osteoclasts, FLS, synovial tissues, plasma, synovium in RA. Some of these are differentially expressed, and LncRNAs are related to RA activity.

5. Conclusion

Emerging evidence shows us that lncRNAs are important regulators in RA. Continuing to explore the functions of lncRNAs in RA, their aberrant expression profile, and determining their role and mode of action will help us understand the underlying causes of the disease. Also, the identified lncRNAs related to the pathogenesis of RA may be potential diagnostic markers or target molecules that regulate RA progression. In the future, LncRNA-based therapeutic tools will likely lead to treatment insights into RA.

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Section 2

Clinical Approach of Rheumatoid Arthritis

Chapter 4

Rheumatoid Arthritis: Severity Classification, Factors Responsible, Pathophysiology, Current and Herbal Treatment

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Abstract

Rheumatoid Arthritis is the autoimmune disorder occurs due to the change in life style, improper diet plans, smoking, excessive alcohol consumption etc. It generally affects the joints and creates swelling and severe pain in joints which leads to further destruction of bone and cartilages. Due to autoimmune responses the factors like Tumor Necrosis Factor-α, Interleukins-1 are introduced to synovial and synovial membrane which creates the swelling and pain. These factors further produce reactive oxygen species and inducing osteoclasts which destruct the bone and cartilages. Along with the drugs the several natural herbal treatments are also available for the treatment of rheumatoid arthritis. This includes varies medicinal plants form which *acacia* species is more potent and efficient. *Acacia Senegal* is the plant which blocks the receptors and decreases the level of tumor necrosis factor-α. Present work on rheumatoid arthritis mainly covers classification, factors responsible, pathophysiology, severity, current treatment and its drawbacks, herbal treatment and its benefits in treatment of Rheumatoid Arthritis.

Keywords: rheumatoid arthritis, swelling, interleukins, cartilages, interleukins, bone erosion, *Acacia Senegal*, herbal treatment

1. Introduction

Bones are the prime constituents of Human Body as they have been affected by chronic diseases [1]. Nowadays, in the developed countries about 1% of population is suffering from the bone related chronic disease; Rheumatoid Arthritis (RA) [2]. Rheumatoid arthritis is a chronic autoimmune inflammatory disease predominantly characterized by inflammation of connective tissue that lines the inside of the joint capsule. Commonly RA It is accompanied by multi-organ disorders, along with pain, swelling, and stiffness of multiple joints. Joint destruction progresses rapidly resulting in irreversible dysfunction and deformation of the affected joints. Large

Sr. No.	Criterion	Definition
1.	Morning stiffness	It is defined as the uncomfortable state occurred at morning time in and around the joints, lasting for at least 1 hour before maximal improvement.
2.	Arthritis of 3 or more joints areas	Physician have to observe the occurrence of swelling or fluid in soft tissue simultaneously in more than 3 joints. Examples are PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
3.	Symmetric arthritis	When the same joint on the both side of body is involved.
4.	Arthritis of hand joints	In this at least a small part of a single hand is involved.
5.	Rheumatoid nodules	As physician observed, Subcutaneous nnodules, over bony prominences, or in juxtaarticular regions.
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.
7.	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on poster anterior hand and wrist radiographs, which must include erosion or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Table 1.
Criteria for classification of RA revised by American rheumatism association in 1987 [12].

	Target population (Who should be tested?) Patients who 1. Have at least one joint with definite clinical synovitis (swelling)* 2. With the synovitis not better explained by another disease	
	Classification criteria for rheumatoid arthritis-based on the score	
A	Joint involvement	Score
	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	>10 joints	5
B	Serology (depends on the results of tests)	
	Negative RF and ACPA	0
	Low positive RF and low positive ACPA	2
	High positive RF and high positive ACPA	3
C	Acute-phase reactants (depends on the results of tests)	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	>6 weeks	1

Table 2.
Rheumatoid arthritis classification criterion in 2010 [13].

numbers of peoples facing swelling and severe pain due to RA. There are several factors which leads to RA, but genuine causes are still unknown [3]. Generally occurrence of RA is due to genetic alterations and environments causes [4]. These genetic alterations are due to factors like change in lifestyle, smoking, autoimmune response excess alcohol consumption, etc. [5]. According to World health organism the Rheumatoid Arthritis is defined as autoimmune, inflammatory disease that is responsible for pain, stiffness, swelling, which further leads to the impairment in its function [6]. These are generally occurs in the joints like carpals, metacarpals and knee joints [7]. The respective joints which are suffered are becoming inflamed, leading to tissue damage, chronic pain, unsteadiness, and deformity [8]. Also the RA affects the eyes, lungs, heart, and mouth [9]. The untreated RA further leads to the bone and cartilage destruction and uncertain and sudden fractures [10]. The symptoms and further destruction can be reduced and prevented by proper treatment but total curation of RA is not yet invented [11]. Rheumatoid Arthritis classified as follow (**Tables 1** and **2**).

2. General classification

Figure 1 [14].

3. Pathophysiology

The worldwide scientists and researchers are only known that autoimmune response is responsible for the RA and genuine pathophysiology is still unknown [15]. So the different researcher gives different pathophysiologies. Form them the important two are explained below [16]. Generally the joints are mostly affected like wrist, knees, hand, ankles and feet. It is the autoimmune disorder means the body attacked by itself [17]. The immune system attacks to the joints and organ tissue [18]. The WBCs moves into the joint. They release chemicals called cytokines which attacks the cell of the synovial membrane. These chemicals cause synovial cells to release the other chemicals. They also cause synovial membrane to grow

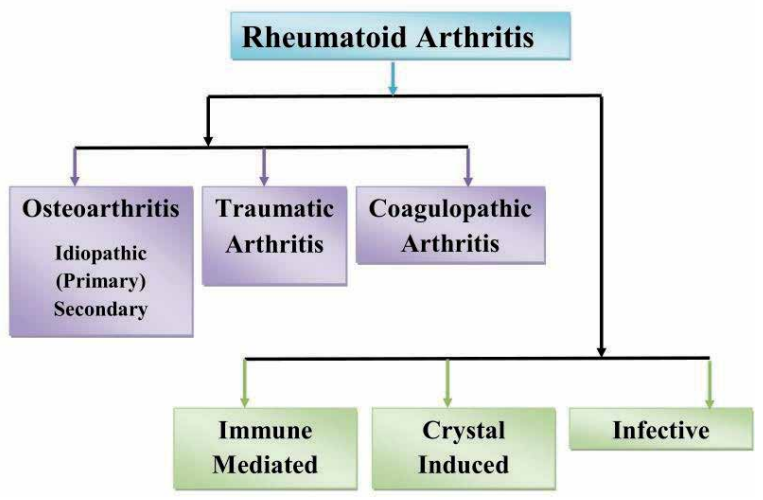

Figure 1.
General classification of rheumatoid arthritis.

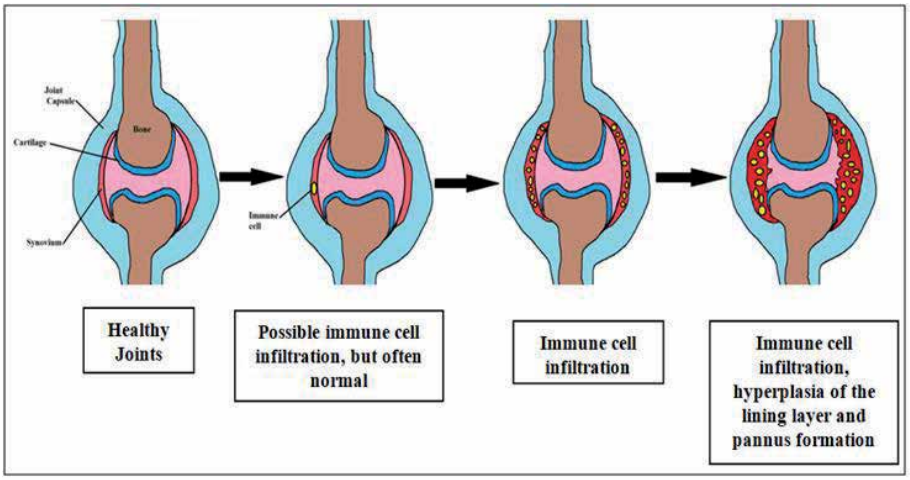

Figure 2.
Pathophysiology of rheumatoid arthritis.

new blood vessels and form a thicken area called pannus [19]. As the pannus grows day by day it invades and destructs the cartilages. Inflammation induces the fluid accumulation in the joint which lead to the further swelling and pain [20]. Due to this the free space between joints get decreases and form ankylosis and in some cases bones get fused to each other causing permanent disability of mobility of it (**Figure 2**) [21].

Another pathophysiology describes that around 7–65% of undifferentiated arthritis get converted into rheumatoid arthritis. In this the characteristic inflammatory mediators like monocytes and lymphocytes leaves the circulation and migrate to the synovium due to any autoimmune response occurs due to the reasons still unknown [22]. As the monocytes matured, the number of macrophases in the synovium gets increases. Some macrophages remain in the synovium further recruiting inflammatory cells. Other migrates towards or onto the hyperplastic synovial lining and get joined to the macrophage like and fibroblast like synovial sites. Simultaneously the APCs interact with the activated T-cells present, signaling the macrophages and they get bind to the synovial sites to release the inflammatory mediators like TNF-α and IL-1. TNF-α and IL-1 signals the additional recruitment of additional inflammatory cells from the blood, these cells also recruits the PMNs which migrate towards and crosses the hyperplastic synovial lining and enters in the joint space [23]. PMN releases the protease and ROs which get destroys nearby cartilages. Fibroblasts like synovial sites releases the additional proteases like MMP-1 and MMP-3 which also destructs the cartilages [24]. The fibroblast like synovial sites may release RANKL leading to nearby osteoclast which destruct the bones. This is the how RA get induced and develops [25].

4. Biosynthesis of TNF-α protein

On the cell membrane there are several receptors are present. There is a type known Toll-like receptors (TLR4) present on the cell membrane. When the lipopolysaccharides (LPS) are going to be attached to lipopolysaccharide binding proteins (LBP) and is transferred to CD14 (receptors of TNF superfamily). It activates two pathways from which one is for internucleus transcription of TNF mRNA and another is for intranucleus translation of TNF-α protein. In first activated pathway

through IRAK (Interleukin1 receptor associated kinase) and IKK (inducible I kappa β kinase) activates the p50 and p65 the NFkβs (nuclear factor kappa light chain enhancer). These NFkβs then get entered into the nucleus. Then due to them first transcription is done and pre-TNF mRNA forms which further converts into TNFmRNA by splicing maturation process. And then the TNFmRNA is exported to intranucleus portion. On other hand in the second pathway the MKK3,6 (mitogen activated protein kinase kinase) is activated and further activates p38. p38 then activates two constituents Mk2 (mitogen activated protein kinase activated protein kinase-2) and MNK1 (a kinase of the MAPKKADK family that can regulate

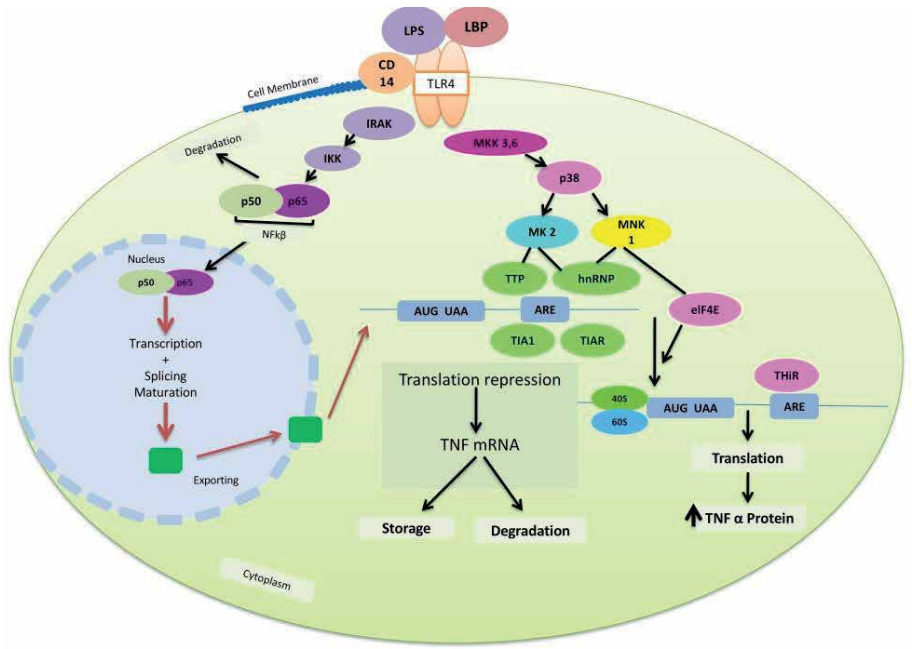

Figure 3.
Biosynthesis of TNF-α protein.

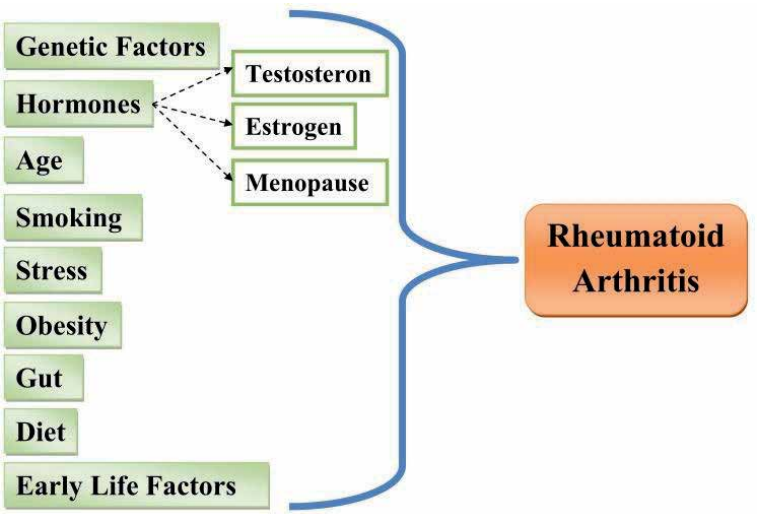

Figure 4.
Risk factors responsible for rheumatoid arthritis.

translation). They further promoted the formation of TTP (tristetroproline-zinc finger protein 36 homolog), hnRNP-A1 (heterogeneous nuclear ribonucleoprotein A1), TIA-1 (T-cell restricted Intracellular antigen 1), elF4E (eukaryotic translation initiation factor 4E), HuR. These all are further going in the process of translation along with the TNFmRNA and forms the TNF-α protein (**Figures 3** and **4**) [26].

5. Risk factors responsible for rheumatoid arthritis

5.1 Genetic factors

If a person having occurrence of Rheumatoid Arthritis is his/her previous generations then he/she will be at high risk of availability of same disorder [27].

5.2 Hormones

There are some hormones present in human body which are responsible for RA. According to CDC (Centre of Disease control and prevention) the women are at high risk of RA as compare to the men [28]. The hormones responsible are as follows:

a. Estrogen: Estrogen is a type of sex hormone which is also present in the male also, according to previously done research works it is proved that after menopause the estrogen received at replacement therapy is responsible for occurrence of RA [29].

b. Testosterone: The disturbed level of testosterone in human body is leads to the RA. Many clinical studies are done on this case in 2018 [30].

c. Menopause: The females after menopause having high physical stress and leads to disability in physical functions which results in symptoms of RA [31].

5.3 Age

According to CDC, persons in and after 60's are at more risk to suffering from RA [32].

5.4 Smoking

Smoking is a very dangerous addictive habit generally occurs in male, it leads to lots of life threatening diseases like lung cancer. It induces the autoimmune responses due to which RA happens [33].

5.5 Stress

As like above mentioned smoking the stress is also affects the immune system of human body and induces autoimmune responses which leads to traumatic experiences and further RA [34].

5.6 Obesity

Nowadays the world's most common disorder is obesity which create the various metabolic syndromes which leads to inflammation and further the RA [35].

5.7 Early life factors

According to the CDC the persons having low economic conditions are having higher exposure to RA. It is directly or indirect links to the factor Diet [36].

5.8 Previous history

The person having any history of occurrence of arthritis in his old generations then he/she might be on the high risk of arthritis.

5.9 Diet

Improper diet which leads to change in lifestyle is also responsible for occurrence of the rheumatoid arthritis [37–39].

6. Treatment

There are lot of research works done but yet no any proper treatment were found that will cure Rheumatoid Arthritis totally from its roots. Only some drugs were

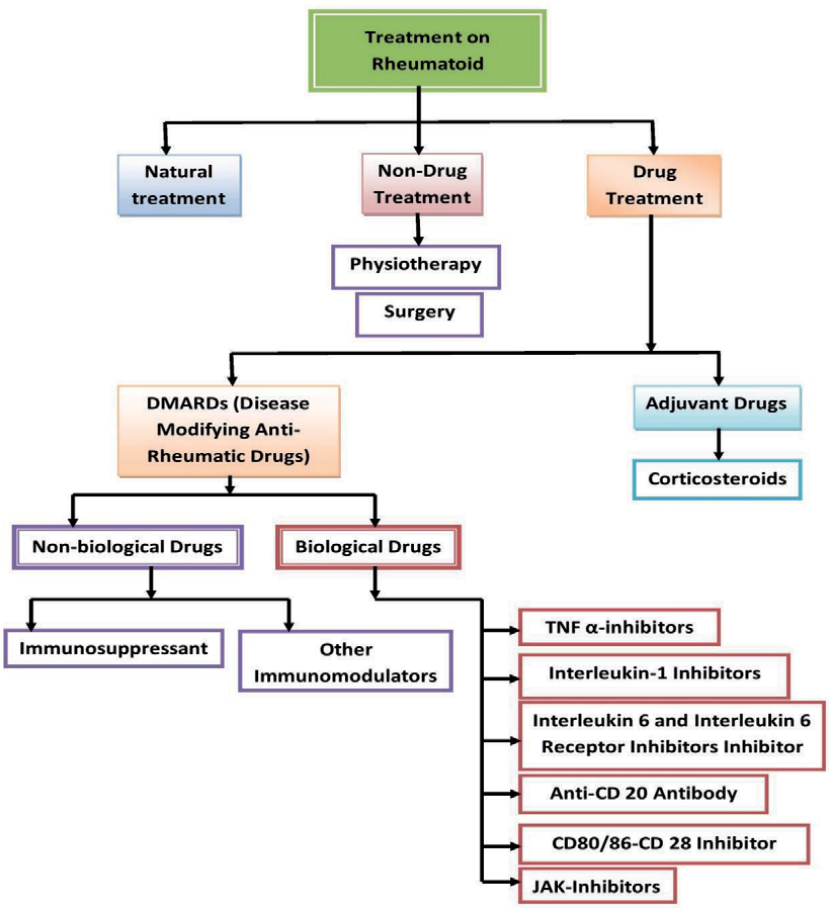

Figure 5.
Current treatment for rheumatoid arthritis.

evolved which reliefs from some of the symptoms and prevent further destructions of bones and cartilages [40, 41]. These drugs are having the side effects too. Some methods and aspects of treatment are as follows (**Figure 5**).

6.1 Natural treatment

There are varies species of plants available worldwide that are used for treatment of Rheumatoid Arthritis. Some majorly used plants are mentioned below with their Scientific name, Family, Local name (**Table 3**).

As like above mentioned plants there are many more plants are available with anti-rheumatic activity. The most efficient plant species is seems to be the Acacia species. Generally the Acacia species are act as a COX-1 and COX-2 inhibitors. The in vitro assay of Acacia species proved that they shows the COX-1 and COX-2 inhibitory action. Some species having activity with the extracts described below. The most potent species of Acacia is *Acacia Senegal* which is also called as Gum Arabica or Hashab gum. It is having properties or activity that decreases the level of TNF-α, ESR, SJC, TJC, VAS, DAS28 (**Table 4**) [42–44].

6.2 Non-drug treatment

6.2.1 Physiotherapy

Physiotherapy is one of the most prominent and painless technique to get rid off from rheumatoid arthritis which comes under non-drug treatment. It is a vital part

Sr. No.	Scientific Name	Family	Local Name
1	*Alpinia galangal Linn.*	Zingiberaceae	Arattai, Perarattai
2	*Anacyclus pyrethrum*	Asteraceae	Akkirakkaram
3	*Aphanamixis polystachya wall*	Meliaceae	Malampuluvan
4	*Aquilaria agallocha*	Thymeleaceae	Agalicundanam
5	*Argemone Mexicana*	Papaveraceae	Kutiyotti
6	*Callicarpa macrophylla Vahl*	Verbenaceae	Nallai
7	*Capparis deciduas*	Capparaceae	Senkam, Sirakkali
8	*Cardiospermum halicacabum Linn.*	Mudukkottam	Modikkottan
9	*Carthamus tinctorium Linn.*	Asteraceae	Senturakam, kusumba
10	*Cassia fistula*	Caesalpiniaceae	Konnai
11	*Catunaregum spinosa*	Rubiaceae	Madkarai
12	*Citrullus colocynthis Linn.*	—	Paitummatti
13	*Commiphhora myrrha Nees*	Burseraceae	Vellaippapolam
14	*Commiphara wightii*	Burseraceae	Kiluvai
15	*Cordial dichotoma Forst*	—	Naruvili
16	*Coriandrum sativum*	Apiaceae	Kottamalli
17	*Euphorbia neriifolia Linn.*	Euphorbiaceae	Saturakkalli
18	*Euphorbia ligularia*	Euphorbiaceae	Llaikkalli
19	*Ficus benghalensis*	Moraceae	Alamaram
20	*Flacourtia jangomas*	Flacourtiaceae	Vaiyyankarai

Table 3.
Natural herbs used in effective treatment of rheumatoid arthritis.

Plant species	Plant Part	COX-1 (DCM extract)	COX-2 (DCM extract)
A. nilitica (L.) Wild. ex Del. subsp. Tomentosa	Bark	46.3 ± 6.7	83.9 ± 4.2
	Leaf	78.1 ± 0.3	89.5 ± 1.8
A. nubica Benth	Bark	39.6 ± 5	90.4 ± 4.6
	Leaf	77.4 ± 4.6	92.7 ± 0.2
A. senegal (L.) Wild. Subsp. senegal	Bark	17.5 ± 7.1	91.6 ± 5.9
	Leaf	71.9 ± 7.43	93.7 ± 3.4

Table 4.
Plant species having COX-1 and COX-2 inhibitor activity.

in the whole lines of treatment of rheumatoid arthritis in cases of both acute and chronic condition. These are several program as follows which are included in the physiotherapy as follows:

1. Exercise – the regular exercise like walking, running, cycling, yoga, swimming etc. are very useful aspects of physiotherapy.

2. Physical therapy – the physical therapy included the use of heat and ice along with the electrical stimulation in transcutaneous region, exercise having range of motion, gentle strengthening moves, etc. which helps to decreases the swelling and pain.

3. Occupational therapy – the person who helps the patients of rheumatoid arthritis in occupational therapy is called as occupational therapist whose work is to identify and detect the problem faced by the modify it as the patient feels compatible while dealing with these stuffs.

4. Mind – body therapies – these therapies are used to stabilize the mind and thinking of patient and to give rest to his/her body. It includes deep abdominal breathing, meditation, muscle relaxation in progressive manner, visualization, tai chi, counseling, acupuncture, hot and cold comfort bath, massage and rest.

6.2.2 Surgery

This is the last line of treatment in rheumatoid arthritis. Drugs are only able to reduce the symptoms and give relief from pain. But when the situation of patient get critical then the surgery becomes mandatory. And this helps in restoration of joint and its movements. There are several surgeries like spinal surgery, hip replacement surgery, knee replacement surgery, total joint replacement, carpal tunnel release, synovectomy, bone and joint fusion surgery [45–47].

6.3 Drug treatment (modern treatment strategies)

In the drug treatment there are two categories in drugs one is DMARDs which is major one and another is Adjuvant drugs which is minor one. The main aim of this type of drug treatment is to minimize the inflammation, swelling and pain in joints of patient. Also it prevent the further bone erosion and damage of articular cartilage after the diagnosis. The drug treatment helps the patient to get relief from the deadly pains and stabilize the joint functions and its motility.

6.4 DMARDs

DMARDs are referred as Disease Modifying Anti-Rheumatoid Drugs or (SAARDs) Slow Acting Anti-Rheumatoid Drugs. From the very old days the first line of treatment for rheumatoid arthritis was use of NSAIDS, but recently after lots of research on various aspects of rheumatoid arthritis the DMARDs are considered to be the first line of treatment as a Modern Treatment for Rheumatoid Arthritis. It is better to take more than two drugs of same class i.e. DMARDs alternatively because the DMARDs loses its potency with prolonged use. DMARDs are of two types one is non-biological type and another is biological type as follows: (Following are the types or classes of drugs are explained in the form of their examples).

6.5 Non biological drugs

6.5.1 Immunosuppressant

6.5.1.1 Azathioprine

Azathioprine get converted into the 6-Mercaptopurine by the enzyme thiopurine methyl transferase (TPMT) and suppress the cell mediated immunity very potently. It comes under purine synthtase inhibitor class. The Azathioprine selectively affect differentiation and function of T-cells and natural killer cells. It also minimizes the inflammation. In the modern treatment the Azathiprine is given with the corticosteroids due its steroid sparing effect (**Figure 6**).

6.5.1.2 Methotrexate

It is the dihydrofolate reductese inhibitor which has very prominent immunosuppressant and tremendous anti-inflammatory property. Methotrexate helps the patient to get relief very rapidly within 3 to 6 weeks. Therefore, it is more preferable than any other medicaments in initial treatment. Among all the DMARDs methotrexate is the first choice due to its most predictable response and long term sustainability. Mostly combined regimens of DMARDs includes methotrexate. If the above DMARDs are failed to treat the patient then the immunosuppressant like cyclosporine, chlorambucil, cyclophosphamide were used [48].

6.5.2 Other immunomodulators

6.5.2.1 Sulfasalazine

It is the drug of choice in second line of treatment or in combined regimen with methotrexate. Sulfasalazine is synthesized from sulfapyrindine and 5-amino salicylic acid, it have the potent anti-infalmmatory activity which is used in bowl and in ulcerative colitis. The exact mechanism of action is still not known. The SSZ variant of sulfasalazine was designed in 1938 specially for the treatment of rheumatoid arthritis. The main pharmacological effects of sulfasalazine are affecting the bacterial flora, inflammatory cell function and immunological process. The approximate mechanism of action of Nf-kB, osteoprotegerin (OPG) and RANK-ligand.

6.5.2.2 Hydroxychloroquin/chloroquin

Hydroxychloroquin is the drug used mostly to treat the malaria patient. Along with malaria it is also used in treatment of rheumatoid arthritis due to its low

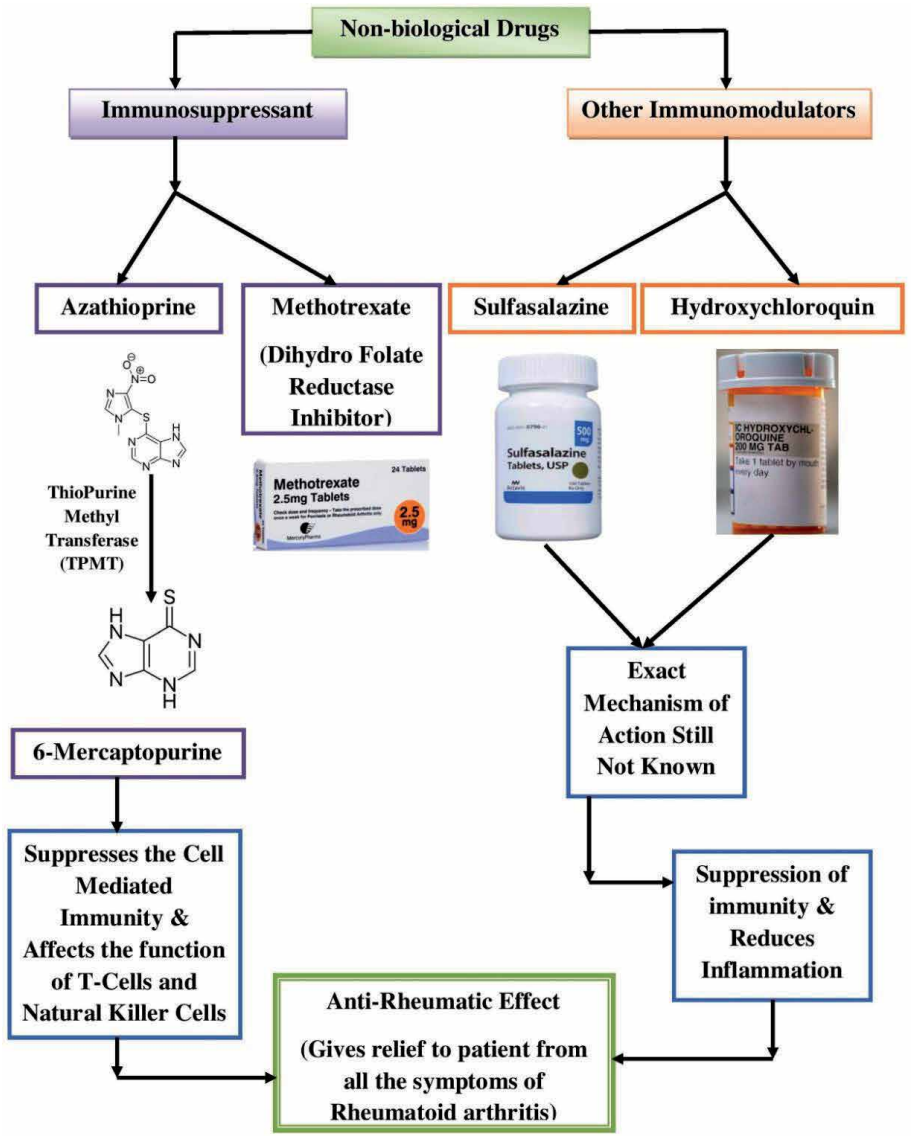

Figure 6.
Non-biological drugs for treatment of rheumatoid arthritis.

toxicity. Its exact mechanism of action is not elaborated yet but approximately it reduces the monocyte interleukin-1 along with inhibition of B-lymphocytes. Also it have some proposed mechanism of actions like stabilization of lysozomes and processing of antigens. This drug is advised only when small quantity of damage to join can recorded and it is must be taken with methotrexate or sulfasalazine [49].

6.6 Biological drugs

6.6.1 TNF-α inhibitors

TNF-α (Tumor Necrosis Factor alpha) is the most important responsible factors for the cause of rheumatoid arthritis. So, in modern treatment the mostly used drug is TNF-α inhibitors (**Figure 7**).

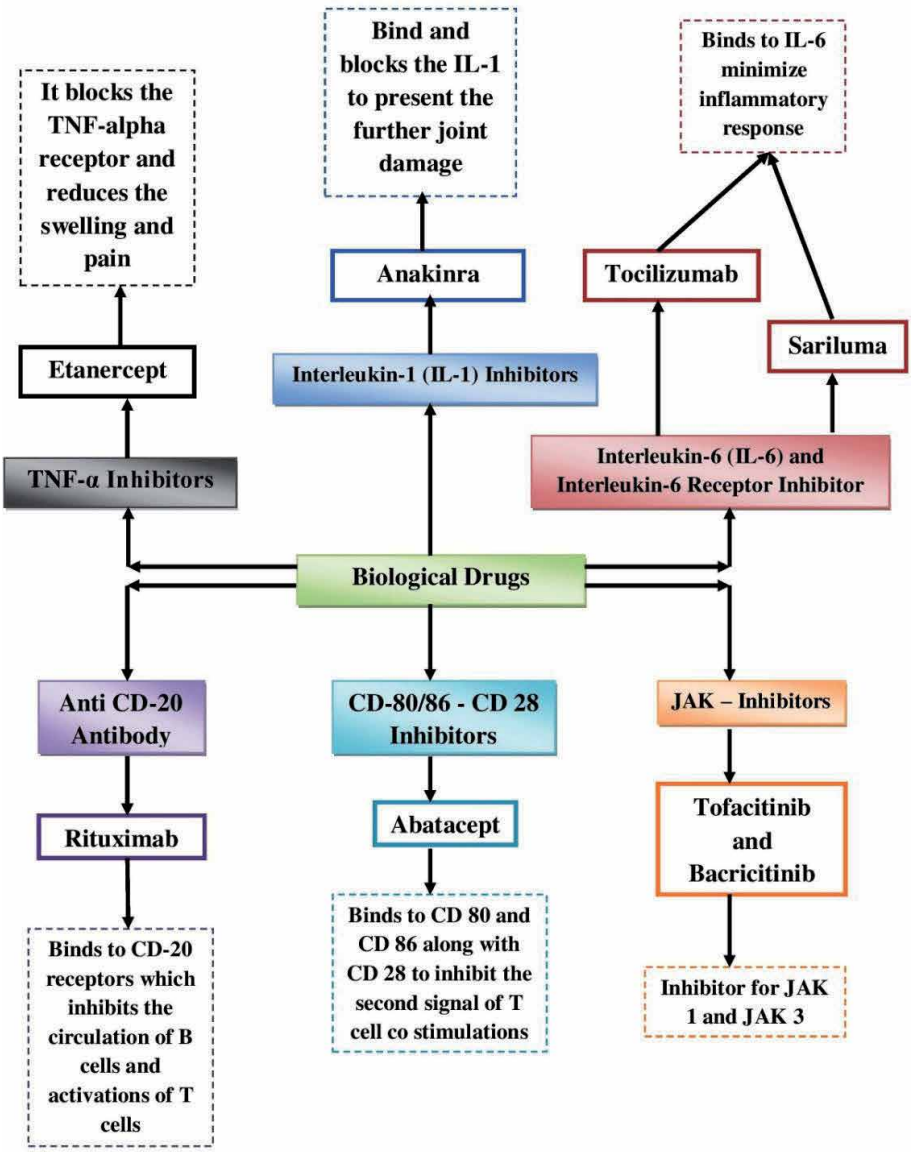

Figure 7.
Biological drugs for treatment of rheumatoid arthritis.

6.6.2 Etanercept

It is the subcutaneous injection which is composed of fusion protein of TNF – Receptor with FC portion of human IgG_1. It binds and blocks the TNF-α from activating the TNF-α receptors. There are also some drugs available in the class of TNF-α inhibitors like infliximab, adalimumab, certolizumab, golimumab.

6.6.3 Interleukin-1 (IL-1) inhibitors

Along with TNF-α, IL-1 is also the important responsible protein in etiology of rheumatoid arthritis. The IL-1 inhibitors are like Anakinra, Rilonacept, Canakinumab.

6.6.4 Anakinra

In 2001, USA and in 2002, Europe first launched this drug which was specially derived for rheumatoid arthritis treatment. This bind and blocks the IL-1 to present the further joint damage. Initially Anakinra was the main drug of modern treatment but nowadays it is used more in the treatment of the gout and polyserosities as compare to rheumatoid arthritis.

6.6.5 Interleukin-6 (IL-6) and interleukin-6 receptor inhibitor

In 1986 scientists was found the key cytokine moiety in the pathogenesis of rheumatoid arthritis named IL-6 which having prominent pro-inflammatory activity. To prevent this IL-6 inhibitors are derived.

6.6.6 Tocilizumab

It is the very first humanized recombinant IgG_1 monoclonal antibody which get binds to both the types of IL-6 that is soluble and membrane bound to block its action and to minimize the initiated inflammatory response.

6.6.7 Sarilumab

It is the second human immunoglobulin G1 IL-6 receptor antagonist monoclonal antibody working as same as above mentioned tocilizumab [50].

6.7 Anti CD-20 antibody

6.7.1 Rituximab

From 2006 onwards the rituximab was used in treatment of rheumatoid arthritis along with methotrexate and TNF-α as a combined dose regimen. It is the chimeric murine-human monoclonal antibody which get binds to CD-20 receptors which inhibits the circulation of B cells and activations of T cells.

6.8 CD-80/86: CD 28 inhibitors

6.8.1 Abatacept

It is the recombinant fusion protein given by in infusion and subcutaneous which is combination of part of FC domain of human IgG with extracellular domain of T cell inhibiting receptor CTLA4. It get binds to CD 80 and CD 86 along with CD 28 to inhibit the second signal of T cell co stimulations. It was given under combined dose regimen with methotrexate.

6.8.2 JAK: inhibitors

JAK (Janus-Kinase) is the cytoplasmic protein tyrosine kinase which is responsible for the signal transduction of the nucleus from the gamma chain (common) of plasma membrane receptor for the IL-2, IL-4, IL-7, IL-9, IL-15, IL-21. These all interleukins are the very important medications of many pro-inflammatory and inflammatory components like cytokines, interferons, interleukin-6. So to prevent and inhibit this the JAK inhibition are approved by FDA in 2012 in USA and by

EMA in European Union in 2017. The two main JAK inhibitors are tofacitinib and bacricitinib. Tofacitinib is the inhibitor for JAK 1 and JAK 3 with large affinity and for JAK 2 and tyrosine kinase 2 in with little affinity. It is used for severe arthritis either in monotherapy or with methotrexate. Also the bacricitinib is also works as same as tofacitinib [51].

6.9 Adjuvant drugs

6.9.1 Corticosteroids

Glucocorticoid is the most potent corticosteroid that can used at any stage in treatment of rheumatoid arthritis in modern treatment. It is used to minimize the swelling, pain and slowing down the joint destruction along with preventions of bone erosion as it have promising anti-inflammatory and immunosuppressant activity. Though it is administered in combination with first and second line drugs in the form of intraarticular injection it does not give total relief from rheumatoid process.

7. Drawbacks of modern treatment strategies

Among the DMARDs the dihydrofolate reductase immunosuppressant are causes the bone marrow depression, oral ulceration and G.I. upset. Methotrexate causes the liver cirrhosis when its is used in prolonged therapy. It is contraindicated in pregnancy, breast feeding, liver disease, active infection, leucopenia and peptic ulcer, hematological abnormalities, congenital deformities in pregnancy. Sulfasalazine produces neutropenia, thrombocytopenia, hepatitis, idiosyncrasy, skin reaction, pheumonitis, agranulocytosis, hemolytic anemia, reduction in male fertility. The regular blood count monitoring is necessary in case of this treatment. In case of treatment with Immunomodulators; due to prolonged use of hydroxychloroquin get accumulated in tissue and produces toxicity and other adverse effects like retinal damage, corneal opacity, rashes, graying of hairs, irritable bowel syndrome, myopathy, neuropathy. TNF-α blockers causes redness, itching and swelling at injection site along with occasional chest infection. Higher use of adjuvant drugs leads to patient becoming the steroid dependent along with over threathening disease and vasculities. On other hand IL-1 causes itching, pain and redness at the site of injection along with severe infections, decrease in WBC and platelets in some patients. The IL-6 inhibiting causes diverticulitis, purulent peritonitis, lowering the GI perforation, fistula, abscess, neutropenia, thrombocytopenia, hyperlipidemia, infections, liver enzyme elevation. Abatacept is not able to give with TNF-α inhibits due to do rise of severe infections. Also it causes hypersensitivity, anaphylaxis, anaphylactoid reactions, tuberculosis, sepsis. There is no any study available regarding that whether the drug is safe for pregnant woman or not. The anti-CD 20 antibodies are responsible for headache, fever, skin rashes, dyspnea, hypotension, nausea, rhinitis, pruritus and mild angioedema along with hypogammaglobinemia. There is very limited information related to the administration of this drug to pregnant woman. Along with this the JAK-inhibitors produces the hypotension, nausea, diarrhea, increase in LDL, HDL and total cholesterol, vein thrombosis, pulmonary embolism, upper respiratory tract infections. The JAK-Inhibitors are contraindicated in the patients with neutropenia, tuberculosis, severe infections, severe liver impairment and pregnancy. To overcome this all drawbacks the use of natural treatment on large scale is prefereable [52].

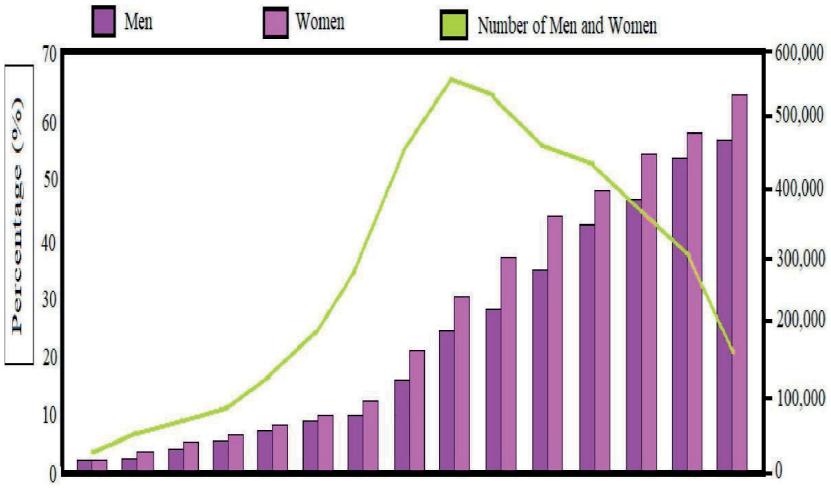

Figure 8.
Survey on rheumatoid arthritis in Canada.

8. Severity

The Rheumatoid Arthritis is most likely available disease now in all over the world [53]. There is one survey run in Canada on "Self-reported prevalence and number of individuals with arthritis by age and sex, household population aged 15 years and older", in 2007 and 2008 which is represented graphically below [54]. From the above graph it is clearly shown that the severity of RA is increased day by day and year by year in Canada in year 2007 and 2008 (**Figure 8**) [55].

9. Severity and survey in India

In India also the severity of RA is on large scale and the yearly surveys are done for its analysis and data were published. Following are some surveys made in various regions of India for RA by Indian Physicians and expert people of RA (**Table 5**) [56, 57].

Sr. No.	Year	Area of survey	Patient population size recorded
1	1988	Pune (Maharashtra)	110
2	1992	Nationwide	11931
3	1993	5 villages of Ballabhgarh township (Haryana)	39826
4	1994	West Bengal	4800
5	1995	Uttar Pradesh	74
6	2001	Bhigwan, Pune (Maharashtra)	5998
7	2003	Jammu (Jammu and Kashmir)	1014
8	2003	Lucknow (Uttar Pradesh)	148
9	2005	New Delhi	81
10	2005	Manipal (Karnataka)	141
11	2006	Lucknow (Uttar Pradesh)	102

Sr. No.	Year	Area of survey	Patient population size recorded
12	2006	New Delhi	211
13	2007	New Delhi	66
14	2007	Northern India	96
15	2007	Lucknow (Uttar Pradesh)	215
16	2007	Chennai (Tamil Nadu)	40
17	2009	Lucknow (Uttar Pradesh)	400
18	2009	Northern India	102
19	2009	Lucknow (Uttar Pradesh)	400
20	2009	Pune (Maharashtra)	8145
21	2011	Hyderabad (Andhra Pradesh; Telangana)	84
22	2011	Village of Ottoor (Kerala)	437
23	2012	Mumbai (Maharashtra)	93

Table 5.
Survey on rheumatoid arthritis by physicians and expert in India.

10. Conclusion

The Rheumatoid Arthritis is chronic autoimmune disorder occurs worldwide due to change in life style, unavailability of proper diet, hereditary characters, excessive alcohol consumption, etc. However the actual reason is still unknown. The Rheumatoid Arthritis is generally occurs in joints causing swelling and severe pain which further leads to destruction of bones and cartilages. First line treatment mainly includes synthetic drugs like Disease Modifying Anti-Rheumatic Drugs; monoclonal antibodies are now available for treatment for Rheumatoid Arthritis. Current treatment is not able to completely cure the Rheumatoid Arthritis form its roots as it has certain side effects such as bone marrow depression, oral ulceration, G.I. upset, skin reaction, pheumonitis, retinal damage, hypersensitivity, anaphylaxis, anaphylactoid reactions etc. So patients suffering from it require complete cure from it which leads to utilization of natural herbs for treatment of RA. Herbal treatment includes medicinal plants along with Acacia species which are mostly preferable because they are more potent, efficient; reduce pain and inflammation precisely along with lesser side effects. Medicinal herbs act is a blockers or inhibitors for the arthritis inducing factors. Due potential benefits of herbal medicines there is tremendous interest growing in medicinal herbs and there is need for more investigate in-vivo applicability. Currently severity of RA is rapidly growing day by day. Best current management pathway for RA contains identification, utilization of medicinally potent herbs along with physiotherapy which mainly include regular exercise like walking, running, cycling, yoga, swimming and acupuncture. As RA chronic disorder which creating permanent disability to joints which may leads to life threatening conditions; social awareness about RA and its remedies are needed.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

TNF-α	tumor necrosis factor
ESR	erythrocytes sedimentation rate
SJC	swollen joint count
TJC	tender joint count
VAS	visual analog score
DAS	disease activity score
RA	rheumatoid arthritis
DCM	dichloromethane
IL1	interleukins 1
PMNs	polymorphic nucleoneutrophills
ROS	reactive oxygen species
MMP1	MetrixMetalo-Protease 1
MMP3	MetrixMetalo-Protease 3
RANKL	receptor activating for nuclear factor kappa β ligands

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Chapter 5

Juvenile Idiopathic Arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common form of chronic synovial joint inflammation in children. It potentially leads to disability and psychosocial outcomes for children and their families. In the absence of appropriate treatment, this can lead to joint destruction and disability. Thus, early diagnosis and aggressive treatment are essential. With the presentation of new biologic DMARDs, based on understanding the disease pathophysiology and molecular pathogenesis, the course of the disease and its outcome have been changed profoundly. In this chapter, the early diagnosis, appropriate treatment, and outcomes approaches are described. These include the latest diagnosis and management options.

Keywords: juvenile idiopathic arthritis, children, chronic arthritis, oligoarthritis, polyarthritis, spondyloarthritis, psoriatic arthritis

1. Introduction

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic childhood disease and one of childhood's most common chronic diseases with unknown etiology and complex genetics. The new nomenclature applies the term juvenile idiopathic arthritis (JIA) [1].

Arthritis means intra-articular swelling or the presence of two signs or symptoms: limited range of motion, pain on motion, warmth, and redness. Intra-articular swelling may be due to intra-articular effusion or an increase in synovial thickness. In terms of the duration of arthritis, it can be divided into two categories: 1. Acute: for less than six weeks, 2. Chronic: more than six weeks [2]. In terms of the location of joint involvement, it can be divided into three categories: 1. Peripheral arthritis: means joints involvement of upper and lower limbs, 2. Axial: includes spinal joints involvement, and 3. Referral: includes the involvement of the hip joint [3]. In terms of the number of joints involved in a disease, arthritis can be divided into three categories: 1. Monoarthritis: means single joint involvement, 2. Oligoarthritis: means simultaneous involvement of four joints or less, and 3. Polyarthritis: it means the simultaneous involvement of more than four joints. In terms of the pattern and timing of arthritis spread, it can be divided into three categories: 1. Migratory: it means the rotation of the involved joints in a short period of several hours to a few days, which means that the affected joint improves and the other joint becomes involved. 2. Additive: this means that another joint or joints are added to the joint involved. 3. Intermittent: involvement occurs occasionally, and at intervals, the patient has no joint symptoms (such as Lyme disease or FMF [4]. In terms of the distribution of involved joints, arthritis can be symmetric or asymmetric. Symmetric arthritis refers to the involvement of the same joint on the opposite side, such as Rheumatoid arthritis, Systemic lupus erythematosus, and RF

positive polyarticular JIA. Asymmetric arthritis is characterized by the involvement of different joints in two sides of the body. This occurs in many childhood arthritis cases such as reactive arthritis, psoriatic arthritis, and Lyme disease. Arthritis can be inflammatory or non-inflammatory. In the case of inflammatory, inflammation of articular structures such as synovium, synovial cavity, and entheses occur. Non-inflammatory arthritis is an articular disease caused by mechanical or structural changes in the joint. These joint diseases can be due to cartilage or meniscus injuries with or without accompanying changes in the subchondral bone or maybe changing in joint anatomy due to congenital, developmental, metabolic, or previous inflammatory diseases [3, 4].

Regarding juvenile idiopathic arthritis, according to the previous definitions, we are faced with chronic arthritis with a period of at least six weeks in the age group under 16 years without an unknown etiology.

2. Epidemiology and immunopathogenesis

Since different criteria and classifications (including previous definitions of JRA, JCA, and JIA) have been presented for this disease over the decades, conducting various epidemiological studies to determine the exact incidence and prevalence of the disease has faced severe challenges. The disease appears to be less common in African-American and Asian populations in the United States [5]. The disease has an average prevalence of about one per thousand children under the age of 16, similar to acute lymphoblastic leukemia and type 1 diabetes in children [6]. In most countries, the ratio of females to males is about two to one or three to one. However, these ratios vary depending on the age of onset and the type of disease. The peak of the disease is between two and four years old, although it varies depending on the sex and type of disease [7].

The pathogenesis and etiology of the disease are unknown. Like many autoimmune diseases, interactions between genetic factors, immune mechanisms, and environmental factors are involved in developing the disease. Patterns consistent with Mendelian or Monogenic inheritance have not been observed in this disease. In many cases, the level of risk to other family members has only slightly increased. HLA types are probably associated with the disease and its subtypes. Patients with early-onset oligoarticular JIA who have a relatively high concordance among siblings are most likely to have isolated associations with these subgroups. Some genes involved in JIA may be a risk factor for the disease but are sometimes neutral or even protective [8].

The primary clinical manifestation of JIA is chronic joint swelling that may lead to deformity of the affected joints due to stretching of the tendons and ligaments around the joint. Enzymes released from inflammatory cells inside the synovium or joint fluid may damage the collagen and proteoglycan matrix in the joint. Osteoclasts activation results from cytokine production by cells in inflammatory tissue, and the final pathway is probably bone demineralization and bone destruction [9].

One of the pathological hallmarks of JIA is a tumor-like spread of inflamed synovial tissue, which is called pannus, leading to further joint destruction. Pannus consists of the synoviocyte proliferation and the invasion of synovial tissue by inflammatory cells (including lymphocytes, macrophages, and dendritic cells). The infiltration of these cells into the synovium is due to vascular factors, cytokines, adhesive molecules, and chemokines. Various inflammatory cells have been found in synovial fluid. As the disease progresses, the pannus expands into the synovial space and attaches to the intra-articular cartilage, where joint destruction eventually occurs [9].

3. Classification

Due to the heterogeneity of JIA disease, its classification remains a challenge. Classification criteria have been developed for research purposes and should not be used as diagnostic criteria at a patient's bedside. However, treatment and prognosis options may still help establish a common language and understanding of disease forms. International League of Associations of Rheumatology (ILAR) recognizes that this disease is an exclusive diagnosis. The characteristics of the disease and its etiology are the uncertainty of the disease onset before the age of 16 and its duration for at least six weeks.

According to ILAR classification, JIA is divided into seven subgroups (**Table 1**).

ILAR criteria are considered as standard, and still, the proposed new systems need further approval. With a greater understanding of the genetics and pathobiology of arthritis, it is hoped that future classifications will suggest more homogeneous JIA groups with biologically distinct diseases [2].

3.1 Systemic JIA

Systemic arthritis is considered a young adult still's disease. Arthritis is present in one or more joints with fever for at least two weeks. The disease most commonly presents with daily fevers, at least three days (quotidian spiking fevers). In addition, the child should have at least one of the following symptoms: evanescent erythematous rash, hepatomegaly or splenomegaly, generalized lymphadenopathy, or serositis.

Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease different from other forms of childhood arthritis and requires different treatments. In this disease, the child has symptoms of systemic involvement, which is less common in other forms of JIA. No autoantibodies are found in the serum of patients, and the primary disorder is in the inherited immune deficiencies system [2].

3.2 Polyarthritis: rheumatoid factor (RF) positive or negative

In addition to the involvement of at least five joints, patients with positive rheumatoid factor (RF) type should have at least two RF-IgM-positive results at least

Systemic arthritis
Polyarthritis: rheumatoid factor negative
Polyarthritis: rheumatoid factor positive
Oligoarthritis: a. Persistent b. extended
Enthesitis-related arthritis (ERA)
Psoriatic arthritis
Undifferentiated arthritis a. Fits no other category b. Fits more than one category

Table 1.
Classification criteria for juvenile idiopathic arthritis: 2001.

three months apart, although this test is often performed only once at the beginning of the diagnosis. Children with first-degree relatives with psoriasis, systemic arthritis, or manifestations of enthesitis-related arthritis are excluded from this category [10].

3.3 Oligoarthritis, persistent or extended

The disease involves a subset of patients previously classified as pauciarticular JRA. The disease is divided into two subgroups:

Persistent arthritis - refers to cases in which a child has one to four joints involved during the first six months of illness, but the number of joints involved never reaches five or more during the disease.

Extended arthritis- refers to children whose number of affected joints extends to five or more after the first six months of disease.

RF positive, first-degree relatives with psoriasis and concomitant or systemic manifestations are excluded from this classification [10].

3.4 Enthesitis-related arthritis (ERA)

This group of diseases refers to cases where enthesitis-related arthritis co-exist or enthesitis alone accompanies two or more of the following:

- Sacroiliac joint tenderness, or inflammatory lumbosacral pain
- Human Leukocyte Antigen B27 (HLA-B27) positive
- First-degree relatives with acute anterior uveitis, ankylosing spondylitis, inflammatory bowel disease, or reactive arthritis
- Acute anterior uveitis
- Arthritis onset in a boy over six years old

Children with first-degree relatives with psoriasis, RF positive, or systemic arthritis are excluded from this group.

This group includes some children formerly known as spondyloarthropathies. Also, some children may develop psoriatic arthritis in the future but do not currently fulfill its diagnostic criteria [10].

3.5 Psoriatic arthritis

Psoriatic arthritis is defined as children who have psoriasis and arthritis together or children with arthritis who have two of the following three:

1. Psoriasis in first-degree relatives
2. Dactylitis
3. Nail disorders, including pitting or onycholysis

Children with manifestations of arthritis associated with enthesitis or systemic, or RF+ are excluded from this group.

3.6 Undifferentiated arthritis

If patients do not meet the criteria mentioned in one of the above subgroups or have rejection manifestations, they fall into this subgroup. Also, if children meet the criteria of more than one group, they will be included in this group [10].

4. Diagnosis

The diagnosis of JIA is based on the history and findings of the physical examination and the exclusion of all other possible causes. Further evaluation, such as plain x-ray, ultrasound, nuclear bone scan, or MRI, is recommended when a physical examination does not prove definite arthritis.

5. Laboratory examination

Laboratory tests that may be performed to rule out other causes of arthritis or to determine the type or activity of the disease include the following [11]:

- Inflammatory markers: level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level
- Complete blood cell count (CBC) and metabolic panel, including serum uric acid and serum lactate dehydrogenase (LDH)
- Liver function tests and evaluation of renal function with serum creatinine levels
- Anti-nuclear antibody test (ANA)
- Rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (Anti-CCP)
- Additional tests: Serum total protein, Serum albumin, Fibrinogen, Ferritin, D-dimer, Angiotensin-converting enzyme (ACE), Anti-streptolysin O (ASO), Anti-DNase B, and urinalysis
- Tests to check for infectious causes, as the case may be.

6. Imaging studies

Radiographic changes in JIA include [11]:

- Swelling of soft tissue
- Osteopenia or Osteoporosis
- Narrowing of joint space
- Bony erosion
- Intra-articular ankylosis

- Periostitis
- Growth disorders
- Epiphyseal compression fracture
- Joint subluxation
- Synovial cysts

These changes are usually seen in children about one to two years after the onset of the disease and if not treated properly.

7. General principles of treatment

The medical treatment includes pharmacological and non-pharmacological treatments performed by a multi-group team. The following are considered in the group of non-drug therapies [11];

- Psychosocial interventions
- Programs to improve school performance (such as academic counseling)
- Nutrition improvement
- Physical therapy
- Occupational therapy

8. Disease course, outcome, and prognosis

JIA is a nomenclature that includes different diseases with different pathophysiology, manifestations, course, and outcome. With early diagnosis and aggressive appropriate step-wise treatment, the long-term outcome of JIA has improved in the last forth decades. There are different criteria for determining disease outcomes. Wallace et al. defined a set of criteria for the evaluation of clinical outcomes in JIA. Inactive disease (according to Wallace) criteria was defined as a state of no active joints, no systemic symptoms, no uveitis, normal erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP), and a physician's global assessment of disease activity indicating no disease activity. Furthermore, there are some different definitions for disease remission. The American College of Rheumatology criteria for complete remission of the disease are as follows [12]:

- Lack of inflammatory joint pain
- Lack of morning stiffness
- Lack of fatigue
- Lack of synovitis

- Lack of damage progression, which is determined by consecutive radiographic examinations

- Lack of high ESR and CRP levels

Also, different risk factors and prognostic factors exist for each of the subtypes. It potentially can cause serious complications, such as musculoskeletal deformities (including joint deformity and contracture), short stature, leg-length discrepancy, osteopenia and osteoporosis, increased risk of infections, cataract, decreased visual acuity, synechia, blindness, and macrophage activation syndrome. Each subtype's expected course, poor prognostic factors, and outcomes will be discussed later in detail.

9. Systemic-onset JIA

9.1 Clinical manifestations and diagnosis

Systemic JIA was formerly known as pediatric still's disease, systemic JRA, or systemic-onset juvenile idiopathic arthritis. This type of JIA is characterized by intermittent spiky fevers, evanescent erythematous rash, and arthritis. This disease is more similar to autoinflammatory diseases and may be different from other types of JIA. Diagnosis can be challenging because there are no specific diagnostic tests, and arthritis, which is essential for a definitive diagnosis, is often absent early in the disease. In addition, infections, malignancies, and other diagnoses should be ruled out before being labeled as these diseases can similarly cause fever, skin rashes, and joint pain. The diagnosis is clinical and is based on quotidian pattern (daily fevers spikes), typical evanescent erythematous rashes, and arthritis is characterized by typical laboratory findings, including leukocytosis with neutrophil predominance, elevated acute phase reactants including thrombocytosis, and high ferritin. In general, unfortunately, the disease does not have a specific diagnostic test. Differential diagnoses include infectious arthritis, other autoimmune and inflammatory disorders, malignancy, and malaria [13].

9.2 Treatment

In children with mild to moderate symptoms and without debilitating symptoms, a non-steroidal anti-inflammatory drug other than aspirin is recommended as initial treatment. In general, a drug test with non-steroidal anti-inflammatory drugs (NSAIDs) alone should not take more than a few weeks. The addition of adjuvant medication is common in children who find or continue to have significant symptoms despite treatment.

Traditionally, many pediatric rheumatologists add a glucocorticoid to the patient who has not responded to initial NSAIDs treatment or who has had a severe disease from the beginning. However, long-term use of glucocorticoids is associated with significant side effects. Biological agents, especially interleukin 1 and 6 blockers, are used as a primary and single treatment with increasing frequency. These factors are effective in reducing clinical symptoms in patients resistant to NSAIDs and glucocorticoids. There are growing findings that suggest that biological agents may also be helpful in the care of children with severe illness instead of glucocorticoids at the time of diagnosis. The decision to start treatment with a biological agent alone or combined with glucocorticoids is initially made considering the type of biological agent used, and after discussing the potential benefits and harms of treatment for the patient and family.

In patients who do not respond to the initial test of treatment with an NSAID alone, or in those whose early symptoms include high fever, other severe systemic symptoms, or debilitating polyarthritis, it is recommended that a biological agent such as Anakinra, Canakinumab, or Tocilizumab is added until a glucocorticoid is taken. Anakinra is used in some at a dose of 2 mg per kilogram of body weight daily up to a maximum of 100 mg. Canakinumab is usually given at a monthly dose of 4 mg per kilogram of child body weight with a maximum dose of 300 mg. Typically, 12 mg per kg intravenous injection or 162 mg subcutaneous injection is used every two weeks for children weighing less than 30 kg. Also, 8 mg per kg intravenous injection with a maximum dose of 800 mg every two weeks or 162 mg subcutaneous injection every week for higher body weights.

It is recommended that glucocorticoids be used when they do not respond immediately to a biological agent. When the current definition of an immediate response varies from center to center, some pediatric rheumatologists wait more than a week to add a glucocorticoid if polyarthritis, fever, and rash persist. They all add a glucocorticoid if there is evidence of severe macrophage activation syndrome or serositis. Both glucocorticoids and biological agents usually persist until disease control. Clinicians may then discontinue glucocorticoids first because the drug is associated with unavoidable intoxication in long-term use. Discontinuation of the biological agent may be possible if the disease is controlled. Prednisolone should be limited to o.5–1 mg/kg, although doses higher than 2 mg/kg or pulsed treatment with methylprednisolone may be necessary in severe cases. The treatment in cases with the polycyclic course and recurrent attacks is similar to the initial treatment. Treatment of the chronic and persistent disease depends on whether the patient has early systemic signs and symptoms (including fever, rash, and serositis), early arthritis, which can be progressive and destructive, or both. Interleukin 1 and 6 blockers are the most effective biological agents for early systemic disease and may also be effective for chronic arthritis. Tumor necrosis factor (TNF) alpha-blockers, concomitant T-cell stimulation blockers (Abatacept), and methotrexate can be used as adjunctive therapies to treat chronic arthritis. Other non-biological disease-modifying anti-rheumatic drugs (DMARDs) such as cyclosporine and tacrolimus, and cytotoxic agents such as cyclophosphamide are complementary choices in cases that do not respond to standard treatment containing biological agents.

The potential toxicity of drugs used in systemic arthritis should be carefully evaluated compared to the progressive, debilitating side effects and often the persistence of uncontrolled disease. Therefore, patients presenting with severe manifestations of the disease or those who resist treatment with NSAIDs should be referred to an experienced pediatric rheumatologist for disease management. Screening and monitoring of the disease are essential in the patients being treated [14, 15].

9.3 Course, prognosis, and complications

The course of systemic JIA is highly variable, although there are three typical pre-biological patterns in the disease: monophasic, polycyclic, and persistent (chronic). In the monophasic pattern, complete remission usually occurs within 4 to 6 months (occasionally in two to four years) and does not recur. In polycyclic or relapsing form, flares of systemic manifestations are with mild arthritis, and among them, remission and inactivity of the disease occur. This period can vary from a few months to several years. Finally, persistent destructive arthritis is often present in the persistent type despite reducing systemic manifestations, usually the most common form of the disease (50%) [16].

Three patterns of chronic disease activity in patients with persistent systemic JIA:

1. Systemic manifestations without or with mild arthritis, including fever, skin rashes, and sometimes recurrent macrophage activation syndrome.

2. Persistent (chronic) systemic manifestations and progressive arthritis.

3. Progressive destructive arthritis despite improvement of systemic manifestations. Despite treatment, some patients develop progressive destructive arthritis.

Systemic JIA-induced morbidity and mortality have decreased with treatment progress, but mortality is still high in patients with severe disease, especially those with recurrent or unknown macrophage activation syndrome and severe pulmonary or vascular complications [17]. Patients with active disease (those with fever, arthritis, high platelet count, persistent need for glucocorticoids) six months after disease onset have a worse prognosis for disease persistence and destructive arthritis [18].

Macrophage activation syndrome is the most common complication of systemic JIA. With the early detection and application of biologic DMARDs such as IL1 and IL6 inhibitors, complications such as severe growth retardation and osteoporosis are currently less common. There may be an increased incidence of rare but severe pulmonary complications that require further investigation.

9.4 Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of systemic JIA that should be treated as a life-threatening emergency. Clinical and histopathological features of macrophage activation syndrome are similar to hereditary lymphohistiocytic hemophagocytosis or HLH. However, diagnostic criteria for it are often not used to diagnose MAS in systemic JIA. Evidence suggests that there is a common genetic component in patients with systemic arthritis and MAS, as well as protein-altering variants in genes associated with HLH [19].

9.4.1 Clinical manifestations

Typically, MAS occurs during the first few days or weeks after the systemic-onset JIA, although it can occur at any time during the disease course. MAS occurs in 10% of children with systemic JIA but can develop subclinically in about 30–40% of other patients. Some patients have recurrent attacks of MAS. Triggers for this syndrome may be viral or bacterial infections or the administration of new drugs, but the initial irritating incident is often not apparent [20].

Children may present with spontaneous bleeding, bruising, liver dysfunction, drowsiness, seizures, coma, or shock. Persistent fever and skin rash (as opposed to intermittent daily fever and the typical evanescent skin rash of mild acute systemic JIA), lymphadenopathy, and hepatosplenomegaly are other common findings. White blood cell count, hemoglobin, platelet count, and serum fibrinogen typically decline abruptly. Liver function tests, triglycerides, and LDH increase rapidly. Ferritin can also reach as high as 10,000 ng/ml or even higher. In addition, a paradoxical decrease in erythrocyte sedimentation rate (ESR) due to fibrinogen consumption occurs, which is a vital diagnostic key. Typically, a bone marrow aspiration reveals multiple benign macrophages that indicate hemophagocytosis. However, not all bone marrow samples from patients with MAS show such a finding and may appear normal [20].

9.4.2 Diagnosis

Early diagnosis of MAS in a patient with systemic JIA may be difficult because systemic JIA flare-ups have similar clinical manifestations. In addition, a review of published literature suggests that patients treated with biologics may have fewer clinical manifestations of MAS, which may make it even more difficult to diagnose; for example, tocilizumab-treated patients have no fever or lower level of fever, and their CRP and ferritin levels are significantly lower. Diagnostic criteria for HLH are often not applicable to MAS in patients with systemic arthritis. Although these syndromes are clinically similar, HLH criteria are so strict that they cannot detect early MAS in patients with systemic JIA when they respond more to treatment. Part of the problem lies in the fact that patients with systemic JIA naturally have significantly increased levels of white blood cells and platelets along with acute-phase reactants such as ESR and fibrinogen so that normal premature levels of these blood tests can be misleading because they are caused by declining levels and is a signal of imminent MAS. For this reason, many efforts are underway to develop applicable clinical diagnostic criteria and scoring tools to diagnose MAS in patients with systemic JIA [21].

The 2016 classification criteria for MAS in systemic arthritis were expanded to identify more valuable criteria by combining consensus methods by experienced individuals and analyzing actual patients' data.

These criteria require increased ferritin and one of the other two criteria. These criteria include [22]:

- Thrombocytopenia (platelets 181,000 or less)
- Elevated liver enzymes (including AST > 48 U / L)
- Hypertriglyceridemia (above 156 mg /dl)
- Hypofibrinogenemia (360 mg/dl or less)

A diagnostic scoring tool to differentiate MAS in systemic arthritis from active systemic JIA without MAS, called systemic MAS scoring MAS / sJIA (MS), was developed and validated in 2019. In this criterion, multinational patient data collected were used to classify the MAS in 2016. Fever is a mandatory criterion for diagnosis and does not fit into scoring, although, as noted above, it may not be present in patients with systemic JIA treated with tocilizumab even in the presence of MAS. This scoring still needs validation in the clinical field and may need to be revised to include biological use in its calculations. This tool can also differentiate between these two diseases with high sensitivity and specificity. The MAS / HLH (MH) score strongly confirms the age of onset, neutrophil count, fibrinogen, splenomegaly, platelet count, and hemoglobin. Having an age of 16 years or less at the onset of the disease and neutrophil of less than or equal to 1400 per liter are the most critical factors in differentiating HLH from macrophage activation syndrome involving systemic JIA [23].

9.4.3 Treatment

When MAS is diagnosed or suspected, treatment should be started urgently with high-dose glucocorticoids, often using a 30 mg/ml methylprednisolone pulse at a maximum dose of 1 gr daily intravenously. There have been case reports of successful treatment with cyclosporine, cyclophosphamide, etoposide, or anakinra. Treatment of resistant MAS cases in patients with systemic JIA is the same as treatment regimens for HLH [24].

10. Oligoarticular JIA

10.1 Clinical manifestations and diagnosis

Children with JIA of the oligoarticular type, formerly known as juvenile rheumatoid arthritis (JRA) of pauciarticular JRA type, have involvement of four joints or less during the first six months after the disease onset. These patients are divided into two main subgroups: 1. Patients who do not have more joint involvement after the first six months of the disease have persistent oligoarticular JIA. 2. Those with four or fewer joints are involved during the first six months of disease onset, but more joints are added over time, resulting in five or more joints eventually becoming involved, known as extended oligoarticular JIA [2].

Oligoarticular JIA is the most common group of JIA, accounting for almost half of all cases. In the USA and Europe, the disease is more common in girls than boys and peaks at two to three years of age. The typical manifestation of the disease is painless limping. Large joints, especially the knees and ankles, are the most commonly involved joints, but the pelvic joints are never the primary joints involved. Except for uveitis, there are no obvious systemic manifestations [25].

Diagnosis of oligoarticular JIA in children is made with arthritis of four joints or less during the first six months of the disease by excluding the other causes of oligoarthritis. There are no diagnostic laboratory tests for the disease. Antinuclear antibodies (ANA) are frequently present in these patients and are associated with an increased risk of iridocyclitis. Patients with an elevated ESR or unexplained anemia are more likely to have a recurrent disease and become an extended oligoarticular JIA. Differential diagnoses of oligoarticular JIA include the other types of JIA such as psoriatic arthritis, polyarticular JIA and ERA, Lyme disease, IBD, pigmented villonodular synovitis, other infectious, autoinflammatory, and autoimmune diseases, and malignancy, all of which may involve four or fewer joints at the onset [26, 27].

Recurrence occurs in approximately a quarter of initially healthy patients. Some patients with the oligoarticular disease eventually develop chronic degenerative arthritis. Manifestations in the first six months of the disease poor prognostic factors include symmetric involvement, ankle or wrist involvement, laboratory evidence of inflammation (elevation of ERS or CRP), radiographic evidence of joint destruction, and hip or cervical joints arthritis [28].

10.2 Treatment

Patients with mild to moderate disease activity, lack of risk factors for poor prognosis, and lack of joint stiffness usually respond to non-steroidal anti-inflammatory drugs and intra-articular injections of glucocorticoids. However, patients with more significant illnesses who do not respond to initial treatment for intra-articular injection or who initially have severe disease activity and poor prognostic risk factors require treatment with methotrexate or other DMARDs. Biological agents such as TNF blockers are used in patients with a moderate or severe disease with poor prognostic manifestations who do not respond to treatment with non-biological DMARDs. TNF blockers are also used in patients with progressive oligoarticular JIA and patients with uveitis [28–31].

10.3 Course, prognosis, and complications

Uveitis is the worst complication of the disease, occurring in approximately a quarter of patients with oligoarticular JIA. Patients with detectable ANA and those

under the age of six at the time of diagnosis are at the highest risk. Mainly, there are no symptoms of uveitis, so routine screening is essential. An ophthalmologist should perform screening and a thorough examination with a slit lamp, and an alternative optometric or fundoscopic examination is insufficient. Complications include cataracts, synechia, glaucoma, band keratopathy, and macular edema (**Table 2**) [32].

The leg-length discrepancy is the second most common complication of oligoarticular JIA. This complication frequently occurs in both bone length and width. Injection of glucocorticoids into the knee and ankle joint early in the course of the disease may prevent this complication [33].

Referral	
• Patients should be referred at the time of diagnosis, or suspicion, of JIA	
Initial screening examination	
• Should occur as soon as possible and no later than six weeks from referral	
• Symptomatic patients should be seen within a week of referral	
Ongoing screening	
• Screening at two-monthly intervals from the onset of arthritis for six months	
• Followed by 3–4 monthly screening for time outlined below:	
○ Oligoarticular JIA, psoriatic arthritis, and enthesitis-related arthritis irrespective of ANA status onset under 11 years	
Age at onset	**Length of screening**
< 3 years	8 years
3–4 years	6 years
5–8 years	3 years
9–10 years	1 years
○ Polyarticular, ANA positive JIA, onset <10 years	
Age at onset	**Length of screening**
<6 years	5 years
6–9 years	2 years
○ Polyarticular, ANA negative JIA, onset<7 years Five-year screening for all children	
○ Systemic JIA and rheumatoid factor positive polyarticular JIA Uveitis risk is very low; however, diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated	
○ All categories, onset >11 years One year screening for all children	
○ After stopping immunosuppression, e.g., methotrexate Two-monthly screening for six months, then revert to previous screening frequency as above	
○ After discharge from screening Patients should receive advice about regular self-monitoring by checking vision uniocularly once weekly and when to seek medical advice Screening may need to continue indefinitely in situations where a young person may be unable to detect a change in vision or be unwilling to seek re-referral Annual check by an optometrist as a useful adjunct	

Table 2.
British society for pediatric and adolescent rheumatology/Royal College of ophthalmology guidelines for uveitis screening in JIA.

11. Polyarticular JIA

11.1 Clinical manifestations

The age of onset of polyarticular JIA onset has a bi-modal distribution. The first peak is between the ages of two and five, and the second peak is between ten and 14 years old. It is more common in girls than in boys of all ages [2].

The clinical presentation of polyarticular JIA varies and tends to show different patterns depending on the age of the disease onset. In children under ten years of age, polyarticular JIA often begins similar to oligoarticular disease with the involvement of one or two joints. The progression of the disease is often subtle until an intercurrent infection dramatically exacerbates the symptoms of the disease. The disease inevitably progresses and spreads to five or more joints during the first six months of disease onset. Joint involvement is typically symmetrical. Older children and adolescents usually have a rapid onset of multi-joint involvement, including a large number of small joints of hands and feet within two to three months of the disease onset [34].

There are no diagnostic laboratory findings for JIA. However, patients may have an ANA-positive test and an increased ESR of 40 mm in the first hour or so, anemia, and hypergammaglobulinemia. In most patients, the Rheumatoid factor is negative. In some patients in this group, rheumatoid factor (RF) or anti-cyclic citrullinated peptide (Anti-CCP) is positive, which is associated with the severity of the disease, symmetrical involvement of small or medium-sized joints, degenerative course of arthritis, and prolongation of the disease with a rheumatoid arthritis-like course. Other autoantibodies are not commonly seen in patients with polyarticular JIA [35].

11.2 Diagnosis

Diagnosis is made in children with arthritis in more than four joints during the first six months of the disease and by rejecting other causes of polyarthritis.

11.3 Differential diagnoses

include several diseases that may be self-limiting or chronic, including other forms of JIA such as psoriatic, systemic, enthesitis-related, reactive arthritis, early-onset rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, sarcoidosis, inflammatory bowel disease, epiphyseal dysplasia, and minocycline-induced autoimmunity [27].

11.4 Treatment and prognosis

Polyarticular JIA treatment aims to treat underlying synovitis and inflammation. Immediate treatment that relieves the patient's arthritic symptoms and protects the patient's function is essential for a better outcome. The treatment regimens chosen depend on prognostic factors, disease activity, as well as physician and family preferences, which are adjusted based on the clinical response. Risk factors include positive RF, positive anti-CCP, and joint degeneration. Disease activity is measured by the clinical Juvenile Disease Activity Score based on ten joints (cJADAS-10). It is recommended that initial treatment with a DMARD be performed in all patients with polyarticular JIA. Methotrexate is preferable to sulfasalazine, leflunomide, or a three-drug combination of methotrexate, sulfasalazine, and hydroxychloroquine. Methotrexate at a dose of 10 mg per square meter of the body per week in patients with low disease activity or an anti-TNF

biological agent with methotrexate in cases with moderate to severe disease activity is primarily used. Indications for using a TNF blocker with or in comparison with methotrexate include the presence of severe polyarthritis, inferior prognostic manifestations, or factors associated with a poor response to methotrexate, such as predominant involvement of the axial joints. The NSAIDs are not suitable as a single drug but as adjunctive therapy to relieve symptoms. Folic acid or folinic acid supplements are used in all children with JIA receiving methotrexate, which has been shown to have beneficial effects, and there is no convincing conflicting data against them. In patients who do not respond to treatment with methotrexate and a TNF blocker, treatment decisions are made on a case-by-case basis. The use of abatacept or tocilizumab is preferable to switching the TNF blocker. Choices include using a combination of DMARDs, other biological agents, or a small molecule inhibitor under the supervision of an experienced pediatric rheumatologist. Adolescents with positive RF and positive Anti-CCP are likely to show early onset of rheumatoid arthritis. For this reason, these children should be treated like adults with moderate to severe rheumatoid arthritis [36].

12. Psoriatic JIA

12.1 Pathogenesis, clinical manifestations, and diagnosis

Psoriatic JIA or psoriatic arthritis is clinically non-homogenous. In children, the age of onset of the disease is bimodal. The first peak occurs mainly in preschool girls and has a clinical picture similar to oligoarticular JIA with a high probability of positive ANA. The second peak is in mid-to-late childhood and resembles adult-onset psoriatic arthritis. The presentation and severity of the disease can be quite different, and the skin manifestations of psoriasis can occur long after the onset of arthritis. Articular involvement may vary from mild enthesitis to polyarticular involvement of the peripheral and axial joints. Inflammation may occur in only one joint or a large number of joints, with or without the involvement of the sacroiliac joints, spine, or peripheral entheses. Dactylitis or sausage-shaped swelling of the fingers is a common manifestation in younger children, while axial enthesitis-related arthritis is more common in older children. Enthesitis refers to inflammation of the joints where ligaments, tendons, capsules, fascia, and other fibrous structures attach to bone. Overt psoriasis Vulgaris may not be present. Nail pitting is more common in psoriatic JIA than skin-limited psoriasis. RF is typically negative and is considered an exclusion criterion. Inflammatory markers include ESR and CRP, and platelet counts may be mild to moderate but are often normal, even in the presence of polyarticular disease. Bone changes and joint space narrowing indicate significant cartilage loss, typically seen only after the advanced disease onset [37].

Psoriatic arthritis is currently diagnosed in children where arthritis occurs in the presence of established psoriasis. However, classic skin rash during presentation does not occur in about half of children with psoriatic arthritis and sometimes occurs even ten years or more after the onset of the joint symptoms. Besides, psoriasis in young children may be mild, atypical, and transient, often mistaken for eczema initially; therefore, diagnostic uncertainty is expected. Laboratory tests and radiologic studies have limited value in diagnosing psoriatic arthritis [37].

Differential diagnoses of psoriatic arthritis mainly include other subtypes of JIA, particularly oligoarticular and RF negative polyarticular and enthesitis-related arthritis. Apart from other types of JIA, differential diagnoses depend on the type of clinical presentation.

12.2 Treatment, prognosis, and outcome

Psoriatic arthritis is a relatively common subtype in JIA, but its clinical presentation can be very varied. Except for confirmation of suspected sacroiliitis by contrast-enhanced MRI, laboratory tests and radiological studies have limited value in managing psoriatic arthritis. Like other types of JIA, initial treatment for psoriatic arthritis depends on summing up all the clinical, laboratory, and radiographic manifestations of the disease to prevent cartilage or bone damage. The standard treatment algorithm for psoriatic arthritis is similar to other JIA cases, with a few exceptions. Some rheumatologists use NSAIDs as the primary treatment for monotherapy. However, NSAIDs do not typically induce remission; therefore, it is generally best used with a DMARD in patients with extensive or moderate to severe disease. Arthritis in the large joints, as well as dactylitis of the fingers, may be treated with glucocorticoid injections. DMARDs are indicated at diagnosis in patients with multiple joint involvements or those who have not remission with intra-articular injection of glucocorticoids. Failure to achieve disease remission is followed by the addition of a secondary DMARD, or more commonly by anti-TNF treatment. Systemic glucocorticoids are generally less commonly used, and antimalarial agents are avoided because of the risk of worsening psoriatic rash. The effectiveness of other biologic agents such as anti-IL-12/23, anti-IL-17, abatacept, apremilast, and Jak inhibitors has been shown in various studies [38].

Axial involvement in psoriatic arthritis is phenotypically similar to ankylosing spondylitis. Treatment should be started in patients with psoriatic arthritis who have symptoms of axial involvement or limited spinal mobility, even if these changes have not yet been shown on plain graphs. Anti-TNF agents are generally most effective, while NSAIDs can relieve symptoms in a group of patients. Other DMARDs have minimal impact. Interleukin-17 blocking agents, such as Janus kinase (JAK) inhibitor, appear to be allowed in adult studies. Monitoring and treatment of uveitis in psoriatic arthritis is similar to other subgroups [38].

Traditional treatment of psoriasis is indicated for skin disease associated with psoriatic arthritis. Usually, skin involvements are not very troublesome because joint manifestations occur early. After all, early use of systemic agents such as methotrexate and TNF inhibitors also has high effects on skin disease [39].

Poor outcomes and long-term disability are generally seen in patients who have a long delay in diagnosis or those who have not started effective treatment, although physicians or families often try to take necessary steps to induce disease remission [40].

13. Spondyloarthritis

13.1 Clinical manifestations and diagnosis

The terms spondyloarthropathy and spondyloarthritis refer to seronegative and related inflammatory diseases characterized by involvement of the spine (sacroiliitis and spondylitis), large joints (asymmetric oligoarthritis, especially of the lower extremities), and the entheses (enthesitis and enthesopathy). Diseases that fall into this category in children include enthesitis-related arthritis (undifferentiated spondyloarthritis), juvenile ankylosing spondylitis (differentiated spondyloarthritis), reactive arthritis, psoriatic arthritis, and arthritis with inflammatory bowel disease [41].

The onset of the disease is gradual but may initially be followed by a febrile illness or a musculoskeletal trauma. Arthritis is usually oligoarticular, asymmetric, and initially involves the large joints of the lower extremity. The knee, ankle, and mid-foot are the most common joints involved during the presentation. Common

manifestations accompanied include painful ligaments or tendons at the junction with the bone (enthesitis), inflammatory back pain or sacroiliac pain, morning stiffness, and limited spine movement [41].

Extra-articular manifestations include anterior uveitis, related skin manifestations, and recurrent gastrointestinal complaints. These manifestations may be associated with undifferentiated spondyloarthritis or suggest an alternative diagnosis, including a systemic disease such as inflammatory bowel disease and mechanical, developmental, and orthopedic disorders other than spondyloarthritis [41].

HLA-B27 is associated with enthesitis-related arthritis and has an increased incidence in all types of spondyloarthropathies. In juvenile ankylosing spondylitis, up to 90%, and in enthesitis-related arthritis, up to 50% can be positive.

13.2 Treatment

Treatment for spondyloarthritis aims to reduce symptoms, control inflammation, and prevent disability. The appropriate treatment depends on which manifestations are present, especially whether spinal involvement and whether spondyloarthritis is a manifestation of a systemic disease such as psoriatic arthritis, reactive arthritis, or inflammatory bowel disease. Traditional treatment with NSAIDs is recommended in all cases. In case of no response and active enthesitis, TNF inhibitor is preferable to methotrexate or sulfasalazine. In cases of TNF blocker contraindication, patients with mild enthesitis and patients with active peripheral polyarthritis, methotrexate or sulfasalazine can be used concomitantly. In cases of chronic active enthesitis, low-dose oral glucocorticoids can be used as bridge therapy in the short term (less than three months). In addition, this treatment can be used in cases of high disease activity, limited mobility, or significant symptoms [36].

14. Conclusions

JIA is the most common cause of chronic arthritis in children. In approach to a child with chronic arthritis, the physician should be alert about the wide differential diagnoses and consider and rule in or rule out the probable causes according to the history and examination. A full history and physical examination will provide a good background for an appropriate approach. Unfortunately, there is not a specific diagnostic laboratory test for confirming the diagnosis. Some important causes such as infections, malignancies, metabolic disorders, endocrine diseases, connective tissue disorders, and immune deficiencies should be in the mind of the physician. Early diagnosis and aggressive treatment are the principles of the management to prevent significant disease complications. Long-term clinical, laboratory, and ophthalmologic follow-up are necessary.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 6

Cardiovascular Risk in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA), one of the most common inflammatory rheumatic diseases. It is defined as a chronic destructive and deforming arthropathy; it also finds its expression through systemic manifestations. RA has an undulating evolution, with remissions and relapses. Atherosclerotic cardiovascular disease represents one of the most common extra-articular manifestations of RA. It is known that the cardiovascular (CV) morbidity and mortality represent one of the leading causes of reduced life expectancy in RA. Patients with RA develop a premature and accelerated atherosclerosis, explaining the high incidence and prevalence of angina, myocardial infarction, congestive heart failure, stroke, peripheral artery disease, and the need for revascularization. Traditional risk factors (arterial hypertension, obesity, smoking, dyslipidemia, insulin resistance and metabolic syndrome, diabetes mellitus, male gender, physical inactivity) interplay with RA-related risk factors, generating endothelial dysfunction, arterial stiffness, carotid plaque, and atherosclerosis. Traditional cardiovascular risk factors alone cannot explain the increased incidence of premature and accelerated atherogenesis. Chronic inflammation, hyperhomocysteinemia, and hypercoagulation act as novel cardiovascular risk factors. Rheumatoid inflammation exerts direct effects on vessels, or by means of altered traditional risk factors. Antirheumatic drugs may promote atherogenesis or by reducing systemic inflammation may decrease cardiovascular risk. EULAR recommendations require annual cardiovascular risk assessment.

Keywords: cardiovascular risk, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA), one of the most frequent rheumatic inflammatory diseases, is defined as a chronic destructive and deforming arthropathy, but it also expresses itself through systemic manifestations [1]. The incidence of RA reaches its peak around 50 years; this disease affects twice as many women than men [2]. Its evolution is undulating, marked by exacerbations and remissions, the burden being variable between patients. This fact makes long-term outcomes different between patients: some have relatively mild disease, while others have marked physical disabilities and reduced quality of life [1].

RA manifests itself in the form of a chronic symmetric polyarthritis that affects predominantly the small joints. But besides articular involvement, which generates severe disability, RA has extraarticular manifestations, which are responsible for

the increase in mortality by 1.5 times compared to that in the general population. Among these extraarticular manifestations, cardiovascular involvement generates increased morbidity and mortality in RA patients. This induces a real challenge in the treatment of these patients [2–7]. RA patients have an increased risk (50% higher than the general population) of premature mortality due to cardiovascular diseases [8–10].

In their meta-analysis, comprising 24 studies of RA mortality on 111,758 patients, Avina-Zubieta et al., reported that the cardiovascular mortality was increased by 50% in these patients. The authors identified that the RA patients with a short duration of disease evolution had had a lower risk of cardiovascular mortality compared to the patients with long evolution of RA [11]. In another study, Avina-Zubieta et al., showed that the patients with RA had a myocardial infarction relative risk of 1.68 (95% CI, 1.40–2.03), and cerebrovascular disease relative risk of 1.41 (95% CI, 1.414–1.4) [12]. Houri Levi et al., revealed in their study done on 12,000 patients with RA that the ischemic heart disease had a greater prevalence among RA patients compared with general population (16.6% versus 12.8%, $p < 0.001$) [13]. The RA patients may develop myocardial infarction at a younger age than the general population [14].

The risk of cerebrovascular events is increased by about 41% in RA patients [13]. Another atherosclerotic manifestation is represented by peripheral arterial disease. Baghdadi et al., studying 30,000 patients with RA, identified a higher incidence of peripheral arterial disease among them than the general population (HR 1.73, 95%CI 1.57–1.91). The association with high blood pressure or diabetes mellitus increased the risk of peripheral arterial disease among RA patients [15].

Heart failure is about 2 times more common in RA patients with a positive rheumatoid factor than in the general population (HR 1.87, 95% CI 1.47–2.39) [1].

In the following sections, the main aspects related to cardiovascular risk in RA are presented.

2. Cardiovascular risk in patients with RA

In European Society of Cardiology guidelines, RA is considered an independent cardiovascular risk factor [16]. Knowing the high incidence of cardiovascular diseases among RA patients, in 2016, the European League Against Rheumatism (EULAR) published a set of 10 recommendations for the screening, identification and management of cardiovascular risk factors in RA patients. These recommendations predicted that the cardiovascular risk scores obtained with the instruments used in the general population be multiplied by 1.5 in patients with RA. It is the task of the rheumatologist to identify and manage the cardiovascular risk factors in RA patients [17]. To date, the optimal control of RA inflammation has not been achieved [18].

High cardiovascular risk in RA patients may be explained by the interaction between traditional cardiovascular risk factors and those determined by RA [7]. But in RA patients, standard cardiovascular risk scores, like Reynold's Risk Score, Systematic Coronary Risk Evaluation (SCORE), and Framingham risk score minimizes the cardiovascular risk [19–21]. Lindharsen et al., demonstrated that the cardiovascular risk is related to the RA severity [14].

The traditional cardiovascular risk factors have a higher incidence among RA patients than in the general population, especially insulin resistance, obesity, diabetes, hypertension, and smoking; however, the presence of increased systemic inflammation has been shown to also provide a detrimental pro-atherogenic role in the RA patients [22]. It was demonstrated that the risk for cardiovascular morbidity

and mortality in RA patients keeps growing even after controlling for insulin resistance, dyslipidemia, body mass index, hypertension, and smoking. In meta-analysis published by Baghdadi et al., the cardiovascular risk induced by traditional cardiovascular risk factors is highlighted as follows: hypertension (RR 2.24, 95% CI 1.42–3.06), hypercholesterolemia (RR 1.73, 95% CI 1.03–2.44), diabetes mellitus (RR 1.94, 95% CI 1.58–2.30), smoking (RR1.50, 95% CI 1.15–1.84), and obesity (RR 1.16, 95% CI 1.03–1.29) [15]. RA-associated chronic inflammation may lead to atherosclerosis acting direct on the arterial walls, or by modifying traditional cardiovascular risk factors, especially insulin resistance and dyslipidemia [1]. Elevated levels of circulating cytokines are identified even before the onset of clinical signs of the disease [9]. Chronic systemic inflammation generates endothelial activation and dysfunction, and a pro-atherogenic and prothrombotic state, responsible of the increased cardiovascular risk in RA patients [23]. It has been identified that systemic inflammation acts on myocardial cells even before the occurrence of specific joint manifestations of RA. Therefore, it is very important that cardiovascular risk assessment be done right at the time of RA diagnosis [7].

Cardiovascular involvement in RA patients is based on two mechanisms: an ischemic one caused by accelerated atherosclerosis, as well as a non-ischemic one, produced by the structural changes of the myocardium, both of them induced by chronic inflammation [2].

3. Inflammation and cardiovascular risk in RA

The link between chronic inflammation and accelerated atherosclerosis is well known in RA patients, several studies supporting this fact [17, 21, 24–27]. Inflammation is implicated in both the development and progression of atherosclerotic plaques in the general population [1]. Chronic inflammation is associated with cardiovascular disease, independent of traditional cardiovascular risk factors [17]. In RA patients, a linear relation between chronic inflammation (elevated erythrocyte sedimentation rate, high levels of C reactive protein) and carotid intima-media thickness, independent of traditional cardiovascular risk factors, has been identified. Higher RA activity, evaluated by means of a composite index DAS28, is associated with higher cardiovascular risk [28]. In their study, carried out for a period of 10 years, Goodson et al., demonstrated the association between inflammation (evaluated by means of CRP levels) and higher cardiovascular mortality in patients with early inflammatory polyarthritis [29]. Agca el al. revealed that the RA patients presented more than twice cardiovascular events than the general population, even higher than the type 2 diabetes patients [30]. RA patients with coronary atherosclerotic disease have an unfavorable prognosis, presenting higher morbidity (recurrent ischemia episodes) and mortality than the non-RA patients [31]. RA patients are more likely to have silent myocardial ischemia and may develop heart failure and sudden death [32]. On the other hand, several studies showed that in the conditions of chronic inflammation, atherosclerotic plaques become vulnerable, unstable, with an increased risk of cardiovascular events [1].

But cardiac dysfunction may have a nonischemic origin, this dysfunction being associated with high inflammatory activity, but not rheumatoid factor positivity [33]. Cardiac dysfunction often goes undiagnosed, especially in asymptomatic patients or those with minor symptoms. Ferreira et al., studying 355 patients with RA, showed that only 7% of them were diagnosed with heart failure, but one third of RA patients met the symptoms of heart dysfunction [34]. The studies have shown that patients with high inflammatory activity (evidenced by elevated serum C-reactive protein levels) have the highest risk of developing heart dysfunction,

suggesting a role of inflammation in the cardiac dysfunction pathogenesis [1, 2]. High levels of C-reactive protein are associated with an increased risk of cardiac dysfunction, independent of the presence of traditional cardiovascular risk factors. The link between RA activity, measured by means of elevated levels of C-reactive protein and cardiovascular risk, indicates the fact that persistent systemic inflammation contributes to increased risk for cardiovascular events [35, 36].

Traditional cardiovascular risk factors acting together with systemic inflammation generate accelerated atherosclerosis and ischemic cardiac events, but systemic inflammation, even in the absence of traditional cardiovascular risk factors, determines the occurrence of cardiac dysfunction, as heart failure with preserved ejection fraction [1].

The involvement of systemic inflammation in heart failure with preserved ejection fraction is proved, acting by means of proinflammatory mediators [1, 35, 36]. This inflammatory environment induces endothelial activation and then dysfunction, and increased recruitment of leukocytes, especially monocytes into the cardiac tissue. In the myocardium, there is a reduction in the bioavailability of nitric oxide and consequently a reduction in cyclic guanosine monophosphate and protein kinase G. These changes lead to cardiac hypertrophy and increased resting tension, finally appearing as diastolic dysfunction [2, 33].

High levels of inflammatory cytokines (TNF-alpha, IL-1, IL-6) can be detected in patients' serum before the onset of RA symptoms [9]. They induce pro-atherogenic and pro-thrombotic states (insulin resistance, atherogenic dyslipidemia, oxidative stress, endothelium activation, and subsequent endothelial dysfunction). These cardiovascular changes appear even before the clinical RA onset [22].

The importance of systemic inflammation in cardiovascular morbidity and mortality of RA patients is revealed by the study published in 2019 by Provan et al., which showed that the RA patients diagnosed before 2003 had significantly elevated cardiovascular mortality compared with the patients diagnosed after 2004, who had a similar cardiovascular mortality risk as the general population [37].

4. Dyslipidemia

RA patients have lipid abnormalities, which promote accelerated atherogenesis. Chronic inflammation modifies lipid pattern in rheumatoid patients, favoring accelerated atherogenesis. In these patients, many studies showed a specific lipid pattern: decreased of total cholesterol, HDL-cholesterol, and LDL-cholesterol, and increased very-low density lipoprotein (VLDL), lipoprotein (a) (Lp(a)), apolipoprotein-B (apo-B), and free fatty acids (FFAs) [22, 38, 39]. Liao et al., described the "lipid paradox" in RA patients: decreased levels of total cholesterol and LDL-cholesterol are associated with high cardiovascular risk. The decreased levels of total-cholesterol are due to low levels of HDL-cholesterol [39]. Sattar et al., reported an inverse relationship between rheumatoid activity reflected by high levels of C reactive protein and low levels of total cholesterol, LDL-cholesterol and HDL-cholesterol [8]. Rheumatoid activity is associated with impaired HDL-cholesterol functions [39]. The impaired antioxidant activity of HDL-cholesterol is correlated with increased oxidized LDL-cholesterol and phagocytosis by macrophages, generating atherosclerotic plaques [40]. High levels of triglycerides are caused by VLDL increase and HDL-cholesterol decrease [8, 38, 40].

Kim et al., reported that the RA patients presented modified structure of lipoproteins, secondarily affecting their functions. The final result is represented by the increase of cardiovascular events incidence [40]. In RA patients, lipoproteins are oxidized and glycated, these processes are associated with a decrease in nitric

oxide generation, endothelial cell death, promoting endothelial dysfunction and atherosclerosis [40].

Ajeganova et al., studying the apolipoprotein pattern in RA patients, identified high levels of apo-B and a higher ratio of apo-B to apo-A, correlated with increased carotid intima-media thickness and the plaques presence [41]. Increased Lp(a) is common in patients with RA, especially when the disease is active. Lp (a) has dual actions: by binding to oxidized phospholipids, it is located in the vascular wall, contributing to atherosclerosis development, and on the other hand, by inhibition of plasmin activity, it promotes a thrombogenic effect [42].

5. Hypertension

Hypertension is known as an important cardiovascular risk factor. In RA patients, the hypertension incidence is between 4 and 73%, this incidence being dependent on the assessed patients and study design [43]. COMORA (COMOrbidities in Rheumatoid Arthritis) study reported a hypertension prevalence in RA patients of 40% [18]. Often, hypertension remains undiagnosed and consequently untreated in patients with RA, contributing to excessive cardiovascular morbidity and mortality [44, 45].

Chronic inflammation, by means of elevated levels of TNF-alpha, IL-1, IL-6, acts on the vascular endothelium, causing nitric oxide reduction, increase in endothelin, and upregulation of angiotensin II type 1 receptor, the final effect being represented by an excessive vasoconstriction and increased total peripheral resistance. Additional contributing factors for hypertension development are represented by genetic polymorphism, physical inactivity, RA medication (nonsteroidal anti-inflammatory drugs, corticosteroids, Leflunomide, Cyclosporin) [1].

6. Insulin resistance, metabolic syndrome, and diabetes mellitus

The existing data support the strong link between RA, insulin resistance and metabolic syndrome [1]. Lindhardsen et al. reported that the chronic inflammation represents the link between RA and atherogenesis [14]. In another study, Baghdadi et al., demonstrated a strong correlation between inflammatory syndrome, RA activity, insulin resistance, and subclinical atherosclerosis revealed by means of carotid intima-media thickness [15]. Metabolic syndrome and RA influence each other, the final result being represented by oxidative stress with secondary endothelial damage [1].

7. Obesity

Obesity is known as an important traditional cardiovascular risk factor. It is important to remind that the adipose tissue is not inert but is very biologically active through the synthesis of TNF-alpha, IL-6, cytokines involved in RA pathogenesis [1].

In RA patients, the prevalence of overweight is about 60%, and the prevalence of obesity is between 18 and 31%. These patients present a higher rheumatoid activity than in RA normal weight patients. But the obesity is associated with other traditional cardiovascular risk factors, as insulin resistance, metabolic syndrome, diabetes mellitus, hypertension, atherogenic dyslipidemia, and inactive lifestyle [46].

The RA patients with low body mass index (<20 kg/m^2) present the elevated risk for cardiovascular disease development. Kremers et al., showed that patients with RA and low body mass index had a higher cardiovascular risk than those with normal weight [47]. Increased inflammatory activity, which characterized active RA, causes an increase in catabolic processes, with a consequent reduction in body weight, settling in the advanced stages of rheumatoid cachexia [1].

8. Smoking

Smoking is known as a traditional cardiovascular risk factor. But the recent data suggested that smoking is involved in RA pathogenesis. Smoking determined the increases the risk of RA. But the RA smoking patients present a higher activity of disease with RF positivity, erosions, nodules, and marked disability. In these patients, the potency of the csDMARD and bDMARDs is low, requiring higher doses of them [1].

9. RA therapy and cardiovascular risk

The therapeutic objectives are represented by the efficient control of the inflammatory process, as well as the prevention of the articular destructions [1]. By controlling the inflammatory process and its consequences on the vascular endothelium, the atherogenesis process is diminished, and consequently, the cardiovascular risk [48]. In order to diminish RA chronic inflammation, joint destruction and cardiovascular risk, EULAR recommended a sustained, aggressive control of disease activity, using several classes of drugs, as nonsteroidal anti-inflammatory drugs, glucocorticoids, csDMARD (conventional synthetic disease modifying antirheumatic drugs), bDMARD (biologic disease modifying antirheumatic drugs), tsDMARD (targeted synthetic disease modifying antirheumatic drug) [17]. All of these drugs, in addition to controlling the inflammatory process, can have side effects that can increase cardiovascular risk [48].

Nonsteroidal anti-inflammatory drugs represent a class of drugs widely used in the RA treatment. These patients used non-selective NSAIDs, or selective COX-2 inhibitors. The use of NSAIDs is associated with increased risk of cardiovascular events, especially in elderly RA patients. These drugs are associated with a high risk of arterial hypertension and atherothrombotic events development [49]. Selective-COX 2 inhibitors are contraindicated in patients with atherothrombotic risk factors, stroke, and ischemic heart disease. Therefore, Rofecoxib was withdrawn from use. But Etoricoxib can be used in RA patients in a dose of 90 mg daily. Due to side effects, these drugs should be used judiciously, but only in combination with DMARDs [1].

Corticosteroids effectively control inflammation, but they have many side effects, especially cardiovascular (uncontrolled arterial hypertension, atherogenic dyslipidemia, diabetes mellitus). The side effects of corticosteroids in RA patients have been evaluated in several studies. Del Rincon et al., demonstrated that the RA patients who received daily doses of glucocorticoids greater than 8 mg had an increase in dose-dependent cardiovascular morbidity and mortality [50]. In their meta-analysis, Roubille et al., showed that the RA patients treated with corticosteroids presented a 47% higher to develop cardiovascular events. The authors emphasized the role of inflammation in the occurrence of cardiovascular events [51]. Hazard ratios (HR) of cardiovascular mortality were 2.27 (95% CI 1.36–3.79) in RA patients who had been treated with oral corticosteroids in daily doses between 8 and

15 mg and 3.21 (95% CI 1.14–8.97) in RA patients who had been treated with doses above 15 mg [1]. The increased cardiovascular risk associated with corticosteroids is dependent on dose and time of use [49]. Based on these facts, EULAR recommends the use of glucocorticoids in RA therapy as the lowest effective dose for the shortest period of time, in order to control the inflammatory process while awaiting csDMARD onset and minimize the risk of cardiovascular side effects [17]. csDMARD (conventional synthetic disease modifying antirheumatic drug) are represented by Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine. bDMARD are classified as TNF-alpha inhibitor (tumor necrosis factor inhibitor: Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Infliximab) and non-TNF-alpha inhibitor (non-tumor necrosis factor inhibitor: Anakinra, Abatacept, Tocilizumab, Sarilumab, Rituximab). tsDMARD (targeted synthetic disease modifying antirheumatic drug) are represented by Baricitinib, Tofacitinib, Upadacitinib. All these drugs have been shown to improve the cardiovascular risk, by the amelioration of sustained inflammation, and lipid profile improvement [39, 52–55].

Reducing inflammation very effectively, Methotrexate (MTX) is the gold standard of RA treatment, showing a reduction of cardiovascular events by 28% [51]. MTX influences the lipid profile, as increase the serum levels of HDL-cholesterol, total cholesterol, and LDL-cholesterol, decrease of lipoprotein (a) level, while the levels of apo-B and triglycerides remain unchanged [7].

Another csDMARD with similar efficacy as MTX in RA treatment is Leflunomide. But this drug is associated with arterial hypertension in 6–10% of treated RA patients. Therefore, it is very important to monitor blood pressure values at the initiation and then during treatment with this drug [56]. The use of this drug is not contraindicated in RA therapy, but it should be avoided in RA patients with uncontrolled arterial hypertension [48].

By interfering with platelet function, SSZ provides cardioprotection in RA patients. HDL-cholesterol levels are increased during treatment with SSZ alone, or in combination with MTX. On the other side, triple therapy with MTX, SSZ and Hydroxychloroquine confers a better lipid profile, consisting of higher HDL-cholesterol levels and lower total cholesterol and LDL-cholesterol levels [7].

By using Hydroxychloroquine (HCQ) in RA therapy, the risk of cardiovascular events has been reduced by 72%. This drug determined an anti-atherosclerotic lipid profile, consisted of lower total cholesterol, LDL-cholesterol and triglycerides, and higher HDL-cholesterol. A rare complication associated with HCQ therapy is cardiotoxicity, manifested in the form of dilated or restrictive cardiomyopathy, or atrioventricular block and bundle branch block. In order to avoid this condition, it is necessary to conduct regular screening using cardiac ultrasound and electrocardiography [7].

Active RA is characterized by increased cytokine levels. By effectively controlling inflammation and reducing cytokine levels, bDMARDs reduce the risk of cardiovascular events [48]. Among them, TNF-alpha has a very important role. Naerr et al., reported that by using anti TNF-alpha therapy, both the RA activity and cardiovascular risk decreased [57]. Halacoglu et al., showed a reduction of 30% in the risk of major cardiovascular events. The beneficial effects of anti TNF-alpha drugs are the consequence of blocking the actions that TNF-alpha has in the atherogenesis appearance [7]. Bergström et al., showed that the anti TNF-alpha therapy increased HDL-cholesterol, total cholesterol, and apo-B, and decreased the levels of Lp(a) [58]. But these drugs can cause or exacerbate heart failure; therefore, they are not indicated in moderate and severe forms of heart failure [59].

Abatacept is associated with the reduction of cardiovascular risk. The study performed by Jin Y et al., showed that the patients treated with Abatacept presented a 20% greater reduction in CV risk compared with TNF-alpha inhibitors [60].

The patients treated with Abatacept presented a significant increase in HDL-cholesterol [61].

Rituximab determined a significant increase in total cholesterol and HDL-cholesterol, and a significant decrease in inflammation (C reactive protein, ESR) and disease activity (evaluated by means of DAS28 score). The levels of LDL-cholesterol have not undergone significant changes [56]. Hsue et al., reported that the therapy with Rituximab had been associated with endothelial function improvement [62].

Tocilizumab decreases inflammation, has a favorable effect on serum fibrinolytic activity and left ventricular systolic function in RA patients, but arterial hypertension is one of side effects of this drug [1, 63, 64]. Curtis et al., analyzing cardiovascular events in RA patients treated with Tocilizumab and anti-TNF-alpha agents, did not identify significant differences between the two groups in terms of myocardial infarction incidence and sudden cardiac death [65].

By using small molecule inhibitors of Janus kinase (JAK), lipid profile pattern is modified in the following manner: levels of total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and apo-B levels are increased, and lipoprotein (a) is reduced (by baricitinib) or unchanged (by Tofacitinib) [53]. It is very important to note that with a dose of tofacitinib 10 mg twice daily, the risk of thrombosis has increased, this risk is not being noticed when reducing the dose at 5 mg twice daily [7].

In their meta-analysis, Ozen et al., showed that the risk of cardiovascular events was reduced by 28% by the use of MTX and by 30% by the use of anti-TNF-agents (Infliximab and Etanercept) use, while corticosteroid therapy increased the cardiovascular risk by 47% [66]. The use of Abatacept has also been associated with a reduction in cardiovascular risk [60].

It is important to note that in order to have cardioprotective effects, the dose of MTX must be higher than 15 mg/week [51]. These high doses of MTX reduce cardiovascular risk by controlling RA activity, but possibly also by direct effects on vascular endothelium [66].

Biologic DMARDs are associated with a lower risk of atherosclerotic cardiovascular disease than csDMARD [66]. Zhang et al., studying the risk of atherosclerotic cardiovascular disease in the RA elderly patients, showed that the risk is higher in patients treated with anti-TNF-agents compared to Abatacept and Tocilizumab [67]. By improving endothelial function, Rituximab would reduce the incidence of atherosclerotic cardiovascular disease [66].

In order to reduce the cardiovascular risk in RA patients, it is necessary to take some steps; at the time of RA diagnosing, the patient must be evaluated in order to detect subclinical atherosclerosis and cardiovascular risk factors. NSAIDs and corticoids should be used at the lowest doses, for the shortest period, and always associated with csDMARD. MTX dose should be over 15 mg/week. Administration of other csDMARDs (non-MTX csDMARD) will take into account the presence of cardiovascular risk factors. bDMARDs should be administered without delay, to control systemic inflammation and, implicitly, cardiovascular risk. But in the case of these drugs, the presence of cardiovascular risk factors will also be taken into account [48, 66, 67].

These are just a few aspects of cardiovascular risk in RA patients. Subsequent research will bring new data that will explain aspects related to cardiovascular risk in RA and will implement new therapeutic strategies to reduce it.

Conflict of interest

None.

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Chapter 7

Rheumatoid Arthritis and Periodontal Disease

Apoorva B. Badiger and Triveni M. Gowda

Abstract

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease (IMID), chronic progressive causing inflammation in the joints and resulting in painful deformity and immobility, especially in the fingers, wrists, feet, and ankles. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or their groups, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, clinical attachment loss, or both. Individuals manifesting both periodontitis and RA may suffer from a unifying underlying systemic dysregulation of the inflammatory response. In the past few years, increasing attention has been given to aspects of oral health in patients with rheumatoid arthritis, especially related to associations with periodontal disease. In this chapter we will be reviewing about the pathophysiology of RA and role of inflammation, periodontal disease: a gateway to RA, oral manifestations of RA, immunogenetics of RA and periodontitis, treatment implications for RA and periodontitis based on common pathophysiology.

Keywords: Rheumatoid arthritis, periodontal pathogens, periodontitis

1. Introduction

The global RA prevalence estimate was 0.46%. Women are affected 2 to 3 times more often than men. Onset may be at any age, most often between 35 years to 50 years, but can also be during childhood. Several risk factors like smoking, genetic association, recovery from bacterial or viral infections, sedentary lifestyles have been associated with the development of RA. In India, an estimated prevalence rate of RA is 0.5%–0.75% [1]. The Surgeon General's report on *Oral Health in America*, published in 2000, documented the significance of dental health on the overall general health and well-being of a patient. Research findings indicate possible relationships between chronic oral infections, such as periodontitis, and systemic disorders, such as diabetes, cardiovascular and lung diseases, stroke, osteoporosis, and rheumatoid arthritis [2]. A recent meta-analysis revealed an increased risk of RA in patients with periodontitis. The cross-sectional study was conducted to assess the impact of periodontitis (PD) on the health-related quality of life (HRQoL) and oral health-related QoL (OHRQoL) of subjects with rheumatoid arthritis (RA) and PD and found that the interaction effect of both diseases significantly conferred impacts on their OHRQoL and HRQoL [3]. Snyderman and McCarty reported common inflammatory mechanisms are shared by RA and periodontal disease (PD). Periodontitis is an inflammatory disease affecting periodontium caused by specific microorganisms like *P. gingivalis* (Pg), Aggregatibacteractinomycetemcomitans

(Aa), *T. denticola*, *T. forsythia*. Interestingly, these bacteria are also noted in the serum and synovial fluid of the joints of RA patients [4]. Mainly Pg and Aa can indirectly cause inflammatory reactions in the body. A study was conducted by Paola et al. on 4461 participants, of whom 103 were classified as having RA. Participants with RA had more missing teeth when compared to non-RA patients. It was concluded that there is a stronger association between periodontitis and tooth loss with RA [5].

2. Pathophysiology of RA & role of inflammation

RA is one of the more common autoimmune disorders, affecting approximately 1% of the population worldwide, and is characterized by dysregulated inflammatory processes in the synovium of the joint eventually leading to the destruction of both cartilaginous and bony elements of the joint, resulting in pain and disability. In a susceptible individual, the interface of environment and genes results in a loss of tolerance of self-proteins that contain a citrulline residue. The recognition of antibodies is directed against citrullinated peptides in RA. Enzymes like peptidyl-arginine deiminases (PADs)cause citrullination to occur. Citrullination is a normal process, vital for normal skin formation and other physiologic functions. But, in RA an autoimmune response develops against citrullinated peptides detected as anti-citrullinated peptide antibodies (ACPA). One of the tests to detect these antibodies detects anti-cyclic citrullinated peptides (anti-CCP). The presence of anti-CCP is>98% specific for the diagnosis of RA; though not all patients with RA will develop anti-CCP antibodies [6].

In the synovial fluid of patients with RA, a significant increase of T cells bearing the CD4+, 4B4+ helper-inducer receptor phenotype, and a significant decrease in CD4+, 2H4+ suppressor-inducer receptor phenotype was found in the peripheral blood of RA patients. The predominant feature is inflammation, mainly in the synovium. The synovial membrane in RA becomes hyperplastic. There is an amplified amount of synoviocytes and are infiltrated with immune and inflammatory cells, particularly macrophages, B- and T-lymphocytes, plasma cells, and dendritic cells. Increased levels of cytokines play a vital role in the dissemination of synovial inflammation.

There is a rising interest in the associations between oral health and autoimmune and inflammatory diseases. Several epidemiologic studies have described associations between rheumatoid arthritis and periodontal disease. Recent clinical studies are increasingly linked with biological assessments to better understand the nature of these relationships. These elicit the body to create antibodies – known as autoantibodies that include rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) in turn produces tumor necrosis factor-alpha (TNF-α), Interleukin (IL)-1, IL-6, IL-8, transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) that damage the body's cartilage, bone, tendons, and ligaments, resulting in the symptoms of RA [7].

3. Periodontal disease: a gateway to RA

In the case of rheumatoid arthritis, the initiating factor is an autoimmune response to structural components of the joint; in periodontitis, the initiating factor is the subgingival biofilm. In both cases, the destructive inflammatory events are remarkably similar, although the pathogenesis varies as a result of the

different anatomy. There has been a longstanding association described between periodontal disease with RA, However, it is now recognized that a specific species of bacteria, esp. *P. gingivalis*, colonizes patients with periodontal disease and marks the progression from gingivitis to aggressive periodontitis that can cause citrullination of proteins the posttranslational modification leading to the production of anticitrullinated protein/peptide antibodies, the most sensitive and specific rheumatoid arthritis biomarker. This gets converted to a citrullinated peptide in presence of the Peptidylarginine deiminase enzyme in turn forming immune complexes activating complement system releasing various inflammatory mediators causing joint destruction [3]. High levels of citrullinated proteins at the infection sites of *P. gingivalis* and their presence and serum levels correlate strongly with disease severity.

Concerning underlying pathophysiology, Chronic Periodontitis and RA share many pathological features and release several mediators that are common to both conditions(interleukin 1-beta and prostaglandin E2). Likewise, collagenase that specifically degrades collagen, activity is greater in GCF of periodontitis patients than healthy controls, also is elevated in RA synovial fluid, gingival crevicular fluid (GCF), and gingival tissue. A systematic review demonstrated that disease activity of RA relates with serum levels of IL-6, TNF alpha, and C Reactive Protein may influence an increase in inflammation leading to bleeding on probing (BOP). Antibodies to cyclic citrullinated peptides are connected with more aggressive and erosive rheumatoid disease [5]. Persistent periodontal disease as a trigger for chronic arthritis in vulnerable individuals via dysregulation in oral microbiota and host immune barriers. This prespective indicates that RA could be a consistent risk factor for chronic periodontitis, in contrary, newer theories emphasize that periodontal disease is a risk factor for RA (**Figure 1**) [1].

Though osteoclast precursors (OCPs) are produced in the bone marrow, circulate in the blood and enter active bone resorptive sites, and differentiate to osteoclasts. Periodontal bacteria-induced systemic IL-6 drives the expansion of OCPs that traffic to sites of bone resorption to boost osteoclastogenesis in response to locally produced RANKL, signifying changes in the bone marrow that link periodontitis to other disorders of bone loss, such as rheumatoid arthritis.

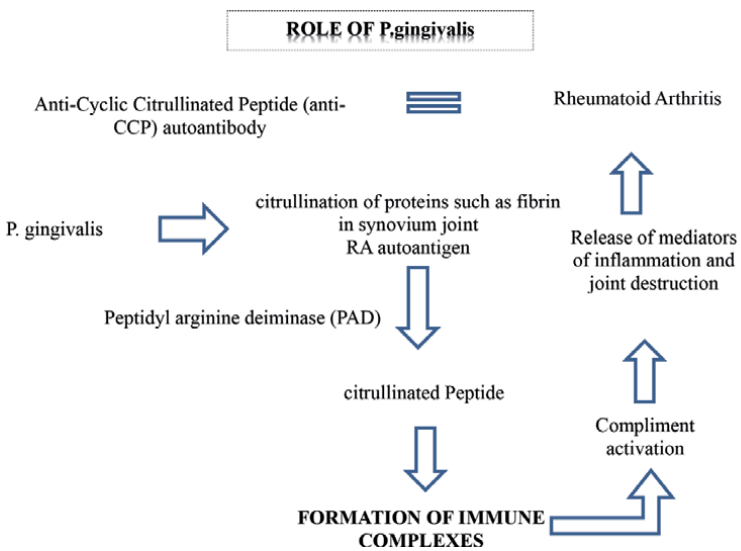

Figure 1.
Role of P.gingivalis in pathophysiology of RA.

Periodontal disease yields an excess of citrullinated protein, that causes a break of tolerance with anti-CCP stimulation. *A. actinomycetemcomitans* induces citrullination in neutrophils by neutrophil extracellular trap(NET) activation and release through leukotoxin A. *P. gingivalis*, which has a specific deiminase enzyme, that could be most liable(Dr. Marotte) Also, research demonstrates it will be critical to address periodontal disease at its initial stage perhaps when it is associated with anti-CCP in preclinical RA, improved oral care and possible vaccination are probable treatment options. Targeting periodontal disease in RA patients or after the effects of anti-CCP is too late to make any changes for the individual. Rituximab and tocilizumab, two medications used to treat RA, also reduce the gingival inflammation and gingival bone destruction in periodontitis cases. However, infliximab enhances gingival inflammation while preventing periodontal bone loss [2].

Systematic review and meta-analysis revealed significantly increased risk of periodontitis in people with RA compared to healthy controls with a significantly raised mean probing depth, risk of bleeding on probing (BOP), and clinical attachment loss. Also, a study reported the presence of *P. gingivalis* and periodontal disease can be a trigger in individuals at risk for developing rheumatoid arthritis. Phase 1 therapy(scaling and root planing) has been effective as a therapy for established rheumatoid arthritis. Periodontal disease could also have probable downstream effects that impact additional related diseases [3, 8].

4. Oral manifestations of RA

The clinical manifestations of periodontal destruction is a result of the complex interplay among etiologic agents like bacterial plaque. Usually, it can be controlled by the body's defense mechanisms without destruction; however, when dysbiosis happens (like increased susceptibility, high bacterial load, or pathogenic infections/systemic infections) periodontal destruction could occur. Also, the recent outbreak of coronavirus infection throughout the world is a matter of global emergency. Patients with comorbidities, in their old age, and with a compromised immune system are at the highest risk of mortality.

Patients with autoimmune diseases, like lupus and rheumatoid arthritis (RA), already have a compromised immune system which is coupled with the prescribed immunosuppressive agents they take—making them more susceptible to infections. Rheumatoid arthritis has been associated with different oral manifestations, such as temporomandibular joint disorders, xerostomia, secondary Sjögren's syndrome, and periodontal disease (PD) [9].

5. Immunogenetics of RA and periodontitis

RA has various features typical of a complex genetic disease, such as multiple gene involvement, genetic variance, and incomplete penetrance. Susceptibility to rheumatoid arthritis (RA) is associated with defined HLA-DRB1 alleles. This specific regulation of DRB1 gene expression in RA patients represents one of the molecular mechanisms involved in the interrelation of HLA DRB1 genes. RA has several features typical of a complex genetic disease, such as genetic variance, incomplete penetrance, and multiple gene involvement. To date, the HLA complex is a strongly associated genetic factor for RA. DNA sequencing demonstrated that the actual disease-conferring portion of the D region of the HLA-DRB1 gene [10].

Various periodontal pathogens are involved in the process of periodontitis. Biofilm of periodontal disease supplies abundant Lipopolysaccharide(LPS).

Local production of IgA and IgM rheumatoid factor(RF) in periodontal disease has been documented. In particular, the HLA antigens A9, A28, BW15, and DR4 are associated with early-onset forms of periodontitis. The severity of RA and periodontal disease are partially due to intrinsic differences in the monocyte/T cell response traits. In both diseases, antigenic challenge (e.g. LPS) to the monocytic/lymphocytic axis would result in the secretion of catabolic cytokines and inflammatory mediators that would dominate. Also, IL-1 Genetic polymorphisms of cytokines have been associated with the susceptibility, severity, and clinical outcomes of inflammatory diseases, such as periodontitis and chronic arthritis [11].

6. Treatment implications for RA and periodontitis based on common pathophysiology

Many systemic conditions can alter the host's susceptibility to periodontitis. For instance, immunosuppressive subjects unable to mount an effective host response to subgingival microorganisms, thereby causing accelerated periodontal destruction. Contrarily, individuals with a substantial rise in the proinflammatory mediators may respond to periodontal pathogens with a boisterous inflammatory reaction causing periodontal tissue destruction. Though the interrelation of many systemic disorders on the periodontium is well documented, evidence suggests that periodontal infection may significantly increase the risk for various systemic diseases or may modify the natural course of systemic conditions.

Reports of the American Dental Association (ADA), American Academy of Oral Medicine (AAOM), British Society for Antimicrobial Chemotherapy (BSAC) American Academy of Orthopedic Surgeons (AAOS), suggest that routine antibiotic prophylaxis before dental treatment is not indicated for most patients with prosthetic joint replacement. However, antibiotic prophylaxis is indicated for almost all patients within the first 2 years after joint replacement patients, rheumatoid arthritis, systemic lupus erythematosus, etc. Many researchers cogitate patients with severe periodontal disease or other dental infections to be at great risk, and antibiotic prophylaxis may be indicated before dental treatment [2].

Several treatment approaches have been introduced to aim the host response to LPS-mediated tissue destruction. Either topically/systemic or in combination with scaling and root planing or surgical therapy. Pharmacologic inhibitors of NF-kB and sp38 MAPK pathways are actively being developed to manage rheumatoid arthritis and inflammatory bone diseases and they have been applied in periodontal disease models with noteworthy accomplishments. MMP inhibits the signal transduction pathways involved in inflammation. With the use of this novel strategy, inflammatory mediators including pro-inflammatory cytokines (e.g., IL-1, TNF, IL-6), MMPs, and others would be inhibited at the level of the cell-signaling pathways required for the transcription factor activation [12].

NSAIDs such as aspirin, naproxen, diclofenac and ibuprofen are the first line of treatment for RA. Also, the use of NSAIDs in managing periodontal disease has been extensively studied and the results are promising. Disease-modifying anti-rheumatic drugs (DMARDs) are second-line drugs used in RA. Effects of administration of systemic gold salts were associated with significantly less periodontal destruction. Chemically modified antibiotics and genetically engineered proteins (monoclonal antibodies and pro-inflammatory cytokines correct the imbalance between the pro-inflammatory and anti-inflammatory cytokines involved in the pathogenesis of RA and periodontitis. Tenidap inhibits cyclooxygenase and PGE2 production with inhibition of IL-1, IL-6, and TNF-a production

that reduces bone resorption and cartilage degradation as activating collagenase and stromelysin in RA patients [2].

Tetracyclines like Doxycycline have been advocated for treatment of patients with systemic diseases such as diabetes, rheumatoid arthritis that has led to improvements in the periodontal health and enhance reattachment or stimulate new attachment of the supporting apparatus and osseous formation. in the future, HMTs will likely be developed as adjunctive treatments for periodontitis. Novel *anti-cytokine drugs* developed for the management of rheumatoid arthritis, a disease with pathophysiology similar to that of periodontitis. Cytokines like TNF-_ have been targeted by TNF-_ antagonists mainly infliximab, etanercept which are effective in treating rheumatoid arthritis [12].

Rheumatic diseases cause patients to seek care for musculoskeletal pain or dysfunction or other problems. Temporomandibular Joint (TMJ) involvement follows the course of most joint involvement. Adherence to articular surfaces, Capsular scarring, and shrinkage may further reduce joint mobility. NSAIDs are routinely used. Education, rest, and physio therapy complete the regimen for treatment. A study by Kononen et al. reported that the subjective symptoms and the clinical signs of CranioMandibular Disorders (CMD) in RA, Psoriatic Arthritis(PA), and Ankylosing spondylitis(AS) are caused mainly by the respective general joint diseases, which directly affect the masticatory system, especially the TMJ. Further, signs and symptoms of CMD are more frequent and severe in RA than in PA or AS [13].

7. Conclusion

RA, being a common autoimmune disease, is associated with inflammation of the joint and, if left untreated, results in joint destruction and resultant disability. Periodontal disease is an infectious process that necessitates bacterial presence and host response that is affected and modified by local, environmental, systemic, and genetic factors. Both RA and periodontitis have remarkably similar pathology. Numerous studies documented interrelationships between them. Individuals suffering from RA more likely to experience significant periodontal problems compared to non-RA patients. With this understanding that the imbalance between pro and anti-inflammatory cytokines in the pathogenesis of RA and periodontitis, emerging therapies have focused on the inhibition of destructive proteases and pro-inflammatory cytokines. These therapies hold tremendous promise in altering the course of progressive forms of RA and periodontitis. Closer attention to oral health in these patients will improve quality of life by providing insights for treatment and prevention.

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Chapter 8

The Regenerative Effect of Intra-Articular Injection of Autologous Fat Micro-Graft in Treatment of Chronic Knee Osteoarthritis

Mohammed Mesfer Al Kahtani, Ali H. Al Yami, Sarah Saleh Al Qahtani and Sihem Aouabdi

Abstract

Osteoarthritis (OA) is one of the most prevalent conditions resulting to disability particularly in elderly population About 13% of women and 10% of men aged 60 years and older have symptomatic knee OA. The proportions of people affected with symptomatic knee OA is likely to increase due to the aging of the population and the rate of obesity or overweight in the general population. There are multiple factors associated with this progressive disease such as obesity, female gender, and repetitive trauma. Pain is the most common symptom in knee OA, a leading cause of chronic disability, clinical diagnosis will be supported by certain radiological findings. There are numerous conservative therapies that help to relive symptoms depend on severity of Osteoarthritis, and knee replacement remains standard of care in advance disease. Fat Micrografting is evolving technique with promising result in selected patients with regenerative and reparative effect of adipocyte-derived stem cell toward damaged cartilage and bone, which supported by clinical evidence.

Keywords: autologous fat micrograft, knee osteoarthritis, intra-articular injection, cartilage degeneration, adipocyte stem cells

1. Introduction

Rheumatic and musculoskeletal diseases (RMDs) constitute a group of more than 150 Conditions that are commonly characterized by progressive lesions and painful symptomatology. Altogether, they account for the leading cause of morbidity and disability worldwide, giving rise to tremendous health expenditures and professional incapacity. Osteoarthritis (OA), one of the RMDs, is a degenerative condition that principally involves the joint's cartilage, leading to its progressive destruction. It is related to aging and lifelong continual stress on the most functional articulations such as the knees, hips, and fingers, and the lower spine region. OA ranks among the ten most disabling conditions in developed countries. The global prevalence of symptomatic OA is estimated as 9.6% in males and 18.0% in

females over 60 years of age. Further, 80% of individuals with OA would experience significant movement limitations, and 25% would have serious handicap to perform routine activities of the daily life [1].

The prevalence of OA varies in different regions of the world, with rates ranging from 3.8–70%, depending on the methodology of studies, whether clinical, radiographic, patient self- reporting, or physician diagnosis [2]. As the incidence and prevalence of OA increase with age, the extending life expectancy results in a growing number of people afflicted with OA, with a proportional risk of disability. In the United Kingdom, 20–30% of the elderly population (aged 60 years and above) are diagnosed with symptomatic OA [3]. In the Middle East countries, including Iraq, Yemen, Saudi Arabia, and Syria, more than one million people are estimated to have OA [4]. Approximately 85% of individuals over the age of 75 experience some symptoms of OA [5].

Knee pain represents more than 80% of the total burden of OA [6]. High body mass Index (BMI) has become an epidemic in the US in recent decades and is a well-known risk factor for knee OA [7]. In Saudi Arabia, a clinically based epidemiological study, at a primary healthcare clinic, by Al-Shammari et al. showed a prevalence of OA as high as 57.2%. Other data by Al Arfaj estimated the prevalence of knee OA as 53.3% and 60.9% in males and females respectively [8, 9].

The treatment of knee OA may use conservative measures including medications, Physiotherapy, and local injections, or surgical approach including total knee arthroplasty (TKA). TKA is highly effective in reducing articular pain and is associated with acceptable functional outcomes. The procedure of TKA is safe and is considered one of the most common and successful procedures in orthopedics.

2. Risk factors

Blagojevicy et al. did a systemic review and meta-analysis to study the risk factors of Knee OA in older patients. They included 85 out of 2233 studies screened. The main risk factors found were obesity, previous trauma, hand OA, female gender and older age [10].

High body mass index (BMI) is associated with development of knee OA, and it was proven that the physical disability of the patients affected by knee OA reduced after weight reduction [11].

Another meta analysis conducted by Muthuri et al. showed that knee injury's history is one of the major risk factors associated with Knee OA and it should be included in any prevention program since it is preventable factor [12]. Genetic factor as shown in different studies is also associated with OA [13]. Increased loading or mal alignment of the joints is considered to be other factors that may lead to OA. So, in summary the risk factors can be classified into patient related factors like BMI, genetic, gender and age and joint related like previous injury, abnormal loading or malalignment [14].

3. Staging

In research, multiple variations of the Kellgren and Lawrence staging system have been used. However, the original one is: [15].

- grade 0 (none): definite absence of x-ray changes of osteoarthritis.
- grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping.

- grade 2 (minimal): definite osteophytes and possible joint space narrowing.
- grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
- grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

4. Management

General and clinical assessment of the patient will help in determining the appropriate. Treatment of osteoarthritis. The assessment of OA effect on patient's function, daily activity, social relationship and quality of life should precede any treatment. The. Management plan has to be discussed with the patient thoroughly including the education of osteoarthritis, benefits and risks of various treatment options.

4.1 Non-surgical management

There are different non-surgical methods to treat joint OA. According to the Osteoarthritis Research society International (OARSI) guidelines published in 2019, patient education and land-based exercise with or without management of dietary weight are core treatments of knee related osteoarthritis. Non-steroid anti-inflammatory drugs (NSAIDs) are recommended in OA.

Management and its topical derivative are strongly recommended for patients with knee OA. COX-2 inhibitors or NSAIDs with proton pump inhibitor should be utilized in patients with gastrointestinal pathology. Oral NSAIDs are not recommended for patients with cardiovascular diseases. Intraarticular injection with corticosteroids or hyaluronic acid is mainly used for knee OA. It is not recommended for poly articular or even hip OA. All these non-surgical methods are associated with different level of evidence in the literature [16].

4.2 Surgical management

Before surgical intervention is considered, the patient should have received the core conservative treatment. Arthroscopic debridement and lavage are not routinely recommended unless there is a clear justification such as mechanical block that can be resolved arthroscopically [17]. After failure of all non-surgical treatments and in advanced joint arthritis, the total joint arthroplasty using artificial joint is the best option. It should be done before the patient gets advanced functional limitations. It is very safe procedure and associated with sound outcome. Pre- and post-operative patient engagement in terms of having proper education and well-structured physiotherapy is crucial to end up with great results. The American Academy of Orthopedic Surgeons (AAOS) in their 2nd edition evidence-based guideline for the treatment of knee OA has published 15 recommendations. This includes self-management exercise programs, weight reduction for painful knee and BMI < 25 and NSAIDs (oral or topical) or tramadol for symptomatic patients. They could not recommend the use of glucosamine and chondroitin, Intra articular Hyaluronic acid injection and arthroscopic lavage and or debridement for patient diagnosed with knee OA. They were unable to recommend for or against the using of knee corticosteroid, growth factor, platelet rich plasma (PRP) intraarticular injections and arthroscopic partial meniscectomy for a torn meniscus in patients with

symptomatic OA. They also have stated that high tibial vulgus osteotomy might be performed for patients with painful medial knee joint OA [18].

5. Fat graft evolution

Neuber presented history of fat transplantation in literature initially in 1893 and he stated that smaller fat parcels tend to undergo less absorption [19], followed by communication from Czerny [20] Lexer [21], and Rehn [22]. In 1911, Bruning was the first to transfer autologous fat into the subcutaneous tissue for the purpose of soft-tissue augmentation [23]. 1950 Peer published 1st book about fat grafting in 300 pages, mentioned that survival rate of fat graft could be 50% and determined the viability of fat tissue which injected [24], in 1980 s liposuction technique evolved which improved technically over time, 1985 Illouz [25] and Fournier [26] developed an comprehensive approach to fat transfer by syringe harvesting, called "microlipoinjection". Fat harvest from liposuction became the simplest and easiest method to pursue fat grafting, which indicated to treat soft tissue depression and contour deformity. 1990 Coleman described steps of fat injection procedure and coins the term Lipostructure [27].

There is numerous indications for fat graft in esthetic and regenerative medicine, Fat grafting technique evolved over period of time and become standard of care use in esthetic and reconstructive cases, in era of regenerative medicine, Lipoaspirate is consider source of fat micrograft which contains adipocyte derived stem cell (ADCS), growth factors, preadipocytes and cytokines demonstrate promising clinical application in wide spectrum of pathology to regenerate and reform damaged biological structure and improve outcome as in Osteoarthritis which consider leading cause to disability particularly in elderly population [28].

6. The use of microfat graft for cartilage repair

Cartilage contain a small number of cells known as chondrocytes, which are responsible for maintaining a large extracellular matrix, 85% of cartilage constitutes water and two categories of molecules: collagenous and noncollagenous [29], The main function of cartilage is to protect underlying bone from friction and act as gliding surface to enable motion, Articular cartilage is characterized as avascular, aneural, and alymphatic and, at maturity, of low metabolic activity [30], which entitle cartilage to special tissue with difficult task to repair it self, It has been demonstrated that early in the process of cartilage damage there is a rapid loss of glycosaminoglycans from the tissue [31]. Thus, most large defects fail to heal, leading to a long-term prognosis of osteoarthritis [32].

7. Surgical technique to harvest fat

Fat is readily available and simple to harvest, with the fat grafting surgery itself shows a low donor-site morbidity, and is inexpensive and repeatable. Liposuction is considered one of the most frequently performed surgical procedures all over the world, Since its introduction in 1982 using a blunt cannula attached to a suction generating device, the procedure has been improved [33]. Current technology for liposuction includes suction-assisted lipectomy, ultrasound-assisted, power-assisted, laser-assisted, and radiofrequency-assisted liposuction [34].

7.1 Harvesting of the adipose tissue

The first step in fat transfer to harvest fat by Many different liposuction techniques, all with the aim of minimizing adipocyte damage and increasing its survival Chosen Donor site is pretreated with a tumescent solution which containing an anesthetic mixture of Lidocaine, Sodium bicarbonate to overcome the acidity of mixture and to reduce pain and discomfort at injection site,epinephrine to control bleeding by vasoconstrictive action and Normal saline, proportionally mixed according to surgeon preference, volume to be injected determine by the desire volume of fat harvest and accordingly 2–3 cc of tumescent mixture to each 1 cc of anticipated fat harvest.

There are a variety of suction methods from which one may choose. The standard techniques are the manual (Coleman technique) or suction-assisted liposuction (SAL). Negative pressure is applied With the Coleman technique and SAL in combination with gentle forward and backward movement of the cannula, causing physical disruption, thus allowing fat tissue harvest. These methods represent the current gold standard, and reports show a lack of stem cell damage and preservation of their regenerative potential [35].

There are multiple modifications of this method, including power-assisted liposuction (PAL), water jet- assisted liposuction (WAL), laser-assisted liposuction (LAL), ultrasound-assisted liposuction (UAL), and VASER (Vibration Amplification of Sound Energy at Resonance).

They all are developed to further facilitate the process of suctioning, with minimal trauma to the donor site and maximal outcome in the requested esthetic result.

Large-bore cannulas decrease the mechanical sheer stress on the harvested cells, and subsequently increase the total number of viable aspirated cells, and Studies have showed an inverse relationship between cellular damage and the diameter of the instrument used to extract fat [36].

8. Processing of lipoaspirate

The goal of processing is to eliminate cellular debris, a cellular oil and excess of infiltrated solution [37]. These elements cause inflammation at the recipient site, which can be unfavorable for the fat graft. Also, blood must be removed as it accelerates the degradation of the transplanted fat.

Sedimentation: little traumatic and gives a large number of vital and intact adipocytes. However, this method contains smaller concentrations of stem cells and a substantial amount of cellular debris and thus making it harmful to graft survival [38].

Filtration techniques: more efficient in producing viable graft material for large-volume fat transfers. One example is Puregraft filtration system; which is a closed-membrane filtration system that was originally designed to prepare fat for isolation of the stromal vascular fraction. Another example of filtration is lipoaspirate filtered with cotton gauze; this results in concentrating the fat and separating it from the infiltrated solution, oil and cellular debris. This method, as compared to centrifugation, showed no significant differences in the viability of transplanted fat cells.

Washing with normal saline: this preserves mesenchymal stem cells as well as a great number of adipocytes.

Centrifugation: considered the most frequently used technique. It separates fat from substances that increase the degradation such as blood, proteases, lipids, lipases, and it may concentrate the adipose stem cell fraction, potentially enhancing

graft survival, Coleman suggested a processing method where centrifugation speed is 3000 rpm for 3 min. This creates multiple layers; the upper level is composed primarily of oil, the middle portion is fatty tissue, and the lowest portion, which is the densest layer, is composed of fluids and blood. This method obtains the highest possible concentration of stem cells within aspirate. It has also the increased content of angiogenic growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). To note that excessive centrifugal force may damage intact adipocytes and on the other hand better graft viability with low centrifugal forces.

9. Microfat graft preparation

Processing micro fat graft that require to process harvested fat graft through multiple micro pores filters that allow micro fat graft to pass through, these filters have different sizes that connected to Leur-leur 1–10 cc syringe.

10. Fat graft injection

Adipose tissue is injected in to the transplantation site through cannulas, where multiple tunnels are created on insertion, and fat is injected during withdrawal of the cannula. Graft through nutrition by tissue fluid absorption can survive up to 48 h. Meanwhile, neovascularization is being established. Therefore, the diameter of the graft should not be more than 2 mm to avoid central necrosis. The osteoarthritic knee joint was injected with autologous intra-articular fat micrograft 15–20 mL through the lateral approach according to the case in an amount that did not produce high pressure inside the joint and did not produce pain to the patients due to tension of the joint capsule [39].

11. Postoperative care

Postoperative care include antibiotics for one week, pain killers, and garment pressure dressing at injection and donor sites, encourage exercise and physiotherapy, massage to reduce swelling.

12. Complications

Infection is the most devastating encounter complication which presented as redness, hotness, increase pain, and purulent collection, treatment depend on severity of infection ranging from I.V antibiotics in addition to incision and drainage.

13. Fat is source of adipocyte derived stem cells (ADSC)

Adipose tissue composed of mature adipocytes (>90%) and a stromal vascular fraction (SVF), which includes preadipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, resident monocytes/macrophages, lymphocytes, ADSC, cytokines and growth factors [40–46], led to a growing interest for the use fat graft as regenerative therapy for common bone and joint diseases, with promising

therapeutic clinical application of ADSC into skeletal system with underlying structure such as Muscle, cartilage, ligament, tendon, and bone with regenerative and reparative potential and ADCs are considered as an ideal source of cell therapy for different types of diseases including bone and joint diseases [47].

14. Adipocyte derived stem cell role in regenerate knee osteoarthritis

Adult stem cells, represented mainly by the mesenchymal stem cells (MSCs) are present in most organs and tissues of the human body; they intend to replace damaged cells as a normal process [48]. These stem cells do not have ethical or legal concerns as compared to the embryonic and fetal stem cells [49]. Mesenchymal stem cells are a promising tool for tissue regeneration. They are multipotent adult stem cells obtained from different sources like bone marrow (BM), adipose tissue, umbilical cord, placenta, synovial membrane [50]. These cells because they are located in fat and synovial membrane, they are most suitable for the treatment of osteoarthritis (OA) [51].

The International Society of Cellular Therapy (ISCT) defines mSCs by three characteristics [52]. They need to be plastic adherent, express specific markers like the CD105, CD90, and negative for CD34, CD45, HLA-DR [47, 53, 54]. MSCs can differentiate to mesodermal lineage cells (osteocytes, adipocytes, chondrocytes) [54]. These cells differentiate also into many other cell types, like myocytes, neurons [55], cardiomyocytes and hepatocytes [56] in vitro and in vivo [57–59].

They are non-immunogenic cells as they lack the expression HLDR receptor, which makes them suitable for allogeneic transplantation [59]. These cells are capable of suppressing lymphocyte reactivity [60] and inhibit the production of inflammatory cytokines in vitro [61]. MSCs express cytokine and chemokine receptors on their cell surface, which allows them to migrate to the site of injury [62]. The ability to suppress the immune response enabled their use in graft-versus-host disease and transplant rejection [63].

Each of the MSCs depending on their origins presents some differences. The BM-MSCs have high differentiation capability, but are difficult to get from bone marrow. The adipose MSCs are easily obtained from adipose tissue with high yield and strong suppressive capabilities [64]. The umbilical cord MSCs are easy to get after birth, they have high self-renewable and differentiation capacities. The synovial-MSCs have high proliferative and differentiation capacities and very low immunogenicity [64].

MSCs from BM from mouse and from human were the first to be identified and are the most studied [54, 58]. Adipose stem cells (ASCs) were first identified as stem cells in 2001, capable to differentiate into cartilage, bone and adipose cells [65].

The age of the donor reflects on the differentiation potential of the cells [66]. Umbilical cord MSCs (UC-MSCs) showed to be highly proliferative and with differentiation potentials [67]. The drawbacks of the BM-MSCs are that the procedure to obtain the cells is painful, costly and does not yield high number of cells for cell therapy [49, 68, 69]. Besides, the procedure for BM isolation can result in potential infections [54].

Synovial-MSCs (S-MSCs) isolated and characterized first in 2001, are also promising tools for the treatment OA due to their natural homing in this site [70]. They were shown to have high chondrogenic differentiation capacities, high expression of type II collagen, compared to other sources of MSCs [71, 72]. S-MSCs are isolated in low numbers from different sites, like styloid fossa and paralabral synovium [73, 74]. They have low immunogenicity with high proliferation potentials [75, 76].

The adipose MSCs (A-MSCs) represent many advantages compared to other sources of the MSCs. They are abundant in the adipose tissue, adipose tissue is easier to get compared to BM, they have strong immunosuppressive capacities [47].

More research is needed to unveil the differences in the traits of A-MSCs isolated from different sites and their implications in therapy. Previously, it was shown that A-MSCs could differentiate from one site to another in term of their cell markers. The A-MSCs isolated from abdominal adipose tissue had high expression in CD31, CD45 and HLA-DR compared to the cells isolated from orbital adipose and had lower expression of CD73, CD90, CD105 and CD146 [77]. MSCs from adipose tissue represent a good and a promising alternative to bone marrow MSCs. They share the same phenotype as MSCs from bone marrow apart from few. They differentiate similarly to BM-MSCs into the three lineages, chondrocytes, adipocytes and osteocytes. Most importantly, they are easily obtained from liposuction aspirate of patients undertaking plastic surgery [65]. Adipose tissue contains greater number of stem cells than bone marrow (10 times higher) [59]. A large number of cells are required for transplantation. Stem cells isolated from adipose tissue or another source like bone marrow, need to be scaled up. At least 2x106 of MSCs is required per kilogram body weight [78].

MSCs from different sites (BM, adipose) tissue are heterogeneous cell population [79]. Although MSCs from bone marrow and from adipose tissue have similar differentiation potential, there are minor differences. ASCs showed higher chondrogenic potential than MSCs from bone marrow [80]. Other study however, showed no significant differences between these two populations for chondrogenic differentiation in 2D culture but the BM-MSCs showed higher chondrogenic differentiation in 3D culture [81]. Proliferative capacities and osteogenic differentiation of the MSCs from bone marrow are reduced with age [82]. According to previous report, MSCs can be affected differently depending on the disease. For example, it was reported that the BM- MSCs from osteoporotic patients had reduced osteogenic activity [82], whereas the BM-MSCs from OA patients did not show any differences with the normal patient [83]. In another, the chondrogenic and adipogenic differentiation of the MSCs were reduced in OA patients but not the osteogenic differentiation [84].

The expression of CD36 differed between donors from no expression to highly expressed [85]. However, all ASC extracted from different donors showed the expression of the CD90, CD73 and CD105. ASCs markers can change in expression depending on the age of cells in culture. CD106 is expressed in MSCs from bone marrow but not in ASCs where this latter expresses CD49b [52]. ASCs and BM-MSCs express CD29 (beta-1 integrin, important factor in angiogenesis) [74] and CD44 (hyaluronate receptor, important for neoextracellular matrix) and CD49e (alpha-5 integrin, important for cell adhesion to fibronectin) [59]. ASCs and BM-MSCs have been shown to secrete angiogenic growth factors, like VEGF, P1GF, bFGF, angiogenin, GM-CSF, MCP-1 and SDF-1alpha (Rehman, 2004; Kinnaird et al.; 2004), these could be involved in increased angiogenesis in ischaemic tissue [59]. CD117 (stem cell factor) a marker for totipotency and pluripotency, was expressed in ASCs and BM-MSCs [85]. Based on the International Society for Cellular Therapy, the minimum criteria to define mesenchymal stem cells are CD105 and CD90, their potential to differentiate to adipocytes, chondrocytes and osteocytes and they are plastic adherent [86]. The expression of the CD34 is only reported on the adipose derived mesenchymal stem cells but the expression decreases in culture [87, 88] and the expression of CD105 increases [89] (Braun et al.; 2013). CD34 is expressed on ASCs before they are isolated from the stromal vascular fraction (SVF) [89] (Braun et al., 2013). The International Society for Cellular Therapy (ISCT) and the International Federation for Adipose Therapeutics

and Science (IFATS) agreed on these changes in phenotype of ASCs in SVF (uncultured) or when cultured [90]. The SVF is referred to the cellular pellet containing ASCs and endothelial progenitor cells without adipocytes and immune cells, [89]. When the SVF is plated, the ASCs adhere to the surface and the rest of the cell population including non-adherent and non-proliferating cells, are removed [89]. ASCs could be isolated from SVF by culture or by magnetic-activated cell sorting (MACS) [89]. The advantage of the MACS isolation is cells can be prepared in few hours as required in clinical application. When cells need to be expanded, isolating the ASCs with culture is the best method. ASCs and SVF could be used for transplant but the number of cells obtained from patients could limit the use of SVF. ASCs could be expanded to a large number of cells, which could be used for autologous transplant or banked for allogeneic transplant [89]. These differences could be due to site differences or due to the lack of standardized isolation method [91].

14.1 Clinical trials with ASCs

MSCs showed to have a big potential in clinical applications. The first clinical trials run on the application of bone marrow MSCs in patients with Hurler syndrome and metachromatic leukodystrophy (MLD) after allogeneic hematopeitic stem cells transplant, showed no toxicity secondary to the bone marrow MSCs transplant and the recovery of some of the symptoms were suggested to be due to the transplanted MSCs [92]. Since then, hundreds of MSCs clinical trials were run on many conditions including neurological diseases, cardiovascular, autoimmune and bone and cartilage diseases [93]. So far, there have been few approved clinical application for the MSCs in different countries. Few examples, are the application of allogeneic MSCs for the treatment of graft versus host disease (GVHD) in Japan, autologous bone marrow MSCs for amyotrophic lateral sclerosis and autologous adipose MSCs for Chron's fistula, human umbilical cord blood-derived MSCs for osteoarthritis in South Korea, and in Europe the application of allogenic adipose MSCs for the treatment of fistulas in Crohn's disease [70].

There are few procedures for the treatment of cartilage injuries; the arthroplasty, microfat grafting and the autologous transplant of chondrocytes but a curative therapy still need to be developed [94, 95].

The autologous chondrocytes implantation is a surgical procedure that involves the isolation of autologous chondrocytes, expanding them in vitro then transplanting them back to the patient [96]. The application of MSCs for knee repair showed to be more effective with fewer side effects from the surgical procedure of the isolation of chondrocytes [96]. There are many clinical trials on the applications of the MSCs for OA [70].

OA is a very common condition in adults, which affects articular cartilage, subchondral bone, synovial tissue and meniscus of the joint. This leads to cartilage degeneration, osteophytes formation, subchondral sclerosis and synovial hyperplasia [97]. OA may be caused by joint injuries, obesity, aging and could be inherited condition [97].

Previous applications of MSCs for cartilage repair showed good outcomes. The BM-MSCs transplant in patients for defects in their knee cartilage and in athletes with the defect in femoral cartilage showed a good recovery of their functions [98].

MSC isolated from bone marrow, adipose tissue, umbilical cord, synovial membrane were previously used for the treatment of OA [64].

Since the discovery of ASCs, they have been used in many clinical trials for different diseases [90]. Success has been reported from different clinical trials using ASCs, but the mechanism of action is still not clear on whether cells would differentiate into the tissue or modulate the immune system [89]. Direct application of the

human ASCs improved cardiac function when injected in animals with myocardial infarction [99]. This effect was believed to be due to trophic factors released by the stem cells and differentiation of the ASCs. Local administration of ASCs accelerated the wound healing in normal and diabetic animals through differentiation into epithelial and endothelial lineage and neovascularization [100]. ASCs were applied to an injured skin due to radiotherapy, showed good healing process compared to the control [101]. ASCs although they have been used successfully in clinical trials, but their effects are not always achieved. There are many reasons that could impact the success of the use of ACS from one trial to another like cell separation, delivery methods, cell homing, engraftment and their survival [89]. Other factors might have an impact on the success of the use of ASCs like the type of liposuction procedure, site of liposuction, age of the patient and the body mass index (BMI). These factors are being investigated. Extraction of fat with different techniques might have an impact on cell viability of stem cells, their proliferation and the phenotype due to the trauma generated during the procedure. It is important to examine the different liposuction techniques and their impact on the ASCs phenotype, proliferation, and stress level for downstream applications either in research or in clinical applications.

15. Conclusion

Knee osteoarthritis is most prevalence musculoskeletal disease which cause functional limitations and affect a person's quality of life, there are known factors related to underling OA pathology such as Obesity, female gender and repetitive trauma to knee, Radiological finding such as subchondral cyst and narrowing of joint space, will support clinical diagnosis and staging of the disease using Kellgren and Lawrence staging system. Which will dictate the treatment modalities, in early stages conservative treatment such as modification of life style, rehabilitation, NSAID. Where advance stage surgical interventions ranging from arthroscopic debridement and lavage in case of blockage to total knee arthroplasty, which is being standard of care in severe condition.

Evolution of fat graft application in wide spectrum of clinical applications and have shown promising outcome to alleviate OA symptoms, where its contain adipocyte stem cells which known with reparative and regenerative process with presence of signal cofactors such as platelets derived growth factors and other growth factors to repaired damaged cartilage, fat graft being harvested from donor site mostly from abdomen, then;lipoaspirate will undergo further processing to isolate pure fat out from oil and fluid layer, then fat graft filtered with connector to reach pure micro fat graft ready to inject into affected knee under sterile process with local anesthesia.

Numerous clinical trials conducted to examine efficacy of microfat graft and ASC injection into knee with OA which demonstrated improvement in the overall condition, and further research with larger samples being in the process of publication to support clinical application and examine safety of patients.

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Chapter 9

The Effect of a Proprioceptive Exercises Programme on Disease Activity and Gait Biomechanical Parameters of Post-Menopausal Women with Rheumatoid Arthritis

Pedro Aleixo, Tiago Atalaia, José Vaz Patto and João Abrantes

Abstract

This study aimed to assess the effects of a proprioceptive exercises programme on disease activity and on ankle kinematic and kinetic parameters of post-menopausal women with rheumatoid arthritis. Twenty-seven post-menopausal women with rheumatoid arthritis were allocated to exercise group (n = 15) or control group (n = 12). Exercise group intervention: proprioceptive exercises (12 weeks; 3 one-on-one workouts/week; 30 min/workout). Control group intervention: stretching exercises (12 weeks; 1 one-on-one workout every two weeks; 30 min/workout). Disease Activity Score (28 joints) was used to assess disease activity. A 3D motion analysis system (9 cameras, 200 Hz) and a force plate (1000 Hz) were used to collect kinematic and kinetic data during a barefoot walking at self-selected speed. For each subjects' foot, 7 trials of the stance phase were collected. One subject withdrawal was registered in exercise group. Post-intervention, exercise group' subjects yielded higher gait speed, shorter stance phase, shorter controlled dorsiflexion sub-phase, and higher ankle power peak ($p < 0.05$), however, they showed no differences in Disease Activity Score, ankle moment of force peak, and variability of biomechanical parameters; control group' subjects showed no differences in all parameters. Proprioceptive exercises seemed to be a safe option to gain gait biomechanical improvements in post-menopausal women with rheumatoid arthritis.

Keywords: rheumatoid arthritis, proprioceptive exercises, disease activity, gait, ankle kinematics, ankle kinetics

1. Introduction

Patients with rheumatoid arthritis (RA) present damaged joints and pain [1], low muscle strength values [2], and cachexia [3, 4], while post-menopausal women represent the greater percentage of these patients [5]. Otherwise, patients with RA [6] and post-menopausal women [7] also present an increased risk of fall. So,

interventions aimed to reduce the risk and to prevent falls seem to be advisable for patients with RA, especially in the post-menopausal women group.

Falls have been associated with different identifiable risk factors [7, 8], which includes an unsteady gait [8] and an ineffective postural stability [9]. Gait and postural stability are dependent of motor control processes, assured by the central nervous system at different levels. According to literature, foot and ankle play a significant role to keep an effective postural stability in bipedal or unipedal activities [10], namely during gait [11, 12]. Furthermore, foot and ankle problems are associated with an increment of the risk of falls [13]. The control of the foot and ankle kinematics is especially important in the gait stance phase [14]. At gait stance phase, the ankle execute, in the sagittal plane, three different angular displacements, which were defined in prior studies as controlled plantar flexion, controlled dorsiflexion, and powered plantar flexion sub-phases [15–17]. These three angular displacements sub-phases are associated with the three objectives of foot control, mentioned in the literature [18, 19], that occurs in the gait stance phase: first, to control the impact on the ground; second, to control the foot as a stable limb; and third, to control the foot to propel the body. Consequently, ankle angular positions, ankle moment of force peak, and ankle power peak during stance phase have been reported as important biomechanical parameters for foot function measurement [20, 21]. Patients with RA have differences in ankle kinematics and kinetics during the gait stance phase, when compared with healthy controls, namely: at ankle angles [20–24]; lower ankle power peak [21, 22]; and lower ankle moment of force peak [21, 23, 24]. Moreover, previous studies [21, 24] correlated lower gait speeds – observed in these patients – with a reduced ankle moment of force peak and ankle power peak. According to the literature [23, 25], an impaired ankle power can reduce the capacity of adjustment and increment of gait speed, leading to a lower functional capacity. A subsequent study [14] specifically compared a group of post-menopausal women with RA with a group of age-matched healthy post-menopausal women. Data from this study showed that these patients yielded a lower ankle moment of force and a lower power performance during the powered plantar flexion sub-phase. The authors of this study concluded that it should be important to improve these kinetic values in post-menopausal women with RA, since they were vital concerning foot and ankle function, functional capacity, and fall prevention. According to the same study [14], post-menopausal women with RA also showed a higher stride-to-stride variability in the ankle moment of force peak. According to the literature, an increment of motor variability was also found in elders with history of falls [26–28], which could be a manifestation of an impaired motor control [29].

The nervous system, composed by the central nervous system and the peripheral nervous system, allows motor control during human movement. The central nervous system controls movement through three different levels (cerebral cortex, brain stem, and spinal cord), which are hierarchically organized, interdependent and connected between them: (1) the most complex voluntary movements are regulated by the cerebral cortex – upper level; (2) postural stability, as well as the automatic and stereotyped movements, are regulated by the brain stem – middle level; (3) movement is also regulated at the spinal cord – lower level [30, 31]. The peripheral nervous system enables the connection of the periphery with the middle and lower levels of the central nervous system [32]. Otherwise, the somatosensory information, composed by the mechanoreceptive, thermoreceptive, and nociceptive information arising from the periphery, also plays an important role in movement control [31]. Proprioception, a subcomponent of the somatosensory information, encompasses the afferent information arising from mechanoreceptors (located at the periphery) and contributes to joint and postural stability control [31]. This proprioceptive information is transmitted to the three levels of the central

nervous system, providing an optimization of the motor control [33]. The reciprocal innervation, an essential mechanism of the spinal cord regulation of the movement, is dependent on the quality of proprioceptive information (e.g., information arising from neuromuscular spindle, Golgi tendon organ, and mechanoreceptors located in joints) [34]. Accordingly, the quality of the movement is reliant on proprioception, both at a global (postural) level and at a local (joint) level [33, 35]. Therefore, a specific exercise programme could be conducted specifically to challenge and improve proprioceptive mechanisms, enhancing motor control processes [36]. This kind of exercise, made with this goal, could achieve the denomination of proprioceptive exercise [37]. According to a systematic review [38], there is evidence that proprioceptive exercises programmes can lead to improvements in proprioception and somatosensory function, namely programmes lasting 6 or more weeks (longer programmes have a greater effect); however, authors also concluded that there was a great variability and lack of detail concerning the training parameters (e.g., weekly frequency and workout duration) defined in the selected studies, making impossible to know the optimal dose–response.

Several interventions to prevent falls in elderly (e.g., exercises programme, educational programme, medication optimisation, environmental modification, and multiple interventions) have been established and evaluated [39]. Exercise programmes can prevent falls in elderly, especially those that include "balance" exercises [40, 41]. "Balance", "coordination", and "postural" exercises were classified as proprioceptive exercises in previous studies [36, 42]. According to a previous study [43], the incidence of falls in elderly was reduced after a proprioceptive exercise program. Thus, exercise is a good contribution for preventing falls; however, proprioceptive exercises, with their specificity, contribute in a more decisive way, stimulating and enhancing motor control processes.

Patients with RA benefit from the safety of the aerobic training, strength training, and from combinations of both. This is evidenced in published systematic reviews and meta-analysis [44–47]. Nonetheless, it was concluded in a prior systematic review [42] that there is a lack of studies that approach the safety and effectiveness of proprioceptive exercises regarding the improvement of functional capacity of these patients. Although these authors had not found any randomized or controlled clinical trial, a more recent systematic review [48] concluded that there is some evidence that, the so called, proprioceptive exercises are safe to apply in patients with RA and helpful in the increment of their functional capacity. In parallel, proprioceptive exercises programmes have revealed effective in elderly regarding improvements of their gait biomechanical parameters [49–51]. Exercise programmes are important to prevent falls [40, 41, 43], however, proprioceptive exercises programmes differs from others by its capacity to stimulate and enhance proprioception and somatosensory function [38]. However, it is noted that to the best of our knowledge, the effects of a proprioceptive exercises programme on gait biomechanical parameters were not studied in patients with RA. Furthermore, researches that evaluate the safety of this kind of exercises, in patients with RA, are also required.

The previous rational supported the twofold aim of the present study. First, it aimed to evaluate the effects of a proprioceptive exercises programme on disease activity of post-menopausal women with RA. Second, it also aimed to evaluate the effects on ankle kinematics and kinetics during the gait stance phase and on its variability.

2. Methods

To achieve the defined aims, a prospective, single-blind, controlled but non-randomized trial study was conducted. The study was concepted in respect of the

Declaration of Helsinki [52] and approved by the Ethical Committee for Health of the Portuguese Institute of Rheumatology, Lisbon, Portugal.

2.1 Participants

The selected post-menopausal women with RA (n = 27) were recruited from the Portuguese Institute of Rheumatology, Lisbon, Portugal, and participated voluntarily in this study. Inclusion criteria were defined as follow, to allow a coherent sample: (1) diagnosis of RA was made according to the 2010 Rheumatoid Arthritis Classification Criteria [1]; (2) patients underwent, for at least 4 weeks before, a stable dose of disease-modifying antirheumatic drugs; this period was necessary to achieve the anticipated effects of medication on joint pain and disease activity; (3) absence of early RA (disease duration <2 years); (4) diagnosis of post-menopausal status [53]; (5) absence of early menopause [54]; (6) absence of an unstable heart condition, chronic obstructive pulmonary disease or cancer; (7) absence of prosthetics in the lower limb joints; (8) nonparticipation in any kind of exercise programme in the last 3 months; and (9) documented ability to walk barefoot and unassisted for >7 m (without current walking aids).

The selected patients were allocated to the exercise group (EG) or to the control group (CG). A power analysis using GPower 3.0.10 software was performed, indicating the need of a sample of 51 subjects in each group, for an independent-samples t-test, to reach a power of 0.8, an effect size of 0.5 with the significance level adjusted to 0.05. Despite the volunteering interest for the study, some patients had logistical difficulties to move to the training centre. Therefore, to reach the greatest possible sample, the allocation process in groups cannot be random. Consequently, this process was defined as following: whenever as possible, the patients were allocated to EG until an n = 15 was attained; the patients who did not have the possibility to meet the workout schedule in EG but had in CG, were allocated to CG; then, the selected patients were allocated to CG, adding to prior allocated patients. Thus, 15 patients were allocated to EG and 12 to CG. The patients read and signed an informed consent form before their participation in the study.

2.2 Exercises programmes

EG' subjects accomplished a proprioceptive exercises programme: 12 weeks; 3 workouts/week; 30 min/workout – 25 min of proprioceptive exercises and 5 min of stretching exercises (15 s/exercise). Proprioceptive exercises were specially designed to improve lower limbs movements, according to the description framework defined in introduction. These exercises can be viewed at http://pera.ulusofona.pt/exercise-programs/exercise-group/ and **Figure 1** presents an example.

An expert of the health and exercise field controlled just one subject in each individual workout (one-on-one session). This expert, who was not blind concerning allocation process, selected the proprioceptive exercises for all subjects (from the defined exercises). The selection of each exercise was made according to its level of complexity and each subject's capacity to perform the exercise. Exercise complexity was increased along the programme period (whenever the exercise was easily performed by the subject). 3 sets of 3 repetitions were performed in each exercise (performed under conditions without fatigue).

The selection of exercises for the CG programme presupposed that these exercises should not have any influence in the evaluated parameters. Thus, CG' subjects accomplished the following programme: 12 weeks; 1 workout every two weeks; 30 min/workout. Each session was composed by stretching exercises for trunk and

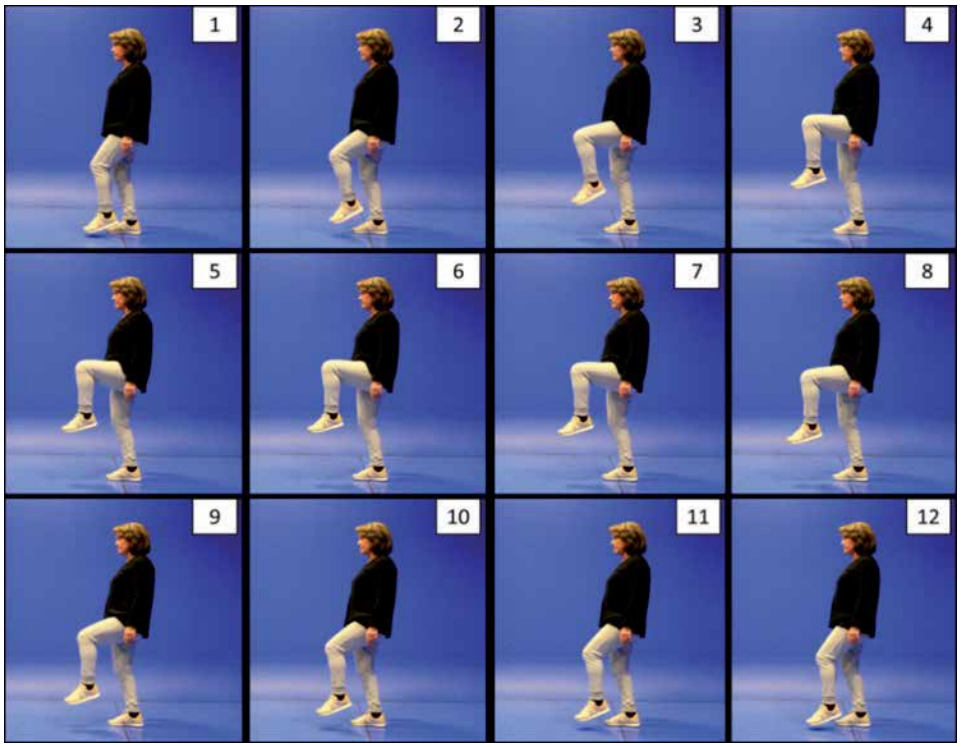

Figure 1.
Example of an exercise used in exercise group (exercise goal: Improve proprioception related to postural stability and local motor control – Lower limb joints of the support leg and hip of the swing leg; exercise description: in single leg stand position, performed flexion and extension of the swing leg hip).

upper limbs (15 s/exercise). At http://pera.ulusofona.pt/exercise-programs/control-group/ are presented these exercises. The training sessions in this group were also performed individually (one-on-one).

2.3 Assessment of disease activity

The Disease Activity Score–28 joints (DAS-28) was used to assess disease activity. DAS-28 score was calculated from: number of swollen and tender joints; visual analogue scale (VAS) to assess global health; and erythrocyte sedimentation rate [55]. One experienced rheumatologist evaluated the number of swollen and tender joints and applied the VAS. Erythrocyte sedimentation rate was assessed in a laboratory. The experienced rheumatologist and the laboratory were blind in relation to allocation process. Although the emphasis of the exercise programme was on lower limbs, most joints included in DAS-28 were located in the upper limbs. Therefore, the number of swollen or tender lower limb joints was also used to assess disease activity. To complement the aforementioned data, subjects answered to a VAS to measure pain perception regarding previous day [56]. This VAS is completed in a comprehensive way to the subjects: at the beginning of every workout session a horizontal straight line of 100 mm was presented in a white paper; the end anchors of the line were labeled as "no pain" on one end and "pain as bad as it could possibly be" on the other end; subjects responded to the VAS by placing a mark through the line already defined; this mark represented the subject's subjective pain perception regarding previous day. The VAS was scored by measuring the distance, in millimeters, between the anchor end labeled as "no pain" and the subject's mark on the line.

The demographic characteristics as well as reproductive and medical history of each subject were also collected by the experienced rheumatologist (age, body mass, height, duration of menopause, nature of menopause, disease duration, and pharmacological therapies).

2.4 Gait biomechanical assessment

An optoelectrical 3D motion analysis was used to assess gait biomechanical parameters. The Vicon® Motion Capture MX System (VICON Motion Systems, Oxford, UK) composed by 9 MX infrared cameras (7 × 1.3 MP; 2 × 2.0 MP), was synchronized with a force plate (model BP400600, AMTI, Watertown, MA, USA).

Each trial session had distinct parts: laboratory preparation, subject preparation, and data collection. The laboratory preparation included the calibration of the system made in accordance with the Vicon® technical specifications. Kinematic data was recorded at 200 Hz and ground reaction force data at 1000 Hz.

Subject preparation started with the collection of anthropometric data and the placement of 39 spherical reflective markers (9.5 mm diameter) that compose the Plug-In Gait Full-Body model (VICON Motion Systems, Oxford, UK). To assure the same measure and marker placement criteria, these tasks were performed by the same team researcher, who was not blind to the allocation process. The collection of the anthropometric data was carried out using a SECA 764 station (Hamburg Germany) and Siber-Hegner instruments (Siber & Hegner, Zurich, Switzerland).

Kinematic and kinetic data was recorded using the Vicon Nexus software (version 1.7.1). The test protocol used the guidelines specified in previous studies [14, 17]: (1) subjects walked barefoot in a gait corridor of 7 m long and 2 m wide, on which the force platform was mounted; (2) at the end of the corridor, the subjects turned around; (3) subjects were asked to walk at a natural and self-selected speed – representing the most comfortable walking speed that minimized possible discomfort that could have been caused if a pre-determined speed was determined [57] and minimized the induction of subjects into a transitioning stage, that is, a stage marked by an increased variability [58]; (4) seven valid trials of the gait stance phase were collected for each foot (trials were considered valid only when one foot stepped entirety on the force plate; this information was not given to the subjects to avoid changes in individual gait patterns); and (5) to avoid gait performance deterioration related to fatigue, subjects rested for 2 min by sitting on a chair every 20 trials.

All trials were processed using the Vicon Nexus software (version 1.7.1) and a quintic spline routine (Woltring filtering) was applied. The next gait biomechanical parameters were evaluated in the stride that started at heel strike on force plate: gait speed (m/s) – determined as described in a previous study [59]; stance phase time (s); time of the controlled plantar flexion sub-phase (s); time of the controlled dorsiflexion sub-phase (s); time of the powered plantar flexion sub-phase (s); ankle angular position in sagittal plane at the – heel strike (°), final of the controlled plantar flexion sub-phase (°), final of the controlled dorsiflexion sub-phase (°), toe off (°) – in these four angular positions, positive values means dorsiflexion and negative values means plantar flexion; ankle angular displacement along the – controlled plantar flexion sub-phase (°), controlled dorsiflexion sub-phase (°), and powered plantar flexion sub-phase (°); ankle moment of force peak in sagittal plane (Nm/kg); and ankle power peak (W/kg).

2.5 Assessment of body composition

For this study, an octopolar bioimpedance spectroscopy analyzer (InBody 720, Biospace, Korea) was used to assess body composition. This equipment analyses

independently five body sections (i.e., trunk, both upper limbs, and both lower limbs). In a previous study [60], the accuracy of InBody 720 was tested using energy X-ray absorptiometry as a reference standard. Data revealed, in females, excellent agreements between InBody 720 and dual-energy X-ray for the quantification of the lower limb muscle mass (intraclass correlation coefficient ≥ 0.83) and percentage of fat mass (intraclass correlation coefficient = 0.93). Therefore, in this study were evaluated the muscle mass values (kg and % of total body mass) and the percentage of fat mass (%). These data was included in this chapter in order to improve the quality of the discussion. These assessments were carried out in accordance with the procedures presented in the equipment user manual [61].

2.6 Statistical analyses

In patients with RA, right and left lower limb joints can be differently affected during the course of the disease. Accordingly, intra-individual differences between lower limbs of post-menopausal women with RA, concerning ankle kinematics and kinetics, were observed in a prior study [14]. Consequently, randomly selected and measured only one lower limb per subject could conduct to loss of valuable information. According to literature [62], the statistical analyses should consider both sides for analyses when right and left lower limbs are independent. Therefore, each limb/ankle/foot dataset was independently considered for the statistical analyses. To this end, the mean and the coefficient of variation (CV) of the biomechanical parameters of each ankle/foot were calculated (from the seven trials collected for the contact of each foot on force plate). These data were inserted in the SPSS software for Windows, version 17 (SPSS, Inc., Chicago, IL), in order to perform the statistical analyses. Variability was studied through the CV.

The t-test's significance level can be almost exact for sample sizes greater than 12, even if the distribution was not normal [63]. Therefore, a two-tailed paired-samples t-test was used to compare baseline and post intervention in each group. For the purpose of comparison between groups after intervention, the differences between baseline and post intervention were viewed as variables. A two-tailed independent-samples t-test was used to compare groups at baseline and post intervention. Differences were considered statistically significant at p values <0.05.

3. Results

One withdrawal was registered in EG: the post-menopausal woman with RA failed to meet the training schedule, precluding her inclusion in statistical analyses. Thus, in the EG only fourteen post-menopausal women with RA were included in the statistical analyses. In EG and CG, the rate of adherence to the programme was 86.1 ± 10.5% and 95.8 ± 27.5%, respectively.

3.1 Clinical, demographic, and body composition data

Table 1 presents the descriptive statistics of the clinical, demographic, and body composition data for EG and CG, at baseline and post exercises programmes. In these parameters no statistically significant intergroup difference was found at baseline.

Most of the post-menopausal woman with RA, in both groups, presented at least one swollen or tender lower limb joint: one in EG and two in CG had no swollen or tender joints to report. One post-menopausal woman with RA in EG and two in CG had an induced menopause (i.e., bi-lateral oophorectomy) – remaining women had a natural menopause. Furthermore, two post-menopausal women with RA in each

Parameters	EG (n = 14)			CG (n = 12)		
	Baseline mean (sd)	Post mean (sd)	p value	Baseline mean (sd)	Post mean (sd)	p value
Age (years)	62.2 (8.8)		—	67.8 (6.6)		—
Disease duration (years)	9.3 (9.5)		—	11.6 (9.9)		—
Duration of menopause (years)	14.8 (8.3)		—	19.0 (9.6)		—
DAS-28 score	4.6 (1.5)	4.0 (1.3)	0.059	4.6 (1.2)	4.2 (0.9)	0.097
Number tender or swollen joints[1]	9.0 (10.3)	6.4 (9.1)	0.069	6.1 (5.2)	3.8 (5.5)	0.084
VAS (mm)	47.0 (18.2)	21.1 (13.9)	0.000	53.0 (14.3)	47.4 (19.8)	0.348
Body mass (kg)	67.5 (15.3)	66.4 (14.6)	0.023	63.2 (10.0)	63.7 (10.1)	0.168
Height (m)	1.53 (0.06)		—	1.52 (0.05)		—
Body mass index (kg/m^2)	29.0 (5.9)	28.5 (5.7)	0.025	27.4 (4.3)	27.6 (4.4)	0.140
Fat mass (%)	36.9 (7.7)	36.1 (8.1)	0.508	34.9 (7.1)	36.0 (6.2)	0.381
Lower limbs muscle mass (kg)	12.0 (0.8)	12.0 (0.9)	0.926	11.4 (0.9)	11.4 (1.0)	0.873
Lower limbs muscle mass (%)	18.2 (2.5)	18.5 (3.1)	0.417	18.2 (2.1)	18.4 (2.5)	0.739

[1]*lower limb joints.*
CG – control group; DAS-28 – Disease Activity Score (28 joints); EG – exercise group; p value – differences between baseline and post intervention were considered statistically significant at p values <0.05; sd – standard deviation; VAS – visual analogue scale to measure pain perception in relation to previous day.

Table 1.
Clinical, demographic, and body composition data at baseline and post intervention.

group were undergoing hormone therapy. Eleven post-menopausal women with RA in EG and nine in CG were using glucocorticoids.

Between baseline and post exercises programmes, both groups presented a tendency to reduction in the DAS-28 score, as well as in the number of tender or swollen lower limb joints. Between the first and last workout session, the EG' subjects presented a decrease of the value of the VAS to measure pain perception regarding previous day ($p < 0.001$). **Figure 2** shows this reduction along the proprioceptive exercises programme sessions. In the CG, no statistically significant difference between the first and last workout session was observed.

Concerning body composition, no differences were observed between baseline and post exercises programmes in both groups.

3.2 Gait biomechanical data

Table 2 describes the gait biomechanical data at baseline and post exercises programmes. At baseline, no statistically significant intergroup difference was found. **Figure 3** presents the curves of the ankle power and ankle moment of force of both groups, during the stance phase.

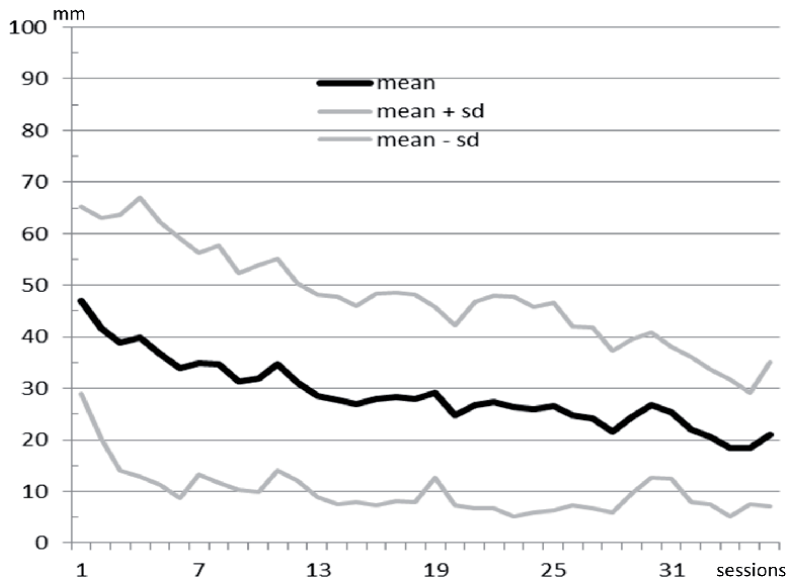

Figure 2.
Mean ± standard deviation curves of the visual analogue scale to measure pain perception regarding previous day [56] – Answered by EG' subjects at each workout session (0–100 mm).

Parameters	EG (n = 28)			CG (n = 24)			p value
	Baseline mean (sd)	Post mean (sd)	Δ mean (sd)	Baseline mean (sd)	Post mean (sd)	Δ mean (sd)	
Gait speed (m/s)	0.97 (0.20)	1.01 (0.18)	0.05 (0.10)†	0.96 (0.24)	0.95 (0.24)	−0.01 (0.07)	0.028*
Stance phase time (s)	0.70 (0.08)	0.67 (0.08)	−0.02 (0.05)†	0.71 (0.11)	0.72 (0.11)	0.01 (0.08)	0.007*
Controlled plantar flexion sub-phase							
Time (s)	0.06 (0.01)	0.06 (0.01)	0.00 (0.01)	0.05 (0.01)	0.05 (0.01)	0.00 (0.00)	0.701
Ankle angular position at beginning of phase (°)	−5.1 (4.0)	−4.3 (3.5)	0.7 (3.0)	−4.9 (3.7)	−4.4 (4.3)	0.6 (2.3)	0.846
Ankle angular position at end of phase (°)	−9.2 (3.6)	−8.9 (3.2)	0.2 (3.2)	−8.5 (4.0)	−8.4 (5.3)	0.2 (2.5)	0.998
Ankle angular displacement (°)	4.1 (2.6)	4.6 (2.3)	0.5 (1.6)	3.6 (1.8)	4.0 (2.5)	0.4 (1.3)	0.803
Controlled dorsiflexion sub-phase							
Time (s)	0.49 (0.07)	0.47 (0.08)	−0.02 (0.04)‡	0.49 (0.11)	0.50 (0.11)	0.00 (0.03)	0.027*
Ankle angular position at beginning of phase (°)	−9.2 (3.6)	−8.9 (3.2)	0.2 (3.2)	−8.5 (4.0)	−8.4 (5.3)	0.2 (2.5)	0.998

Parameters	EG (n = 28)			CG (n = 24)			p value
	Baseline mean (sd)	Post mean (sd)	Δ mean (sd)	Baseline mean (sd)	Post mean (sd)	Δ mean (sd)	
Ankle angular position at end of phase (°)	13.1 (3.3)	11.9 (3.9)	−1.1 (3.5)	13.6 (3.8)	13.8 (3.4)	0.2 (1.9)	0.124
Ankle angular displacement (°)	22.3 (3.5)	20.9 (4.7)	−1.4 (3.7)	22.1 (5.6)	22.1 (6.1)	0.0 (2.6)	0.135
Powered plantar flexion sub-phase							
Time (s)	0.15 (0.02)	0.15 (0.03)	0.00 (0.02)	0.16 (0.03)	0.17 (0.03)	0.01 (0.03)†	0.060
Ankle angular position at beginning of phase (°)	13.1 (3.3)	11.9 (3.9)	−1.1 (3.5)	13.6 (3.8)	13.8 (3.4)	0.2 (1.9)	0.124
Ankle angular position at end of phase (°)	−9.3 (7.1)	−10.3 (6.0)	−1.1 (4.6)	−8.6 (6.7)	−9.4 (6.9)	−0.8 (3.5)	0.793
Ankle angular displacement (°)	22.4 (6.2)	22.2 (5.3)	−0.1 (4.6)	22.2 (6.4)	23.1 (6.9)	0.9 (3.9)	0.372
Ankle moment of force peak (Nm/kg)	1.12 (0.18)	1.16 (0.19)	0.03 (0.16)	1.08 (0.22)	1.09 (0.22)	0.01 (0.08)	0.587
Ankle power peak (W/kg)	2.34 (0.91)	2.60 (0.79)	0.27 (0.55)†	2.27 (1.10)	2.27 (0.98)	−0.01 (0.32)	0.043*

Ankle angular position is positive during dorsiflexion and negative during plantar flexion; CG – control group; EG – exercise group; p value – differences between groups concerning Δ; sd – standard deviation; Δ – difference between baseline and post exercises programme.
†p < 0.05 (differences between baseline and post intervention.
‡p < 0.01 (differences between baseline and post intervention).
**p < 0.05.*

Table 2.
Gait biomechanical data at baseline and post exercises programmes.

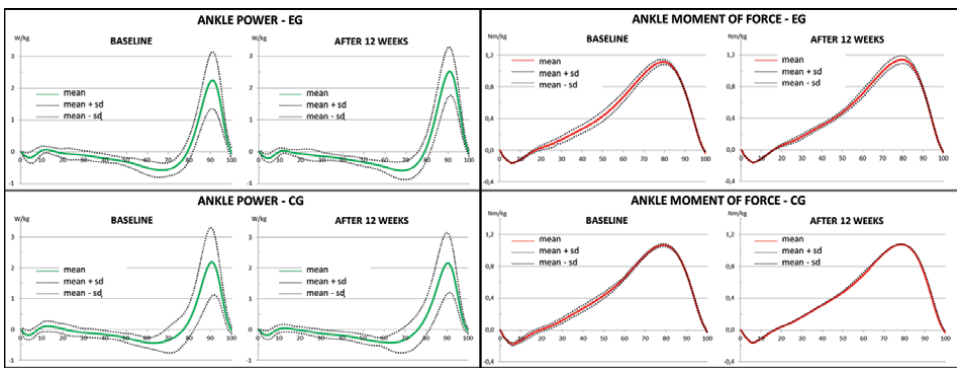

Figure 3.
Mean ± standard deviation curves of the ankle power and ankle moment of force of both groups, during the stance phase (normalized to 100% of the stance phase).

Between baseline and post intervention, EG' subjects yielded a higher gait speed (p = 0.027), a shorter stance phase (p = 0.014), a shorter controlled dorsiflexion sub-phase (p = 0.009), and a greater ankle power peak (p = 0.016). A trend towards

reduction in ankle angular position at final controlled dorsiflexion sub-phase and in ankle angular displacement during controlled dorsiflexion sub-phase were observed in EG ($p = 0.090$ and $p = 0.059$, respectively). In the other gait biomechanical parameters of the EG' subjects, no statistically significant intragroup differences were found.

In CG, no statistically significant differences were found in gait biomechanical parameters after intervention, except for an increase of the time of powered plantar flexion sub-phase ($p = 0.043$).

Contrary to baseline, intergroup differences were found after intervention in gait speed, stance phase time, time of controlled dorsiflexion sub-phase, and ankle power peak ($p < 0.05$).

Variability of the gait biomechanical parameters showed no statistically significant intergroup or intragroup differences at baseline and post exercises programmes.

4. Discussion

A number of systematic reviews and meta-analysis [44–47] described the safety of using aerobic exercises, strength exercises, and the combination of both in patients with RA. Nonetheless, there was a need of researches that evaluate the effects of proprioceptive exercises on disease activity of patients with RA. Therefore, the first aim of this study was to describe the effects of a proprioceptive exercises programme on the disease activity of post-menopausal women with RA. Data from this study (DAS-28 and number of swollen or tender lower limb joints) showed no disease activity increase as a result of the exercise programme implementation; quite the reverse, data showed a trend towards reduction. Moreover, EG' subjects presented a reduction of the pain perception between the beginning and ending of the proprioceptive exercises programme. These results indicate that is safe to use proprioceptive exercises in post-menopausal women with RA.

A second aim was to evaluate the effects of the programme on ankle kinematics and kinetics of post-menopausal women with RA, during the gait stance phase. To the best of our knowledge, this was the first study that researched this topic in patients with RA, and specifically in post-menopausal women with RA. Data showed that a proprioceptive exercises programme had effects on ankle kinematics and ankle kinetics, as well as on gait speed, i.e.: higher gait speed, shorter stance phase and controlled dorsiflexion sub-phase, and higher ankle power peak. Otherwise, CG' subjects presented no changes post intervention. These results corroborated those of a prior study [50], which also found an increase of gait speed in elderly women after the participation in a proprioceptive training programme. Moreover, elderly also improved postural control after a proprioceptive exercises programme [49, 51]. However, none of them studied the effects of these programmes on ankle kinematics and kinetics during gait. As concluded in a recent study [14], post-menopausal women with RA should improve ankle kinematic and kinetic parameters during the propulsive phase of gait, which are important parameters for foot function, functional capacity, and fall prevention. Therefore, data presented in this study showed that a proprioceptive exercises programme had effects on those parameters, namely on the stance phase duration, controlled dorsiflexion sub-phase duration, and ankle power peak value. Thus, the improvement in foot function after the proprioceptive exercise programmes seems to point out that using this kind of interventions is indicated as an option for therapy in post-menopausal women with RA.

According to literature [14, 21–24], a lower ankle power and moment of force peaks were observed in patients with RA, and specifically in post-menopausal women with RA. Therefore, interventions to improve these gait biomechanical parameters are desirable, with exercises programmes being a possible option, namely proprioceptive exercise programmes. In the present study, post-menopausal women with RA yielded a higher ankle power peak as a result of the proprioceptive exercises programme; nonetheless, the ankle moment of force peak showed no change. Thus, the proprioceptive exercises programme enhanced joint power of the post-menopausal women with RA during the powered plantar flexion sub-phase, a parameter that may play an important role in the risk of fall. Otherwise, the inability of this programme to enhance muscle mass and ankle moment of force peak may indicate another reason is behind of the better performance during the powered plantar flexion sub-phase. According to a systematic review [38], there is evidence that proprioceptive exercises programmes can lead to improvements in proprioception and somatosensory function. According to this, we can speculate that the reason for a better performance was an improvement of proprioception and motor control as a result of the proprioceptive exercises programme.

Another aim was to evaluate the effects of the proprioceptive exercises programme on the ankle biomechanical variability. According to literature, an increased stride-to-stride variability was attributed to a probable loss of motor control [29] and post-menopausal women with RA yielded an increased variability of the ankle moment of force peak [14]. In this study, it was conjectured that the variability of the ankle moment of force peak could be decreased as consequence of the proprioceptive exercises programme; however, data showed no differences between pre and post intervention. Thus, another question arises, which can be answered by future research: "Could other kind of exercises programmes change variability of ankle kinematic and kinetic parameters during the gait stance phase?"

Strength training enhanced muscle mass of patients with RA [64, 65], however, the effect of a proprioceptive exercise programme on muscle mass was unknown. Between baseline and post exercise programmes, data showed no changes in low limbs muscle mass, pointing that these types of programmes had no effect on this parameter. Nonetheless, more research is required to clarify this question. On the other hand, post-menopausal hormone therapy, vitamin D and protein intakes, and menopause nature can influence muscle status [66, 67]. The use of hormone therapy could influence positively muscle status, whereas an induced menopause (e.g., bilateral oophorectomy) could be responsible of a greater impairment of muscle status. These parameters were not considered along the selection and allocation processes; nevertheless, data revealed that both groups of post-menopausal women with RA presented similar characteristics. Higher vitamin D and protein intakes could restrict muscle fiber atrophy; nonetheless, these variables were not evaluated in this study and thus, it can be considered as a limitation.

The presence of higher fat mass values could predispose to hypertension, diabetes, and risk for cardiovascular disease [68] and patients with RA showed high percentages of fat mass [69–72]. Fat tissue is an important font of inflammatory cytokines that could contribute to the systemic inflammation [72]. Following this deduction, it would be important to reduce fat mass in patients with RA, and to achieve this, physical exercise appears as an important strategy. However, the proprioceptive exercises programmes assessed in our study had no effect on fat mass of post-menopausal women with RA. To the best of our knowledge, this was the first study that researched this issue. Previous studies researched the effects of other types of physical exercise on fat mass of patients with RA. Two studies showed no change of the fat mass after strength training programmes [65, 73]. Otherwise, a combined strength and endurance training programme decreased the subcutaneous

fat thickness and this should not be dissociated from the inclusion of aerobic exercises in the training programme [74]. Accordingly, aerobic exercises are the best option for decreasing fat mass [75]. The importance of proprioceptive exercises is recognized with the findings showed in the present study; however, as described in literature [64], an exercise programme for patients with RA must contain aerobic, strength, mobility and proprioceptive exercises to achieve all benefits.

According to the literature [47], exercises programmes for patients with RA should be cautiously designed to the individual. The methodology of our exercise programme followed this indication. However, according to a number of systematic reviews [44–48], most studies that evaluated the effects of physical exercise on patients with RA applied group training sessions in their programmes. Consequently, it is imperative to emphasize the kind of exercise programme used in the present research (an individualized and personalized exercise programme). In the present study, the one-on-one workout sessions could have contributed to the high adherence rates of the programmes and to the observed results. Moreover, the clinical community can easily apply a similar programme due to the type of equipment used, i.e., low-cost equipment.

In accordance with the aforementioned, the use of proprioceptive exercise in clinical practice with women with RA is suggested, especially in patients in the following situations: patients with low physical activity; after periods of immobility; in recovery phases from an active disease; in aftercare for joint replacement surgery (total hip or knee prosthesis); in elderly patients, those with rheumatoid cachexia, those with a history of falls; after the first fracture; and in patients with moderate to severe osteoporosis.

5. Conclusions

A proprioceptive exercises programme had effects on the ankle biomechanical performance of post-menopausal women with RA, during the gait stance phase: increasing ankle power peak and shortening controlled dorsiflexion sub-phase. The programme also increased gait speed and shortened stance phase, although it had no effects on body composition. Finally, it seems to be safe in post-menopausal women with RA.

Conflict of interest

The authors declare no conflict of interest.

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Section 3

Traditional Methods of Treatment of Rheumatoid Arthritis

Chapter 10

Traditional Treatment for Rheumatoid Arthritis

Krushna Chandra Sahoo

Abstract

The most prevalent musculoskeletal disorder is rheumatoid arthritis (RA). The main concern with RA is extreme fatigue, pain, and weakness. Patients having severe pain are compelled to take medications containing a variety of indigenous substances. These indigenous substances, on the other hand, exacerbated illnesses and delay in seeking appropriate healthcare. Treatment is delayed due to a number of reasons, including patients' lack of access to trained healthcare professionals, delays in referral to a rheumatologist, and patients' belief on traditional healing practices. The choice of inappropriate healthcare providers often causes a delay in referral to a rheumatologist. Self-medication and seeking treatment from traditional healers are often compelled the patient to engage in a variety of traditional practices. Cultural values have a significant influence on care-seeking behavior. Since healthcare promotion is dictated by community demands, the healthcare system should understand the contextual phenomena behind common practices for better health education. This chapter will address the beliefs and values that underpin traditional treatment, the sources of traditional learning pathways and ethical aspects of traditional practice.

Keywords: rheumatoid arthritis, musculoskeletal disorder, traditional healing, indigenous treatment practices, use of animal products, care-seeking pathways

1. Introduction

Rheumatoid arthritis (RA) is one of the most common inflammatory musculoskeletal disorders, causing chronic pain in patients [1–6]. It is also a chronic destructive inflammatory disease characterized by the presence and consistency of an inflammatory infiltrate, resulting in joint architecture destruction and impairment of function [1–6]. The fingers, wrist, feet, and ankles are the most commonly affected by RA, and the chronic inflammation causes permanent joint destruction and deformity [1–6]. The main concern with RA is the pain, and its persistence frequently has negative health consequences [5–8]. As a systemic disease, RA has extra-articular manifestations in systems such as the pulmonary, ocular, and vascular systems, as well as other organs or structures that may be affected by the inflammatory process. As a result, timely and rational rheumatoid arthritis treatment is critical [8–10]. Nonetheless, despite greater recognition of the benefits of timely treatment, there is always a delay in obtaining treatment from appropriate healthcare providers among patients [11]. The delays in diagnosis and referral to a tertiary health care facility or specialist, such as a rheumatologist, causes worsening disease conditions and complicating care-seeking pathways [12–18].

2. Rheumatoid arthritis, and complementary and alternative medicines (CAM)

Rheumatoid arthritis is one of the most painful diseases, and patients seek a variety of treatment options, including complementary and alternative medicines (CAMs) [19–26]. CAM has grown in popularity among RA patients worldwide; CAM use is widespread among RA patients and is projected to increase further [2, 9, 27, 28]. The use of CAMs by people living with RA in the United States has been reported to range between 28 and 90 percent [21, 22]. The lifetime prevalence of CAM use in RA patients is 38 percent [29]. CAMs include a wide range of traditional or indigenous practices as well as a variety of products. Herbal treatments, homoeopathy ingredients, and various animal products are among the products available. Massage therapies, acupressure, acupuncture, electro-acupuncture, electrical stimulation, laser therapy, and mind–body therapies are among the indigenous treatment methods [7, 14, 17, 24, 26, 30, 31]. Many different types of physical activity are generally used and encouraged. Homeopathy employs ingredients in high concentrations that are not typically found in conventional medicines or treatments [7].

The fundamental question is why CAMs are not fully integrated into mainstream medical care, even in countries like China and India, which are known to be the birthplace of these traditional CAMs [7, 24, 26, 31]. The reasons could be scientific, political, or economic [19]. However, the most common argument is that traditional complementary and alternative medicine or therapies often create a barrier to scientific scrutiny [19]. The effect of CAMs with slight alterations and combinations can be demonstrated to be similarly effective and can suggest better patents; thus, research does not garner much private funding. The majority of studies are underpowered or poorly designed. As a result, pharmacovigilance research should concentrate on issues such as drug interactions and CAM intervention [19]. However, the most significant barrier to CAM research is a lack of funding and qualified experts to research these products. Currently, these CAMs are being subjected to scientific scrutiny [19]. Whatever the reason behind the popularity of CAMs, it is critical to understand which type of CAM is safe and effective for patients with RA [21, 22]. Physicians should be well informed and at ease discussing common complementary and alternative therapies, particularly their effects, side effects, and potential interactions with conventional RA treatments. Many patients may not volunteer for their use of CAM, so physicians must conduct systematic inquiries during consultations. This should be given extra attention in elderly patients with comorbidities.

3. Various indigenous healing practices

Traditional RA treatment includes the use of plant products or herbal remedies [22, 32, 33], animals or animal products [14, 22, 32, 34–37], and the application of alternative therapies [2, 7, 22, 32, 38, 39]. Traditional approaches to RA treatments include herbs/juices, spiritual practices, topical applications, movement-based therapies, and practitioner-based modalities [32]. These traditional treatments are used as a home remedy and were primarily encouraged or suggested by family members, neighbours, or relatives. The majority of the time, however, these traditional treatments are prescribed by local traditional healers. Traditional medicines are used in a variety of ways, including eating, drinking, tying, anointing, banding, massaging, and fumigation. It was eaten often fresh. The other methods of preparation were cooking, burning, crushing, grinding, wrapping, powdering, or drying. **Table 1** shows a detailed list of the animals and animal products that are used in traditional RA care.

Authors	Scientific name of the animal	Preparation Procedure
Samal et al. 2020 [14]	*Ocyceros birostris* (Indian Grey Hornbill)	Body (boiling with spices)
	Centropus sinensis (Crow pheasant)	Body (boiling with cumin seeds)
	Herpestes edwardsi (Indian grey mongoose)	Body (rotten for 4–5 days mixed with curd and eating)
	Capra aegagrus hircus (Goat)	Boiling and eating
	Canis aureus indicus (Indian jackal)	Body (rotten for 4–5 days mixed with curd and eating)
	Lumbricus terrestris (Earthworm)	Grinding curd and spices and eating
Kendie et al. 2018 [34]	Capra aegagrus hircus L. (goat)	Milk (drinking)
	Sus scrofa (pig)	Meat (eating)
	Crocodylus spp. (crocodile)	Bile (drinking anointing)
	All spp. of leeches	Head (massaging)
Altaf et al. 2017 [35]	Felis domesticus (cat)	Fat (massaging)
	Bubalus bubalis (buffalo)	Fat, milk, flesh (eating)
	Hemiechinus collaris (gray long eared desert hedgehog)	Body (massaging)
	Hystrix indica (Kerr Indian crested porcupine)	Fat (massaging)
Geisler and Cheung 2015 [32]	*Gallus Gallus domesticus* (chicken)	Cartilage Juices (eating)
	Fish oil	Oil (eating)
Alves and Alves 2011 [36]	*Apis mellifera* (Africanised honey bee)	
	Acheta domesticus (house cricket)	
	Paragryllus temulentus Saussure (cricket)	
	Palembus dermestoides (peanut beeatle)	
	Leporinus piau (Black piau)	
	Carcharhinus porosus (smalltail shark)	
	Rhizoprionodon lalandii (Brazilian sharpnose shark)	
	Rhizoprionodon porosus (Sharpnose shark)	Sun-dried, grated and crushed to powder then administered as tea or taken during meals
	Sphyrna lewini (Scalloped hammerhead)	
	Oncorhynchus mykiss (redband trout)	
	Astyanax bimaculatus (Twospot astyanax)	
	Megalodoras uranoscopus (catfish)	
	Platydoras costatus (catfish)	
	Pterodoras granulosus (catfish)	
	Oxydoras niger (catfish)	
	Electrophorus electricus (electric eel)	
	Hoplias malabaricus (trahira)	
	Gadus morhua (atlantic cod)	
	Ginglymostoma cirratum (nurse shark)	
	Phractocephalus hemioliopterus (redtail catfish)	

Authors	Scientific name of the animal	Preparation Procedure
	Zungaro zungaro (black manguruyu)	
	Pristis pectinata (smalltooth sawfish)	
	Pristis perotteti (largetooth sawfish)	
	Prochilodus nigricans (black prochilodus)	
	Sphoeroides testudineus (checkered puffer)	
	Phyllomedusa bicolor	
	Iguana iguana (common iguana)	
	Tupinambis merianae (lizard)	
	Tupinambis teguixin (lizard)	
	Boa constrictor (boa)	
	Eunectes murinus (anaconda)	
	Epicrates cenchria (Brazilian rainbow boa)	
	Oxyrhopus trigeminus	
	Drymobius margaritiferus	
	Caudisona durissa (neotropical rattlesnake)	
	Micrurus ibiboboca	
	Lachesis muta (bushmaster)	
	Phrynops geoffroanus (geoffroy's side-necked turtle)	
	Phrynops tuberosus	
	Mesoclemmys tuberculata (toadhead turtle)	
	Caretta caretta (loggerhead turtle)	
	Eretmochelys imbricate (atlantic hawksbill)	
	Lepidochelys olivacea	
	Dermochelys coriacea (Leatherback turtle)	
	Rhinoclemmys punctularia (spot-legged turtle)	
	Podocnemis expansa (amazon river turtle)	
	Podocnemis unifilis (yellow-spotted river turtle)	
	Chelonoidis denticulate (yellow footed tortoise)	
	Caiman crocodilus (common cayman)	
	Caiman latirostris (cayman)	
	Paleosuchus trigonatus	
	Buteogallus urubitinga	
	Ardea cocoi (white-necked Heron)	
	Coragyps atratus (black vulture)	
	Crax globulosa (wattled Curassow)	
	Ortalis vetula	

Authors	Scientific name of the animal	Preparation Procedure
	Glaucidium brasilianum	
	Rhea americana (greater rhea)	
	Agouti paca (spotted paca)	
	Balaenoptera acutorostrata (minke whale)	
	Bubalus bubalis (water buffalo)	
	Ovis aries (sheep)	
	Lycalopex gymnocercus	
	Canis latrans	
	Cerdocyon thous (crab-eating fox)	
	Dusicyon thous (Crab-eating fox)	
	Ateles geoffroyi	
	Ateles paniscus	
	Mazama cf. gouazoupira (gray brocket)	
	Tolypeutes tricinctus (Brazilian three-banded armadillo)	
	Sotalia fluviatilis (gray river dolphin)	
	Sotalia guianensis (guianan river dolphin)	
	Didelphis albiventris (common opossum)	
	Didelphis virginiana	
	Puma concolor (mountain lion)	
	Hydrochaeris hydrochaeris (capybara)	
	Inia geoffrensis (amazon river dolphin)	
	Conepatus semistriatus (striped hog-nosed skunk)	
	Conepatus chinga (hog-nosed Skunk)	
	Cyclopes didactylus	
	Myrmecophaga tetradactyla (collared anteater)	
	Procyon cancrivorus (crab-eating raccoon)	
	Physeter catodon (sperm whale, cachelot)	
	Tapirus terrestris (Brazilian tapir)	
	Trichechus inunguis (amazonian manatee)	
Efthimiou and Kukar 2010 [22]	Omega-3 PUFAs (fish oil)	Eating
Padmanavan and Sujana 2008 [37]	*Melursus ursinus* (bear)	Fat (massaging)
	Herpestes fuscus fuscus (brown mongoose)	Penis (eating with roasted)
	Bubalus bubalis (buffalo)	Ghee (eating and massaged)
	Varanus bengalensis (monitor lizard)	Fat (massaging)
	Panthera pandus (panther)	Fat (massaging)
	Panthera tigris (tiger)	Fat (massaging)
	Python reticulates (python)	Fat (massaging)

Authors	Scientific name of the animal	Preparation Procedure
	Cervus unicolor (sambar deer)	Fat (massaging)
	Palamnaeus swammerdami (scorpion)	Whole body (boiled and massage with gingiley oil)
	Vespa orientalis (wasp)	Body (ground with honey and salt and applied)

Table 1.
Animal or animal products use for treatment of RA.

Herbal medicines were mostly prescribed or used in powder form. In the majority of cases, patients used roots and tubers to reduce joint swelling. They took herbal remedies in the form of liquid and powdered plant products. Herbal medicines have been used as anti-inflammatory treatments for the treatment of RA [22]. The herbal remedies or plants used for treatment of RA are given in **Table 2**.

A multi-country study conducted in the United Kingdom, Germany, the United States, Australia, and Canada found that self-management of RA with pacing, heat, cold, and rest without medical advice reduced intense pain [4]. A study in the Dominican Republic looked into the religious and environmental theories of arthritis etiology. According to their participants, arthritis was caused by God's will and due to contact with contaminated water; they believe that by praying, and avoiding

Authors	Name of the plants or herbs
Geisler and Cheung 2015 [32]	*Curcuma longa* (turmeric)
	Zingiber oYcinale (ginger)
	Prunus avium (cherry)
	Ricinus communis (castor oil)
Yang et al. 2013 [33]	Black cohosh
	Angelica sinensis
	Licorice
	Tripterygium wilfordii
	Centella asiatica
	Urtica dioica
Efthimiou and Kukar 2010 [22]	*Camellia sinensis* (green tea)
	Celastrus aculeatus
	Lepidium meyenii
	Uncaria (cat's claw)
	Tripterygium wilfordii (thunder god vine)
	Perna canaliculus
	Curcuma longa (turmeric)
	Curcuma phaeocaulis
	Zingiber oYcinale (ginger)
	Semecarpus anacardium Linn.

Table 2.
Use of herbal remedies for treatment of RA.

Authors	Application of alternative therapies
Khanna et al. 2017 [38]	Seven days fasting followed by vegan diet
	An elimination diet plan
	Provision of elemental diet
	Supplementation of dietary fibers and whole grains
	Use of specific fruits and spices
Zhao et al. 2017 [7]	Fish and plant oils
	Herbs and traditional Chinese medicine
	Supplements and diet regimes
Geisler and Cheung 2015 [32]	Use of magnets or copper bracelets
	Movement based therapies – yoga, pilate's, tai chi
	Acupuncture
	Energy healing
	Reflexology
	Massage
	Eating dark chocolate, and lecithin rich food
	Eating honey and apple cider vinegar
	Eating horse liniment
	Meditation, prayer, biofeedback, relaxation
Ernst and Posadzki 2011 [2]	Magnets therapy
	Homeopathy
	Avocado-Soybean Unsaponifiables (ASU)
	Tai chi
Graham et al. 2011 [39]	Foot orthoses
Efthimiou and Kukar 2010 [22]	Acupuncture
	Electro-acupuncture
	Bee-venom acupuncture

Table 3.
Application of traditional alternative therapies for RA.

contact with contaminated water, RA can be cured [40]. Patients used heat and physical therapies, supplementation, traditional medicines, and prayer to get relief from RA [27, 28]. It was also observed that patients would sometimes practice hot compression by applying mustard oil to the affected areas [14]. The various applications of traditional alternative therapies for RA are provided in **Table 3**. Traditional healers have given powders or ash to RA patients on occasion [14]. According to a study conducted in the United States of America, 70% of patients never mention traditional treatments to their physicians, which is regarded as an invisible mainstreaming of alternative care [21, 22].

4. Key reasons for traditional healing practices and its consequences

Patients with RA have a wide range of health-care options, including self-medication with home remedies, traditional or indigenous healing practices,

traditional herbal treatment, and treatment from informal healthcare providers (untrained or unqualified providers), trained prescribers, and specialists [10, 13, 14, 23]. Patients' pain frequently prompted medication decisions, which were frequently purposeful and multifaceted [7, 15]. Because of their fatigue, pain, and disability, people with musculoskeletal disorders are among the highest self-reported users of CAMs, particularly traditional treatments [41]. The swelling and joint damage that characterize active RA are the end results of complex autoimmune and inflammatory processes involving components of both the innate and adaptive immune systems, which compel them to seek care from multiple providers, especially in LMICs. Furthermore, foot deformity is common (80%) among RA patients, leading to foot ulceration [39]. The traditional treatment used by RA patients to alleviate or recover from severe pain [11–15, 42–45].

Traditional healers are preferred because of the lack of trained healthcare providers and patients' trust in indigenous healing approaches, as well as the ease of access to care and patients' faith in traditional healing [11, 23]. The patient's care-seeking behaviour and treatment preferences vary depending on their education, culture, and beliefs [13, 27, 28]. Self-medication and seeking care from traditional healers frequently force people to engage in various indigenous practices. The studies revealed that there are two key factors responsible for the gap between onset of symptoms, definite diagnosis and appropriate health care or treatment from the right providers. These factors include poor health literacy among the patients and inaccessibility to modern health care systems or unavailability of trained providers, which often happens in rural and remote areas, where more than one-third of the patients live. Furthermore, these factors frequently result in a delay in care pathways or a proper referral system, aggravating disease conditions [11]. The major underlying reasons for treatment delay were the influence of ethnicity, such as folk beliefs, family and friends, and dietary manipulation [43].

Depression is the most common comorbidity in RA, and it has a significant impact on the quality of life [1]. It has been documented that some patients used traditional CAM therapy in addition to other modern antidepressants to recover from RA-related psychiatric disorders, particularly depression and anxiety [1]. The satisfaction with support was associated with adaptive behaviour, whereas disappointment was associated with maladaptive behavior [5, 13, 14]. Furthermore, the primary motivators of indigenous practice were easy access to healers and no prescription fees; the primary demotivators were high prices and ineffective treatment. Furthermore, the RA causes productivity loss; one of the major concerns was RA-related work-disability – permanent disability and temporary job loss [18]. For example, a study in Lithuania found that RA patients were 24 percent less likely to be employed than the general population [18]. Some of the patients sought care through multiple health care providers, and even received traditional treatment in order to avoid disability and RA-related productivity loss [18].

Treatments are frequently influenced by the patients' perspective and experience with the illness, such as the likely duration of disease onset, symptomatology, severity, diagnosis, urgency of care, and available facilities [46]. A meta-ethnography study of RA patients revealed that many were unsure about the severity and duration of the disease [47]. Patients' seeking care in various care practices during the disease period has a significant impact on disease cure [13, 48]. There were few positive outcomes from indigenous treatment; in many cases, patients experienced negative outcomes such as disease severity, side effects from incorrect treatment, and frequent delays in receiving appropriate care [13, 14]. As a result, improving the quality of life of RA patients is critical. Community literacy and mass screening would both contribute to the early detection and management of RA. It is

critical to understand patients' perspectives in order to develop a more effective health care delivery model.

5. Empirical knowledge on traditional healing

Cultural factors are regarded as vital components in the promotion of conventional therapies; the use of traditional RA management has been influenced by cultural factors [7, 27]. Traditional cultures recognized the importance of belief healing requirements and devised complex rituals to elicit expectancy and participation from healers, patients, and the local community. Traditional healing techniques have been an integral part of nearly all societies' healing rituals since the beginning of time [36]. The sources of empirical knowledge of traditional healing were based on either learning from or motivated by family, relatives or local community members or with the attraction and preference of local traditional healers [14, 15, 27]. This was mostly due to an article of faith on severe pain reduction, or to witnessing others being cured, or to societal pressure. The key knowledge pathway of indigenous RA treatment was ancient tales, customs, and belief or faith in religious or traditional healers.

Many countries around the world have deep roots in traditional healing practices. According to the World Health Organization (WHO), traditional medicine is used for primary health care by 3/4 of the world's population [49]. Indigenous cultures are often known for their oral tradition – healing and medicine knowledge transmitted orally from one generation to the next [49]. Moreover, there is great diversity in indigenous cultures worldwide. Specific healing practices are practiced by one community may not be accepted by another. The treatment practices are often difficult to generalize without scientific proof. Understanding people's beliefs about etiology, feelings, thinking, and the content of lay beliefs is critical in medical sociology [49]. However, it is difficult to verify indigenous knowledge by scientific or adequately evaluated assumptions underlying such treatment practice as a basis for its' typical criteria and philosophies [50]. The convictions of the patients about etiology were often based on faith [40, 42, 48]. However, misleading assumptions frequently result in a community's health being jeopardized.

6. Health system responsibilities and preparedness

The absences of adequate facilities in rural and remote areas, as well as a lack of patient awareness, were major motivators for indigenous approaches to RA treatment. When patients do not have adequate access to modern care, they rely on traditional healers for primary care [51]. There is compelling evidence that community members frequently prefer self-medication to traditional providers for many health issues [51]. As a result, there is a need for RA management at primary health care centres with a proper referral system [13]. Patient-centered care models are essential for effective treatment [52]. The primary need for RA patients is physician consultation through active listening and professionalism with chronic pain management [42]. Inadequate community literacy on RA is the major reason for proper treatment [36, 44]. Patients with RA must be well informed and educated on modern treatment, which is a critical component of care [10, 12]. Furthermore, public health practitioners' understanding of indigenous health concepts may be beneficial in reducing unnecessary treatment burden and care complexity [53].

In countries where much effort has been put into building a single uniform health service delivery system, the pluralistic health care system is ignored. In the

meantime, understanding the pluralistic medical system is critical to improving community health. India has a pluralistic medical culture with a well-documented history and practice of alternative medicine – Ayurveda, Yoga, and Naturopathy (AYUSH) [54]. Furthermore, multidisciplinary holistic approaches that focus on context-specific health determinants are important for understanding the cultural influence on RA care seeking pathways [13, 55, 56].

7. Conclusions

Patients with RA seek immediate care from multiple traditional providers with a wide range of products and services with no gatekeeping. The most significant concern expressed by practitioners, policymakers, and researchers is the safety and efficacy of traditional treatments, which can be addressed by conducting a thorough examination of the products in common use. Primary health centres are the entry point for retaining RA patients; the availability of RA-trained providers at primary health centres, along with a proper referral system, is critical for convalescing care-seeking pathways. Furthermore, community education on early symptoms, diagnosis, and proper treatment is critical.

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Conflict of interest

The author declares there is no conflict of interest.

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Chapter 11

Action Mechanisms of Antirheumatic Herbal Medicines

Nima Nakisa and Mahboobeh Ghasemzadeh Rahbardar

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory and debilitating joint disorder that causes severe impairment and reduces the quality of life. The available synthetic medicines used as standard therapy for RA have numerous side effects that can compromise their therapeutic outcomes. Thus, the demand for alternative and complementary medicines is increasing. A search of English articles in PubMed, Scopus, Google Scholar, and Web of Science databases was carried out on probable mechanisms of action of herbs with the antirheumatic property. Herbal medicines stated in folk medicine face acceptance concerns by the medical community because of the lack of scientific documents regarding their physio-pharmacological mechanisms. This chapter aims to review the possible antirheumatic effects of various herbs, including *Rosmarinus officinalis* L., *Curcuma longa*, and *Crocus sativus*, their related mechanisms, and preclinical applications, in order to recall the therapeutic properties of herbal medicine. However, more clinical trials are required to confirm the safety and efficacy of these antirheumatic herbal medicines.

Keywords: rheumatoid arthritis, antirheumatic, herbal medicine, folk medicine, complementary drugs, physio-pharmacological effects

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that can strike men and women at any age [1]. About 1% of the world's population has been affected by RA, which has resulted in progressive articular damage, permanent impairment, and even reduced life expectancy [2]. Genetic and environmental factors have important roles in the aetiopathogenesis of RA [3]. The pathophysiology of RA is complex and mainly focuses on autoimmune response and inflammation [4]. The reactive oxygen species (ROS) damage proteins such as collagen and denature immunoglobulins that both might become autoantigens in RA [5]. Autoantibodies against immunoglobulin G (IgG) (also called rheumatoid factors (RFs)) and autoantibodies against citrullinated peptides (ACPAs) are two types of autoantibodies that can cause complement activation in RA patients [6, 7]. It was suggested that increased circulating ACPAs can promote bone loss by activating macrophages, producing B cells, organizing immune complexes or binding membrane citrullinated vimentin [8–11] which consequently ease the shift from autoimmunity to inflammation. Inflammation of the synovial membrane in RA is made up of both innate and adaptive immune cells [12]. The majority of immune responses are regulated by cytokines and chemokines including interleukin-6 (IL-6) and

tumor necrosis factor (TNF) which can induct or intensify the inflammatory response of the synovial compartment [13].

Disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are currently available drugs for RA [14]. Antirheumatic medications that are currently available for RA treatment target the inflammation and tissue swelling resulting from the disease. However, the majority of patients still experience extreme pain and physical impairment. These drugs are ineffective in preventing cartilage degradation and joint damage [15]. It was also reported that taking two or more biologic DMARDs at the same time, or a biologic DMARD with a nonbiologic DMARD, increases the risk of severe infections or cancer [16]. Other investigations have also illustrated the cardiovascular [17] and ocular [18] adverse effects of antirheumatic drugs. Therefore, the development of safe, fast-acting antirheumatic medicines is required.

Complementary and alternative medicine methods are now thought to provide adjuvant therapies to improve the chances of full remission of RA [19, 20]. Several herbal medicines have displayed pre-clinical and clinical antirheumatic properties including *Curcuma longa* L., *Rosmarinus officinalis* L., and *Crocus sativus* through their antioxidant, anti-inflammatory, anti-proliferative, and antinociceptive properties (**Figure 1**).

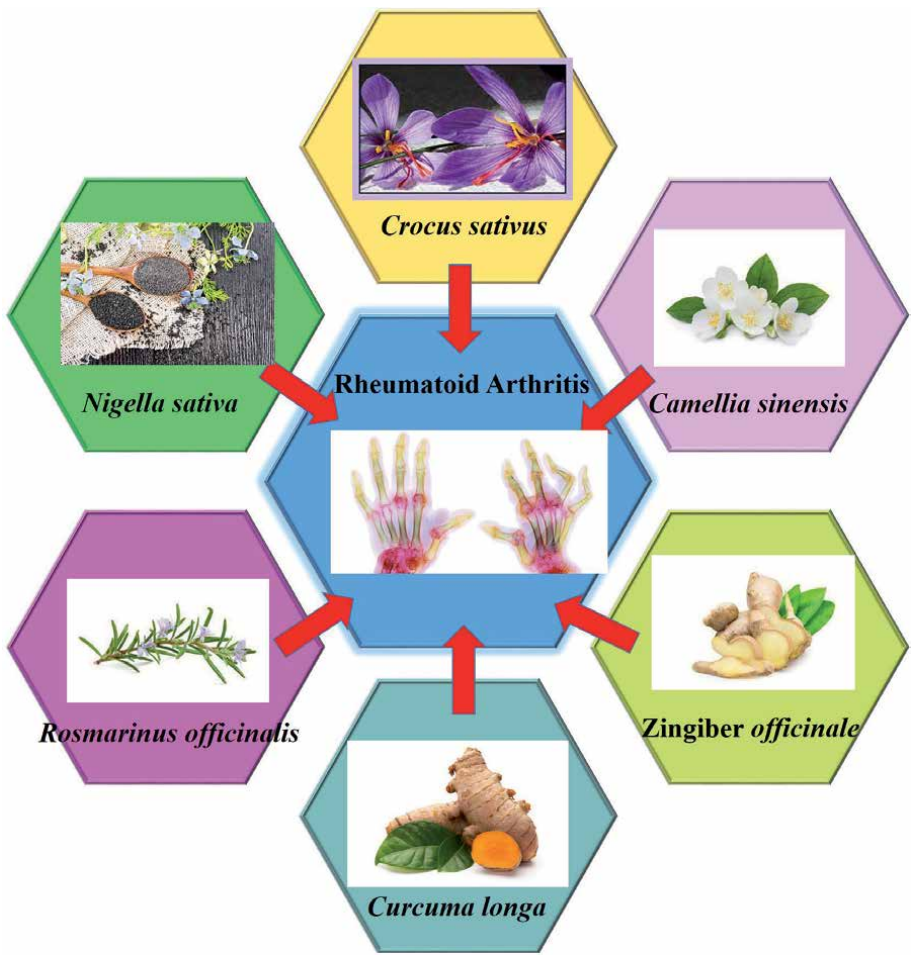

Figure 1.
Some herbal medicines with antirheumatic property.

Thus, searching for herbal medicines with antirheumatic properties could be an advantageous method to find effective antirheumatic medicines with fewer side effects. The detailed information about medicinal herbs and their physio-pharmacological mechanisms of action is summarized in this chapter.

2. Methods

The present chapter mainly emphasizes the published original articles implicating the therapeutic and beneficial effects of herbs on rheumatoid arthritis. The data (Google Scholar, PubMed, and Scopus) search has been carried out by searching related keywords, including "rheumatoid arthritis", "rosemary", "*Rosmarinus officinalis* L.", "turmeric", "*Curcuma longa* L.", "*Crocus sativus* L.", "saffron", "*Zingiber officinale*", "ginger", "*Nigella sativa*", "black seed", "black cumin", "*Camellia sinensis*", and "green tea". No time limitation was considered.

2.1 Herbal antirheumatic medicines

In folk medicine, numerous plants have been used because of their antirheumatic properties. Researchers are currently focusing on evaluating and characterization of different plants and their components to treat RA. The aim of this section of the chapter is to review the mechanism of action of a number of medicinal plants that have antirheumatic properties.

2.2 *Rosmarinus officinalis* L. (rosemary)

A former study indicated that administration of water-soluble compounds of rosemary reduced oxidative stress (by enhancing the glutathione (GSH) level and the GSH/glutathione disulfide (GSSG) ratio) and inflammation (paw edema, number of leukocytes in the femorotibial joint cavities, secondary lesions score, adrenal glands, inguinal lymph nodes, and popliteus lymph nodes weights) in rats with adjuvant-induced arthritis [21]. Carnosic acid, a major phenolic compound isolated from rosemary (5 mg/kg, 2 weeks, i.p.), administration to collagen-induced arthritis rats inhibited inflammation response and joint destruction by decreasing the amounts of TNF-α, IL-1β, IL-6, IL-8, IL-17, matrix metalloproteinase-3 (MMP-3), and receptor activator of nuclear factor kappa-B ligand (RANKL) [22] (**Table 1**). Moreover, it was observed that a methyl ester derivative of rosmarinic acid, a constituent of rosemary (50 mg/kg/day, 15 days, i.p.), has a potent anti-arthritic property in collagen-induced arthritis mice via its anti-inflammatory and immunosuppressive effects [34].

Another study has reported that rosmarinic acid triggers apoptosis via mitochondrial pathway in activated T cells taken from rheumatoid arthritis patients [35].

2.3 *Curcuma longa* L. (turmeric)

A clinical trial was carried out on 45 patients with RA to investigate the antirheumatic effect of curcumin at the dose of 500 mg for 8 weeks. Curcumin improved disease activity and the American college of rheumatology scores [36]. Another clinical trial reported that curcumin in a turmeric matrix (250 mg, twice daily, 90 days) was an advantageous agent in managing RA by its analgesic and anti-inflammatory properties. Curcumin improved erythrocyte sedimentation rate, C-reactive protein, visual analog scale, rheumatoid factor, and American College of Rheumatology responses in comparison with the control group [37]. It was also seen that administration of CuroWhite™, a novel hydrogenated curcuminoid

Herbal medicine	Antirheumatic Mechanism(s)	Reference
Rosmarinus officinalis L.	↑ GSH level	[21]
	↑ GSH/GSSG ratio	
	↓ Number of leukocytes in the femorotibial joint cavities	
	↓ TNF-α, IL-1β, IL-6, IL-8, IL-17, MMP-3, RANKL	[22]
	↑ Apoptosis	[23]
Curcuma longa L.	↓ Erythrocyte sedimentation rate	[24]
	↓ C-reactive protein	[25, 26]
	↓ PGE2, COX-2, TNF-α, and IL-1	
	↓ Bcl-2	
	↑ Bax, caspase 3, 9	[27]
	↓ MAPK/RANK/c-Fos/NFATC1	
Crocus sativus L.	↓ Erythrocyte sedimentation rate	[28]
	↓ C-reactive protein	
	↓ TNF-α, IFNγ	
	↓ MDA	[29]
	↓ Lipid peroxides	
	↑ Catalase and glutathione peroxidase	[30–33]
	↓ IL-1β, IL-6, IL-17, IL-8, NF-κB	
	↑ SOD, GR	

Bax: BCL2-associated X; Bcl-2: B-cell lymphoma-2; COX: cyclooxygenase; GSH: glutathione; GR: glutathione reductase; GSSG: glutathione disulfide; interferon gamma (IFNγ), IL: interleukin; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde, MMP: matrix metalloproteinase; NFATC1: Nuclear Factor of Activated T Cells 1; NF-κB: nuclear factor kappa B; PGE2: Prostaglandin E2; RANKL: receptor activator of nuclear factor kappa-B ligand, SOD: superoxide dismutase; TNF: tumor necrosis factor.

Table 1.
Antirheumatic mechanisms of action of R. officinalis *L.,* Curcuma longa *L., and* Crocus sativus *L.*

formulation, at the dose of 250 mg and 500 mg for 3 months ameliorated RA by its anti-inflammatory and antinociceptive effects which was confirmed by improving erythrocyte sedimentation rate, rheumatoid factor, visual analog scale, and C-reactive protein [25]. A recent clinical study reported that administration of curcumin (200–1000 mg) to patients with RA decreased pain, fatigue, stiffness, and swelling [26]. The results of a clinical trial indicated that the prescription of BioSOLVE Curcumin™ (250 mg, 12 weeks) to patients with RA improved the American college of rheumatology-20, Western Ontario and McMaster universities osteoarthritis index and visual analogue scale score [28].

A turmeric extract devoid of essential oils was given to Wistar female rats in an animal model of streptococcal cell wall-induced RA. Injections of an extract containing 4 mg/kg/day total curcuminoids intraperitoneally for four days prior to arthritis induction significantly reduced joint inflammation in both the acute (75%) and chronic (68%) phases [38]. A previous investigation stated that the administration of *C. longa* extract (30, 60, and 110 mg/ml/kg, 4 weeks) prevented degenerative alterations in the joints and bones of collagen-induced arthritic rats [30]. It was also observed that turmeric (200 mg/kg, 28 days, p.o.) significantly reduced the incidence and severity of arthritis by increasing the production of anti-inflammatory agents and decreasing the amount of pro-inflammatory cytokines, as well as stimulating the anti-oxidant defense system [31]. Furthermore, turmeric

(containing 60% v/v alcohol) mother tinctures decreased hind paw swelling in carrageenan-treated rats [32].

The findings of an *in vitro* study indicated that curcumin inhibited the production of prostaglandin E2 (PGE2) and induced apoptosis in synovial fibroblasts of patients with RA by reducing the level of B-cell lymphoma-2 (Bcl-2), an anti-apoptotic protein, upregulated the amount of BCL2-associated X (Bax), a pro-apoptotic protein, and activated caspase-3 and caspase-9. Besides, curcumin attenuated the cyclooxygenase (COX)-2 mRNA expression level [23]. The findings of another research confirmed that curcumin could inhibit the osteoclastogenic potential of peripheral blood mononuclear cells from patients with RA by suppressing the mitogen-activated protein kinase/Receptor activator of nuclear factor-kappa B/c-Fos/Nuclear Factor of Activated T Cells 1 (MAPK/RANK/c-Fos/NFATC1) signaling pathways, and it was suggested that curcumin might be an effective therapeutic agent for treating bone deterioration in inflammatory diseases including RA [24]. In another investigation, human fibroblast-like synoviocytes isolated from RA patients were treated with the IC_{50} of the curcumin. Curcumin downregulated the expression of the inflammatory response gene. Moreover, the authors suggested that prescribing curcumin along with the usual therapies could increase the quality of life in RA patients [39].

The data of an *in silico* study disclosed that herbal compounds present in turmeric have strong inhibitory properties against the pro-inflammatory cytokines including TNF-α and IL-1. It was also proposed that turmeric has therapeutic potentials to be used for treating RA [40].

2.4 *Crocus sativus* L. (saffron)

A clinical trial was carried on 66 women with RA to assess the effect of saffron (100 mg/day, 12 weeks) supplementation on their metabolic profiles and clinical outcomes. According to the obtained data, saffron considerably reduced the number of swollen and tender joints, pain intensity, and disease activity score compared to baseline values. Moreover, erythrocyte sedimentation rate was significantly improved and high-sensitivity C-reactive protein, TNF-α, interferon-gamma (IFNγ), and MDA levels reduced [41].

In an *in vivo* study, the efficiency of saffron was assessed on adjuvant-induced arthritic mice. As the results showed the daily administration of the saffron extract (25, 50, and 100 mg/kg, 47 days, p.o.) decreased the amount of lipid peroxides level and increased the activity of catalase and glutathione peroxidase [42]. The effect of saffron ethanolic extract (25–600 mg, 12 days, every other day, i.p.) was studied in an adjuvant-induced arthritis rat model. The results revealed that saffron ethanolic extract chiefly at the higher concentrations meaningfully attenuated tibiotarsal joint and paw diameters in comparison to the control group. It has also been suggested that saffron ethanolic extract could be potentially used as an anti-arthritic agent in managing inflammation in RA [43]. An investigation examined the effect of saffron extract (50, 100 mg/kg, 47 days, p.o.) on adjuvant-induced arthritis in mice. It was observed that saffron could remarkably reduce TNF-α and IL-1β levels. It also increased superoxide dismutase (SOD) and glutathione reductase (GR) activity [44]. Another *in vivo* study was planned to determine the effect of crocin, a carotenoid constituent of saffron, on the rat RA model. It was seen that intradermal prescription of crocin (6.25, 12.5, and 25 mg/kg, 28 days) pointedly alleviated the paw swelling, decreased arthritis score, the thymus index, the inducible nitric oxide synthase (iNOS) production, and the serum amount of TNF-α, IL-1β, and IL-6 [27]. Moreover, it was reported that crocin (40 mg/kg, 36 days, p.o.) shows therapeutic potential for RA, by mitigating the symptoms and preventing the expression of

pro-inflammatory factors including TNF-α, IL-17, IL-6, and IL-8 in ankle tissues and serum of collagen-induced arthritic rats [29]. It was also illustrated that crocin treatment (50 mg/kg, a week, i.p.) significantly decreased the amounts of TNF-α, IL-1β, and IL-6 in collagen-induced arthritic mice through blocking nuclear factor kappa B (NF-κB) signal activation by its interaction with IκB kinase (IKK) [33] (**Table 1**).

2.5 *Zingiber officinale* (ginger)

A former clinical trial was carried out on 6 patients with RA who took ginger powder (0.5–1 g/day, 3 months). It was found that all six patients reported pain relief, improved joint mobility, decreased swelling, and morning stiffness after three months of continuous ginger intake. There were no side effects recorded by any of the participants, and they all seemed to be happier and more engaged in their daily lives [45]. Another study investigated the effect of ginger on 56 RA patients. The findings revealed that after taking ginger (50 g/day raw/fresh, 3 months-2.5 years) more than three-quarters of participants reported pain and swelling relief to varying degrees. Also, all the subjects with muscular discomfort experienced pain relief. The authors suggested that at least one of the mechanisms by which ginger exerts its beneficial effects is thought to be linked to inhibition of prostaglandin and leukotriene biosynthesis, implying that it acts as a dual eicosanoid biosynthesis inhibitor [46]. The results of another study demonstrated that ginger powder (1500 mg, 12 weeks) administration ameliorated RA by reducing disease manifestations through controlling immunity factors, for instance enhancing the gene expression of forkhead box P3 (FoxP3), as well as attenuating RAR-related orphan receptor gamma (RORγt), and T-bet genes expression [47].

Prescription of *Z. officinale* (> 50 mg/kg/day, 26 days, i.p.) amended the disease incidence, clinical scores, cartilage destruction, swelling and temperature of the joint in rat collagen-induced arthritis. It also reduced serum levels of IL-1β, IL-2, IL-6, TNF-α, and anti-collagen type II (CII) antibodies [48]. The anti-inflammatory property of the essential oil of ginger was assessed in an experimental model of RA in female rats and it was observed that ginger essential oil (28 mg/kg, 28 days, i.p.) ameliorated chronic joint inflammation. These findings indicate that the anti-inflammatory properties of ginger are due to a combination of secondary metabolites, pungent-tasting gingerols, and aromatic essential oils, rather than only the phenolic compounds that have been studied previously [49]. A recent document explained that oral administration of zingerone, an active constituent of ginger (25 mg/kg, 3 weeks), to adjuvant-induced RA rats considerably decreased the amounts of NF-κB, transforming growth factor-beta (TGF-β), TNF-α, IL-1β, IL-6, and high-sensitivity C-reactive protein (hs-CRP), and significantly enhanced IL-10 levels. Moreover, zingerone restored the amounts of antioxidant enzymes [50]. Cedrol, a ginger active component, has been shown to improves RA by decreasing inflammation and preventing Janus kinase 3 (JAK3) phosphorylation [51].

Ginger extract was found to be an advantageous anti-inflammatory agent in an *in vitro* model on cultured fibroblast-like synoviocytes from RA patients by inhibiting the production of cytokines [52].

2.6 *Nigella sativa* (black seed, black cumin)

The efficiency of *N. sativa* oil was studied in the management of RA. The subjects of the treatment group took *N. sativa* oil capsules (500 mg, twice a day, 1 month). The results disclosed that the disease activity score, the number of swollen joints, and the duration of morning stiffness remarkably reduced compared with the

placebo group [53]. Assessing the effects of *N. sativa* oil extract (500 mg, twice a day, 8 weeks) on oxidative stress status and inflammatory cytokine response in patients with RA indicated that the serum amount of IL-10 augmented in the *N. sativa* group, besides serum malondialdehyde (MDA) and nitric oxide (NO) levels decreased compared with the baseline [54]. Another clinical trial reported that administration of *N. sativa* oil (1 g/day, in two divided doses, 2 months) to 43 female patients with mild to moderate RA led to a significant decrease of the serum hs-CRP amount and the number of swollen joints. A moderately similar T helper cells ($CD4^+$ T cell) percentage was detected in the *N. sativa* oil and placebo groups. *N. sativa* also decreased CD8+, and amplified CD4+CD25+ T cell percentage and the CD4+/CD8+ ratio in comparison with the baseline and placebo group [55] (**Table 2**).

Evaluating the effects of thymoquinone, the volatile oil of black cumin (2.5, 5 mg/kg, 14 days, p.o.), on RA model in rats disclosed that signs of inflammation on the claw and the amounts of TNF-α, as well as IL-1β decreased in treatment groups

Herbal medicine	Antirheumatic Mechanism(s)	Reference
Zingiber officinale	↓ Prostaglandin and leukotriene	[47]
	↑ FoxP3	
	↓ RORγt, and T-bet	[48, 50]
	↓ IL-iβ, IL-2, IL-6, TNF-α, NF-κB, TGF-β, hs-CRP, and anti-CII antibodies	
	↑ IL-10	[51]
	↓ JAK3 phosphorylation	
Nigella sativa	↑ IL-10	[54]
	↓ MDA	
	↓ NO	
	↓ hs-CRP	[55]
	↓ CD8+	
	↑ CD4+CD25+ T cell, CD4+/CD8+ ratio	[56]
	↓ TNF-α, IL-iβ	[57]
	↓ PGE2, TNF-a, IL-ib, IL-6, IFN-c, TNF-α-induced phospho-p38 and phospho-JNK	[58]
	↓ MPO, elastase activity, lipid peroxidation, articular nitrite content	
	↑ GSH and SOD	
	↓ NFκB, TLR2, and TLR4	[59]
Camellia sinensis	↓ Oxidative stress	[60]
	↓ Blood leukocytosis and erythrocyte sedimentation rate	[61]
	↓ Free radical levels	[62]
	↓ IL-iβ, IL-6, IL-8, and COX-2	[63]

CD4+ T cell: T helper cells, CII: collagen type II, COX: cyclooxygenase; FoxP3: forkhead box P3; GSH: glutathione; hs-CRP: high-sensitivity C-reactive protein; IFN-c: Interferon-c; IL: interleukinJAK3: Janus kinase 3; JNK: c-Jun N-terminal kinases, MDA: malondialdehyde, MPO: myeloperoxidase; NF-κB: nuclear factor kappa B; NO: nitric oxide, PGE2: Prostaglandin E2; RORγt: RAR-related orphan receptor gamma; SOD: superoxide dismutase; TGF-β: transforming growth factor-beta, TLR: toll like receptor; TNF: tumor necrosis factor.

Table 2.
Antirheumatic mechanisms of action of Zingiber officinale, Nigella sativa, *and* Camellia sinensis.

[56]. Thymoquinone (5 mg/kg, 21 days, p.o.) treatment in the collagen-induced arthritis in Wistar rats could considerably reduce the amounts of pro-inflammatory mediators including PGE2, TNF-a, IL-1b, IL-6, Interferon-c (IFN-c), and increased IL-10 level. Thymoquinone also decreased arthritis scoring and improved bone histology [57]. Administration of the aqueous methanolic extract of black seed (400, 500 mg/kg, 20 days, p.o.) to arthritic rats decreased myeloperoxidase (MPO), elastase activity, lipid peroxidation, articular nitrite content, and increased GSH and SOD amounts [64]. In another rat model of RA, *N. sativa* oil (0.91, 1.82 mL/kg (798, 1596 mg/kg, respectively), 25 days, p.o.) was administered to animals. *N. sativa* oil exhibited anti-inflammatory, anti-nociceptive, and anti-arthritic properties that were significant in comparison with the untreated arthritic rats [59]. The results of an *in vivo* study demonstrated that thymoquinone (10 mg/kg, 28 days, i.p.) administration arthritic rats attenuated the macroscopic arthritic score, pannus formation, synovial inflammation, bone erosion and CRP amount. Moreover, mRNA levels of IL-1, TNF-α, NFκB, TLR2, and TLR4 were reduced [60].

An *in vitro* study explained that thymoquinone inhibited TNF-α-induced phospho-p38 and phospho-c-Jun N-terminal kinases (JNK) expression in RA synovial fibroblast [57].

2.7 *Camellia sinensis* (green tea)

Evaluating the therapeutic effects of green tea (0.5, 1.0 g/kg, 24 days, p.o.) on articular/extra-articular difficulties in rat adjuvant-induced arthritis revealed that the arthritis severity and complications besides oxidative stress ratio in synovial fluid were significantly reduced [61]. In another *in vivo* study, adjuvant-induced arthritic rats received green tea aqueous extracts (0.5 and 1.0 g/kg, p.o.) for 28 or 14 consecutive days starting from day 0 or 14 of arthritis induction, respectively). It was observed that the high dose of green tea amended synovial joint inflammation, reduced blood leukocytosis and erythrocyte sedimentation rate, and changes in weight/cellularity of lymphoid organs. It also decreased the systemic production of pro-inflammatory cytokines and the expression of chemokine receptor-5 in synovial tissues [65]. Aqua-alcoholic extract of green tea (50, 100, 200, 400 mg/kg, 14 days, p.o.) was prescribed to collagen-induced arthritic rats. The findings showed that green tea was useful in reducing the ratio of oxidative stress by controlling the amounts of antioxidants, decreasing free radical levels, and restoring normal hematopoietic cascade [58]. The therapeutic potential of green tea was evaluated in an experimental model of RA in Lewis rats. The data showed that green tea reduced paw edema, bone erosion, and inflammatory responses in joints of treated rats. It also reduced telomerase activity in comparison with the control group [62].

In an *in vitro* study, crude aqueous *C. sinensis* (50, 100, 200, 400 μg/ml) infusion and decoction revealed anti-arthritic properties in protein denaturation and membrane stability methods [66]. It was also found that catechins derived from *C. sinensis* (epigallocatechin-3-gallate, epigallocatechin, and epicatechin) inhibit the IL-1β signaling pathway and consequently decrease the amounts of pro-inflammatory mediators such as IL-6 and IL-8, as well as COX-2 in primary human RA synovial fibroblasts [63] (**Table 2**).

3. Conclusion

Herbs are spread in different geographical and ecological throughout the world. Since the olden days several traditional herbs have been utilized for treating plenty of ailments. The number of medicinal plants that have antirheumatic properties is

comparable to potent synthetic antidepressants. The antirheumatic effects of plants have been linked to their antioxidant, anti-inflammatory, analgesic properties. Furthermore, polyherbal formulations might be more effective due to their possible additive and/or synergistic effects and could be employed for ameliorating mild to moderate RA. As a result, it is possible to conclude that medicinal plants are at the center of nature and that more research is required to determine their therapeutic value.

Abbreviations

ACPAs	autoantibodies against citrullinated peptides
Bax	BCL2-associated X
Bcl-2	B-cell lymphoma-2
$CD4^+$ T cell	T helper cells
CII	collagen type II
COX	cyclooxygenase
DMARDs	disease-modifying anti-rheumatic drugs
FoxP3	forkhead box P3
GSH	glutathione
GR	glutathione reductase
GSSG	glutathione disulfide
hs-CRP	high-sensitivity C-reactive protein
IFN-c	Interferon-c
IgG	immunoglobulin G
IFNγ	interferon gamma
IKK	IκB kinase
IL	interleukin
iNOS	inducible nitric oxide synthase
JAK3	Janus kinase 3
JNK	c-Jun N-terminal kinases
MAPK	mitogen-activated protein kinase
MDA	malondialdehyde
MMP	matrix metalloproteinase
MPO	myeloperoxidase
NFATC1	Nuclear Factor of Activated T Cells 1
NF-κB	nuclear factor kappa B
NO	nitric oxide
NSAIDs	anti-inflammatory drugs
PGE2	Prostaglandin E2
RA	rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa B
RANKL	receptor activator of nuclear factor kappa-B ligand
RFs	rheumatoid factors
RORγt	RAR-related orphan receptor gamma
ROS	reactive oxygen species
SOD	superoxide dismutase
TGF-β	transforming growth factor-beta
TLR	toll like receptor
TNF	tumor necrosis factor

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Chapter 12

Ayurveda Concepts of Joint Diseases

Ayagama Pitadeniyage Anoma Jayasiri

Abstract

Prevalence of bone related diseases are very high in the world today, among them arthritis is very common form of disease suffers millions of people, problematic for individually and economically to the society due to the long term disability. If not properly manage leads to joint replacement surgical procedures which are very common and high in cost. Aim of this chapter to make attention in application of Ayurveda medicine for betterment of the world population. Ayurveda explain theories in origin of these diseases, causative factors, eteopathogenesis and management steps mostly using herbal drug products mentioned in eight divisions of Ayurveda. Main common two diseases sandhigatha vatha correlated with osteoarthritis and amavatha correlated to rheumatoid arthritis well described with proper management procedures with many other bone and joint diseases. Different theories were discussed with the aid of philosophical backgrounds which facilitate these medical theories. These are five element or panchabhutha theory, three dosha concept or theory of three governing energies of the body, saptha dhathu concept or body bearing tissues, concept of agni or metabolic power. Different treatment plans were described as treatment options for cure and prevention of human being as a complete medical system.

Keywords: Herbal products, rejuanation, prevention, amavatha, arthritis

1. Introduction

Millions of people around the world suffer many kinds of bone and joint diseases. It was reported that five million people suffer from osteoarthritis and 12000 of children were from juvenile arthritis. In modern medicine described disorders of connective tissues, joints and bones that cause musculoskeletal pain and stiffness are predominant features [1]. Same as in modern medical field Ayurveda medical system also identified the commonest form of joint disease known as sandigatha vatha that correlated to osteoarthritis manifested with pain.

This information described well in history of the Ayurveda medicine included in literature which goes thousands of years back. Ayurveda, define as the science of life coming from ancient to this era as a system of natural way of healing to the world population. This medical system old at least 5000 years which come from time of (1500–1000 BC) but address the health problems appears today and benefited to promote good health and longevity while cure the diseases. When study about the historical background until 700 BC, this science has been orally discussed between sages and physicians [2]. There after two main texts were assembled to discuss medicine part by Charaka called Charaka Samhitha [3] and surgery concepts

were discussed by Susrutha in his text Susrutha Samhitha [4] later some texts were written and they were included to separate time periods until come to present stage, as pracheena kala (ancient period), madya kala (medieval period) and nuthana kala (modern period). Two Ayurveda authentic texts were available known as Charaka Samhitha which described etiology, symptomatology, pathology, prognosis and management of diseases written by physician Charaka and Susrutha Samhitha deals with surgical instruments and procedures written by surgeon Susrutha.

Ayurveda medical system mainly divided into main 08 branches known as Ashtanga Ayurvea (sub divisions). These divisions correlated to modern medical stream named as shalya thantra (surgary), shalakya thantra (ENT), kayachikithsa (general medicine), bhutha vidya (holistic medicine), agada thantra (toxicology), rasayana thantra (geriatrics), vageekarana therapy (aphrodisiac procedures) [5]. All these fields deals with every aspect of theories related to Ayurveda medicine on causative factors of diseases, treatment lines, preventive measures, prognosis, deformities and rehabilitation procedures. Except to these many literature were contributed to the field by ancient Ayurveda scholars including large amount of drugs as sauces from plant kingdom, mineral and animal kingdom among them Bhava Prakasha is one important text which was written in adhunika kala (modern period) [6]. Most of these literature described various facts relevant to joint diseases with treatment options in Ayurveda, this chapter also designed to give a view about joint diseases as Ayurveda approach.

2. Ayurveda concept of health

There are main two objectives of Ayurveda as medical system well explained par with the definition to a healthy person explained by the World Health Organization. Two objectives comprised preventive and curative aspects of living human beings. Ayurveda deals not only with body but also with the mind and spirit as well. In Ayurveda medicine well described the features of a healthy person. Firstly he or she must have three main energies (*tridosha*) that governing the body in balance state the term which implies *samadosha* (balanced three *doshas*) which act as main three pillars to stable the body in healthy state, by involve in body functions. *Agni* or metabolic power of the body is another factor that needs to be in balance state of a body. *Dhathu* or tissues seven in number are the components that bare the body of a person as per the Ayurveda view that need to be in balance state to give healthy life. Waste products of the body (*mala*) also need to be in balance state to appear a person in healthy manner. Except to these physical structures clear mental state as well as balance mind good spiritual soul need in a person to spend a healthy life as described in Ayurveda system of medicine. With these three energies maintain metabolic activities by the *agni* (metabolic power) help the interactions are processed inside the body constituents based on the theory of *panchabhutha* (five element theory of Ayurveda). *Panchamahabhuthas* are the material basis of the universe so as for the living body. The gross body of a living being consist of this five elements and life processes due to consciousness. Par with the philosophical explanations five *mahabhuthas* (*Panchabhutha* i.e. *Pruthvi, Ap, Thejas, Vayu, and Akasha* which correlated to atomic levels of structure that constitute the vegetable, animal and mineral kingdoms) along with consciousness called six *dhathus* (components) that a human being is comprise [5, 6]. This is the scientific background that implies in definition of healthy person related to the mind. On combination with consciousness, five elements, out of their some portions, constitute three *doshas* in order to perform and regulate the physiological process of the body [5, 6]. The changes in physiological functions can be given rise due these reasons as mal practices of food

patterns, behavioral nature of a person environmental, seasonal changes as well as traumatic conditions can be affect to change this balance state of a person and create diseases in the body that make individual mentality unstable.

2.1 Ayurveda approach in origin of diseases

According to Ayurveda, most diseases connected with the psychophysiological and pathologic changes in the body are caused by imbalance states in three *doshas* (ie, *vata, pitha and kapha*) these three energies which governs the body by maintaining the balance of body constituents and help in homeostasis in internal environment [7]. Each energy is responsible for certain type of body functions such as *Vatha* (Air/motile force) energy of movements, functions of nucleus, neurological activities, and natural urges stool/urine or gases etc. *Pitha dosha* (Fire/Agni) is responsible the functions of energy of metabolism, digestion with transformation, functions of mitrochondria, hormonal and enzymatic activities. Third category of energy is the *kapha* (Water/fluid component) that involves body functions of energy of lubrication structure, functions of protoplasm, secretory activities, and functions of the fluid contents of the body. These three energies govern the body bearing structures as well as functions of those structures. Another factor is tissues (*dhatus*) that bare the body, that seven in number correlated to the physical structures of the body such as rasa (plasma), *raktha* (blood), *mansa* (muscles), *medas* (fat tissues), *asthi* (bones), *majja* (bone marrow) and *shukra* (sperms/ovum). Three waste excretory products of the body known as *mala* (stools), *mutra* (urine) and *sweda* (sweat). Mainly *agni* (metabolic/fire) is an important concept describe in Ayurveda which mainly involve as causative factor for diseases, if it is in imbalance or mal function state known as *ama* (i.e. undigested state of foods in digestive tract which causes diseases/formation due to dearranged *agni*) which is mainly involved in certain type of joint diseases also. Important 13 agnis are activating in tissues, organs and systems of at different places of the body. Main type is *jataragni* (digestive power) activate in the digestive tract that correlated to enzymetic actions of gastrointestinal tract. Twelve other *agnis* (metabolic fire/power) are established in different places of the body and functionally contributed to internal homeostasis. Each tissue levels composed their owned metabolic powers namely dhatwagni 07 in number as *rasa dhathvagni*, *raktha dhathwagni*, *mansa dhathvagni*, *medas dhthvagni*, *asthi dhathvagni*, *majja dhathvagni*, *shukra dhathvagni* those involves in process of tissue metabolism. There is another important category of metabolic power is activated in micro channels and cellular level of the body named based on five element theory of Ayurveda as *panchabhuthagni* [8]. When these micro metabolic powers are not properly activated at cellular levels micro channels of the body *(srothas)* will not function properly, they blocked *(avarodha)* channels and tissues as well as organs then cause diseases. Main other concept of this medical system identified which cause the root for diseases produced *ama* within the body that can get mixed with *doshas* and formed complexes named as *sama vatha, sama pitha and sama kapha* which give rise symptoms of diseases [9]. Accoring to Ayurveda concepts *ama* means unripe substance produced under the weakened state of Agni (digestive power). Features of this *ama* state are *visha* (toxic), slimy in nature, has unpleasant odors, heavy in nature and has/represent various colors [9–11].

As per the view of this system of medicine development stages of a disease is describes based on five element theory, *saptha dhatu* and concept of *agni* described early paragraph. As the body composition and functioning energetic three doshas and the body tissues (*dhathus*) comprises from similar physical properties, there is relationship between doshas and tissues (*dhathus* synonym as *dushya*) in origin of a disease identified as combination these two components and named as *dosha dushya*

sammurchana (combination of vitiated dosha with tissues) according to this combinations demonstrate the symptoms of each disease in process of eatiopathogenesis [12]. Categoriztion of idiseses done according to this relationship between these *doshas* and *dhathus* (tissues seven in number) known as *dosha-dushya* complex that can be seen as symptoms in a patient.

Treating the diseases there are different conceptual theoretical background is established in this medical system. Mainly it described remove the causative factors of diseases such as diet, seasonal changes, correction of generating *ama* are some steps can be practically apply to breaking down the stages of etiopathogenesis and remove the *ama* by applying relevant medicaments. As an example rheumatoid arthritis which involve not only the joints but also certain other systems also in angle of Ayurveda view that cause when *samavata* mixed with rasa dhathu then causes Amavatha (rheumatoid arthritis), combination of *samapitta* and *raktha dhathu* produces *vatarakta* disease. *Ama* is a substance having a toxic nature and this toxic substances reacts with joint and bone elements causing the diseases. If *Ama* is not produced, there will be no bone joint disease either, this is the theory behind this medical science, that implies it has been mentioned that synonym given for diseases the word *ama*.

2.2 Involvement of Dosha in born and joint diseases in Ayurveda

Born and joint diseases in Ayurveda mentioned with related concepts texts written in ancient to modern period. These information were stated by modern Ayurveda scholars after further study well they mentioned that three main joint manifestations were identified and treated. They are *Sandigatha Vatha* (osteo arthritis), *Amavatha* (rheumatoid arthritis) and *kostukashirsha* (pain with swelling of knee joint) [9] symptoms of these conditions can correlate to structural changes of modern clinical cases. Two of them are *polyarthritic* clinical entities having a range from acute to chronic. *Sandhigata vatha* is the commonest form of articular disorder. It is a type of disease which mainly occurs in oild age people due to the dryness of the tissues which limits daily activities such as walking, dressing, bathing making patient disabled. Because this is a type of *vatha* category of disease can be lead to dangerous if located in a vital point, same situation occurs in an old person difficult in cure. Therefore in identifying prognosis by detect early symptoms is very important because this is very common type of disease. As it is *vatha* type of disease *shula* (pain) is the cardinal feature of the disease associated with *sandhishotha* (swelling), lack of movements of the joints or painful movement of the joints, sometimes loss of function and dislocations are possible. *Vatha raktha* is a condition give rise symptoms of pain, fasciculations, swelling, dryness of the affected part with discoloration, itching, contraction are seen, predominantly in larger joints, but begins from the smaller joints both the *vatha* (motile force) and *raktha* (blood) are in predominant positions. This condition influenced by *ama* combined with *pitha dosha* that known as *sama pitha* and manifest the symptoms accordingly. *Kostukashirsha* is the other common form of disease naming according to its appearance of the knee joint after affected knee joint of the person known jackals head due to the swelling and same time person feels sever pain.

Modern period literature described the relationship between *ama* and joint disease to give a better diagnostic outlook. Rheumatoid arthritis which is a whole multitude of joint manifestations that given rise to joint malfunctioning disease correlated to *Amavata* decribed in Ayurveda [13]. Ayurveda diagnosis can be done only study the *dosha* involvement, causative factors, symptoms,malfunctioning of the affected part and finally can be treat using herbal drugs use in the field with the help of Ayurveda pharmacodynamic properties with the aid of drug actions [14].

When considering structure–function relationship and *dosha* involvement need to mention the five verities of three *doshas vatha*, *pitha* and *kapha* is very important. There are 5 varities of three *doshas* which were located at specific places of the body and give its contribution to the proper functions of that area of the body [15, 16] were well described in Ayurveda texts and that types are tabulated in **Table 1**.

Each and every type of *dosha* located at its own site facilitate its action to that relevant body parts. These types of each *dosha* is well responsible to cover all the functions of the body, when consider the structure and functions of the joints *(sandhi) Shleshaka kapha* component is the main part that give the actions related to its structure in the locomotive system [15, 16].

Sandi samslesha (bindings of joint) is described as one of the functions of *kapha* that described in Ayurveda view. Susrutha postulates similar views and while describing the functions of *kapha*, mentions of Sandisamshleshanam (lubrication of the joint), *snehana* (promotion of uncouthness), *purana* (storage or filling), *stayikrit* (stability) which are directly connected properties pertaining to *sandhis* (joints). The text written in *pracheena kala Ashtangahrida samhitha* mentioned that among other functions shleshma promotes, sthirathwa (sturdily), *snighdhatwa* (viscosity) as well as hates (binding) actions that are specifically applied to joints. Keeping various components of it in firm unity that makes it possible to function as a single unit, further *shleshaka kapha* protects it's articulation and opposes any force that might cause it's separation and disunion. According to the literature it becomes clear that *Shleshaka kapha* is predominant in joints and keeps them well lubricated and nourished. These explanations correlated with structure (including synovial fluid) and functions to integrate as medical systems were mentioned in this paragraph.

In the disease state of *sandhis* (joints) one or more above functions seen to be deviate it's normal in functioning due to the pathological changes and give person abnormal feeling. The bone ends are covered by hyaline cartilage, avascular tissue which provides a smooth, low friction surface allowing joint movement. Normal articular cartilage is a smooth bluish translucent material which is composed of chondrocytes, proteoglycans, collagens and water that correlated to structure and functions of *Shleshaka kapha* variety explain in Ayurveda. It is very important to identify the bone and joint related diseases with proper classification of these in Ayurveda by integrating its application for treatment options due to high prevalence of these disease conditions. Disorders of the joints are among the most disabling of conditions. They cause serious morbidity to the affected individual same way major economic importance to both the patients and society [15–18].

2.3 Types of bone and joint diseases in Ayurveda

In this chapter mainly discuss about the joint diseases, Ayurveda literature mostly discuss about three joint related diseases such as *Vatha raktha, Sandigatha vatha* and

Verities of *Vata Dosha*	Verities of *Pitha Dosha*	Verities of *Kapha Dosha*
Prana vata	*Pachaka pita*	*Bodhaka kapha*
Vyana vata	*Alochaka pita*	*Kledaka kapha*
Samana vata	*Ranjaka pita*	*Shleshaka kapha*
Udana vata	*Brajaka pita*	*Avalambhaka kapha*
Apana vata	*Sadhaka pita*	*Tharpaka kapha*

Table 1.
Categories of three Doshas.

Kostukashirsha but except to these in different texts written from ancient time to modern period discussed other bone related diseases and joint diseases. They have named according to the structural manifestation, *dosha* involvement, place that symptoms, structural changes can be seen, relevant to its tissues that mainly affected.

They are *Sandigatha vatha* (it is a *vatha dosha* category of condition that pain is the main feature of this, which mainly occurs in old age due to *dhatukshaya* or dryness of the tissues, which limits everyday activities such as walking, dressing, bathing making patient disabled*), Vata raktha* (swelling, dryness of the affected part with discoloration, itching, contraction are seen, predominantly in larger joints), *Kostuka shirsha* (pain and swelling in the knee joint), *Avabahuka* (pain with restriction in movements of the upper arm), *Vatakantaka* (pain at calcanium area), *Grudrasi* (pain along the hip joint and thigh that causes difficulty in walking, pain is the main symptom), *Khalli* (loss of function and paralysis, specifically affecting the leg), *Urustambha* (severe pain, loss of function and loss of temperature sense in the affected limb), *Hanusthamba* (mainly due to trauma, dislocation of tempero mandibular joints, loss of movement is seen), *Asthimajjagata vatha* (severe crushing pain in bones and joints, discolorations are possible, loss of muscular power and strength with gradual thining of the affected limb), *Visvachee* (loss of function of the hand due to the dryness of structures at wrist joint which cause pain that radiates from the proximal to distal hand), *Amavatha* (mainly affects bigger joints, appears symptoms of anorexis, vomiting, malaise, indigestion), *Raktha vatha* (cause due to vitiation of rakta dhatu, slightly similar to Vata rakta in its clinical presentation), *Visha vatha* (cause due to infections), *Jara vatha* (cause due to old age, this included to natural bony degeneration due to senility), *Jirna vatha* (manifest due to degenerative processes), *Pada bransha* (characterized by loss of function of the affected foot among the eighty types of *vatha rogas*), *Vatha khuddatha* (one among the eighty types of *vata rogas*), *Gulpha graha* (stiffness in the ankle joint is the predominant feature), *Uru sara* (severe pain, loss of function and loss of temperature sense in the affected limb), *Janubheda (*type of pain localized in the knee joint), *Pangulya* (person felt to limp a sign due to any causes, such as trauma, dosha), *Thrika graha* (stiffness at the macro iliac joints), *Prushta graha* (stiffness in the spine), *Bahu shosha* (wasting is the predominant sign in this condition, at the shoulder), *Griva sthambha* (Stiffness in the neck), *Asthyavrutha vatha* (Obstruction of *vatha* due to *asthi dhatu* causes penetrating pain, stabbing pain and lassitude), *Kaphavrutha vatha* (*Vyana vatha* is being obstructed by kapha dosha, pain felt at the small joints and the patient feels heaviness in the body) [17, 19, 20].

When observe these different types of bone joint diseases discussed in Ayurveda texts it shows some are appear as *vatha* category of diseases, some are causes due to traumatic conditions and involve the bones or joints. Therefore some scholars who were searched for these in modern period looked into that and categorized into certain classifications. They mentioned three disease conditions namely *Sandigatha Vatha, Vatha raktha* and *Kostukashirsha* were the mostly discussed disease conditions in literature, also these conditions common in clinical practice [21], therefore clearly mentioned involvement of *dosha*, causative factors, prognosis and deformities prominent diseases, then classification explained accordingly as mentioned here.

Rheumatoid arthritis is a critical disease condition which the person is highly disabled if it is not properly managed. In Ayurveda system of medicine this disease well described in modern period texts that correlated to name as Amavatha which is a disease that systemic involvement as well as local involvement can be seen in large joints. It mainly affect bigger joints, presenting symptoms of anorexia, vomiting, malaise, indigestion etc. causative factor is due to the malfunction of digestive power. In the patients it presenting swelling with predominant pain as the symptoms with many other complaints. In ancient literature term 'Ama' the word

comprises Amavatha used to denote a state of illness cause 'visha' padartha (toxic matter) which produces due to malfunction of digestive power. Also malfunction of the metabolism of the body benefited this disease process. Texts and the scholars of modern period of Ayurveda history described views about arthritis or joint diseases by indicating variety of clinical presentations. They stipulated the possibility of occurs several interrelated entities with possibly different etiologies related to joint diseases as mention here. They are Rasa Vata (a synonym for Amavatha), Raktha Vatha (a similar condition to Vatha raktha in ancient texts), Visha vatha (a condition similar to acute infective arthritis in modern medicine), Jirna vatha a condition with sandhi jadya or ankylosis due to old age, Jara vatha similar to degenerative arthrosis, Sandhika jwara to rheumatic fever. Same manner Amawatha correlated with its symptoms to Rheumatoid arthritis and according to the causative factors and disease involvement different treatment measures were prescribed such as to correct the digestive power and digest the ama and facilitate to absorb to the system, and then avoid the manifest in the locomotive system. Different treatment measures were described for this to manage the disease process help of drug actions such as deeepana (appetizer), pachana (digestive) drugs, local treatments according to the involvement of joints external drug preparations are applied to relieve pain and swelling with improve the joint movements.

2.4 Classification of bone and joint diseases

Based on the clinical features these diseases classified according to the causative factors, involving places, and symptoms by compairing structurural and functioning features in modern medicine [1, 17, 19], manifest in diseased person which is important in treating and management of bone and joint diseases, par with Ayurveda treatment plans, here it has been mentioned according to the based on or predominance of each factor.

2.4.1 According to causative factors

1. Based on names.

   Sandigatha Vatha, Kostukashirsha, Avabahuka, Vatha kantaka, Grudrasi, Khalli, Asthi majjagata Vatha, Hanu bramsa, Visvachee.

2. Traumatic

   Vatha kantaka, Hanu bramsa, Grudrasi, Avabahuka.

3. Based on dosha involovement

   Sandigatha vatha, Khalli, Visvachee, Gudegatha Vatha, Asthi majjagata vatha, Ama vatha.

4. Based on origin of *Ama*

   Amavatha, Vatha raktha, Urusthambha,, Raktha vatha.

5. Based on toxic factor

   Visha vatha.

6. Based on time factor

   Jara vatha, Jirna vatha.

2.4.2 According to symptoms

1. Based on Pain.

   Sandigatha vatha, Asthi majjagata vatha, Vatha kantaka, Amavatha, Urusthambha.

2. Based on swelling

   Kostukashirsha.

3. Based on inflammation

   Amavatha, Vatha raktha, Urusthambha.

4. Base on malfunction

   Avabahuka, Khalli, Visvachee, Grudrasi, Hanu bransha.

5. Based on deformities

   Kostukashirsha, Pada bransha, Bahu shosha.

2.4.3 According to the place specifically affected

1. Joint predominancy.

   Hanu bransha, Sandigatha vatha, Grudrasi, Amavatha, Vatha raktha, Avabahuka, Vatha kantaka, Khalli, Visvachee.

2. Bone predominancy

   Asthi majjagata vatha, Urusthambha.

3. Muscle with joint predominance

   Amavatha, Kostukashirsha, Avabahuka, Grudrasi, Vatha kantaka, Khalli, Visvachee.

4. Ligaments & joint predominance

   Vatha raktha, Khalli.

2.5 Ayurveda treatment options for bone and joint diseases

To manage these diseases different therapeutic measures are used according to the Ayurveda system of medicine. In clinical practice medicinal materials in form of single drugs as well as poly-herbal formula are used. Body has been buildup of dietetic materials, the drug materials giving to manage the diseases also constituted same physical properties identified by Ayurveda influence of philosophical literature, also the aid of these theoretical concepts drugs are prescribed based on their actions. Body treatment is correlated to management process of a disease in Ayurveda defined as *chikithsa* which has a broad meaning related with the body. Literary meaning of body, described based on philosophical backgrounds that stated body derives and develop from nutrient materials and it is a collection of nutrients. To maintain its balance status there should be equilibrium in metabolic functions. These functions are governing by the three energy flows (*vatha, pitha,*

kapha) with the help of different *agnis* (metabolic power) in the body. These processes activate in the body and responsible to maintain the internal environment in balance state by avoiding cause any imbalance which originated a disease. Therefore treatment defined as *chikithsa* that implies collection of suitable procedures which can be normalizing the imbalance state of internal environment of the body.

Collectively these procedures lead to promoting and preservation of health in healthy person and curing disease in the sick person which highlights curative, preservative, rehabilitative and preventive aspects to manage diseases which in same manner applied to the joint diseases. Based on theoretical aspects different treatment lines are applied to manage joint diseases. They are avoiding causative factors such as dietary mal practices, mal practices in behavior, correct expose to seasonal changes. Pacifying visited *doshas* mainly *vatha samana* using drugs pertain drug action of *vedana stapana* to relieve pain with other medicaments for correct rearranged body functions according to the causative factors [14, 21, 22]. Excretion of disease causative factor known as *ama* by digestion of *ama* into the system using suitable drugs. Cleansing the obstructed channels (*srothas*) by five bio purificatory process known as *Panchakarma* using suitable drugs [23]. Facilitate diseased person if the condition caused due to the aging process by *rasayana* (rejuanation) therapy which is a main branch of Ayurveda. Whether person needs the rehabilitation yoga therapy or meditation can be advice to the patient. Finally all these treatment options can be apply as local or systemic therapeutic applications according to the patient condition as well as the nature of the disease.

3. Conclusions

Three energies governing the body functions to maintain the balance state of internal body environment. *Vatha dosha* as motile force and neurological activities. *Pitha dosha* responsible for metabolic, enzymatic and hormonal actions. *Kapha dosha* represents fluid component and its actions. Common form of joint diseases are osteo arthritis and rheumatoid arthritis respectively correlated to sandhigatha vatha and amavatha, for management these conditions herbal products, body purificatory processes, rejuanation procedures with yoga exercises can be used as therapeutic options.

Conflict of interest

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Notes/thanks/other declarations

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Rheumatoid arthritis (RA) is a chronic autoimmune disease generating joint pain and damage in which inflammation plays a major role. RA joints are inflamed and stiff. Symptoms include joint swelling and warmth causing fatigue affecting life's health-related quality. Still, there are many other medical conditions that can also be associated with your symptoms and signs. This book is not a substitute for a diagnosis from a healthcare provider. Yet, understanding your symptoms and signs and educating yourself about health conditions is important and can contribute to having the healthiest possible life. Herein, Professor Hechmi Toumi offers an edited volume with detailed new information on RA pathogenesis and explains both approaches and treatment options: recent clinical research and traditional methods.

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