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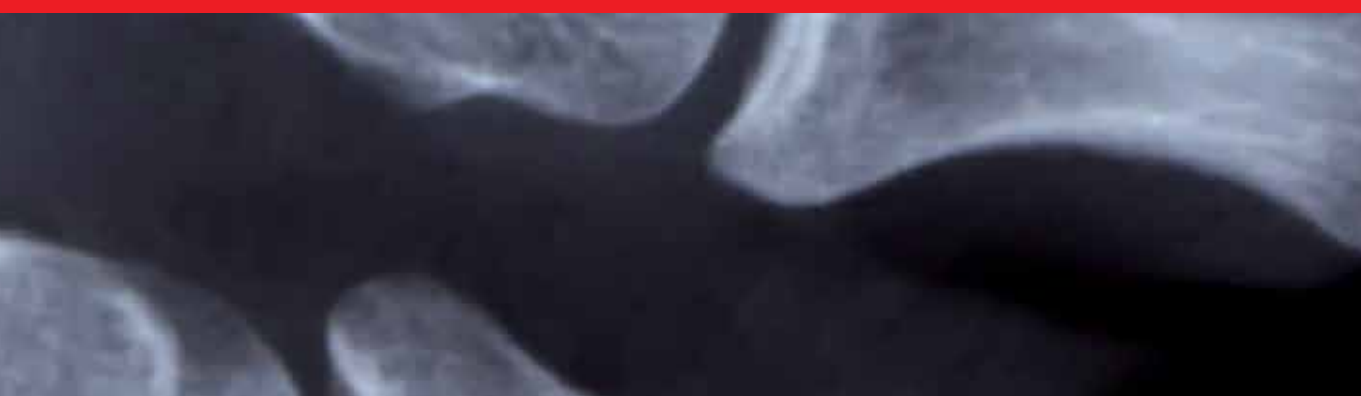
Osteoarthritis Biomarkers and Treatments

Edited by Hechmi Toumi and Marija Mazor



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IntechOpen Book Series

Osteoarthritis Biomarkers and Treatments

Volume 2

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Scope of the Series

This book series presents new concepts of pathogenesis, including genetic, epigenetic determinants and epidemiology of rheumatic diseases. It focuses on current classification criteria, recommendations for the diagnosis and treatment of rheumatic diseases. The goal of the series is to explain various aspects of disorders associated with impaired immune response and autoimmunity processes. It also discusses risk factors associated with the development of autoimmune diseases, as well as latest discoveries and future perspectives of this extremely dynamic field of internal medicine - rheumatology.

Contents

Preface

Because the regenerative ability of cartilage is limited due to its avascular nature and low replenishment rate of colla- gen type-II, osteoarthritis (OA) is one of the top five most disabling conditions that affects more than one-third of the population older than 65 years of age. Recently, ORSI recommended that the optimal OA treatment regimen should consist of both medications and non-drug treatments. Currently, painkillers and anti-inflammatory drugs are often prescribed in association with weight loss and/or physiotherapy. When these options are no longer able to control symptoms, intra-articular injections of corticosteroids, hyaluronic acid or Platelet-Rich Plasma are alternatives. Non-pharmaceutical treatments start with bracing, weight loss and muscle strengthening through different types of physical activity. Recently, physical exercise became the cornerstone of osteoarthritis therapy and several natural medicines have been examined in clinical trials. Foods for treating arthritis include Omega-3 foods, high-antioxidant and fibre foods etc. The first part of this book examines the changes in bone and OA biomarkers in response to OA-diseased joints. The second part is a description of both OA clinical treatment approaches and natural supplements.

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Section 1

OA Biomarkers and Treatments

Chapter 1

Value of Biomarkers in Osteoarthritis

Yaşar Mahsut Dinçel

Abstract

Biochemical markers in osteoarthritis are molecules that occur during the physiological cycle of the bone and cartilage matrix, and they can be detected in body fluids. The most important goal of marker metrology in osteoarthritis is that cartilage damage can be recognized at the early stage when it has not yet been detected radiologically. In addition to early recognition, follow-up of disease activity, determination of disease severity, prediction of prognosis, and evaluation of response to treatment are other purposes of marker measurement. Type II collagen is the most important structural element of joint cartilage and is relatively specific to hyaline cartilage. The main event in osteoarthritis pathophysiology is the damage of the Type II collagen network. For this reason, researches aimed at detecting osteoarthritis-specific and specific biochemical markers have focused on Type II collagen. CTX-II is currently the most investigated and promising biomarker in relation to osteoarthritis clinic.

Keywords: biomarkers, CTX-II, fibulin-3, osteoarthritis, Type II collagen

1. Introduction

Osteoarthritis (OA) is a multifactorial, dynamic disease process characterized by erosion in the joint cartilage, bone hypertrophy at the joint edges, subchondral sclerosis, synovial membrane, and biochemical and morphological changes in the joint capsule. It is more common in the elderly [1].

The diagnosis of OA is classically performed by radiological imaging methods that support clinical findings. However, primary OA developed without any trauma, especially those without any traumas, started many years before the radiological findings became evident and the pathology is often not revealed early. The progression of the disease is often slow and is spread over the years. Radiological findings in OA can provide indirect information about the cartilage tissue. For this reason, radiological methods are not sensitive especially in the early stage [2, 3]. Early diagnosis allows the joint to treat OA conservatively without interruption.

Imaging methods in OA provide information about the accumulated image that already existed in the past, rather than the current assessment of how far the disease has progressed. Therefore, there is a need for alternative methods that can detect joint changes in a quantitative, reliable, and sensitive manner. Biochemical markers can serve this purpose. For this reason, recent research on OA has focused on the development of disease-specific biochemical markers, with an increasing number of publications in this area in recent decades [4]. Biochemical markers, which stand

out among laboratory methods, will be discussed in this section in the context of recent developments.

A good biochemical marker, which is specific to the disease, reflects the disease activity at that time, is susceptible to posttreatment changes, predicts the outcome of the disease, and has knowledge of its metabolism and biological properties [5]. Clinical use of the markers should be based on a number of criteria such as clearance rates, circadian differences, diet, physical activity, and drug use [6].

Biochemical markers in OA are molecules that occur during the physiological cycle of the connective tissue matrix and can be detected in body fluids. One of the most important purposes of biochemical markers measurement in OA is the recognition of cartilage damage at the early stages when it has not yet been detected radiologically. In addition to early recognition, follow-up of disease activity, determination of the severity of the disease, prediction of prognosis, and evaluation of response to treatment are other purposes of marker measurement [7].

Until now, no notable findings of a laboratory for primary OA have been reported. Routine laboratory tests, including the highly sensitive CRP, cannot provide definitive information regarding disease activity in OA. Although the quantitative values of CRP may increase in synovitis in case of inflammation, the results are usually normal. Similarly, the serum levels of antinuclear antibodies, rheumatoid factor, and complement components are normal. These laboratory findings are important in terms of differential diagnosis from other diseases with arthritis and metabolic disorders [7].

In OA, the synovial fluid is noninflammatory, pale yellow, and brittle. It is mononuclear cell-weighted, with a small number of leucocytes. The viscosity of the liquid is normal. Excess synovial fluid may suggest that the course of the disease is going worse [7].

New diagnostic methods are being developed for early diagnosis since OA has positive responses to early-stage treatment interventions. Biochemical markers showing bone and cartilage recurrence in recent years have been shown to be useful in identifying patients at risk for high joint deterioration [8]. They have also been reported to be compatible with magnetic resonance (MR) imaging [9, 10]. There is evidence that these markers can distinguish not only the cartilage surface change in knee OA but also the specific forms of damage to the bone and the surrounding soft tissue. For this reason, different combinations of markers may play an important role in the prognosis of the disease.

Despite the lack of specific laboratory methods in diagnosis, many biomarkers have been recently developed for the diagnosis and follow-up of OA. The joint is a complex structure of bone, cartilage, and synovial tissue; for this reason, it is useful to use the markers of these three constructs when determining the degree of the degeneration of the insert. The extracellular matrix of bone, cartilage, and synovial tissues forms mainly collagens. These are Type I (bone and synovium), Type II (cartilage), and Type III (synovium) collagens. Collagen is found together with aggrecan and other glycoproteins. The speed of construction and destruction of the cartilaginous structure is slow, so the cartilaginous structure has a long half-life. Extracellular matrix, mainly composed of collagen in normal conditions, balances between construction and continuous renewal. However, when the speed of construction cannot capture the speed of destruction, the cartilaginous structure gradually loses its integrity [11].

In general, cartilage, proenzymes, active proteinases, proteinase inhibitors, matrix fragments that are released by proteinases, and antibodies developed by the organism against cartilage components are among the markers of cartilage cycling in pathologies involving joint cartilage. Among these markers, the proteoglycans most frequently researched are the smaller fragments of the structure

that eventually result in proteolytic destruction. Knowledge of the biochemistry and immunological properties of the proteoglycans has allowed the measurement of proteoglycan components and degradation products with more sensitive methods [12].

Nowadays, these methods can be used to measure proteoglycan degradation products in the serum and synovial fluid inflammation and degenerative joint diseases. Some studies have found that there is a correlation between proteoglycan levels in the synovial fluid and severity of the disease [12].

Several biochemical markers such as Type II collagen, proteoglycans, hyaluronan, cartilage oligomeric matrix protein (COMP), and matrix metalloproteinases (MMPs) have been investigated in relation to OA and radiological progression, and frequently conflicting results have been obtained [13].

In some studies with COMP, it was concluded that OA progression was positively related, while in other studies, it was shown that it was affected by factors such as age, ethnicity, and BMI (body mass index), which had a weak relationship with the narrowing of the joint space and disease progression. In addition, it is reported that cartilage is not specific, and it is also found in structures such as the synovium and meniscus [14].

Glucosyl-galactosyl-pyridinoline (Gly-Gal-Pyd), Type I, and Type III are cross-links of the collagenous roof. It is found in the synovial tissue and has been identified in in vitro studies that have occurred during the cartilage destruction process. In a study conducted, urinary Gly-Gal-Pyd levels were found to correlate strongly with pain and disability scores and radiological disease stage in patients with knee OA [15].

Type II collagen is the most important structural element of the joint cartilage and is relatively specific to hyaline cartilage. The main event in OA pathophysiology is the damage in the Type II collagen network. Therefore, investigations aimed at detecting OA-specific and specific biochemical markers have focused on Type II collagen [15].

Experimental arthritis models are exploring cartilage metabolism in a variety of ways. In one study, an increase in synovial fluid proteoglycan fragments in the experimental OA model showed concordance with the severity of arthritis [12].

The use of biomarkers in OA has some significant purposes. One of these is the predetermination of patients with rapid cartilage destruction in order to prevent joint destruction in the future because the period of the radiographic degeneration of the joints and the diagnosis of OA are usually detected in the advanced stages of cartilage damage from the molecular point of view. In addition to early recognition, monitoring of disease activity and determination of disease severity, prediction of prognosis, and cartilage degradation should be tracked in order to monitor the efficacy of new drugs developed as cartilage protectants [16].

Some criteria must be considered for a biomarker measurement to be valid in OA. First of all, it is necessary to know what kind of pathology the specimen measured reflects since there are different types of markers for tissue damage, tissue repair, anabolic or catabolic processes, or pathologies at the cell or tissue level. It is also important that the measured indicator is indeed the marker to be measured. For this reason, the method should be well investigated and the most appropriate method should be selected according to the conditions. Furthermore, the biomarker measurement results should be compatible with the clinical and radiological findings of the disease and with the pain-function score. It should also reveal the smallest change in the severity of the disease [16].

In order to understand the clinical benefit of biomarkers, it is necessary to initially standardize the measurement method used. Sample receipt time, purchase and storage conditions, and each biomarker circadian rhythm should be known.

Some may be affected by factors such as physical activity, age, and gender. For example, C-terminal cross-linked Type II collagen (CTX-II) and serum COMP (sCOMP) from cartilage markers show very little circadian variation [11].

At the later stages of OA, cartilage damage to the tissue occurs at a high rate, making it difficult to interpret when the marker is detected at a very low concentration. Serum can change the levels of biomarkers with foods such as hyaluronic acid. At the first hour after feeding, hyaluronic acid levels reach the highest point. For this reason, the serum levels of biomarkers in OA should be checked on an empty stomach. Metabolism of biomarkers, kidney excretion, and drugs can also be affected. The level of urine CTXII is affected by ibuprofen [11].

The levels of certain biomarkers such as COMP, chondroitin sulfate, and urine CTX-II may vary with age and sex, as well as joint pathology. In addition, a patient's ethnicity and BMI may affect the baseline measurement values of biomarkers. There are different classifications for biomarkers to be used in OA. These may be direct and indirect markers, cartilage, bone and synovial tissue, or markers of synthesis and destruction. It is more accurate to classify OA in comparison to the tissues from which they originate if the bone and the synovial tissue as well as cartilage are thought to have contributed to the development and the course of OA [16].

2. Metabolic processes of osteoarthritis during which biomarkers emerge

In osteoarthritis, significant changes that cause an inflammatory cascade which in turn triggers the chronic overproduction of factors at the metabolic level occur. These factors may aggravate osteoarthritis. Biomarkers are metabolic processes of all kinds which develop during the inflammatory process in osteoarthritis.

Hyaline cartilage structure is principally composed of water, collagen, and proteoglycans, which include sparsely distributed chondrocytes. Chondrocytes provide a balance between the anabolic and catabolic activities that protect the aggrecan structure [17]. Deprivation of the cartilaginous matrix results in an imbalance between the cartilage synthesis (anabolic) and resorption (catabolic) processes in the joint. Mechanical strain causes upregulation of cytokines like interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) with a rapid transcription through a shock sensor system in chondrocytes and tendons [18]. The mechanical strain resulting from normal activity or therapeutic exercise in fact inhibits this upregulation and helps in the remodeling of the cartilage through collagen synthesis. The upregulation of cytokines causes induction of MMPs which enzymatically disrupts the cartilage structure [19]. In addition, mechanical strains cause microcellular damage which leads to the release of extracellular membrane particles and intracellular microtubule elements into the joint [20].

These mechanical strains also produce other metabolic changes such as the release of arachidonic acid from the phospholipids in the damaged intra-articular cell membranes after phospholipase A2 (PLA2) action [21]. The continuous strain together with the metabolic processes causes inflammation in the joint tissues. The main cytokines that cause degradation in the synovia are the IL-1, IL-6, IL-17, and TNF-α [22]. Other elements and side products which further increase the cartilage degradation and play a role in osteoarthritis include insulin-like growth factor 1 (IGF-1), transforming growth factor beta1 (TGF-β1), and chondrodegradative enzymes [23].

In cases of acute or chronic joint damages, arachidonic acid is the primary fatty acid produced by the metabolic conversion of the cell membrane phospholipids through PLA_2. Through other enzymatic activities, arachidonic acid transforms into

various inflammatory mediators such as cytokines and eicosanoids, which lead to a progression of the disease.

During the metabolic conversion of arachidonic acid into inflammatory metabolites, the two most important enzymatic pathways are the 5-lipoxygenase (5-LOX) and cyclooxygenase (COX) [24]. These parallel pathways produce the leukotrienes, prostaglandins, thromboxanes, and prostacyclins, which play a significant role in the onset and progression of the inflammatory response. The conversion of arachidonic acid through COX-2 leads to production of prostaglandins, which are physiologically important mediators in tissue repair and prostacyclins [25].

The metabolic transformation of arachidonic acid through 5-LOX, another inducible enzyme, leads to the production of leukotrienes. Leukotriene B4, specifically, is a chemoattractant and a fatty acid metabolite that causes damage in the cells and tissues [26]. Leukotrienes initiate the production of new reactive oxygen species. The upregulation of the inflammatory cascade of cytokines causes permanent disruption of the cell membrane, thus leading to formation of more arachidonic acid [27].

Matrix metalloproteinases produced from chondrocytes are zinc-containing proteinases which degrade the cartilage. In particular, the expression of MMP-1 and MMP-13 is induced by IL-1β, which in turn causes the degradation of Type II collagen [28].

Chondrocytes also produce the reactive oxygen species. The production of reactive oxygen species causes damage on the components of the cartilage matrix and induces apoptosis [29]. Another form of transformation is the nonenzymatic lipid peroxidation of arachidonic acid. When arachidonic acid is exposed to reactive oxygen species, the molecule is oxidized to three main products: F2-isoprostanes, 4-hydroxynonenal, and malondialdehyde [30]. All three molecules directly destroy the hyaline cartilage. Chondrocytes also produce the reactive oxygen species like xanthine-hypoxanthine system, hydroxyl radicals, peroxide, and hydroxyproline [31].

Each of the biochemical products produced along the sequence of inflammatory cascade in osteoarthritis mentioned briefly above is investigated as a biochemical marker in the early diagnosis, during treatment and later during follow-up of the disease.

3. Biochemical markers of bone origin

The bone matrix consists mainly of Type I collagen molecules linked by pyridinoline (PyD) and deoxypyridinoline (D-PyD) cross-links. The degradation of Type I collagen can be assessed by pyridinoline cross-links in the urine. NTX-I and CTX-I, the epitopes of N-terminal and C-terminal cross-link telopeptides, are the most studied bone resorption markers. Bone formation and degradation markers shown in **Table 1** can be affected by regional subchondral bone structure defects [32, 33]. Serum and urine concentrations may vary due to age, menopause, osteoporosis, and other bone diseases. Bone markers in osteoarthritis give incompatible results due to several factors that can affect the results.

Bone	Production	Demolition
Type I collagen	N- and C-propeptides (PICP and PINP)	Pyridinoline (PYD), deoxypyridinoline C-terminal and N-terminal telopeptides (CTX-I, NTX-I)
Noncollagen protein	Osteocalcin Bone alkaline phosphatase	Sialoprotein (BSP) Tartrate-resistant acid phosphatase (TRAP)

Table 1.
Biochemical markers of bone origin used in OA.

Urine C-terminal and Type I collagen telopeptide levels (CTX-I) were higher in cases with a rapid onset of osteoarthritis than slow-onset events [34]. Bone sialoprotein (BSP) is a product of active osteoblasts located in the junctions of mineralized cartilage and subchondral bone tissue. Elevated levels of serum BSP reflect the bone matrix cycle [35].

There is evidence that combined measurement of COMP and BSP may be a prognostic marker to determine the development of OA in chronic knee pain cases [36]. Osteocalcin, an important component of bone noncollagen matrix, is released during mineralization. This measurement gives information about bone formation. It is important to demonstrate subchondral bone metabolism [16].

During cartilage damage, changes in the bone metabolism occur and the molecules of the bone increase in body fluids. In general, elevated serum BSP reflects the bone matrix cycle [33].

Serum and urine levels of bone markers may vary due to menopause, osteoporosis, and other bone diseases. It is an important question in terms of OA performance [37].

Bone markers have shown more pronounced circadian rhythm changes and more concentrated on cartilage and synovial tissue markers in recent years due to inconsistent results.

3.1 Biochemical markers of cartilage production

The main event in the pathophysiology of OA is the destruction of the Type II collagen nerve which is formed by COL-2 α1 fibrils. For this reason, OA studies have focused on Type II collagen. Type II collagen is only 1% of all collagen in the body, and the normal cycle is slow. Type II collagen, predominantly found in the joint cartilage, is synthesized procollagen in chondrocytes (**Table 2**). Subsequently, the extracellular fluid is released, where the procollagen carboxy-terminal and amino-terminal propeptides (PIICP and PIINP, respectively) are separated from the parent construct, and mature collagen synthesis is completed. These are important indicators of collagen synthesis in the articular cartilage. And the levels of cartilage tissue, serum, and synovial fluid can be measured [11].

PIICP and PIINP may be the most common Type II collagen [12] in the cartilage (**Table 2**). COL-2 molecules are synthesized as propeptides from the carboxy-terminal and amino-terminal regions of the extracellular domain before forming fibrils. These peptides are cysteine-rich PIINAP, a prokaryotic Type II C-terminal propeptide (PIICP), a procollagen Type II N-propeptide (PIINP), and a second form of PIINP. They are indicators of chondrocyte synthase activity. It has been detected that serum PIINAP levels are inversely correlated with the loss of cartilage induced by MR or radiography in patients with OA [38].

Cartilage	Production	Demolition
Type II collagen	N- and C-propeptides (PIICP, PIIANP, PIIBNP)	PYD, CTX-II Type II collagen fragments
Aggrecan	Chondroitin sulfate epitopes	Keratan sulfate epitopes
Aggrecan and noncollagenous proteins	Glycoprotein-39 (YKL-40) Cartilage-derived retinoic acid-sensitive protein	COMP SLRPs

Table 2.
Biochemical markers of cartilage origin used in OA.

The development of OA in the synovial fluid of individuals with knee injuries has reached maximum levels of propeptide levels in the preradiological period [39].

In a study by Garnero, serum PIIANP levels in OA patients showed a decrease [14]. The increase in the urine CTX-II levels with serum PIIANP levels may indicate that joint destruction develops more rapidly. PIICP levels give hope to early detection of OA.

Nine amino acid peptides (COL2-1) and their nitrated form (COL2-1 NO2) of Type II collagen are localized peptides in the collagen network of the triple helix structure and show oxidative degradation of this helix structure. In a 3-year follow-up study in patients with knee OA, it was observed that initial increases in urine levels were associated with high disability assessed by the Western Ontario and the McMaster University Osteoarthritis Index (WOMAC) [40]. These results suggest that the urinary levels of COL2-1 and COL2-1 NO2 may reflect the clinical severity of OA. However, a significant association of COL2-1 NO2 with CRP and an increased synovial inflammation requires caution in the differentiation of other arthritic patients [5].

Another name for YKL-40, a cartilaginous marker, is glycoprotein-39. In advanced stage OA, serum and synovial fluid are present in high amounts. Elevated serum levels were detected in hip OA. YKL-40 levels may also increase depending on other pathologies, especially inflammation. For this reason, inflammation can also be considered as a marker [41].

3.2 Biochemical markers of cartilage destruction

The most well-known marker in the demolition reagents is COMP. Increasing levels are thought to indicate that OA is advancing. Since COMP is synthesized not only by cartilage but also by synovial cells, tendon fibroblasts, and osteoblasts, the increase may be due to cartilage destruction or synovial inflammation. In the knee OA, the COMP level is synovitis grade compatible, but it is shown that OA is not compatible with the grade. The absence of COMP specificity may limit the use of OA-RA (rheumatoid arthritis) to assess changes in joint damage [42].

4. Type II collagen destruction products

There is a consensus that Type II collagen degradation products can be used as markers in the diagnosis and follow-up of OA and RA [43]. C2C and C1-2C are new epitopes formed after destruction of Type II collagen speckle collagenases. For this reason, it can give opinion on the destruction of cartilage. The levels of C1-2C were found higher in OA cartilage than in normal cartilaginous tissue [11].

CTX-II is also a Type II collagen degradation product and an important indicator of cartilage damage. Urine CTX-II levels were elevated in RA and OA, and high levels were found to be compatible with joint erosion [43]. In patients with knee OA, urine CTX-II measurement has shown that it may be useful in determining the prognosis of joint damage, and they have been found useful as a determinant for rapid degeneration of joint cartilage [44].

In another study, it was determined that the urine CTX-I and CTX-II and sCOMP levels can determine patients with focal cartilage lesions in the early stages of knee OA [45]. At the beginning of OA, new epitopes emerged from the triple helix of collagen collapsed by collagenases. The C-terminal telopeptide, one of these epitopes, is now the most searched for association with OA clinic and is most promising as a specific marker for OA [44]. In many studies, OA was found to be particularly high in urine levels compared to controls and that it can be used as a

diagnostic marker [46]. Another publication has shown that high CTX-II levels are associated with radiological progression of the knee and hip in OA and that they increase eight times the risk of progression in these individuals [44].

Bettica et al. found a relationship between urinary CTX-I and knee OA development in terms of cartilage derivation markers [34]. Urine CTX-II has been reported as a good marker of knee and hip OA progression [47, 48].

5. Oligosaccharides

Chondroitin sulfate and keratan sulfate are oligosaccharides that bind to the aggrecan protein and are the first molecules in which cartilage formation and degradation are evaluated. The affinities of these oligosaccharides depend on the length and sulfation of the molecule and thus may vary from person to person. It is present at high concentration in the circulation during prolonged disease and significant loss of cartilage. Although cartilage is at the highest concentration in the tissue, chondroitin sulfate and keratan sulfate epitopes can be found in the cartilage as well as in the extracellular matrix of the molecules outside the acceptor. For these reasons, their use as a marker in clinical evaluation and treatment follow-up is very limited.

Biglycan, decorin, fibromodulin, and lumican are small leucine-rich proteoglycans (SLRPs). The destruction of these small proteoglycans, along with the large molecule of cartilage-like aggrecan, suggests that it is active OA [11].

6. Biochemical markers of synovial tissue construction

6.1 Hyaluronan

It has been shown that radiological progression is faster in OA patients with high serum hyaluronan (sHA) levels [49]. It is not useful as a marker in everyday practice due to its distinctive circadian rhythm [37].

6.2 Highly responsive CRP

Osteoarthritis becomes defective in the chondrocyte metabolism and therefore there is an increased interest in acute phase proteins in OA, despite a common systemic manifestation of RA in nature. It has been reported that high-sensitivity CRP (hs-CRP) levels may be a prognostic feature of rapid progressive hip and knee OA (**Table 3**). In a study conducted to investigate the association between hs-CRP

Synovial tissue	Production	Demolition
Type III collagen	Type II N-propeptide (PIINP)	PYD, CTX-I, NTX-I Glucosyl-galactosyl-pyridinoline (Gly-Gal-Pyd)
Noncollagenous proteins	Hyaluronan, YKL-40, COMP	
Proteases and inhibitors	Tissue matrix proteinases (TIMP 1, 2)	Matrix metalloproteinases (MMP 1, 2, 3, 9)
Systemic infection	Highly sensitive CRP	

Table 3.
Biochemical markers originating from the synovial tissue used in OA.

and the OA severity and size in patients with advanced hip and knee OA, the severity of pain in the advanced OA patient group, although not the extent of OA, was associated with hs-CRP [50]. In a study designed to determine whether the levels of IL-6, TNF-α, and CRP in the normal population could be an adjunct marker in radiographic knee OA, the prevalence and incidence of radiological knee OA and the circulating levels of IL-6 were found closely related [51].

7. Biochemical markers of synovial tissue demolition

7.1 Matrix metalloproteinases (MMPs)

Matrix metalloproteinases have been measured mainly in studies related to RA. The metalloproteinase enzyme group may cause collapse of the extracellular matrix elements by acting as collagen and Type II collagen [10]. The tissue inhibitors of metalloproteinases (TIMPs), which are natural inhibitors of metalloproteinases, are released from both chondrocytes and synovial cells. The synovial fluid and serum MMP-1 and MMP-3 levels have been shown to be elevated in patients with hip or knee OA. It has been reported that MMP-1 and MMP-3 levels can be detected not only in RA and OA but also in other adult states such as systemic lupus erythematosus [52]. MMP-3 has been reported radiographically to predict narrowing of the joint space [53].

7.2 Glucoside-galactose-pyridinoline

In the extracellular matrix, collagen Type II fibrils are placed in triple alpha helix. They are present at very low levels in the cartilage and other tissues found abundantly in the human synovium, thus showing an increase in urine Gly-Gal-Pyd levels in knee OA [54].

8. Other biochemical markers

Metabolic changes associated with obesity are possible causal agents for OA. Leptin is released primarily from adipocytes but is also released from chondrocytes and production increases in the cartilaginous form of OA. Leptin levels in synovial fluid are a possible metabolic factor in the pathogenesis of OA.

The role of markers such as leptin and IL-6 in obese-associated hip OA is unclear. In a study, it was determined that metabolic and ambulatory mechanisms may play a role in the etiology of hip OA and that the relationship between bone composition and the narrowing hip joint space was mediated by leptin, particularly in women [53].

Proteomic studies, which reveal the protein content of the cell tissue and biological fluids, distinguish related proteins and show functional changes in proteins have become more prominent in recent years [55]. In 2011, studies describing new proteomes in the urine, serum, and chondrocyte vesicles of OA patients were published [56]. In one of these studies, two fragments of fibulin-3 (Fib 3-1 and Fib 3-2) were shown to increase in the urine of OA patients.

Fibulin-3 is a proteome closely related to the TIMP, which plays an important role in the pathogenesis of OA. While it is suggested that they are biomarkers with high sensitivity and specificity, more work is needed to confirm them [57].

Deamidated COMP (D-COMP) hip joint was associated with OA radiological severity, but the same relationship was not detected with knee OA. It was suggested that D-COMP may be a biomarker specific to the hip joint [58].

It is thought that soluble leptin receptor (sOB-R) may be a marker of cartilage damage because of the significant relationship between the basal sOB-R level and low osteocalcin and PIIANP levels [59].

Since sOB-R is an adipokine receptor, it may be a promising marker for clarifying the relationship between obesity and pathogenesis of OA, especially in load-bearing joints [60].

9. Clinical evaluation of the osteoarthritis biomarkers present

Osteoarthritis Research Society International (OARSI) has published a series of recommendations for the use of soluble biomarkers in clinical trials. Publications supported by OARSI summarize the basic steps for a biomarker to be used as a drug development tool and various situations that OA biomarkers can be used [61, 62]. The Foundation for the National Institutes of Health/Osteoarthritis Initiative (FNIH/OAI) has published the results of an analysis on soluble biomarkers in a study that investigated the use of biomarkers as a drug development tool [61, 62]. The FNIH/OAI researchers found that time-dependent concentrations of urine C-terminal telopeptide of Type II collagen (uCTX-II), sHA, and serum N-terminal telopeptide of Type I collagen (sNTX-I) over a 24-month period were associated with subject cases that had both progressive pain and radiographic progression of knee OA over a 4-year period. Baseline levels of uCTX-II and sNTX-I predicted pain progression and radiographic progression. Plans are underway to qualify these biomarkers using samples and data from already-completed DMOAD (disease-modifying osteoarthritis drugs) trials.

Over the past years, several biomarkers have been tested in samples taken from patients with OA of various degrees. However, the number of newly found biomarkers was limited; most of them were already discovered molecules including MMPs, interleukins, adipokines and joint-related serum biomarkers, MMP-mediated degradation of C-reactive protein (CRPM), MMP-mediated degradation of Type III collagen (C3M), cartilage oligomeric matrix protein (COMP), HA (hyaluronic acid), N-terminal propeptide of collagen IIA (PIIANP), COL2-3/4 C-terminal cleavage product of Types I and II collagen, uCTX-II, MMP-3, and urine-nitrated Type II collagen degradation fragments (uCOL2-1 NO2).

The first analytical data came from the OAI. Eighteen biomarkers believed to be associated with OA were tested in the 129 blood or urine samples collected from OA patients [61]. The results showed that three commercially available biomarkers were related to age: sHA, P2ANP, and C1,2C. Similarly, uCTX-II, MMP-3, uCOL2-1 NO2, and sHA showed gender-related differences [61]. In a study, the concentration levels of sCOMP, sCTX-II, sMMP-3, sPIIINP, and sHA were identified in 79 patients who had cartilage damage and underwent knee arthroscopy or total knee replacement [63]. PIIANP, serum CTX-II, HA, and COMP levels were measured; however, only the concentration levels of HA and COMP were found significantly higher in OA patients with cartilage damage in the early term. These results suggest that the concentration levels of sCOMP and HA may be used in predicting the early-term cartilage lesions in the knee.

In a study on CRP [64], 58 cases of knee OA and 33 controls were examined for CRP and MMP-derived collagen types C1M, C2M, and C3M. The knee OA cases had elevated levels of C1M, C2M, and CRP and significantly lower level of C3M in comparison to controls.

Over the past few years, a limited number of studies have attempted to validate the existing OA biomarkers in the context of a clinical DMOAD study. Karsdal et al. [65] studied uCTX-I, uCTX-II, and serum osteocalcin. After 24-months, the biomarkers declined in all patients who had a positive Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain response to calcitonin. However, in another calcitonin study [65], the pain and biomarker responses after 24 months were not significant and the radiographic responses between the two studies were also different. This made it difficult to confirm these biomarkers for pain or radiographic response. The authors of the clinical trial of calcitonin have concluded that a precisely successful DMOAD study will be necessary to confirm the predictive and surrogate biomarkers for OA drug development.

Researchers have come up with studies that examine large OA cohorts dealing with the predictive ability of established OA biomarkers [66, 67]. In one of these studies, the sHA was associated with the joint space width (JSW) in the Iwaki Health Promotion Project over a period of 5 years [66].

In a Chingford cohort study [67] with a 20-year data history of radiographic knee OA progression in a group of middle-aged women with a Kellgren and Lawrence (KL) score of 0 at baseline, the high sCOMP levels were significantly related to painful radiographic OA development in the knee. The increase in the risk of radiographic knee OA was found in relation to sCOMP during the 5-year follow-up of 493 cases. In another report [68], 5 years of data from the Rotterdam study cohort were used to determine the relationship between the incidence of OA and KL score progression and biomarkers. As reported by Van Spil et al. [68], uCTX-II and sCOMP were found to be significantly associated with the incidence and progression of OA. The researchers investigating the 5-year data from the Cohort Hip and Cohort Knee (CHECK) study found that some biomarkers measured at the baseline were related to the incidence and progression of OA in the knee. Interestingly, uCTX-II and sCOMP were the most consistent biomarkers associated with the presence, incidence, and progression of knee OA.

UCTX-II and sCOMP had a positive effect on the presence and progression of OA in the knee. Both biomarkers showed negative correlation with knee OA. The authors suggested that the low cartilage and subchondral bone turnover in the earliest stages of knee OA may explain this second finding [67].

Over the past years, the mechanisms and benefits of inflammatory biomarkers in the pathogenesis and progression of OA have also been studied. The data from the Rotterdam study showed that CRP was independently associated with the incidence and progression of OA, similar to uCTX-II and sCOMP, and CRPM showed positive correlation to the progression of OA [69].

In a meta-analysis of the knee, hip, and hand OA studies from 1992 to 2012 [70], no correlation between the pain symptoms of OA and hs-CRP levels was found. However, radiographic findings showed strong correlation with hs-CRP levels. As shown in another study, inflammatory macrophages in the joints of knee OA patients might be a potential source of inflammation that triggers CRP production [71].

Soluble markers of the synovial fluid (SF) and inflammatory macrophages (CD14 and CD163) were shown to be associated with abundance of active macrophages in the knee joint as measured by EC20 SPECT imaging. These soluble markers were associated with narrowing of the joint space, osteophytes, and severity of the knee pain [72].

The best known inflammation markers have been confirmed in a study by Attur et al. [73]. Previously, proinflammatory mediators such as IL-1β, TNF-α, and COX-2 in peripheral blood leukocytes have been shown to identify the patients under risk for knee OA [74]. In a cohort of symptomatic knee OA patients prospectively evaluated for 24 months, an increase in the peripheral blood transcripts regarding

the basal levels of IL-1β, TNF-α, and COX-2 was shown to predict the narrowing of the joint space [73]. In another study assessing the samples taken from symptomatic knee OA patients under prospective evaluation for 24 months, the authors concluded that the levels of plasma interleukin-1 receptor antagonist (IL-1Ra) were positively correlated with the severity and progression of knee OA [75].

In addition to the above findings, reduced serum and uncarboxylated matrix Gla protein (ucMGP) levels were detected in OA patients. The mean serum ucMGP levels in knee OA patients were significantly lower than the healthy controls and showed negative correlation with radiographic severity [76].

Mabey et al. reported that the IL-4 and IL-6 levels in OA patients were significantly higher than the controls and showed positive correlation with radiographic severity [77].

In a study conducted on 138 OA patients [78], adipsin (complement factor D), leptin, adiponectin, resistin, and serpin E1 levels in the serum and cartilage volume with MRI were measured at the baseline and after 24 months. The elevated levels of adipsin and leptin were correlated to the increased cartilage volume in the global knee and medial femur. Adiponectin levels showed negative correlation with the cartilage volume in the medial compartment and femur. No correlation between resistin and serpin E1 and cartilage volume was detected.

10. Conclusion

In conclusion, biochemical markers, especially Type II collagen production, demolition, and synovial tissue markers, are important contributors in the early diagnosis, treatment, and follow-up of OA. Numerous biochemical markers that can potentially predict the progression of OA are still under research, but the progress is slow. For a molecule to qualify as a marker, it must be biologically and methodologically sensitive and specific. COMP, antigenic keratan sulfate, hyaluronan, YKL-40, Type III collagen N-propeptide, and urine Gly-Gal-Pyd are the most promising biochemical markers. The only predictor of cartilage loss determined by MR in the knee OA is sCOMP [79].

Early identification of OA with possible identification of new biochemical biomarkers with proteomic studies in the future seems possible. More comprehensive randomized and controlled studies of biomarkers will provide useful information in early diagnosis, prognosis, and response to treatment in OA.

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Section 2

OA Treatments Options

Chapter 2

Osteoarthritis as a Chronic Inflammatory Disease: A Review of the Inflammatory Markers

José Fábio dos Santos Duarte Lana and Bruno Lima Rodrigues

Abstract

Osteoarthritis (OA) is the most prevalent joint disease and a common cause of joint pain, functional loss, and disability. In addition to macroscopic features, such as cartilage degradation with subchondral bone remodeling, hypertrophy of the joint capsule, and osteophytes formation, several cellular and molecular alterations are present in OA, which lead to a chronic low-grade inflammation. Inflammatory mediators observed in OA joints are thought to be the downstream effectors of the pathogenesis of the disease. Although cytokines are among the most extensively studied mediators of inflammation, such as IL-1β and TNF, there has been an increase in studies showing the contribution of chemokines and adipokines in OA progression. This fact is supported by recent progress, which has considerably improved knowledge of the factors involved in the development of OA and the mechanisms responsible for its progression. Therefore, the aim of this chapter is to discuss the involvement of the inflammatory response in OA maintenance, focusing on the main inflammatory markers observed in studies with OA.

Keywords: osteoarthritis, immune response, inflammation, biomarkers, cytokines

1. Introduction

Osteoarthritis (OA) is a common disease that can affect joints from any part of the body, and it represents a major cause of disability and joint pain worldwide [1, 2]. OA most commonly affects the knee, hip, and shoulder, and it was estimated that more than 25 million people in the USA were affected by some form of OA in the last decade [3]. In addition, OA presents a high susceptibility to affect female gender, elderly people, and obese individuals [4].

The progression of OA leads to cartilage degradation with subchondral bone remodeling, hypertrophy of the joint capsule, and osteophytes formation, causing pain [1, 5, 6]. Although the development of OA is considered a heterogeneous process, which comprises a number of genetic and environmental causes, the presence of local causes, such as trauma and hypermobility of the joint, may worsen OA [2, 7].

The accurate identification of osteoarthritic features has been studied in order to radiographically grade the stages of OA. The Kellgren-Lawrence classification is the most widely used, especially in clinical researches. This classification evaluates the appearance of osteophytes and cysts, joint space loss, and sclerosis, and it grades the severity from 0 to 5 points. The radiological features found in OA joints were

graded as follows: (1) formation of osteophytes on joint margins or on tibia spines for knee OA; (2) periarticular ossicles in relation to distal and proximal interphalangeal joints; (3) narrowing of joint cartilage and sclerosis of subchondral bone; (4) pseudocystic areas with sclerotic walls in the subchondral bone; and (5) altered shape of the bone ends [8]. Some of these criteria were adopted by the World Health Organization (WHO) as the standard for studies on OA.

Current options for the treatment of OA focus on reducing pain (non-steroidal anti-inflammatory drugs—NSAIDs) and joint viscosupplementation (intra-articular injections of hyaluronic acid) [1]. Besides presenting a short-term effect, the chronic use of some of these medications, especially NSAIDs, may cause serious adverse events, including toxicity and risk of thromboembolism [9, 10]. In severe cases, surgical procedures, mostly joint replacement, are suggested [1]. Novel alternative therapies, called orthobiologics, have emerged from the need of tissue regeneration. Clinical trials using orthobiologics, which comprise platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), fat graft (Biofat), and expanded mesenchymal stem cells, have shown promising results for the treatments of OA from any origin [11–14].

Moreover, monoclonal antibody (mAb) therapy represents one of the alternative treatments that aim to control inflammation and slow structural progression [15]. This approach focuses on blocking specific molecules responsible for the maintenance of OA. Preclinical studies with ADAMTS mAbs reported a significant decrease in histological scores after 3 months of treatment [16]. Adalimumab is an anti-TNF-α therapy used in diverse immune-mediated diseases, and it presents a protective role for OA as it reduces the severity of the cartilage lesion and improves the structure of subchondral bone [17]. Since IL-1 family may induces the production of metalloproteinases (MMP), it has also become a target for mAb therapy, and, in a randomized controlled trial with patients who presented knee OA, it was reported great improvement on pain relief [18].

In addition to macroscopic features, several cellular and molecular alterations are present in OA, such as catabolism and anabolism events; hypertrophy and, consequently, death of chondrocytes; and impaired autophagy process [19]. Also, a chronic low-grade inflammation interplayed with immune system has been considered to present a crucial role in the maintenance of OA [1]. This fact is supported by recent progress, which has considerably improved the knowledge regarding factors involved in the OA development and the mechanisms responsible for its progression.

2. Osteoarthritis and immune response

The inflammation observed in OA is believed to involve innate immune response prior to a mild degree of adaptive immunity [20]. During tissue damage, a group of endogenous molecules, called damage-associated molecular pattern (DAMP), signals the immune cells to induce a protective response against the tissue, causing tissue repair. However, a prolonged signaling of DAMP to immune cells leads to an exacerbated cytokine release, which can be destructive to the tissue [21, 22].

Innate immune cells activated by DAMP include macrophages and mast cells, which have shown to present (displayed or demonstrated) a key role in the pathogenesis of OA. Mast cells are considered regulators of vascular permeability, and they may play a crucial role in OA joint inflammation as they facilitate leukocyte infiltration [23].

Macrophages exhibit a functional plasticity based on the environment in which they are located or present [22]. However, their chronic activation can lead to the

production of proinflammatory cytokines, which worsen the osteoarthritic joints [24]. *In vitro* studies of human OA synovium-derived cells showed that macrophage depletion results in diminishing of inflammatory response by decrease of proteolytic enzyme expression, such as metalloproteinases (MMP) This fact is supported by *in vitro* studies with cell culture suspension of human OA synovium, which reported that, after macrophage depletion, there was a decrease in the production of inflammatory response by less activity of proteolytic enzymes, such as metalloproteinases (MMP) [25]. Although macrophages may also present a protective role, as they are known to secrete transforming growth factor β (TGF-β), which would enhance cartilage repair, intra-articular injection of TGF-β in mice knee led to osteophyte formation and fibrosis [26].

In addition, natural killer (NK) infiltrates are commonly found in synovial tissue from patients who underwent joint replacement surgeries, and a subset of NK cells ($CD56^{bright}$) was found to be greatly expanded in patients with inflammatory arthritis who have not undergone joint replacement surgeries. However, the effect of these cells on the development of OA has not been elucidated yet [27–29]. NK cells secrete protease enzymes called granzyme type A and B, which correlate to cytolytic potency. Granzymes can be released during degranulation of cytotoxic cells and, when delivered intracellularly to the target cells, they induce apoptosis. Granzyme A also stimulates the production of tumor necrosis factor (TNF-α), IL-6, and IL-8, while granzyme B may intensify the degradation of extracellular matrix [30, 31]. Tak et al. identified both types of granzymes in synovia from OA and rheumatoid arthritis. However, another study later showed that NK cells within OA synovia were granzyme negative with potential to produce the interferon-γ (IFN-γ) when expanded with IL-2 and stimulated with cytokines known to trigger IFN-γ production in blood NK cells, such as IL-12 and IL-18 [27, 32].

The presence of IFN-γ has a role in the bone resorption and consequently in the osteoclastogenesis process, but the studies have shown controversial results in this regard: *in vitro* evidence reported that IFN-γ, via TRANCE pathway, strongly suppresses osteoclastogenesis in culture of mononuclear phagocyte cells, which are the osteoclast precursors [33], whereas in culture of peripheral blood it may enhance osteoclast production as IFN-γ increases superoxide generation by neutrophils [34]. In addition, experimental studies in which IFN-γ receptor was silenced suggested a more rapid onset of collagen-induced arthritis [35]. Although IFN-γ plays a key role in angiogenesis, there is no evidence that this cytokine is able to promote angiogenesis in OA.

Proteins from complement system have been found to play a role in OA, especially in early stages, as they were upregulated in both synovial membrane and fluid [23, 36]. Additionally, the deposition of the membrane attack complex (MAC, C5b-9) is correlated with the presence of inflammation on histology of synovial membrane, and it was present in chondrocytes in late OA [36]. MAC can lead to chondrocyte destruction as it stimulates catabolic events through the increase of leukocytes and, consequently, the production of MMP [23]. Also in the studies with experimental knockout models for C5 and C6, the joint damages were attenuated [36].

Cellular infiltrates from adaptive immune response have also been observed in synovial fluid from OA joints. Although the main cell type present in this infiltrate is CD3+ T cells, both CD4+ and CD8+ cells have also been found in OA [37]. Th1 cells, and consequently their secretory cytokines, such as IL-2 and INF-γ, appear to be expressed five times greater than Th2 in most of OA patients [37]. Based on lymphocyte aggregates, there is a suggestion of an active cell-mediated immune response since T-cells in lymphocytic aggregates in OA synovium were shown to bear early (CD69), intermediate (CD25 and CD38), and late (CD45RO) activation markers [38].

3. Inflammatory markers in osteoarthritis

3.1 Cytokines

Inflammatory mediators observed in OA joints are thought to be the downstream effectors of the pathogenesis of the disease. Cytokines are among the most extensively studied mediators of inflammation. Several cytokines have been reported to play a role in the progression of OA, such as TNF, IL-1β, IL-6, IL-15, IL-17, IL-18, IL-4, and IL-10. Although their precise mechanism of action has not been completely elucidated yet, it has been proposed that their presence influences cartilage homeostasis as they induce catabolic events as well as inhibit anabolic processes [21, 39, 40].

3.1.1 IL-1β and TNF

Interleukin (IL)-1β and tumor necrosis factor (TNF) are considered the major mediators in the pathophysiology of OA. They both are secreted not only by immune cells, especially mononuclear cells, but also by chondrocytes and osteoblasts. In OA joints, these cytokines are increased in both synovial fluid and membrane. They are known to drive the inflammatory cascade, and their increased expression induces catabolic events as they enhance MMP [39]. IL-1β and TNF downregulate the synthesis of major extracellular matrix (ECM) components by inhibiting anabolic activities of chondrocytes [40] and reducing type II collagen production [41].

IL-1β is activated through the binding of its specific receptor type I (IL-1RI). Overexpression of IL-1RI in cartilage proximal to the macroscopic injury in OA joints resulting in increased binding of IL-1β was observed [42]. IL-1β has also been reported to be responsible for the catabolic events present in OA: its expression combined with TNF induces the production of MMP-1, -3, and -13 and stimulates the production of aggrecanases (ADAMTS)-4 and -5 in human and bovine chondrocytes [43, 44]. TNF receptor type I (TNFRI) is overexpressed in OA chondrocytes [45]. High levels of TNF-α in cartilage explants seem to inhibit the synthesis of proteoglycan and stimulate resorption [40].

In OA joint, IL-1β and TNF amplify the arthritic condition by inducing the production of proinflammatory cytokines, such as IL-6, IL-8, and monocyte chemoattractant protein 1. In addition, chondrocytes treated with IL-1β and TNF increase the production of nitric oxide (NO), cyclooxygenase 2 (COX-2), and prostaglandin E2 (PGE2), which contribute to articular inflammation and cartilage destruction as they enhance MMP activity, inhibit the production of anabolic products such as collagen and proteoglycan, and induce chondrocyte apoptosis [39].

The catabolic events observed (the catabolic events that occur due to the presence of...) in the presence of IL-1β and TNF are mediated through the activation of signaling pathways, including nuclear factor-κB (NF-κB) signaling. NF-κB pathway induces the expression of the genes related to the inflammatory mediators cited above and also contributes to the induction of MMP-1 and -13 and ADAMTS-4 [46]. However, some signaling pathways are involved in the downregulation of the IL-1β and TNF effects in OA, such as peroxisome proliferator-activated receptor-γ (PPAR-γ). The activation of PPAR-γ seems to reduce the progression of cartilage lesion in experimental models of OA as it assists the downregulation of inflammatory and catabolic responses mediated by IL-1β and TNF [47, 48].

3.1.2 IL-6

IL-6 is a proinflammatory cytokine, whose signaling pathway involves the activation of receptors, such as membrane-bound IL-6 receptor (IL6R), soluble

IL-6R (sIL-6R), and gp130, followed by the activation of STAT1 and STAT3 pathways [39]. In physiological conditions, the production of IL-6 by chondrocytes is considerably low. However, the exact mechanism of IL-6 action in OA is unknown, but its production can be stimulated by the number of cytokines and growth factors present in OA, including IL-1β, TGF-β, and PGE_2 [25, 49].

Increased levels of IL-6 in synovial fluid and serum have been correlated with the severity of lesions in X-ray imaging [50]. *In vitro* studies have shown that IL-6, in combination with IL-1β and TNF, upregulates the production of MMP-1 and -13 in human and bovine chondrocytes and induces proteoglycan and type II collagen degradation [51, 52]. The effect of IL-6 in studies with animal models has shown uncertain results. IL-6 knockout mice revealed more advanced degenerative changes compared to wild-type animals [53]. However, when IL-6 was injected in the joint cavity of IL-6-deficient mice, the reduction in the loss of proteoglycans in the acute phase of inflammation was observed [54].

One of the most considered active components in OA is the change in subchondral bone tissue, and IL-6 has been a critical mediator in this regard. Its effect, together with IL-1β and TNF, is based on promoting osteoclast formation and, consequently, bone resorption [55]. In response to IL-6, osteoblasts stimulate the production of receptor activator of NF-κB ligand, IL-1β, and PGE_2, which activate osteoclasts [56]. In addition, osteoblasts activated by these cytokines produce MMPs, which adversely affect the surrounding cartilage [57].

3.1.3 IL-15

Despite a better documented involvement in rheumatoid arthritis [58], the knowledge regarding IL-15 and its action in OA is still poor. It acts based on the stimulation and proliferation of T cells and NK cells, and it may also induce the production of MMP [59]. IL-15 levels are elevated in synovial fluid in early stages of OA, and this concentration correlates with pain and severity of lesions seen on X-ray imaging [60, 61].

3.1.4 IL-17

Due to its inflammatory effects, IL-17 family has been implied to play a role in OA [62]. IL-17 is mainly stimulated by CD4+ T cells and mast cells, which are present in the cellular infiltrates observed in OA joints [63]. Within the joints, IL-17 primarily targets chondrocytes and fibroblast-like synoviocytes, which express IL-17 receptor (IL-17R) on their surface [64]. It was reported that IL-17 is able to inhibit proteoglycan synthesis by chondrocytes and increase the production of MMPs [65]. Also, high levels of IL-17 in both serum and synovial fluid were correlated with radiographic lesions in OA [66].

The genetic correlation between IL-17 and OA was suggested: a polymorphism in the gene IL-17A G-197A could be associated with the susceptibility to the development of OA [67]. In addition, IL-17 is produced by a specific T cell lineage called T helper 17, and it is able to cause hypertrophy of synovial membrane as its presence influences the secretion of vascular endothelial growth factor (VEGF), which leads to excessive blood vessel formation [68]. It can also indirectly affect cartilage by inducing the production of cytokines responsible for tissue degradation, such as IL-1β, TNF, IL-6, NO, and PGE_2 [64].

3.1.5 IL-18

The active form of IL-18 results from the activation of caspase-1, which has been reported to be elevated in articular cartilage and synovium of OA, leading to great

promotion of IL-18 and IL-1β. The production of IL-18 in joints is mainly determined by chondrocytes, osteoblasts, and macrophages [69]. IL-18 affects cartilage by upregulating the production of IL-18Rα on chondrocyte surface and stimulates excessive production of MMP-1, -3, and -13 [70]. Also, IL-18 negatively influences the production of proteoglycans, aggrecan, and type II collagen and may cause morphological changes typically observed in apoptotic processes [71, 72].

The increased concentration of IL-18 observed in synovial fluid, synovium, cartilage, and even blood serum from patients with OA has been correlated with the severity of lesions seen in radiographic imaging [73]. Also, studies have correlated the development of OA and lumbar disc degeneration with polymorphisms in the gene encoding IL-18 and its receptor (IL-18R) [74, 75].

3.1.6 IL-4

Anti-inflammatory cytokines also present a role in the maintenance of OA. IL-4 is associated with chondroprotective effects as it is shown to reduce MMP production and, consequently, inhibit the degradation of proteoglycans in the articular cartilage [76]. However, chondrocytes from OA joints have shown a decreased susceptibility to this IL-4 protective effect, leaving the cartilage unprotected, quickening the degeneration via the action of the proinflammatory cytokines cited above [77]. In addition, a polymorphism in the gene encoding IL-4 and its main receptor (IL-4Rα) could predetermine the development of OA in hand and knee joints [78, 79]. It was also further reported that, when compared with healthy patients, OA patients present an elevated level of soluble IL-4Rα (sIL-4Rα) [80].

The activation of IL-4 depends on intracellular signal transduction by gradual phosphorylation of IL-4Rα, which leads to the expression of several proinflammatory genes [81]. IL-4 production is mainly determined by T cells, especially Th2, which are present in the cellular infiltrates observed in OA [37]. It was reported that IL-4 alone or in combination with IL-10 is able to reduce the production of diverse proinflammatory mediators, such as IL-1β, TNF-α receptors, IL-6, PGE_2, and COX-2 [82–84].

3.1.7 IL-10

Due to its anti-inflammatory features, IL-10 is another cytokine that presents chondroprotective effects, and it is linked to the release of IFN [62]. *In vitro* studies have shown increased proteoglycan and type II collagen syntheses after the administration of IL-10 in chondrocytes [62]. The protective effects that IL-10 exhibits are likely due to a stimulation of the synthesis of IL-1β antagonist and a tissue inhibition of MMP-1 (TIMP-1) [85]. Also, IL-10, as well as IL-4, reduces apoptotic events in chondrocytes and production of MMP [86, 87].

IL-10 induces the expression of bone morphogenetic protein-2 and -6 (BMP2 and BMP6), which are related to chondrogenesis as they belong to TGF-β family [88]. Together with BMP production, IL-10 activates signaling pathways, such as NKX-3.2/SOX9, that induce the differentiation of mesenchymal stem cells into chondrocytes [89]. Also, by reducing the expression of TNF-α receptors, IL-10 is able to attenuate the effect of TNF-α on synovial fibroblasts. A decrease in COX-2 production was also noted in the same study [90].

The secretion of IL-10 can be influenced by physical exercises. Patients with and without OA had synovial fluid and periarticular tissue harvested from their knee before, during, and after they underwent exercise practice for 3 hours. A significant increase in IL-10 levels was observed in these patients after the exercise. Although it is not clear what exact mechanism led to this result, this observation is

likely attributed to an increase in intra-articular pressure and subsequent effects on cellular secretion [91, 92].

3.2 Chemokines

Chemokines comprise small proteins that act as chemoattractants to assist cells to migrate to injured tissue. Diverse chemokines have gained attention in the development of OA. Some of them including their receptors, such as IL-8, CCL5, CCL19, CCR1, CCR2, CCR3, and CCR5, may induce the production of MMP-3 by chondrocytes and increase the breakdown of cartilage matrix components, which trigger the onset of OA [60, 93]. However, some chemokines might present a protective role in OA, such as stromal cell-derived factor-1 (also called CXCL12), whose main function is to recruit mesenchymal stem cells to the injured area in order to promote tissue repair [94].

Several chemokines were reported to be overexpressed in OA, such as IL-8/CXCL-8, GROα/CXCL-1, MCP-1/CCL-2, RANTES/CCL-5, MIP-1α/CCL-3, and MIP-1β/CCL-4. Some of these chemokines are stimulated by IL-1β, which is upregulated in OA, and they induce MMP production upon binding to their ligands, causing tissue degradation [93]. Levels of INF-γ-inducible protein 10 (IP-10), also called as CXCL-10, in plasma and synovial fluid have been correlated with radiographic knee OA. CX3CL1, a serum fractalkine, has also been reported to be significantly elevated in severe knee OA in a study that compared OA patients with healthy patients [95].

To support the role of macrophage in the inflammatory response observed in OA, MCP-1, also known as chemokine ligand-2 (CCL2), has been reported to recruit macrophages into adipose tissue and atherosclerotic lesions [96]. Also, MCP-1 levels in both serum and synovial fluid has been associated with self-reported pain and disability in patients who present knee OA [97]. In addition, it was observed that, in severe knee OA, the levels of macrophage-derived chemokine (MDC) and IP-10 in synovial fluid were elevated, while eotaxin levels, an eosinophil chemotactic protein, were lower when compared with healthy patients [98].

3.3 Adipokines

Adipokines have been associated with the incidence and severity of OA [99]. *In vitro* studies reported that the presence of adipokines, such as leptin, adiponectin, visfatin, and resistin, increases the production of inflammatory mediators and also induces chondrolysis [99]. Although the exact mechanism of how these cytokines derived from adipose tissue act on arthritic joints has not yet been elucidated, researchers have studied the role of fat pad as a local inflammation mediator in OA, particularly in knee OA due to the infrapatellar fat pad, which has proven to be infiltrated with macrophages, lymphocytes, and granulocytes [100]. These findings support the thought that obesity supports the development of OA more through biochemical pathways rather than biomechanical overload risks on a weight-bearing joint.

3.4 Lipid mediators

The COX-2 enzyme is responsible for the production of lipid mediators, including PGE2 and leukotrienes, and it is also upregulated in OA joints. In addition, the overexpression of COX-2 in OA has been associated with the increased production of IL-1β, TNF, and IL-6 via toll-like receptor-4 (TLR-4) [101]. Besides assisting the production of MMPs and other functions already cited above, PGE_2 is also involved in apoptosis and structural changes that characterize arthritic disease [102].

Leukotrienes have also been investigated for their role in OA. These mediators are converted from arachidonic acid, which also produces PGE_2 via the activity of the enzyme phospholipase A2 [21]. Leukotrienes, mainly leukotriene B4 (LTB4), are present, to a lesser extent, in OA synovium, bone, and cartilage. Also, LTB4 has been reported to stimulate the production of IL-1β and TNF in arthritic synovium [103].

4. Conclusions

The cumulative evidences over the years have shown that increased expression of proinflammatory cytokines, in particular IL-1β, TNF, and IL-6, in cartilage as well as synovial fluid and membrane, has played a key role in the pathogenesis of OA. Inflammatory processes linked with immune responses have characterized OA as a complex disease and not as a simple age-related cartilage degeneration as it is thought to be. The understanding of individual roles of inflammatory mediators and their compounds is of utmost importance to target new therapies for OA, since the current options are elusive and may be noneffective, invasive, or even capable of presenting serious side effects. Due to advancements in molecular tools, the overall aim would be to dissect the role of each cytokine in the pathophysiology of OA and, together with drug delivery systems, to develop specific anticytokine therapy, given that inflammatory responses contribute substantially to OA maintenance.

Conflict of interest

The authors have no conflict of interest to declare.

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Chapter 3

Fat Tissue's Graft in Osteoarthritis Treatment: Indications, Preparations, and Results

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Abstract

Osteoarthritis (OA) represents one of the most common causes of joint pain and disability with related changes in bone morphology. In last years, this pathology is steadily increasing due to the continuous increase in the average life expectancy and the rate of active population. In recent years, there have been many conservative treatments for symptomatic gonarthrosis in order to reduce pain and delay or avoid the implantation of a knee prosthesis. The most studied and used was infiltrating treatment. Our group has been paying attention to regenerative medicine for many years, focusing on the characteristics of adipose tissue and the presence of multipotent mesenchymal cells, particularly in the vascular stromal area. Mesenchymal stem cells (MSCs) of adipose tissue can commit toward the chondrogenic, osteogenic, adipogenic, myogenic, and neurogenic lineages. Our group has continued the studies in this field by submitting this to treatment patients with grade II–III arthrosis according to the scale of Kellgren-Lawrence or patients with IV degree of such scale inoperable for internal reasons. To date, with a 4-year follow-up, our results are satisfactory in terms of pain reduction, improvement in joint function, and recovery of daily and sports activities.

Keywords: osteoarthritis, fat tissue, joint, adipose stem cells, conservative treatment

1. Introduction

Osteoarthritis is a common degenerative joint cartilage disorder associated with hypertrophic bone changes and loss of joint cartilage integrity [1]. It causes pain, stiffness, and reduction of the associated function, consequently, disability with relative difficulty for the patient in carrying out the normal daily activities [2]. Risk factors are represented by genetic factors, female sex, post-traumatic conditions, age, obesity, etc. [3–6]. Treatment is therefore aimed at reducing symptoms, improving quality of life, and preventing its progression. Treatment options can be classified into:

- Conservative treatment, such as lifestyle education, pain therapy and physiotherapy, and infiltrative therapy.
- Surgical treatment, traditionally represented by arthroplasty and osteotomy and in some cases by arthroshaving [2].

Several national and international OA management guidelines recommend that patients should be first introduced into pathways that provide conservative treatment options and then directed to surgical treatment only when the conservative treatment does not allow the desired therapeutic achievement [7–10].

2. Epidemiology and causes

It represents the most common joint disease in the world, even if the frequencies vary from country to country: it affects more than 40 million individuals only in the United States and about 4 million in Italy, thus representing the main cause of disability at a national level. Therefore, OA is responsible for direct and indirect medical costs for society: clinical visits by primary care physicians or specialists, drugs, and surgical interventions represent direct costs; comorbidity and time lost from work due to the effects of disability are the examples of indirect costs. This clinical condition is more evident among the elderly, who may lose their independence and then need assistance during their daily activities, thus increasing the economic burden [11–13]. The lifetime risk of developing symptomatic osteoarthritis of the hip is 18.5% for men and 28.6% for women. For symptomatic knee OA, it is around 45%. Therefore, the risk of being subjected to a total hip or knee prosthesis at the age of 50 results to be high, with values of 7.1–11.6% for the hip and 8.1–10.8% for the knee [14, 15].

OA has a multifactorial etiology, and it is a disease that affects not only the quality of all synovial joint structures but also the function and quality of surrounding tissues and the pathway of nociceptive signaling. The causes that lead to the onset of osteoarthritis are largely unknown. On the other hand, it is believed that in most cases, many factors that alter the joint balance are involved. Schematically, the joint balance can be maintained if a normal load is exerted on a normal cartilage. Therefore, all factors capable of modifying this balance, acting either on the load or modifying the characteristics of cartilage, can be considered risk factors for osteoarthritis. In most cases, there is a combination between the genetic predisposition of the individual and the influence of environmental factors, especially those that act on the load, such as mechanical stress, obesity, malformations, trauma, and microtrauma. The precocity of the onset and the type of evolution may then depend on the number of factors involved, on their size and on the duration of their action. The OA can be divided into primary and secondary forms. The primary form, or idiopathic, manifests itself in intact joints without any triggering factor. Aging plays a fundamental role in this form of OA: the joint wear causes damage to the cartilage and, associated with an abnormal repair mechanism, the disease manifests itself. In the secondary form, OA is caused by a predisposing factor. In general, any violation of the integrity of the chondrocyte matrix has the potential to cause OA. However, some considerations aside highlight age as a risk factor. Although we all know that the frequency of arthrosis increases with age, arthritis is currently considered not to be a disease of aging. In fact, not all the elderly has this disease. It is therefore probable that the genetic tendency that an individual has in the predisposition to contract sooner or later some diseases, including arthritis, can be accentuated and accelerated by the risk factors. Obviously, among the elderly, the duration of exposure to these risk factors is higher, so the consequences are more evident.

Some risk factors are not changeable, such as age and genetic predisposition, while others, such as mechanical ones, overweight, etc., are considered modifiable and therefore, a rarely feasible consideration for other rheumatic diseases [16, 17].

Attention must also be given to another attachment of the joints overlapping the OA for clinical and disability: osteonecrosis. Osteonecrosis is estimated to be the cause of 10% of all total hip arthroplasty performed in the United States.

However, differentiation between these conditions can be difficult, particularly at the beginning of the pathological process [18, 19].

It is a disease characterized by the interruption of the normal supply of bone blood resulting in "death" bone. At this point, the healing response may be inadequate and then the joint surface collapses with the subsequent degenerative arthritis [18].

Osteonecrosis is more common in patients under the age of 40 and has no sexual preference. Among the risk factors acquired for osteonecrosis, alcohol abuse, smoking, and trauma are more common in men, while rheumatic diseases, such as systemic lupus erythematosus, are more commonly found in women. Therefore, the predilection of sex in osteonecrosis is highly influenced by the associated risk factors [20].

OA develops with the combination of biochemical, cellular, and mechanical processes [21].

OA is associated with biochemical events mediated by cytokines, proteolytic enzymes, and other proinflammatory substances responsible for osteolysis, subchondral bone sclerosis, osteophytosis, articular erosion of the cartilage, and thickening of the synovial membrane [22, 23].

Following the break of the cartilaginous matrix, due to proteolysis, the cartilage weakens and becomes subject to fibrillation and erosion, resulting in the release of proteoglycans and collagen fragments in the synovial fluid. This process induces an inflammatory response in the synovium, which causes further degradation of the cartilage. When the cartilage weakens, it begins to thin out, causing a reduction in joint space. Cartilage damage also causes the appearance of periarticular osteophytes. The exact mechanism of pain generation in OA is not well understood, but is probably related to an interaction of different mechanisms [21, 24].

From a purely biochemical point of view, OA is the result of an imbalance between the peptides that promote the synthesis of components of the ECM (extracellular matrix) of the articular cartilage and those that induce the remodeling of these components. [25–31].

The result of these catabolic cascades is the persistence of the synovitis, with initial cartilage damage and induction of remodeling of the subchondral bone [32, 33]. The pathogenesis of OA is therefore composed of a network of overlapping complex molecular mechanisms, which entail damage to the articular tissue. These mechanisms depend on the equilibrium of expression of the catabolic and anabolic articular molecules.

3. Therapy

The goals of therapy in OA can be defined as "short-term," represented by pain control, stiffness control, and reduction of inflammation and "medium-long term," represented by the arrest or slowing of progression, by deformity prevention, and restoration of function.

For the pursuit of these objectives, many strategies can be used, both pharmacological and nonpharmacological, which often need to be coordinated with each other to be really effective. In fact, in addition to the introduction of new drug therapies, the importance of general measures, such as patient education to the

knowledge of the disease and the consequent implementation of some measures such as weight loss and gymnastics or the use of unloading orthoses is recommended [10, 34, 35].

For conservative treatment, today we have several strategies available that, as mentioned, where possible, must be evaluated and taken into account in relation to the clinical condition of the patient.

An increasingly important role in the conservative treatment of OA is represented by the infiltrative therapy that in recent years has proposed a wider range of solutions: from intra-articular anti-inflammatory therapy as a palliative treatment to an infiltrative solution that can restore joint homeostasis or that can possibly activate a regenerative process into the joint.

Intra-articular corticosteroid injections may be indicated after failing NSAIDs and acetaminophen, but some researchers suggest only using them once every 3 months for a maximum of 2 years due to negative potential side effects [36].

The mechanism underlying the anti-inflammatory efficacy of corticosteroid is multifactorial, but generally involves blocking antigen opsonization, leukocytic cell adhesion, and cytokine diapedesis within the capillary endothelium. Corticosteroids also attenuate the effects of IL-1, decrease leukotriene and prostaglandin release, and inhibit metalloproteases and immunoglobulin synthesis [37].

The duration of action of intra-articular corticosteroid injections remains controversial, with various studies quoting anywhere between 1 and 24 weeks. There is consensus that steroids provide relief to patients for approximately 1 week after injection.

Adverse effects of corticosteroid injections do exist; however, Handler and Wright first described radiographic evidence of destruction of the knee joint and cartilage after several corticosteroid injections [38]. The incidence of joint infection following corticosteroid administration is rare, but may be as high as one in 3000 patients, with an associated mortality rate of approximately 11%. Additional known complications include pain, skin atrophy, tendinopathy, and systemic hyperglycemia [39].

The use of this procedure results in an inconclusive recommendation strength [10].

4. Hyaluronic acid injections

HA plays a fundamental role in maintaining elasticity and viscosity of the synovial fluid and integrity of the connective tissues such as joints [40, 41]. Several studies have shown that HA is a chondroprotector: it synthesizes proteoglycan and glycosaminoglycan, and it has anti-inflammatory, mechanical, subchondral, and analgesic actions [40].

5. Platelet-rich plasma

Platelet-rich plasma (PRP) is the most investigated biological treatments [42–44] due to the capacity to reduce inflammation and consequently a reduction of pain [45–47]. PRP exerts its biological effect with neoangiogenesis and migration of macrophages and mesenchymal cells and regulates cell differentiation and the activity of different cell lines, promoting tissue regeneration. PRP is controversial for the treatment of OA, because there is insufficient evidence to recommend the use of it [48–50].

Despite the growing interest in this biological approach for cartilage regeneration, the knowledge on this topic is still preliminary [51].

6. Biological use of fat tissue

The promise of mesenchymal stem cells (MSCs) to give birth to a new era of medicine was strong, thanks to the ability of these cells to do self-renewal and multipotent *in vitro* differentiation into mesodermal cell subtypes. To be honest, recent studies have demonstrated that a good portion of the thrilling *in vivo* clinical results is due to the trophic, paracrine, and immunomodulatory activities of MSCs instead of their differentiation ability [52]. Differently from drug concept where the effect is dependent from concentration, MSCs are self- and site-regulated and they release a multitude of bioactive factors in variable concentration in response to the local messages of the microenviroment. The main trophic activity exerted by MSCs is the release of growth factors and other chemokines to induce the homing and proliferation of cellular progenitors and to promote angiogenesis. These factors are transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), endothelial growth factor (EGF), fibroblast growth factor 2 (FGF-2), and insulin-like growth factor 1 (IGF-1)—all of these are proteins able to accelerate cellular growth and division of progenitors [53]. Moreover, IGF-1, EGF, and the vascular endothelial growth factor (VEGF) are able to recruit endothelial cells and promote new vascularization [54].

MSCs can derive from many tissue sources, and among these, the more manageable for clinical practice is bone marrow and adipose tissue. Even if the MSCs from bone marrow (BM-MSCs) were discovered first and have more clinical experience, there is higher interest on adipose tissue—not only for the ease and low morbidity of harvest but also because it has a higher MSCs frequency. In a bone marrow aspirate, there are 6×10^6/ml nucleated cells and, among these, only 0.001–0.01% are MSCs; on the other hand, a lipoaspirate contains $0.5–2.0 \times 10^6$/g nucleated cells where the MSCs frequency ranges from 1 to 10% based on the donor site. Since the adipose tissue has a total of $0.5 \times 10^4–2 \times 10^5$/g of MSCs, it means that there is a 500-fold higher concentration of MSCs in comparison with bone marrow [55]. Moreover, it has been demonstrated that the proliferation and differentiation properties of stem cells from adipose tissue (ADSCs) are less impaired by age in comparison with BM-MSCs [56].

ADSCs can be exploited with three different methods. The first, the only option where we can properly name them as true ADSCs, is the cell culture and optional cell expansion *in vitro*. By selecting the cells that are able to stick to the plastic, it is possible to obtain cell that expresses mesenchymal markers (CD105+, CD73+, CD90+, CD45−, CD34−, CD11b−, CD14−, CD79a−, and HLA-DR−) able to differentiate into the three mesodermal lineages (bone, cartilage, and fat). This option has serious limitation in the clinical practice due to regulatory issues because it can only be performed into good manufacturing practice facilities that manipulate these cells like an experimental drug (it is named advanced cellular therapy). Notably, concentrated BM-MSCs outperform cultured cells since they are more practical and efficient and less harmful and expensive [52]. The second method is enzymatic digestion of adipose tissue that gives in the hands of operators a heterogeneous cell population that contains, beside MSCs, endothelial cells, leucocytes, and preadipocytes. This final product of enzymatic digestion is named stromal vascular-fraction (SVF). Finally, autologous ADSCs can be exploited through the processing and fragmentation of adipose tissue (FAT, *fragmented adipose tissue*). While the SVF is a heterogeneous cell population where each cell is separated from the others and the efficacy is dose-dependent, the FAT is a proper minimally manipulated tissue that entrust more on cell quality instead of cell quantity. The FAT is composed of tissue cluster of variable diameter where the SVF cells are embedded and attached to an undisrupted tissue architecture made of vasculature and extracellular matrix sustained by a scaffold made of adipocytes. This natural scaffold protects cells from anoikis (death cause by the lack of cellular adherence) and other harmful stress.

The MSCs embedded into these clusters have high vitality and can still differentiate into the three mesodermal lineages as a proof of their multipotency. To prove that quality is superior to quantity, it has been demonstrated in an animal model of critical limb ischemia that an injection of 500 μl of FAT (which contain 2×10^4 ADSC) restores limb perfusion better than a single injection of 1×10^6 isolated ADSC [57].

During the First World War, the fat was used to heal soldier wounds and its application was very heterogeneous until 1990 where Sidney Coleman defined precise guidelines. The evolution of surgical techniques associated the volumizing effect of lipofilling to the regenerative properties of natural adipose tissue, favoring the processing, the reduction, and the purification of the tissue to raise the survival of grafts and magnify the regenerative potential of MSCs. Also reducing the volume of grafts and the diameter of injection needles had helped the hosting tissue to decrease stress and trauma, thus provoking less inflammation and ameliorating again graft survival [58]. Adipose tissue is now used with lipofilling techniques in hard-to-heal wounds and in all cases characterized by mortified tissue (burn, compression, and radiation) linking the regenerative potential also to an esthetic effect. Wound healing professionals use lipofilling to treat ulcers resistant to classical therapies and advanced dressing and also for the treatment of critical limb ischemia and diabetic patients [59]. In orthopedics, intra-articular lipofilling has become a fashionable and innovative strategy to fight osteoarthritis, thanks to the ability of this tissue product to reequilibrate the articular homeostasis and to reduce the inflammation of the synovial membrane [60]. The integrity of the extracellular matrix can also exploit the shock absorber function of adipose tissue reducing the stress between cartilage surfaces. The paracrine effect of MSCs can also promote cartilage repair when mechanical conditions of the articulation are stable. The anti-adhesive properties of adipose tissue were exploited in the surgery of tendons and nerves to limit the formation of fibrotic and scarring tissue, thus also limiting the relapse incidence. Finally, adipose tissue was also studied in pain management for the intradiscal infiltration for the treatment of low back pain associated to black disc.

7. Lipofilling

The technique of liposculture is originally created for esthetic purposes. Autologous fat transfer has recently become an increasingly popular surgical procedure: harvesting, refinement/processing, and transfer of subcutaneous tissue to provide relatively pure and intact parcels of fat are paramount for successful lipofilling. Usually, we use local anesthesia with sedation or epidural anesthesia. Rarely, we use general anesthesia.

- Incisions with a n°11 blade are made in the donor site. When possible, incisions are placed in wrinkle lines, folds, or fatty areas (abdomen flank, thigh, and knee).

Instruments for lipofilling cause minimal trauma to fatty tissue during placement.

- Cannulas vary in shape (curved or no-curved) and length (7–12 cm).

Liposuction: special blunt-tip, maximum diameter 3 mm, with small holes near the tip

  - Coleman I is used near a blood vessels or nerve. This cannula is capped on the tip with a lip that extends 180° over the distal aperture.

- Coleman II is used in other circumstances. This cannula is not completely capped and has a lip that extends over the distal aperture about 130–150°.

- Coleman III is used for the scars or fibrous tissue treatments. This cannula is flat on the end to allow for dissection of the tissue.

- Coleman V is a dissector used for scar's treatment.

Transplantation: small blunt-tip

- Infiltration cannula is a blunt 17G cannula with one or two distal aperture proximal to the tip: no fatty tissue should be infiltrated during the advancement of the cannula; fatty tissue is left in the pathway of the retreating blunt cannula (this method permits stable and regulated placement with minimal irregularities or clumps of tissue).

8. Surgical technique

8.1 Harvesting of adipose tissue from a suitable donor site

Many different techniques have been proposed for harvesting of adipose tissue: the fundamental aim is minimizing adipocyte damage and increasing the survival of adipose tissue. Incisions with a n°11 blade are made in the donor site, when possible in wrinkle lines, folds, or fatty areas (abdomen, flank, thigh, and knee).

There are many different natural fat deposits: it is important an accurate preoperative examination of the patient.

The abdomen is the most common site of fat harvesting; it is also common in the trochanteric region (saddlebags) and in the medial/internal part of the thighs and knees.

The main techniques for fat harvesting are vacuum suction, syringe suction, or surgical excision.

8.1.1 DRY technique

Other surgeons advocate a "dry" fat harvesting: cell viability has been similar to "wet" fat harvesting nut, and this technique may lead to a greater requirement for analgesic.

8.1.2 WET technique

In 1993, Klein proposed a new method called tumescent technique in which a fluid solution (Klein's solution) was injected into the donor site improving the safety of large-volume liposuction (it eliminated the need for general anesthesia and reduced surgical hemorrhage).

Another technique is the "Berlin autologous lipotransplantation", which involves the use of a water-jet system to harvest the fat tissue and collect it in a closed container: minimal bruising and postoperative pain, faster harvesting time, and greater sterility.

In the course of fat harvesting, a blunt cannula is inserted through an incision into fatty tissue engorged with tumescent fluid (Klein's solution)

- Negative pressure liposuction is faster than 10 ml syringe aspiration (low pressure) and is an effective method for aspiration of large amounts of fat, but it causes massive destruction of adipocytes, greatly reducing the survival of fat graft.

- Conventional liposuction with high negative pressure may cause disruption of 90% of adipocytes structures.

Cannula size may also impact the viability of harvested adipocytes. Performing biopsy and lipoaspiration with large-bore cannulas could reduce the risk of cellular rupture by preserving native tissue structure.

So the size of cannula must be large enough to preserve adipocytes and stromal cells and their anatomical relationship without limiting diffusion of nutrients.

Coleman described a technique for fat harvest that minimized trauma to the adipocytes.

He used 3-mm incisions (n°11 blade), a 3-mm blunt edge, 2 hole harvesting cannulas (3 mm) connected to a 10-ml Luer-Lock syringe. The cannula is pushed through the harvest site (abdomen, flank, thigh, knee, or other sites with excess adipose tissue) as the surgeon uses digital manipulation to create a gentle negative pressure.

A combination of lower negative pressure and the curetting action of the cannula through the tissues allows parcels of fat to move into the syringe. At the end, the syringe is disconnected from the cannula and replaced with a plug that seals the Luer-Lock end of the syringe.

8.2 Processing

The most commonly used methods to process fat tissue are centrifugation, sedimentation, washing, and filtration. Comparative studies investigating the effects of fat processing with different techniques have showed no significant differences in fat retention.

The goal of fat processing is:

To eliminate contaminants that can cause inflammation at the recipient site, which can be detrimental for the fat graft. These elements include cellular debris, free oil, and other nonviable components of the lipoaspirate such as hematogenous cells.

- Blood must be extracted in order to improve degradation of the transplanted fat.

- Since the debris will be absorbed after a few hours, its injection could be confused with volume correction.

- Moreover, many authors report an improvement in graft viability by maximizing the number of ADSC in the graft material.

8.3 Ensuring graft viability

Centrifugation is the most widely used technique for postharvest fat processing and has previously been considered the criterion standard. Coleman's technique consisted in centrifugation (3000 rpm for 3 minutes) to separate the different components as follows:

- Upper level: least dense and consists primarily of oil.

- Middle: primarily fatty tissue.

- Lowest: blood, water, and aqueous elements.

The supernatant fat and the lower aqueous layers are discarded, leaving concentrated viable fat cells.

That is an optimal method to obtain the highest concentration of stem cells and increased angiogenic grow factors (FGF and VEGF). It separates adipocytes from blood cells and enzymes (lipids, proteases, and lipases). Sedimentation allows obtaining a large number of vital intact adipocytes [61].

Washing methods has the goal of removing superfluous tumescent fluid and all elements that can be detrimental for the fat graft.

- Lipocell technique is a new procedure that allows eliminating blood, oil, cellular debris, or other nonviable components and obtaining a pure lipoaspirate. This technique preserves a large number of mesenchymal stem cells and a large number of adipocytes.

Filtration allows elimination of contaminants by maintaining viable adipocytes and a lot of ADSC, thus obtaining a viable graft material for large volume fat transfers.

- Pure graft filtration is a new technology that uses a closed-membrane filtration system for preparation and isolation of stromal vascular fraction and its mechanism is known to work by principles similar to a dialysis unit.

8.4 Implantation/fat injection

Principles of fat reimplantation are found on optimal recipient site vascularity to increas fat survival.

Graft can survive up to 48 hours by tissue fluid absorption.

Neovascularization progresses 1 mm/day; therefore, a deposit diameter greater than 2 mm should be avoided to prevent central necrosis. With a skin incision like a diameter of the cannula, the graft is put at the level of the anatomical region involved. Cannulas with small gauge will reduce tissue trauma, bleeding, and hematoma.

Through multiple access sites, multiple tunnels are created on insertion, but fat is injected only during withdrawal of the cannula.

In our experience, mainly concentrated on the knee involves the constant association of a diagnostic and surgical arthroscopy; in fact, in the majority of cases, there are meniscal lesions (flap type) or unstable chondral lesions which, if left untreated, could lead to failure of the grafting procedure alone.

9. Complications

All steps in surgical technique (harvesting, processing, and transplantation) are important. Complications are few, rare, and minimal. Viability of fat cells is crucial. The chances of survival are higher if the fat graft is less manipulated and reinjected as fast as possible.

- Donor site complications related to lipoaspirate technique: bruising, swelling, hematoma, pain, paresthesia, infection, pathologic scarring, contour irregularities, cellulitis, and damage to the underlying structures.

- Failure of fat graft in recipient sites could cause fat necrosis, oil cysts, calcifications, reabsorption of fat, and intravascular injection with fat embolism.

Early identification of local sepsis.

10. Conclusion

In conclusion, there are several treatments for knee OA including nonpharmacological and pharmacological treatments.

Among the nonpharmacological ones, patient education and self-management strategies, advising weight loss and strengthening programs are included.

Regarding the pharmacological treatment, the NSAIDs can be used in the short-term therapy but their effect is limited in time.

Another employed strategy to manage knee OA is represented by joint injections of corticosteroids, hyaluronic acid, PRP, and even stem cells [47].

The reason for using ASCs in orthopedics is derived from tissue engineering studies that enhance their ability to differentiate into osteoblastic or chondrocyte using appropriate culture media and bioengineered structures that can accommodate cells as a biological scaffold.

The studies of Hattori and colleagues showed an osteogenic differentiation (by electron microscope, with histological evaluation and by the capacity of osteocalcin secretion) analogous to BMSC using a beta-tricalciophosphate scaffold [62, 63].

Always Hattori and colleagues in 2008 proposed new strategies for the in vitro expansion of ASCs. In most cases, the expansion was obtained with fetal bovine serum (FBS) which, in subsequent clinical applications, could have caused infections or immunological reactions caused by the proteins present in the FBS [64].

For this reason, Hattori and colleagues have demonstrated, with studies on the mouse, that it is possible to obtain the expansion of the ASC with the same differentiation potentials, using a small amount of autologous serum containing type I, FGF-2 collagen and thus opening the way to possible therapeutic applications.

Promising is the application in the treatment of cartilaginous lesions. In 2007, Masuoka and colleagues used a three-dimensional honeycomb scaffold of atelocollagene (ACHMS scaffold) with ASCs for cartilaginous lesions in rabbit's knees; as a control group, they used the only ACHMS-scaffold or nothing [65]. Twelve weeks later, histological analyzes have highlighted that only in cases where ASC + ACHMS-scaffold had been used, there was hyaline cartilage with high expression of type II collagen. It should be also noted that the ASCs, as mentioned above, have the ability to release factors of tissue growth and/or regeneration and cytokines. These substances play an important role in chemotaxis, in promoting tissue regeneration, cell differentiation, and neoangiogenesis.

Regenerative medicine opens the way for a new therapeutic frontier, as it now allows an improvement in symptoms and in the functionality of the joints. On the other hand, further studies are needed, major follow-ups, targeted clinical trials, and finally the possibility of a second look to evaluate and validate the real regenerative capacity of this treatment.

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Section 3

Natural Treatments for Osteoarthritis

Chapter 4

Herbal Medicinal Products in the Treatment of Osteoarthritis

Zoran Maksimović and Stevan Samardžić

Abstract

Osteoarthritis (OA) is the most common form of arthritis, which represents a substantial economic burden for society and significantly affects patients' quality of life. Current conventional treatments of OA may be insufficiently effective and unsafe. In an attempt to overcome these limitations, many patients use herbal medicinal products (HMPs) and dietary supplements. A considerable number of herbal drugs and preparations (e.g., willow bark, *Salicis cortex*; devil's claw root, *Harpagophyti radix*; blackcurrant leaf, *Ribis nigri folium*; nettle leaf/herb, *Urticae folium/herba*; meadowsweet/meadowsweet flower, *Filipendulae ulmariae herba/flos*; rosemary leaf/oil, *Rosmarini folium/aetheroleum*; and juniper oil, *Juniperi aetheroleum*) are traditionally employed to relieve minor articular pain. Active constituents (e.g., sesquiterpene lactones, triterpenic acids, diarylheptanoids, iridoid glycosides, phenolic glycosides, procyanidins, and alkaloids) are not often fully known. Experimental studies suggest that herbal extracts/compounds are able to suppress inflammation, inhibit catabolic processes, and stimulate anabolic processes relevant to OA. Therapeutic benefit of most HMPs is expected solely from the experience of their long-standing traditional use. Efficacy and safety of several HMPs were assessed in clinical trials. The growing body of preclinical and clinical evidence provides rationale for the use of herbal products in the treatment of OA. However, at present, they cannot be recommended to patients with confidence.

Keywords: osteoarthritis, herbal medicinal products, medicinal plants, mechanism of action, active constituents, clinical efficacy

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis and the main cause of disability in elderly. Due to the aging population and obesity (major risk factors), its prevalence increases. It is estimated that symptomatic OA of knee affects approximately 12% of the older population (≥60 years). Symptomatic OA of hand (6.8%, ≥26 years) and hip (9.2%, ≥45 years) is also frequent. OA can influence patients' quality of life significantly, as it is usually accompanied with the pain and loss of physical function. OA often affects knees, hips, hands (distal and proximal interphalangeal joints and the base of thumb), cervical and lumbosacral spine, and feet (first metatarsal phalangeal joint). It is characterized by failure of all joint structures. Articular cartilage loss is the most prominent feature of the disease, but subchondral bone, synovial membrane, associated muscles, and ligaments are also affected. On cellular level, catabolic function of chondrocytes prevails over their

anabolic activity. This imbalance is promoted by pro-inflammatory cytokines, which stimulate chondrocytes to produce enzymes (collagenases and aggrecanases) able to degrade extracellular matrix composed of collagen type II and proteoglycans. Several mediators (e.g., TNF-α, IL-1β, NO, and PGE_2) play an important role in the pathogenesis and progression of OA [1, 2].

Conventional treatment of OA encompasses non-pharmacotherapeutic approach (e.g., physiotherapy, correction of malalignment, weight control, and patient education), pharmacotherapy, and surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs) are medicines used most often for the relief of osteoarthritic symptoms. Although NSAIDs are relatively efficient, their prolonged use or their use in susceptible individuals can cause serious side effects such as gastrointestinal toxicity, cardiovascular events, edema development, reversible renal insufficiency, and modest increase of blood pressure. Topical formulations of NSAIDs are slightly less efficient than the oral ones, but their advantage lies in better safety profile. However, irritation of the skin often occurs at the application area [1].

Some patients experiencing unsatisfactory efficacy and side effects of conventional therapy try to overcome current treatment deficiencies by using modalities of complementary and alternative medicine. In that regard, herbal medicinal products (HMPs) and dietary supplements have become considerably popular for alleviation of OA symptoms [3]. Besides expected direct effects, important indirect benefit of their use may be the decrease of required doses of concomitantly administered conventional drugs, as this may result in reduced side effects. At present, available scientific data are insufficient to support the use of these products in clinical management of OA. The aim of this review is therefore to present current knowledge on herbal treatment options in the therapy of OA, i.e., active constituents of plants and mechanisms of their action relevant to OA, advice for patients using herbal products, and results of clinical trials, if available.

2. Herbal medicinal products for oral use in the treatment of osteoarthritis

Willow bark (*Salicis cortex*) is whole or fragmented dried bark of young branches or whole dried pieces of current-year twigs of various species of genus *Salix* including *S. purpurea* L., *S. daphnoides* Vill., and *S. fragilis* L. [4]. Herbal teas (infusion and decoction), powder, dry aqueous extracts, liquid hydroalcoholic extract, and tincture of willow bark are traditionally used for minor articular pain relief. Duration of the treatment is restricted to 4 weeks. In the case of hypersensitivity (to the willow bark, salicylates, or the other NSAIDs), asthma due to hypersensitivity to salicylates, active peptic ulcer disease, third trimester of pregnancy, glucose-6-phosphate dehydrogenase deficiency, children and adolescents younger than 18 (risk of Reye's syndrome), severe liver or renal dysfunction and coagulation disorders, the use of *Salicis cortex*-based HMPs is contraindicated. Concomitant application of salicylates and other NSAIDs is not recommended, unless advised by the physician. Willow bark preparations may interact with anticoagulants. Their use is not recommended in the first and second trimester of pregnancy, as well as during lactation. Side effects include allergic reactions and gastrointestinal symptoms [5]. The main constituents of willow bark with respect to the pharmacological action are phenolic glycosides (e.g., salicin, salicortin, 2′-O-acetylsalicortin, and/or tremulacin) [6, 7] although the other secondary metabolites (e.g., polyphenolic compounds) may also participate in the total anti-inflammatory activity [8]. Phenolic glycosides are considered as prodrug compounds that are metabolized to salicylic acid in gastrointestinal tract and liver. Beneficial effect is a result of

cyclooxygenase inhibition and diminished production of prostaglandins [9]. Two randomized controlled clinical trials provided low-quality evidence that short-term treatment with standardized willow bark extracts (daily doses corresponded to 240 mg of salicin) was not efficient in reduction of pain and improvement of physical function in patients with OA of hip and knee [3, 10]. Additional well-designed sufficiently powered studies are needed in order to estimate willow bark clinical effect.

Devil's claw root (*Harpagophyti radix*) consists of cut and dried, tuberous secondary roots of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne. [4]. Herbal tea and liquid or solid dosage forms containing different devil's claw root preparations (e.g., dry aqueous or hydroalcoholic extracts, liquid or soft hydroalcoholic extracts, tincture, powder) are used for the relief of minor articular pain, exclusively based upon long-standing traditional use. Patients with known hypersensitivity to devil's claw root or active gastric/duodenal ulcer must not use these products. Additionally, in cases of gallstones, a physician should be consulted prior to use of devil's claw root preparations. Undesirable effects include hypersensitivity, as well as adverse reactions of the central nervous system and gastrointestinal tract [11]. *Harpagophyti radix* contains bitter iridoid glycosides (harpagide and harpagoside), triterpenoids, polyphenolic acids, phenylethyl glycosides, and flavonoids [7]. Devil's claw root preparations exhibited anti-inflammatory activity *in vitro* by decreasing production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and PGE_2 in LPS-stimulated human monocytes [12] and by reducing levels of matrix metalloproteinases (MMP-1, MMP-3, MMP-9) in IL-1β-stimulated human chondrocytes [13]. Aqueous extract of *H. procumbens* downregulated expression of COX-2 and iNOS in the mouse fibroblasts and, as a result, decreased PGE_2 and NO generation [14]. Harpagoside, similarly to devil's claw root extracts, suppressed expression of IL-6 and MMP-13 in human chondrocytes, probably via the inhibition of transcription factor activator protein-1 (AP-1) activity [15]. Antiosteoarthritic properties of three devil's claw root preparations were the subject of four randomized controlled clinical trials. In two studies investigating Flexiloges® (ethanolic (60%) extract, DER 4.5–5.5:1, daily dose 960 mg), there was no improvement in pain scores. However, the pain-relieving activity of Arthrotabs® (aqueous extract, DER 1.5–2.5:1, daily dose 2400 mg) was noticed in another study. Finally, one study indicated that Harpadol® (cryoground powder, daily dose 2610 mg) was comparable to diacerhein in reducing pain [10].

Blackcurrant leaf (*Ribis nigri folium*) is a dried leaf of *Ribes nigrum* L. [4]. Phytochemical analysis showed that it contains polyphenolic compounds (flavonoids, proanthocyanidins, hydroxycinnamic acid derivatives) and traces of essential oil [6]. Blackcurrant leaf is used in traditional medicine to reduce minor articular pain [16]. Hydroalcoholic extract of this herbal drug exerted beneficial effects in carrageenan-induced acute inflammation, cotton pellet granuloma, and Freund's adjuvant-induced arthritis in rats. It also acted as an antinociceptive agent in the acetic acid-induced writhing test in mice [17]. Prodelphinidins (*Ribis nigri folium* constituents) stimulated synthesis of type II collagen and proteoglycans, and decreased the generation of PGE_2 in human chondrocytes [18]. Documented anti-inflammatory, analgesic, and anabolic effects give credence to reported folkloric use.

Meadowsweet herb (*Filipendulae ulmariae herba*—whole or cut, dried flowering tops) and meadowsweet flower (*Filipendulae ulmariae flos*, syn. *Spiraeae flos*—dried flowers) are herbal drugs obtained from *Filipendula ulmaria* (L.) Maxim. (syn. *Spiraea ulmaria* L.), which are traditionally used in treatment of minor articular pain [4, 19–21]. They are characterized by high content of polyphenols, particularly flavonoids and ellagitannins. Phenolic glycosides and salicylic acid are also present [6, 22]. *In vitro* anti-inflammatory action of

meadowsweet preparations was mediated by inhibition of complement activation, reduction of the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and, to a certain degree, inhibition of cyclooxygenase and PGE_2 generation [6, 23, 24]. In animal model of carrageenan-induced acute inflammation, lyophilized flower infusion of *F. ulmaria* exerted analgesic activity [25]. There is no literature data related to clinical effects of meadowsweet in OA.

Nettle leaf (*Urticae folium*) is whole or a cut dried leaf of *Urtica dioica* L., *Urtica urens* L., or their mixture [4], whereas nettle herb (*Urticae herba*) is dried cut or fragmented aerial part of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures, collected or harvested during the flowering period [26]. Both herbal drugs are employed in folkloric medicine for alleviation of minor articular pain. Side effects include gastrointestinal and allergic reactions [26, 27]. Constituents of nettle leaf and/or herb are caffeic acid esters, flavonoids, minerals, free amino acids, etc. [6]. Reputed benefit of nettle preparations in the treatment of OA complaints is supported by experimental findings that they suppressed activation of transcription factor NF-κB and inhibited IL-1β-stimulated production of MMP-1, MMP-3, and MMP-9 in human chondrocytes [28, 29]. Furthermore, oral intake of nettle leaf extract by healthy volunteers, during a three-week period, reduced production of pro-inflammatory cytokines (TNF-α, IL-1β) in whole blood *ex vivo* after LPS challenge [30].

Ash leaf (*Fraxini folium*) is by definition a dried leaf of *Fraxinus excelsior* L. or *Fraxinus angustifolia* Vahl (syn. *Fraxinus oxyphylla* M. Bieb), or of hybrids of these two species or of a mixture [4]. It is employed in ethnomedicine as herbal tea (infusion or decoction) to reduce minor articular pain [31]. Constituents occurring in ash leaf are coumarins, iridoids, secoiridoids, flavonoids, lignans, simple phenolic compounds, etc. [32]. Evidence from pharmacological studies that could explain recorded traditional use is scarce. Certain support was provided by experimental observation that esculin, a coumarin present in both species, decreased NO production in macrophages by inhibition of transcription factor NF-κB activation. Additionally, esculin was able to suppress inflammatory response (reduce levels of TNF-α and IL-6) induced by injecting LPS to mice [33].

Mixture of avocado and soybean unsaponifiables. Antiosteoarthritic properties of a mixture of avocado and soybean unsaponifiables (ASU) were extensively examined in the past. Phytochemical analysis of its composition revealed the presence of phytosterols (β-sitosterol, campesterol, and stigmasterol), fat-soluble vitamins, triterpene alcohols, and possibly furan fatty acids. Experimental studies provided significant evidence of ASU anabolic and anticatabolic action in cartilage. ASU stimulated the synthesis of extracellular matrix components (collagen and aggrecan) and inhibited production of pro-inflammatory molecules (TNF-α, IL-1β, IL-6, IL-8, MIP-1β, NO, and PGE_2) probably by interfering with signaling of transcription factor NF-κB. Cartilage degradation may be decreased as a result of ASU ability to inhibit matrix metalloproteinases (MMP-2, MMP-3, and MMP-13) and stimulate expression of tissue inhibitor of metalloproteinases-1. Beneficial activity may also be related to the capacity of ASU to affect levels of transforming growth factor-β and vascular endothelial growth factor [34]. Four randomized controlled clinical studies recruiting 651 participants provided moderate-quality evidence that ASU proprietary product Piascledine® (mixture of unsaponifiable fractions of fatty oils of *Persea gratissima* (P) and *Glycine max* (G), 1/3 P + 2/3 G; daily dose 300 mg) generated small improvement in osteoarthritic symptoms with questionable clinical significance, after a treatment lasting 3–12 months. Adverse events of herbal intervention were not probably increased compared to the placebo group. Moderate-quality evidence showed that Piascledine® in higher daily dose (600 mg) also reduced OA symptoms. Available data did not support assumption

that it significantly improved joint structure. There is limited evidence that it prevented joint space narrowing [10].

Indian frankincense (*Olibanum indicum*) is an air-dried gum-resin exudate, obtained by incision of the stem or branches of *Boswellia serrata* Roxb. ex Colebr. [4], which is used in the treatment of OA [35]. To assure optimal absorption, it is recommended to use Indian frankincense preparations with food. Cases of neutropenia were documented after long-term use of dry extract in a daily dose of up to 10 g. It contains pentacyclic triterpenic acids, i.e., β-boswellic acid (BA), 11-keto-β-boswellic acid (KBA), and acetyl-11-keto-β-boswellic acid (AKBA) [35]. These secondary metabolites could be responsible for the therapeutic activity, particularly BA that reaches relatively high concentration in the human plasma. BA, KBA, and AKBA acted as inhibitors of mPGES-1 and, hence, PGE_2 synthesis. They reduced the activity of cathepsin G [36], a serine protease whose relevance in OA has been suggested in a recent study [37]. The suppressing effect of AKBA on production of TNF-α in monocytes was also reported [36]. Crude *Boswellia serrata* extract downregulated inflammatory cytokines (TNF-α, IL-1β, and IL-6) in peripheral blood mononuclear cells [38]. Results of investigations using animal models of inflammation and arthritis (e.g., adjuvant arthritis in Lewis rats, formaldehyde-induced arthritis in rats, dextran-induced edema in rats, and carrageenan-induced edema in rats and mice) are in accordance with the *in vitro* observed anti-inflammatory activity [36]. Two randomized placebo-controlled clinical trials conducted with Indian frankincense proprietary product 5-Loxin® (standardized to contain at least 30% AKBA) indicated that oral application of this enriched extract in a daily dose of 100 mg decreased pain and improved function in OA patients (n = 85) after 90 days treatment. The results of studies examining proprietary product Aflapin® (enriched with non-volatile oil and standardized to contain at least 20% AKBA) are consistent. New studies may change the estimations [10]. Concentration of MMP-3 in synovial fluid of patients using 5-Loxin® decreased, suggesting that therapeutic activity could be linked to the attenuation of cartilage destruction [39].

Pycnogenol® is standardized bark extract of French maritime pine (*Pinus pinaster* Aiton) rich in polyphenolic compounds (procyanidins, taxifolin, catechin, and phenolic acids) [40]. Pharmacokinetic studies demonstrated that certain anti-inflammatory constituents of Pycnogenol® (ferulic acid and caffeic acid) and procyanidins gut microbiota metabolite δ-(3,4-dihydroxy-phenyl)-γ-valerolactone were able to reach synovial fluid [40, 41]. δ-(3,4-Dihydroxy-phenyl)-γ-valerolactone concentration-dependently reduced nitrite production and iNOS expression. Its affinity to accumulate in macrophages, monocytes, and endothelial cells were demonstrated [42]. Investigation conducted in patients with severe OA showed that expression of matrix metalloproteinases (MMP-3 and MMP-13) and IL-1β in chondrocytes was decreased after intake of Pycnogenol®, as well as level of ADAMTS-5 in serum [43]. Plasma obtained from volunteers taking Pycnogenol® orally for 5 days decreased activation of transcription factor NF-κB in macrophages and inhibited COX-1 and COX-2 [44, 45]. Additionally, gene expression of COX-2 and 5-LOX, leukotriene biosynthesis, and phospholipase A_2 activity in polymorphonuclear leukocytes (isolated from the blood of volunteers) were reduced [46]. Moderate-quality evidence obtained from three randomized controlled clinical trials indicated that Pycnogenol® (daily doses 100 or 150 mg) decreased pain and improved physical function in patients with OA of knee and that it probably reduced consumption of NSAIDs. The effect size after three-month treatment was estimated to be large and clinically important. However, quality of evidence is insufficient to make any firm conclusion. It should be noted that the content of marker compound (procyanidins) differed in the investigated products [3, 10].

Rosehip (*Rosae pseudofructus cum fructibus*) is obtained from *Rosa canina* L. It represents pseudofruit, composed of achenes enclosed in a fleshy receptacle or hypanthium. Phytochemical investigations revealed that rosehip contains sugars, organic acids, pectins, procyanidins, catechins, flavonoids, carotenoids, triterpene acids, unsaturated fatty acids, and a galactolipid [7, 35]. *R. canina* hip preparations inhibited activation of transcription factor NF-κB, decreased expression of matrix metalloproteinases (MMP-1, MMP-3, MMP-9, and MMP-13) in chondrocytes, suppressed expression of COX-2 in human monocytes and chondrocytes, decreased generation of PGE_2 and NO in murine macrophages, and reduced levels of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) and chemokine CCL5 in various assays. Dried powder of *R. canina* hips given to animals during 3 weeks exerted activity in rat arthritis model (monoiodoacetate-induced) and suppressed production of MMP-3 and MMP-13. Rosehip preparations also displayed activity in animal models of acute inflammation [47]. Active constituents belong to different groups of compounds; e.g., galactolipid was able to modulate chemokines (CCL5 and IL-8), matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) and aggrecanase ADAMTS-4 expression, whereas fatty acids (linoleic and linolenic) inhibited cyclooxygenases [47, 48]. It seems that reputed antirheumatic effect of rosehip is a sum of actions of several individual constituents. Data obtained from three clinical trials examining effects of rosehip powder provided modest and somewhat conflicting evidence that orally administered product (daily dose 5 g) is superior to placebo in the treatment of osteoarthritic pain [10].

Turmeric rhizome (*Curcumae longae rhizoma*) consists of whole, peeled, shortly boiled or steamed and dried rhizome of *Curcuma longa* L. (syn. *C. domestica* Valeton) [4]. Characteristic constituents are curcuminoids (phenolic diarylheptanoids), essential oil rich in turmerones (sesquiterpene ketones), and polysaccharides. It is popular in Ayurveda and Chinese medicine as an anti-inflammatory agent [7]. Curcumin *in vitro* prevented the apoptosis of chondrocytes and decreased the production of matrix metalloproteinases and monocyte chemoattractant protein. It also suppressed expression of pro-inflammatory cytokines, cyclooxygenase, and PGE_2 in chondrocytes. These effects were probably mediated by inhibition of IkB phosphorylation and thus transcription factor NF-κB activation. Regulation of AP-1 and protein kinase C was described as well. *In vivo* curcumin suppressed carrageenan-induced edema and formaldehyde-induced arthritis [49, 50]. Meta-analyses of randomized controlled trials indicated that curcumin was able to decrease circulating levels of pro-inflammatory cytokines TNF-α and IL-6 [51, 52]. Curcuminoids and *Curcuma longa* extract decreased oxidative stress in patients with OA, which suggested that antioxidant activity participated in turmeric beneficial action [53, 54]. A four-week multicenter randomized double-blind controlled clinical study showed that ethanol extract of turmeric rhizome (daily dose 1500 mg, 75–85% curcuminoids) was not inferior compared to ibuprofen (daily dose 1200 mg) in the management of knee OA. The number of side effects was similar in both groups, but incidence of gastrointestinal side effects was significantly higher in patients treated with ibuprofen [55]. Authors of a systematic review and meta-analysis concluded that a short-term treatment with curcumin and extract of *Curcuma longa* produced significant and clinically meaningful reduction of pain and improvement of physical function in patients with OA of knee. The quality of evidence was estimated to be very low to moderate. Characteristics of available studies limit possibility to make firm conclusion on the efficacy of turmeric rhizome preparations [3].

Ginger (*Zingiberis rhizoma*) is dried, whole or cut rhizome of *Zingiber officinale* Roscoe, with the cork removed, either completely or from wide, flat surfaces only [4]. It is characterized by the presence of essential oil and a mixture of pungent

tasting phenolic compounds (gingerols, gingerdiols, gingerdiones, dihydrogingerdiones, and shogaols) [7]. In a recent *in vitro* study, it has been shown that ginger extract was able to attenuate oxidative stress and reduce succeeding cell death of chondrocytes resulting from a mitochondrial apoptosis [56]. Ginger preparations also inhibited LPS-induced PGE_2 formation in U937 cells and decreased levels of TNF-α and IL-1β in murine peritoneal macrophages [57]. *In vivo*, they suppressed carrageenan- and fresh egg albumin-induced edema in rats and exhibited analgesic action in models of chemically and thermally induced pain in mice [58, 59]. Ginger essential oil reduced acetic acid-induced writhing response in animals [57]. Intraperitoneally administered 6-gingerol exhibited analgesic and anti-inflammatory action, i.e., decreased formalin-induced licking time in late phase and suppressed carrageenan-induced edema and acetic acid-induced writing response [60]. *In vitro* assay showed considerable potential of 6-gingerol to inhibit prostaglandin biosynthesis [61]. Therapeutic effect of ginger in patients with OA was investigated in two randomized controlled cross-over clinical studies. In one trial, ibuprofen treatment was reported to be more effective than acetone extract of ginger root (DER 20:1, daily dose 510 mg) in terms of pain reduction and consumption of NSAIDs. Available data did not allow reanalysis. Another trial showed that CO_2 extract of ginger root (daily dose: 1000 mg of extract, 40 mg of gingerol) significantly differed from placebo after a six-month study [10]. Although clinical trials investigating ginger were performed, its clinical benefit at this moment cannot be assessed with confidence.

Cat's claw (*Uncaria tomentosa* and *U. guianensis*), South American vines that share the same common name, are used traditionally to treat inflammatory conditions (e.g., arthritis) [62]. Active constituents of these medicinal plants are considered to be oxindole alkaloids (isorhynchophylline, rhynchophylline and their N-oxides, mitraphylline) and the quinovic acid glycosides [63]. According to the monograph of the World Health Organization, cat's claw bark (*Uncariae cortex*) consists of the dried stem bark of *Uncaria tomentosa* (Willd.) DC. (Rubiaceae) [64]. *In vitro* studies in murine macrophages showed that *U. tomentosa* and *U. guianensis* preparations suppressed TNF-α and PGE_2 formation [62] and that aqueous bark extract of *U. tomentosa* inhibited activation of transcription factor NF-κB [65]. The observed anti-inflammatory activity was further supported by *in vivo* experiments. *U. tomentosa* bark extracts (spray-dried hydroalcoholic and aqueous freeze-dried) suppressed carrageenan-induced paw edema in mice [66]. Using *in vivo* model of acute inflammation, fractions of *U. tomentosa* bark extract yielded quinovic acid glycoside as one of pharmacologically active compounds [67]. Mitraphylline, pentacyclic oxindole alkaloid, decreased blood levels of pro-inflammatory cytokines (IL-1β and TNF-α) in the LPS-challenged mice [68]. Double-blind placebo-controlled study in 45 patients within 4 weeks compared pain-relieving property of freeze-dried aqueous extract of *U. guianensis* bark (daily dose 100 mg) to placebo. A significant decrease in activity-related OA knee pain occurred in a group receiving *U. guianensis* preparation in the first week of trial. On the other hand, *U. guianensis* preparation did not reduce the pain at rest or at night. Serious side effects were not observed [62]. Clinical data were insufficiently reported for reanalysis [10]. Preclinical studies suggested that *U. tomentosa* (especially pentacyclic chemotype) could exert immunostimulatory action; therefore, patients under risk of transplanted organ rejection should be advised not to use cat's claw products [63].

Bromelain is a mixture of proteolytic enzymes obtained from the fruit and stem of pineapple (*Ananas comosus* L.) and other species of Bromeliaceae family [7]. Experimental evidence suggests that bromelain anti-inflammatory properties may be mediated by its ability to decrease levels of bradykinin and PGE_2 and to modulate cell surface adhesion molecule implicated in arthritis. Investigations in animals

confirmed that bromelain acted as an analgesic agent [69]. Anti-osteoarthritic property of orally administered bromelain (daily dose 500 mg) was compared with therapeutic activity of diclofenac (daily dose 100 mg) in a randomized single-blind active-controlled pilot study in 40 patients with mild-to-moderate knee OA. After a four-week treatment, there was no difference in symptoms relief between bromelain-treated and diclofenac-treated groups [70]. Bromelain (800 mg/day) was also compared with placebo in a randomized double-blind three-month long pilot study that included patients with moderate-to-severe OA of knee. The authors suggested that bromelain was not efficacious as an adjunctive treatment, but, due to the trial limitations, proposed that new studies should be performed [71]. Recent systematic review of clinical trials, examining dietary supplements used in the management of OA, has shown that the short-term treatment with bromelain was not effective in alleviation of pain and function improvement. Evidence quality was low [3].

Purified purple passion fruit peel extract, obtained from South American climbing vine *Passiflora edulis*, contains considerable amounts of flavonoids and anthocyanins. Its therapeutic effects (daily dose 150 mg) in patients with OA of knee were examined in a randomized double-blind placebo-controlled short-term study. The observed reduction of pain and improvement of physical function were significant and clinically meaningful. The quality of provided evidence was moderate [3, 72].

3. Herbal medicinal products for topical use in the treatment of osteoarthritis

Capsicum (*Capsici fructus*) is a dried ripe fruit of *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small-fruited varieties of *Capsicum frutescens* L. [4]. With respect to its medicinal properties, the most important compounds are capsaicinoids (capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicins I and II, caprylic acid vanillylamide, etc.). Triglycerides, carotenoids, ascorbic acid, flavonoids, and a complex mixture of volatile compounds are also present [35]. Standardized products of capsicum (semisolid or liquid dosage forms, medicated plasters) are intended for the relief of muscle (e.g., low back pain) and osteoarthritic pain. They should be used continuously until relief of pain is achieved, but not longer than 3 weeks and with a subsequent, at least two-week break period. Its use is contraindicated in cases of broken skin, wounds, eczema, and hypersensitivity to herbal substance or capsaicinoids. The plasters and semisolid dosage forms are not intended for concomitant use with other products for external administration. Topical application of capsicum HMPs initially causes skin irritation that is manifested by erythema and warmth sensation. Next stage is characterized by prolonged (hours to weeks) desensitization to pain stimuli. Side effects include skin hypersensitivity and allergic reactions [35, 73]. Capsaicin acts as an agonist of vanilloid receptors on C-type nerve fibers and thus it leads to depletion of neuropeptide substance P and consequent antinociception [7]. Standardized product containing capsicum tincture (Capsica gel®, 0.0125% of capsaicin) was investigated in a cross-over, randomized, placebo-controlled trial recruiting 99 patients with the OA of knee, within 9 weeks. Gel (2 inches) was applied topically three times per day. The conducted study provided moderate-quality evidence that the product probably did not decrease pain and improve function. Adverse events were common and included skin irritation and burning sensation [74, 75]. Creams containing higher concentration of capsaicin (0.025–0.075%) are indicated in the treatment of OA symptoms [1].

Arnica flower (*Arnicae flos*) is, whole or partially broken, dried flower-head of *Arnica montana* L. [4]. This herbal drug is employed traditionally for relief of bruises, sprains, and localized muscular pain. Semisolid and liquid dosage forms based on arnica preparations (tinctures or ethanolic liquid extract) are applied cutaneously. The use of arnica HMPs is contraindicated in patients with known hypersensitivity to arnica and other plants belonging to Asteraceae family. They should not be applied on broken skin. Reported side effects include allergic skin reactions [76]. Main constituents of arnica flower-heads are pseudoguianolide-type sesquiterpene lactones helenalin and 11α,13-dihydrohelenalin [7]. Contribution of these secondary metabolites to the anti-inflammatory effect is likely as it was shown that helenalin and 11α,13-dihydrohelenalin had the ability to interfere with the activation of transcription factor NF-κB [77]. *In vitro* experiments conducted on the pig skin indicated that sesquiterpene lactones can penetrate into it, and thus further support this assumption [78, 79]. Better permeation through stratum corneum (the outermost layer of the skin) was achieved when sesquiterpene lactones were applied in the form of arnica tinctures than as pure compounds [78]. Arnica flower preparations at low concentration/s were able to reduce levels of pro-inflammatory cytokines (IL-1 and TNF-α) in human mononuclear cells and of mRNA of matrix metalloproteinases (MMP-1 and MMP-13) in human and bovine articular chondrocytes [80, 81]. Whole plant methanolic extract suppressed expression of iNOS and COX-2 in LPS-stimulated murine macrophages [82]. Presented literature data may help to rationalize the use of arnica in management of diseases with underlying inflammation. Moderate evidence from a single, double-blind randomized controlled clinical trial showed that topical application of arnica gel (A. Vogel Arnica Gel®, 50 g herbal tincture/100 g gel, extraction solvent 50% ethanol, and DER 1:20) three times per day probably decreased pain and improved function related to hand OA as ibuprofen gel (5%), with a similar number of adverse events [74, 83].

Rosemary leaf (*Rosmarini folium*) is whole, dried leaf of *Rosmarinus officinalis* L. [4]. Its chemistry is characterized by the presence of essential oil, phenolic diterpenes (e.g., carnosol, carnosolic acid, and rosmanol), hydroxycinnamic derivatives, flavonoids, and triterpenoids [6]. Rosemary leaf bath additive is applied as an adjuvant to relieve minor muscular and articular pain, exclusively based upon long-standing traditional use [84]. Several rosemary compounds exhibited anti-inflammatory action *in vitro*. Rosmarinic acid decreased levels of PGE_2 and NO in rat chondrocytes [85]. Phenolic diterpene carnosol decreased concentrations of PGE_2 and NO, and reduced gene expression of iNOS, IL-1α, IL-6, and CCL5 in LPS-stimulated macrophages. In addition, it interfered with transcription factor NF-κB activation and influenced expression of anabolic and catabolic genes in chondrosarcoma cell line SW1353 and in primary human chondrocytes [86].

Comfrey root (*Symphyti radix*) is obtained from *Symphytum officinale* L., a traditional medicinal plant that can be found throughout Europe, parts of Asia, and as a naturalized plant in North America. It contains allantoin, mucilage polysaccharides, phenolic acids (e.g., rosmarinic acid), glycopeptides, amino acids, triterpene saponins, and pyrrolizidine alkaloids with 1,2-unsaturated necine ring structures. Identity of active principles is not sufficiently known although it is assumed that allantoin and rosmarinic acid play an important role in biological activity [87]. Taking into account considerable hepatotoxic and carcinogenic potential of pyrrolizidine alkaloids, their content in comfrey products has to be specified, as daily exposure has to be below 0.35 μg [88]. Anti-inflammatory action of comfrey preparations was demonstrated in preclinical studies when they dose-dependently inhibited complement activation and suppressed carrageenan-induced rat paw edema [87]. Moderate evidence from a double-blind, randomized, bicenter,

placebo-controlled trial with 220 participants indicated that comfrey root gel Kytta-Salbe® f probably reduced pain related to knee OA after 3 weeks of external application (6 g daily, 3 × 2 g) [74, 89]. Investigated proprietary product contained 35% of liquid extract (DER 1:2, ethanol 60% V/V, allantoin 0.2–0.5%) and <0.35 ppm of pyrrolizidine alkaloids [89].

Essential oils such as juniper oil, *Juniperi aetheroleum*; rosemary oil, *Rosmarini aetheroleum*; eucalyptus oil, *Eucalypti aetheroleum*; peppermint oil, *Menthae piperitae aetheroleum*; sweet birch oil, *Betulae lentae aetheroleum;* and wintergreen oil, *Gaultheriae aetheroleum* are employed for external treatment of articular pain and rheumatism. They are used in the form of bath additives and semisolid and liquid dosage forms. When applied to skin, essential oils act as irritants, which cause local increase of blood flow, reddening of the skin, and sensation of warmth thus antagonizing pain. Juniper oil must be avoided in the case of severe renal diseases [6, 7, 90, 91].

4. Conclusion

Osteoarthritis (OA) is a slowly developing degeneration disease affecting joint cartilage and adjacent tissues. It is one of the most prevalent diseases and most common causes of disability in the elderly, associated with worsening symptoms of joint pain, stiffness, and limitation of articular movement. Therefore, it imposes a significant functional and economic burden not only on affected patients but also on health-care systems.

Contemporary therapy protocols involve an array of non-pharmacological, pharmacological, and surgical measures. Although non-pharmacological treatments represent a basis for OA treatment, pharmacotherapy is considered to be an important adjunct. Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently a cornerstone in OA pharmacotherapy. None of the therapeutic options are curative, but the aim of treatment is to relieve the pain, improve quality of life, and reduce the loss of physical functionality.

NSAIDs often have serious adverse effects, with gastrointestinal complications as the most frequently reported. Some patients do not respond well to conventional medical therapy. Facing unsatisfactory efficacy and adverse effects of conventional therapy, they try to overcome current treatment deficiencies by using herbal medicinal products.

Preclinical studies showed that a number of herbal extracts and respective constituents exhibited pharmacological properties that could be relevant for their beneficial effect in OA. They interfered with cytokine (IL-1β, TNF-α, and IL-6), PGE_2, and NO production, modulated biosynthesis and activity of collagenases and aggrecanases, stimulated formation of extracellular matrix, and inhibited activation of transcription factor NF-κB. Active constituents are not often defined satisfactorily, but it could be said that they belong to various groups of secondary metabolites such as sesquiterpene lactones, triterpenic acids, galactolipids, diarylheptanoids, iridoid glycosides, phenolic glycosides, procyanidins, and alkaloids. Trials in humans support observations from *in vitro* and animal studies.

Unfortunately, this area is still far under-researched and needs further and better attention. Existing studies were frequently based on flawed research design, unclear and incomplete selection criteria, inadequate definition of the herbal interventions, or post hoc manipulation of data to support the authors' preferred conclusions [10]. The same authors urge on high quality and adequately powered clinical studies, advising future researchers that particular attention should be given to the detail of study design, which would ensure that participant samples are well

defined according to American College of Rheumatology (ACR) criteria and that participants are recruited without bias [10]. Furthermore, herbal preparations should be reported in detail, including dose, extraction method, and chemical characterization of active principle(s). Finally, study results should be recorded using reliable, valid outcome measures that combine pain and functional impairments in the identification of treatment response (as proposed by OMERACT-OARSI initiative) for comparing the efficacy of different medicinal plant products [10].

Herbal medicines that have been shown to be effective in the treatment of pain associated with OA could help lowering or ceasing the consumption of NSAIDs, reducing at the same time the incidence and severity of their adverse effects. This would also produce necessary long-term safety data, which are needed for most of the herbal medicinal products.

Currently available data are insufficient to acknowledge their use in OA treatment as clinically proven (i.e., with demonstrated efficacy and safety). However, it could be stated that the body of evidence is growing and that expectations on arrival of reliable, efficient, and safe herbal products, fulfilling the criteria of modern medicine in the near future, seem reasonable.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 5

Cardiovascular and Functional Capacity of Patients with Knee Osteoarthritis

Zuhal Kunduracilar and Kartal Selici

Abstract

Patients suffer from pain and disability and have associated reductions in muscle and cardiopulmonary function. Patients with knee and hip OA have a 15–20% decrease in aerobic capacity. The reduced aerobic capacity of patients with lower limb osteoarthritis affects their independence in performing everyday activities. More research is needed to determine the optimal types and dosing of aerobic conditioning with osteoarthritis. Persons at risk for osteoarthritis have one or more of the following risk factors: age over 50, female gender, a first-order family member with OA, previous history of a major knee or hip injury or surgery, obesity, history of joint trauma, or a job requiring bending and carrying. Hip osteoarthritis can also be secondary to developmental defects. Disability not only reduces the quality of life for individuals but also jeopardizes their ability to live independently; it increases the risk of hospitalization, institutionalization, and mortality and is a major driver of healthcare costs due to arthritis.

Keywords: osteoarthritis, cardiovascular disease, aerobic capacity, functıonal capacity

1. Introduction

Hypertension, diabetes mellitus, cardiovascular diseases, and osteoarthritis (OA) are the leading diseases of the most common disease clusters [1, 2]. Knee OA is a common health problem in the general population [3]. It is characterized by the abrasion of joint cartilage, changes in the extracellular matrix, subchondral bone ossification, and osteophyte formation [4]. The socioeconomic load of OA, which has a serious morbidity and disability rate, is very heavy. In the United States, 30.8 million patients with OA caused a medical expenditure of over 340 billion dollars between 2008 and 2011 [5]. The worldwide prevalence of symptomatic knee OA is increasing [6].

The most common localization of OA is the knee joint, and symptomatic knee OA affects 24% of the general population [7]. The fact that hypertension, diabetes, and cardiovascular diseases are found together with OA has led to the speculation of a metabolic "OA phenotype" [2]. It was hypothesized that obesity, dyslipidemia, impaired fasting blood sugar, and hypertension contribute to the incidence and progression of OA, which, in turn, led to another hypothesis that OA is an independent metabolic risk factor for cardiovascular diseases [8, 9]. A series of cross-sectional

studies showed a positive relationship between OA and cardiovascular diseases and metabolic syndrome [2, 10, 11].

In 2017, Kendzerska et al. in a study comprising 18,490 patients with 10.0% hip OA, 15.3% knee OA, and 16.3% hand OA found that 31.9% cardiovascular events occurred in approximately 13.4 years in these patients, especially in the knee OA group. They also mentioned that the walking difficulty in knee OA severely increased the risk of a cardiovascular event.

Many cardiovascular events could be prevented by managing OA, with an increase in the cardiovascular capacity and mobility [12]. A low socioeconomic level has been reported to be directly related to the incidence of age and obesity [13, 14]. A low income level, educational status, prolongation of life, and obesity were the important factors in the increase of OA in Brazil [15]. De Rezende et al. in their study comprising 198 patients with OA imparted a training to 150 of them. The physical activity level before the training was mild in 11 participants, moderate in 12 participants, and high in 2 participants, and after the training, it was mild in 74 participants, moderate in 40 participants, and high in 9 participants [15].

2. Motivators and obstacles of physical activity in patients with knee OA

Physical activity is especially accepted as a treatment method for patients with cardiovascular, vascular, and metabolic diseases. The World Health Organization recommends daily recreational or leisure activities, transportation, profession, household chores, games, sports, and planned exercises in the context of family and community activities [16]. Patients with OA typically have lower levels of physical activity compared with the general population [17].

In 2017, Kanavaki et al. conducted a systematic review of qualitative evidence on the inhibitors and facilitators of physical activity in knee and hip OA. A total of 5449 studies were identified; of these, 2657 abstracts were screened and 51 full texts were evaluated. Seven authors were contacted for more information. Ten studies with qualitative metadata that included 173 middle-aged patients were reviewed. The selected studies were found to be of moderate and high quality. The results suggested that half of the studies did not have a clear data analysis or were not well defined and only a few provided the desired characteristics. In the present study, the inhibitors and facilitators were examined under three conceptual headlines: physical health, interpersonal and psychological factors, and socioenvironmental factors. Facilitators in physical health included mobility, getting rid of symptoms, and health. Facilitators in interpersonal and psychological factors included beneficial exercise, information about exercise, maintaining motivation despite OA, organizations, prioritization, personal effort, responsibility, and the will to be physically more active. Facilitators in social environment included support from health professionals and social support to make the physical activity easier. Inhibitors in physical health included pain and other symptoms and perceived functional limitations. Inhibitors in interpersonal and psychological factors included non-effective physical activity, harmful or suspicious activity, loss of motivation, and loss of behavioral regulation. Inhibitors in social environment included lack of advice and encouragement from health workers, social comparison as demotivation, and lack of social support [18].

In 2017, Gay et al. conducted a qualitative study on the motivation and inhibitors for physical activity in patients with knee OA. A total of 27 patients with a mean age of 67 years were included in the study, of which 17 were women. The physical motivators for physical activity included well-being, reduced pain, and self-perception;

personal activity included life style and psychological well-being; social activity included relationships and opinions of friend circles; and for environmental activity included living conditions. The motivators were found to differ according to gender. Inhibitors for physical activity were as follows: psychological—fear of pain and lack of motivation and physical—knee pain and asthenia. Moreover, life events such as potential depression and hospitalization were also identified as inhibitors for physical activity [19].

Nociceptive and neuropathic pain accompanying the disease leads to disorders in mood and sleep, which, in turn, lead to a decrease in the quality of life [20]. In 2017, Aşkın et al. conducted a study comprising 60 patients with knee OA with neuropathic pain and found that 66.7% had significantly reduced functional capacities and quality of life as a result of the clinical evaluation carried out with the chair stand test. Although inhibitors and facilitators increase the effectiveness of treatment in the development of cardiovascular and functional capacity within OA management, they also help decrease the symptoms in a shorter period of time, contribute to the quality of life, and thus facilitate the decrease of morbidity-induced deaths [21].

3. Comorbid diseases in OA

In a recent meta-analytic study by Hall et al., 40% of patients with OA were found to have cardiovascular diseases and 10–14% of those who had diabetes mellitus together with OA also suffered from obesity and metabolic syndrome [22, 23]. Calders et al. performed a systematic review and meta-analysis in which 17 studies were examined. In this study, worsening OA-related pain was associated with comorbid disease. Studies also found that heart disease, hypertension, and diabetes mellitus associated with OA led to a further deterioration in physical functioning [24].

Chronic inflammation is a global major health problem that affects tens of millions of people in North America and Europe [25, 26]. The long-term use of nonsteroidal anti-inflammatory drugs in OA increased the blood pressure and even leads to heart attack, stroke, heart failure, arrhythmias, and sudden cardiac death. The presence of these diseases accompanied by OA increased the danger even more [27]. Among joint-related diseases, patients with osteoarthritis (OA) are the most prone to develop hypertension. This situation constitutes a risk factor for cardiovascular and cerebrovascular diseases [28]. Patients with OA have an increased risk of experiencing a stroke because of a decrease in the mobility [29]. With increasing elderly population, obesity and decreased physical activity have increased the incidence and prevalence of OA, which, on the other hand, have accelerated vascular comorbidity [30]. Along with vascular diseases, the overlap of OA prevalence has also raised the question of possible common mechanisms and the development of preventive and therapeutic strategies for this situation [31].

The chronic or intermittent increase in systemic inflammation suggests a connection between OA and vascular diseases. OA is a noninflammatory systemic chronic disease. Systemic inflammatory mechanisms in OA are still being discussed [8, 31, 32]. For example, chronic and low-grade inflammation occurs with age, and OA is a disease that more often occurs with an advanced age. However, changes also occur in the blood immune system in these patients who were suggested to have a systemic change in the inflammatory process that is associated with OA independent of age [31, 33–35]. Among OA and cardiovascular diseases, there are inflammatory cytokines (e.g., interleukin-6) [36, 37], oxidative pathways [38, 39], and C-reactive protein containing [31, 40, 41] common inflammatory mediators.

Inflammation leads to vascular endothelial dysfunction in places with previous cardiovascular events. Impaired flow-mediated dilation responses in patients with OA in this group showed a weak vascular endothelial function. This situation might be a marker for peripheral vascular dysfunction [31, 42].

Osteoprotegerin (OPG), which is a systemic vascular mechanism, a key in the bone resorption modifier, and associated with vascular endothelia, is one of the precursors of early atherosclerosis. OPG plays a role in both bone remodeling and atherosclerosis. OPG serum levels were found to be high in patients with advanced OA. A high OPG level may lead to the progression of OA and dysfunctional vascular remodeling [31, 43]. Khazraji et al. emphasized in a compilation study, examining the relationship between OA and cerebrovascular disease, that the common relationship between cerebrovascular hemodynamics and cognitive functions in people with and without OA risk needs to be explored [31].

The decrease in aerobic capacity in the lower extremity OA negatively affects independence in daily life activities. Studies have shown that various aerobic exercises, such as walking, running, cycling, aquatic exercises, and aerobic dance, have a positive effect on pain, joint stiffness, functional capacity, and aerobic capacity in patients with hip and knee OA [44]. Studies have stated that walking in patients with OA can improve aerobic capacity and physical activity without increasing the stress in the joints and can be used safely [45]. In 2011, Escalante et al. conducted a systematic review of the effect of exercises on functional aerobic capacity in patients with lower extremity OA. The study found that although aerobic exercise programs were recommended for patients with knee and hip OA, only a few randomized control studies were performed. They have stated that there was no consensus in terms of the content, duration, and frequency of the exercise programs, and the exercise programs including tai chi, aerobic, and mixed exercises had better results compared with hydrotherapy [45].

Although swimming is the ideal exercise for patients with OA, only a few studies have investigated the effect of regular swimming on vascular dysfunction and inflammation. Similar studies have shown that ground-based exercises have similar benefits. Alkatan et al. conducted a randomized controlled study with middle-aged patients with OA in 2016. One group was given supervised swimming and the other group cycling training for 12 weeks. After the training, central arterial stiffness determined by carotid femoral pulsation wave velocity decreased in both groups. Also, according to simultaneous ultrasonography and applanation tonometry, the carotid artery stiffness decreased. In the swimming group, the evaluation of the brachial flow-mediated dilation showed a development in vascular endothelial functions, but no change was observed in the cycling group [42].

4. Factors affecting cardiovascular function and functional capacity

Garza et al. conducted a study in the year 2017 with 33 patients aged more than 40. All the patients were diagnosed with OA. They have founded that decreased ischiotibial muscle flexibility reduced the functional capacity, also flexibility and functional capacity increased and pain decreased through exercise [46]. Obesity is considered to be one of the most important and potentially preventable risk factors for OA. Besides the mechanical load of obesity on OA, leptin, visfatin, adiponectin, and resistin were found to have metabolic effects on the pathogenesis and progression of adipokines and others. Obesity has an important role in the reduction of functional capacity in OA, as a result of the disability [47].

Difficulty in walking in people with hip and knee OA constitutes a great risk for all-cause mortality and cardiovascular events [48, 49]. In 2016, Hawker et al.

conducted a study using 1996 patients (with a mean age of 71.4 years) with hip and knee OA and found that 77.7% had hypertension, 54% had cardiovascular diseases, 42.9% had obesity, and 15.3% were smokers. The HAQ walking difficulty score in these patients was found to be two-third. This interval showed that these patients had medium-to-serious disabilities. Of these patients, 54.9% used a walking aid. An average of 6.1 years later, 184 people (51.3%) experienced one or more complications specific to diabetes; 5.7 years later, 191 patients experienced cardiovascular events [50].

5. Approaches to increase cardiovascular function and functional capacity

Besides facilitating weight loss in the management of knee OA [51, 52], exercise is strongly recommended because of its positive changes in symptoms and functional capacity [53, 54]. The aquatic environment allows an individual to exercise because it reduces the load on the joints. Recent studies compared ground-based exercises with aquatic exercises in terms of lower extremities of patients with OA and found that aquatic exercises statistically significantly reduced the pain [55]. Kunduracılar et al. investigated the effect of two different aquatic exercises on pain, functional and exercise capacity, and balance with a program that lasted for 4 weeks, 5 days a week, implemented on 89 patients diagnosed with OA. They applied ground-based exercises together with lower extremity aquatic exercises to one group and ground-based exercises together with upper and lower extremity exercises and body exercises to the other group. The control group was only given ground-based exercises. All three groups were positively affected in terms of pain, balance, and functional capacity. However, the second group, where both exercises were given, was found to have the best outcome in terms of increased functional and exercise capacity [56]. Bernad-Pineda et al. conducted a study comprising 1849 patients with knee (61.5%) and hip (19%) OA in 2014 and found that a decrease in quality of life also led to a decrease in functional capacity [57].

The studies showed that exercise played an important role in the management of OA-related symptoms and also contributed to the functional capacity in the everyday life activities of the patients. In 2017, Peeler et al. went on with the hypothesis that unsafe and ineffective exercise practices might exacerbate the symptoms in the joint. They used a new treadmill, without the risk of exacerbation during exercises, in patients with pathology in the lower extremities, within a low-load exercise training that allows lower body positive pressure (LBPP). The treadmill uses a waist-high air chamber filled with positive air pressure (i.e., LBPP) to accurately and reliably diminish body weight during exercise. The 12-week LBPP-supported treadmill program in this study comprising 31 patients increased the functional capacity of the patients and allowed them to freely carry out their daily activities. The study concluded that the 12-week LBPP-supported treadmill program was a safe exercise for patients with mild and medium OA without exacerbating the symptoms [58].

Another way to strengthen the muscles via exercise is the whole-body vibration (WBV). In recent years, WBV has been used frequently to improve muscle performance [59]. Many studies have documented that WBV is very effective in increasing the functional capacity and metabolism in age-related muscle atrophies [60, 61]. In this training, contrary to the other exercise programs, less pressure was put on the joint. Recent studies have shown that this technique was statistically more successful in reducing symptoms and regaining functions in patients with OA [62]. Bokaeian et al. in a study in 2016 applied strengthening training for the quadriceps and hamstring muscles to a group with knee OA (n = 139) and the

WBV technique along with the strengthening exercises to another group (n = 15) in three sessions per week for a total of 8 weeks. The results showed an increase in quadriceps muscle strength and functional activity [63]. In 2017, Waller et al. conducted a 4-month program of postmenopausal high-intensity aquatic resistance training, which included 87 postmenopausal patients with mild OA, to examine its effect on body composition and walking speed of the patients. After the study, the patients were followed up for 12 months. The findings revealed that the walking speed increased and the cardiovascular system developed; however, while the gains in the increased walking speed were maintained, the cardiovascular gains were lost in the 12-month follow-up [64].

6. Conclusion

In conclusion, the assessment of cardiovascular and functional capacity and the inclusion of training programs in the treatment of OA reduced the load of the disease. Besides, these programs could reduce the frequency of comorbid illnesses, hospital admissions, and deaths associated with OA. It could increase the quality of life of the patients and is believed to make positive changes on survival. However, further studies in this regard might be more beneficial, and OA grievances should be prioritized in health policies.

Conflict of interest

The authors declare no conflict of interest.

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Section 4

Bone Changes in OA

Chapter 6

Evaluating the Relation between Bone Marrow Lesions and Synovitis with Pain and Structural Damage in Hand Osteoarthritis

Nidhi Sofat and Soraya Koushesh

Abstract

Osteoarthritis (OA) is the most prevalent arthritis worldwide and is a condition affecting the whole joint. Changes in subchondral bone, cartilage integrity and synovitis are recognised during OA progression. Although advances have been made in our understanding of OA pathophysiology, there are no current treatments that delay or halt the progression of the disease. Treatments are largely based upon physical therapies to improve function, anti-inflammatory agents for pain symptoms and joint replacement surgery for late stage disease in large weight bearing joints. There is an urgent need to better understand the pathophysiology of OA that could translate into improved treatments for this condition. In recent years, more advanced imaging techniques including magnetic resonance imaging (MRI) have led to an improved understanding of changes at the bone-cartilage interface in OA, with recognition that loss of integrity at the cartilage-bone junction and development of bone marrow lesions (BMLs) in the subchondral bone are associated with OA pain in large epidemiological studies. In this book chapter, we review the evidence for the role of BMLs and synovitis, particularly in the pathophysiology of hand OA. Based on a systematic review of the literature, we have identified 15 articles reported on BMLs and synovitis in hand OA, which will be discussed in this chapter.

Keywords: hand osteoarthritis, bone marrow lesions, synovitis, joint space narrowing, osteophytes, pain

1. Introduction

Osteoarthritis (OA) is the most common debilitating arthritis worldwide, with a preponderance for affecting the knee, hip, hand, spine and feet. It is a leading cause of physical disability and pain in our ageing populations worldwide. The rising epidemic of obesity is also contributing to the increasing incidence of OA, with a greater impact on the quality of life of sufferers and healthcare costs in many systems worldwide [1].

In large epidemiological cohorts of OA, hand OA (HOA) in particular causes a significant disease burden. The Framingham Study reported hand OA to have a prevalence of 27.2% [2]. The same study reported that women were more likely to develop hand OA symptoms in comparison to men [3]. In a large European study of

7983 people, 25% of participants with hand pain showed significant hand disability, with 24.2% of subjects reporting OA of any joint and 28.3% subjects having a manual occupation [4]. Such studies demonstrate the significant symptom burden and functional impairment that hand OA places in human populations worldwide.

Pain and loss of function in OA are as a result of pathological changes in the entire joint structure. Specifically in hand OA, structural changes leading to pain and functional impairment include cartilage damage, subchondral bone sclerosis, subchondral cysts, synovitis, osteophyte formation, erosions and bone marrow lesions (BML) [5]. In the clinic, underlying joint damage can be observed clinically as joint deviation and deformity, swelling e.g. formation of distal interphalangeal (DIP) and proximal interphalangeal (PIP) joint swelling and loss of function [5]. In addition to DIP and PIP joint involvement in hand OA, the thumb first carpometacarpal (CMC) joint can also be involved, which functionally can cause severe functional impairment (**Figure 1**). Although mechanical factors with manual occupations are a major risk factor for hand OA, other factors including increasing age and obesity contribute significantly to disease burden [6].

Current therapies for hand OA include improving physical function and strengthening exercises [7], supportive aids including taping devices [8] and pain management [9]. Pain relieving agents currently include topical or oral therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics and capsaicin [10]. Intra-articular therapies include corticosteroids and hyaluronic acid in suitable cases [11]. Since there are currently no proven disease-modifying therapies for hand OA, there is a huge unmet need to better understand disease pathophysiology, which could lead to the development of improved therapies for hand OA.

Imaging studies in recent years have provided useful insights into the pathophysiology and progression of hand OA [12]. Historically, imaging of the hand in OA has favoured plain radiography (**Figure 1**), but more recently US and MRI have been used in clinical studies to evaluate radiographic changes in HOA. Modalities of imaging used have included plain radiography and magnetic resonance imaging (MRI). Plain radiography is consistently able to identify a number of structural

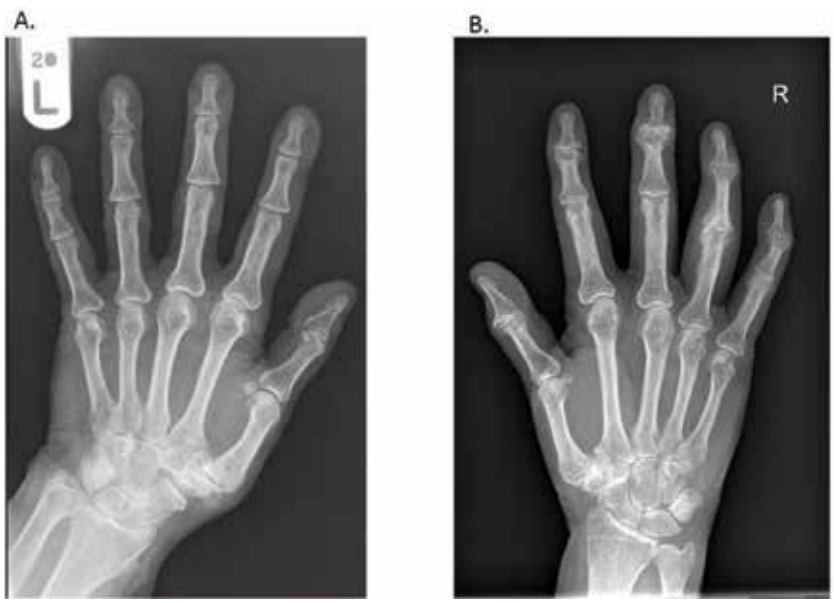

Figure 1.
Plain radiographic changes in hand osteoarthritis due to thumb first carpometacarpal joint involvement (A) and proximal and distal interphalangeal joint involvement (B).

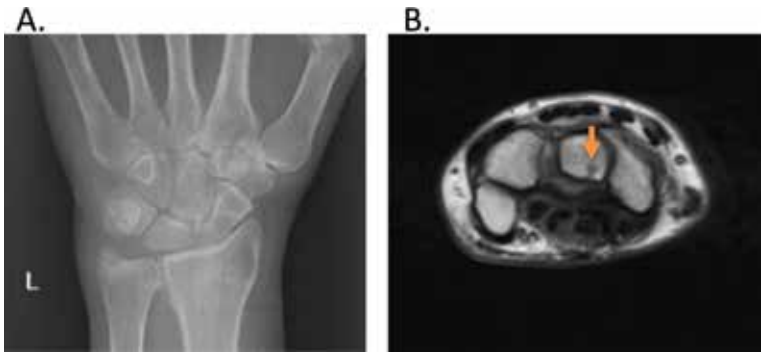

Figure 2.
Correlation of plain radiographic changes with MRI bone marrow oedema. (A) Wrist joint showing early joint space narrowing and sclerotic changes. (B) Bone marrow oedema in carpal bone on corresponding MRI scan of the wrist in the same patient (arrow).

changes such as joint space narrowing and osteophyte formation [13]. However, other joint tissue structures including synovitis and subchondral bone marrow lesions, which are linked to pain, may not be easily visualised by plain radiography.

Numerous cross-sectional studies have proposed radiographic features to be strongly associated with pain and functional impairment [14] which may be better visualised by MRI evaluation for hand OA [15]. MRI has now become widely accepted as a reliable imaging modality for identifying bone marrow lesions (BML) (see **Figure 2**) and synovitis in OA [16], with a large number of studies already conducted in knee OA [17]. With respect to the hand, fewer clinical and imaging correlative studies have been conducted. Studies conducted in the Oslo hand OA cohort has shown MRI features, including BML and synovitis, to be strongly associated with joint tenderness, making these potential targets for future treatments [18, 19].

Although several studies have now been published with respect to radiographic changes including BMLs, cartilage damage and synovitis associated with structural progression and pain in knee OA in particular, there is no systematic review reporting hand structural changes including MRI, synovitis and cartilage damage in hand OA. In this chapter we sought to summarise existing knowledge on studies evaluating BML, cartilage damage and synovitis in hand OA specifically, since these structural changes are associated with pain in hand OA. We aimed to investigate the most frequent imaging modalities reported in the published literature, which included plain radiography and MRI.

2. Search strategy for systematic review

A systematic literature search was conducted through the following electronic databases: Pubmed (from 1996), EMBASE via Ovid (from 1996), Medline via Ovid (from 1996) and Web of Science via Ovid (from 1970) to June 2018. The inclusion criteria for keyword searches were: bone marrow lesion(s) (BMLs), osteoarthritis (OA), imaging, synovitis, and pain. We included studies that observed the associations between BMLs, synovitis, osteophytes and the development of osteoarthritis pathophysiology under magnetic resonance imaging. Initially, it was agreed to conduct a systematic review comprising of all joints affected by osteoarthritis. After careful search, we found that no previous authors had summarised imaging studies on the progression of BMLs and/or synovitis in HOA by systematic review. We agreed to summarise all available literature in HOA relating clinical features to imaging findings to date by systematic review. For exclusion criteria,

the search strategy results were screened through the titles by two reviewers NS and SK. Studies were excluded if they were: reviews, letters to the editor, case reports, case series or studies which were not in the English language. All searches were restricted to human subjects. No limits were applied to the sex and age of the subjects. Both reviewers independently screened through the abstracts to exclude any irrelevant articles and eligible full articles were obtained to further analyse the criteria for review. Studies were eligible if they examined BMLs, synovitis and other structural changes using imaging techniques in participants with hand OA. Following the initial search, studies reporting data on hand OA only were included in the systematic review reported herein.

3. Results

3.1 Data extraction

The literature flow is depicted by using the Preferred reporting items for Systematic reviews and Meta-Analyses (PRISMA) diagram in **Figure 3**. Following database searches, 2831 articles were extracted for title screening. Following exclusion of duplicate studies and obvious exclusions, 2796 papers were removed and the remaining 35 studies were selected for abstract screening.

Of the 35 studies selected for screening, 19 did not meet the inclusion criteria (bone marrow lesion(s), osteoarthritis, imaging, synovitis, and pain). Full text articles were obtained for 15 studies and independently reviewed by the same two reviewers (NS and SK) for relevance and quality. Following full text review, one study was removed as it was the abstract of a full publication already included for review. A total of 15 studies were included in this systematic review. The data extracted from each study included: country of study, number of participants, structural changes, type of MRI scanner used and pain scores assessed. A summary of the studies and their demographics is shown in **Table 1**. The structural changes described by each study is summarised in **Table 2**.

3.2 Study characteristics

The mean age for all studies was 64.4 [18–32]. Most studies (n = 13) were performed on both genders, although the majority of the subjects in each study were female. Only two studies [26, 32] had female subjects only and one study did not report the gender of the participants [25]. Of these studies, 13 were from observational cohort studies: the Hand OSTeoarthritis in secondary care (HOSTAS) [27, 29–31] the Oslo hand OA cohort [18–23, 25, 32] and a clinical trial: the digital osteoarthritis in refractory hand OA (DORA) study [28]. All articles examined BMLs and various subchondral features using MRI. The strength of the magnetic field was 1.5 T in four studies [27, 29, 26, 30]. Eight studies used a 1.0 T system [18–23, 25, 32] whereas one study [28] used the 0.2 T system in two patients only. Only one study used a 3.0 T system [24] while one study did not report the MRI system used [31].

3.3 Data from cohort observational studies

In the HOSTAS study, 87 subjects with primary hand OA were included, of which 82% were women [27]. All participants had radiographic measures and MRI scans conducted, with Kellgren-Lawrence grading (KL) (0–4) and OARSI grading methods [osteophytes 0–3, joint space narrowing (JSN)] for radiographic severity collected. Radiographic progression over the 2-year period was considered as

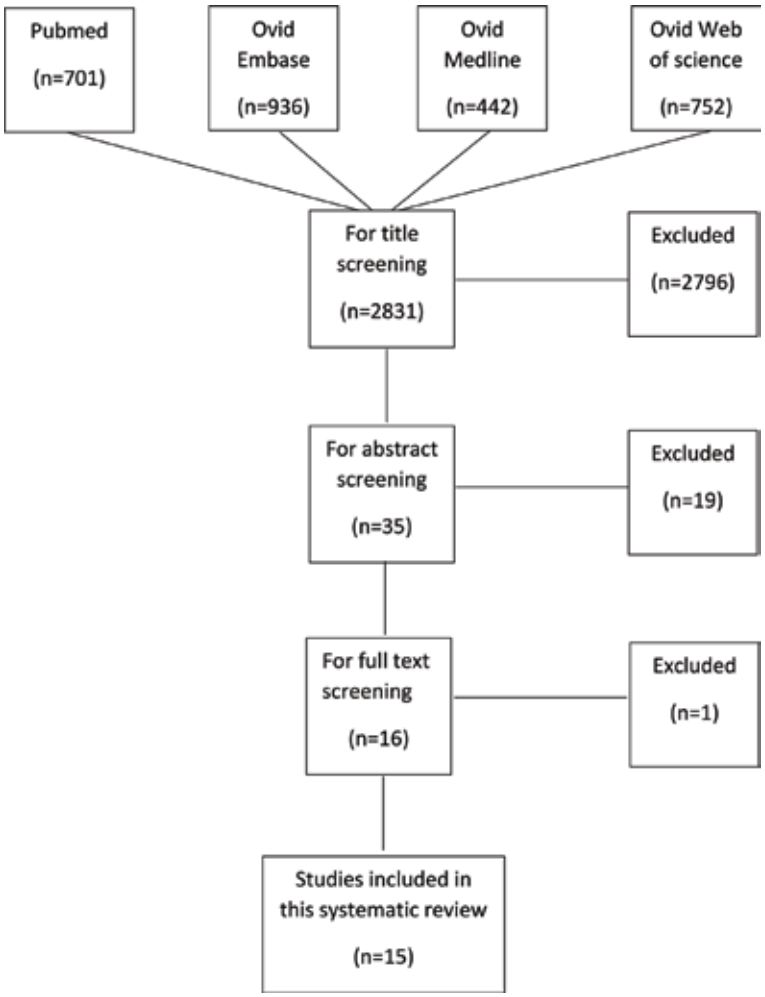

Figure 3.
PRISMA flow diagram for systematic review.

an increase in score of ≥1. Associations between MR features and radiographic progression were explored after adjusting for age, sex, body mass index (BMI), synovitis and BML. The group analysed 696 joints in their study, to find that BMLs and synovitis were both associated with radiographic progression by plain radiography and MRI. In comparing plain radiographic versus MRI changes, BMLs grade 2/3 were associated with KL progression, while BML grade 1 was not. Synovitis also showed graded associations with KL radiographic progression.

A number of studies have been reported by the Oslo Hand OA cohort, which was initially established in 2001. This cohort underwent extensive evaluation from 2001 to 2003, with further follow-up from 2008 to 2009. A number of observations of pain and functional characteristics in relation to imaging scores have been reported in this cohort. In their first report, Haugen et al. [18] reported the associations between MRI features and measures of pain and physical function in hand OA. Eighty-five participants (77 women) with mean age 68.8 (5.6) years underwent contrast-enhanced MRI of the interphalangeal joints (dominant hand) and clinical joint assessment. One investigator read the MRIs for presence/severity of changes including osteophytes, joint space narrowing, erosions and BMLs. A reliable scoring system previously developed by the authors was used to assess changes [20].

Publication	Number of participants and mean age	Country	Clinical outcome measures	Imaging modalities measured
Haugen et al. [18]	85 (91% women) Mean age = 68.8	Norway (Oslo HOA)	AUSCAN FIHOA AIMS-2 Grip strength	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [19]	70 (90% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [20]	10 (90% women) Mean age = 69.5	Norway (Oslo HOA)	Not applicable	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [21]	106 (92% women) Mean age = 68.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [22]	70 (90% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN Grip strength	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [23]	74 (91% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Kortekaas et al. [24]	16 [13 with erosive hand] (62% women) Mean age = 57.0	Norway	Pain assessed during physical examination	Plain radiograph 3.0 T MRI Ultrasound
Haugen et al. [25]	20 (95% women) Mean age = 65.8	Norway (Oslo HOA)	AUSCAN	Plain radiograph 1.0 T MRI
Ramonda et al. [26]	11 (100% women) Mean age = 59.0	Italy	AUSCAN VAS Dreiser FIHOA	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Damman et al. [27]	87 (82% women) Mean age = 59.0	The Netherlands (HOSTAS)	Not applicable	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Roux et al. [28]	18 (77.8% women) Mean age = 64.4	France (DORA)	VAS Dreiser FIHOA	Plain radiograph Kellgren-Lawrence Scoring 0.2 T MRI (2 patients)
Liu et al. [29]	105(83% women) Mean age = 59.4	The Netherlands (HOSTAS)	AUSCAN VAS SF-36 MHQ	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Kroon et al. [30]	289 (83% women) total - 202 (84% women) = MRI subjects −87 = Ultrasound subjects (excluded from review) Mean age = 60.1	The Netherlands (HOSTAS) (LUMC)	AUSCAN VAS	Plain radiograph MRI 1.5 T Ultrasound

Publication	Number of participants and mean age	Country	Clinical outcome measures	Imaging modalities measured
Kroon et al. [31]	524 (86% women) Mean age = 61.9%	The Netherlands (HOSTAS)	AUSCAN VAS SF-36 HADS	Plain radiograph Kellgren-Lawrence Scoring MRI system not reported
Wolski et al. [32]	21 (100% women) Mean age = 69.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI

Table 1.
Publications included in systematic review by clinical outcome and imaging measures.

Publication	Structural changes
Haugen et al. [18]	BML, synovitis, flexor tenosynovitis, osteophytes, erosions, attrition, malalignment
Haugen et al. [19]	BML, synovitis
Haugen et al. [20]	BML, synovitis, flexor tenosynovitis, osteophytes, jsn, erosions, malalignment, cysts, collateral ligament
Haugen et al. [21]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, malalignment, cysts, erosion, attrition
Haugen et al. [22]	BML, synovitis, erosion, central erosion
Haugen et al. [23]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, malalignment, cysts, erosion, attrition, collateral ligament
Kortekaas et al. [24]	BML, synovitis, osteophytes, JSN, erosion
Haugen et al. [25]	BML, synovitis, erosion, cysts, osteophytes, cartilage space loss, malalignment
Ramonda et al. [26]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, cyst, malalignment, erosion
Damman et al. [27]	BML, synovitis, flexor tenosynovitis, osteophytes, joint space narrowing (JSN), cysts
Roux et al. [28]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, cyst, malalignment, erosion
Liu et al. [29]	BML, synovitis, flexor tenosynovitis, cyst
Kroon et al. [30]	BML, synovitis, osteophytes, JSN, effusion
Kroon et al. [31]	BML, synovitis
Wolski et al. [32]	BML, synovitis, osteophytes, JSN, cyst, malalignment, attrition, erosion, sclerosis

Table 2.
Structural changes in hand osteoarthritis publications reviewed.

A number of questionnaires and clinical examination of the hands were used to assess pain and physical function. Joints were palpated by a rheumatologist to assess the presence of tenderness. To evaluate pain and function in the hands, patients completed self-administered questionnaires including the Australian/Canadian (AUSCAN) hand index, functional index of hand osteoarthritis (FIHOA) and the Arthritis Impact Measurement Scale 2 (AIMS-2). In addition, grip strength was screened for by the use of a hand dynamometer. Linear regression analysis adjusted for age and sex was used to examine the association between MRI abnormalities,

pain questionnaires and grip strength. Logistic regression was used to further validate linear regression analysis by evaluating associations between MRI features and tenderness of the joints. All features were associated with tenderness of the joints, attrition, osteophytes, synovitis and erosions in the PIP and DIP joints respectively. In the multivariate model, BML and synovitis showed a significant association with joint tenderness (both after adjustment for age, sex and radiographic severity) independently of each other. The MRI summed scores were not significantly associated with AUSCAN pain/physical function and the AIMS-2 hand/finger subscales. Conversely, MRI summed scores for osteophytes and attrition were the only MRI-defined features that were associated with grip strength ($B = -0.39$; $p < 0.001$) and FIHOA ($B = 0.58$; $P = 0.005$), respectively.

Studies from the same group have aimed to validate scoring systems for MRI-assessed changes in the hand [20] and demonstrated that MRI-detected changes, including synovitis, BMLs and joint space narrowing are predictors of radiographic progression in hand OA [22]. More recently, the same group have reported that MRI-defined synovitis and BMLs are related to changes in joint tenderness in a 5-year longitudinal study of the Oslo hand osteoarthritis (OA) cohort [19]. A total of 70 participants (63 women, mean (SD) age 67.9 (5.5) years) were included. The investigators evaluated BMLs and contrast-enhanced synovitis in the distal and proximal interphalangeal joints on 0–3 scales in n = 69 and 48 patients respectively. The goal was to investigate tenderness of each joint and MRI features in a longitudinal manner. With the use of generalised estimated equations (GEE), the same joints that showed no tenderness at baseline visit were assessed during the follow up visit to determine whether incident/increasing BML and synovitis scores were correlated with de novo tenderness [19]. In joints that showed tenderness during baseline visits, the investigators assessed whether decreasing synovitis and BML were positively correlated with the loss of joint tenderness, adjusting for sex, age, BMI, changes in radiographic OA and follow-up time. The investigators found that the same joints in participants which showed no joint tenderness at their baseline visit were associated with joint tenderness upon increasing/incident BML and synovitis. An increase in incident synovitis was detected in 45 out of 220 joints whereas BML were detected in 47 out of 312 joints.

3.4 Correlation of MRI changes with plain radiography

Several studies have evaluated the reliability of MRI scanning in assessing structural changes in hand OA in relation to clinical symptoms. Korteekas et al. [24] evaluated 16 participants with HOA. The study group had a median age of 57, 62% of the group were women and 13 had erosive OA. In the study, finger joints in the right hand were studied using a 3 Tesla MRI scanner with contrast using gadolinium. Pain was assessed on the same day of MRI examinations and radiographs.

The authors found that detection of synovial thickening for MRI was 43% and for US it was 42%. The most prevalent MRI features were osteophytes, BML and erosions. In contrast to radiographs, MRI scanning was more sensitive at detecting structural changes. A correlation coefficient of 0.43 was found for synovial thickening between US and MRI and it was 0.49 for osteophytes. US was found to be more sensitive for the detection of osteophytes, whereas MRI was more sensitive at detecting synovial thickening. Pain upon palpation was associated with structural changes including synovial thickening, collateral ligaments, BML, erosions and osteophytes.

Other studies have also demonstrated that MRI is a reliable and reproducible method for detecting HOA changes in the interphalangeal joints [23] and thumb base first carpometacarpal joint [30]. Interestingly, in thumb base OA, structural damage was more strongly associated with pain than synovitis [30]. In the HOSTAS

study, which was a large study of 92 participants with HOA [29], interphalangeal and thumb base joints were evaluated to demonstrate that MRI-identified BMLs in HOA were associated with pain and also interacted with synovitis. Findings in DIP/PIP and thumb base HOA have also been replicated in erosive hand OA [26]. With respect to bone texture, roughness in proximal bone texture in finger joints has been shown to be associated with MRI-defined osteophytes in finger joints without radiographic OA, which could assist in detecting early HOA changes.

In a clinical trial of hand OA, Chevalier et al. [33] evaluated French participants in the digital osteoarthritis in refractory hand OA (DORA) study. This multi-centre study recruited 99 participants and randomised 85 to placebo or adalimumab anti-TNF therapy. Mean age was 62 years, 855 were women, with the mean level of pain at baseline of 62 mm by the visual analogue scale (VAS) for pain. The primary outcome measure was the percentage of patients with an improvement of more than 505 in global pain (VAS) between baseline and 6 weeks' therapy. At 6 weeks, there was no significant difference in VAS pain outcomes between the adalimumab and the placebo groups [33]. In a smaller sub-study analysis of the DORA study, Roux et al. [28] evaluated the clinical findings and imaging measures from the DORA study. The group reported that of the 18 participants recruited and 144 joints studied, MRI-measured synovitis in the dominant hand was not correlated with radiological scores, clinical or biological markers of inflammation. A strong correlation was reported between other MRI features including joint space narrowing and osteophyte formation. Serum IL-1 was also associated with structural damage and impaired function.

3.5 Hand OA in the context of inflammatory arthritis

An important issue in hand arthritis studies is the co-existence of OA and rheumatoid arthritis (RA) in many patients. The factor of co-existing OA and RA in people with hand arthritis has recently been addressed by Loef et al. [34]. The group investigated the effect of TNF inhibitors (TNFi) on incidental and progressive hand OA in subjects with recent-onset RA over a 10 year follow-up. Plain radiographs of 262 subjects with RA (mean age 52 years, 66% women), from the BeSt study had osteophyte scoring conducted. Osteophytes in the DIP/PIP joints were scored using the Osteoarthritis Research Society International atlas (0–3; summed score 0–54) and according to Kellgren-Lawrence (KL) score (0–4; summed score 0–72) at baseline and 10 year follow-up. The use of TNF inhibitor treatment was assessed at 3 monthly visits. The group evaluated associations between TNF inhibitor treatment and HOA using generalised linear regression models and estimating equations. A total of 58% of patients were treated with TNFi with a median duration of 42 months. There were 55% of patients who had hand OA in any IP joint at baseline. For individual patients, TNFi duration did not affect incidental hand OA. However, on a monthly basis, TNFi treatment resulted in a reduced relative risk (RR) of hand OA progression in the DIP joints (relative risk (RR) 0.987 (95% CI 0.978, 0.996) but not in the PIP joints. The study concluded that TNFi treatment was associated with a reduced risk of hand OA progression in DIP joints but not in PIP joints after 10 years. The effect sizes in this study were small and were limited to DIP joint involvement, but suggest that TNF alpha can influence disease course in HOA.

4. Discussion

This systematic review has identified studies from the literature which demonstrate that joint space narrowing, osteophytes, synovitis and BMLs are all structural

changes in HOA that are associated with significant symptomatic burden of pain and functional impairment. MRI and US have been shown to be effective imaging modalities that detect more structural changes that plain radiography alone. MRI allows examination of the joint as a whole organ to directly visualise intra-articular structures significant to the progression of OA such as BMLs, synovitis, osteophytes and erosions in relation to radiographic changes and pain. Our systematic review has also found that synovitis and BMLs in HOA which are detectable by MRI and US in particular, are associated with progression in symptoms over time and therefore may represent valid targets for future interventions aimed at modifying these structural changes. Joint space narrowing and osteophyte formation were also identified to have good correlation between plain radiography and MRI/US identified changes. Future novel therapeutics would benefit from correlation with changes in synovitis, BMLs and joint space narrowing in relation to pain and functional outcome for HOA.

Our systematic review has found that a number of different cohorts around the world demonstrate structural changes observed in HOA. However, the majority of the studies were in European populations. Future studies in distinct Ethnic groups around the world would be helpful to compare and contrast data from existing published studies.

Since HOA has a higher prevalence in females, as reflected by the preponderance of women participants in the studies we identified, future studies which report changes in male participants with HOA, with data on occupation, since manual occupations are known to have a higher risk of HOA, are to be welcomed to compare and contrast the changes observed.

Emerging data from the articles we have reviewed suggest that people with HOA could potentially be stratified for imaging-based structural changes e.g. subjects showing inflammatory changes as evidenced by US or MRI-defined synovitis that could be targeted by NSAIDs or intra-articular steroid injections, or a predominant bone-cartilage damage profile, evidenced by the presence of MRI-defined cartilage loss, joint space narrowing and bone oedema that could be targeted using novel therapeutic agents. Imaging modalities such as MRI and/or US that demonstrate additional structural changes not visualised by plain radiography could aid in improved stratification and development of novel therapeutics for HOA in the future.

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