Editorial

Osteoarthritis - Current Insights in Pathogenesis, Diagnosis and Treatment

INTRODUCTION

Osteoarthritis (OA) is the most frequent chronic joint disease and is the leading cause of pain and disability in the population all over the world. The primary OA occurs without known cause and typically affects the weight-bearing joints (knees and hips) as well as hands (distal and proximal interphalangeal joints, first carpo-metacarpal joint), feet (first metatarsophalangeal joint) and spine. Age, genetic predisposition, obesity, female sex, great mechanical stress are the main risk factors for the development of OA. The high prevalence as well as the significant medical and social cost of OA has stimulated the research of the rheumatologists in this field in the recent years. Thus, great progress has been achieved regarding pathogenesis, diagnosis and treatment of OA.

OSTEOARTHRITIS – CELLS AND MEDIATORS

Classically considered as a degenerative joint disorder that affects primarily the articular cartilage, it is currently established that inflammation, albeit at significantly lower level as compared with inflammatory arthritides, is present in different joint tissues e.g., cartilage, bone and synovium. Thus, OA is a disease of the whole joint that results from imbalance between the catabolic and anabolic processes in the articular cartilage with low-grade inflammation in the cartilage, bone and synovium as well as with development of secondary reparative compensatory changes leading finally to joint dysfunction.

Activation of innate immunity has been proved in OA, contrary to rheumatoid arthritis, which is associated with activated both innate and adaptive immune system. Innate immune responses are induced by the so-called pattern-recognition receptors (PRRs) including the family of toll-like receptors. PRRs encompass a wide range of surface, endosomal, and cytosolic receptors that besides microbial patterns (pathogen-associated molecular patterns) also recognize multiple endogenous molecules released from tissue damage (damage- or danger-associated molecular patterns) [1].

It has been elucidated that several cellular types are involved in the pathologic process in OA e.g., chondrocytes, osteocytes and osteoblasts in the subchondral bone, synovial lining cells and mononuclear cells in the synovial membrane [2].

The target of pathologic process in OA is the articular cartilage, which in normal conditions is composed of extracellular matrix, containing mainly collagen type II, and also collagen type IX and XI, proteoglycans – mainly aggrecan and the leading cell type – chondrocytes.

In OA, there is accumulation of shorter proteoglycans, decreased synthesis of type II collagen, and increased production of collagen type X. A constant feature is the up-regulation of cartilage degrading enzymes - matrix metalloproteinases (MMPs) such as collagenase-1 (MMP-1), stromelysin (MMP-3), gelatinase (MMP-9), matriksin (MMP-7), and collagenase-3 (MMP-13) and ADAMTS metalloproteinases produced mainly by chondrocytes, but also by osteocytes and synoviocytes. The target of ADAMTS metalloproteinases is aggrecan (ADAMTS-4 plays a major role). The target of collagenase-1 and 3 (MMP-1, MMP-13) is collagen type II respectively. In contrast, the level of tissue inhibitors of MMPs is decreased.

The key inducers of catabolic processes in OA are Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α). IL-1β and TNF-α are synthesized by the same cell types e.g., chondrocytes, osteocytes, cells forming the synovial membrane, and mononuclear cells that were previously present in the joint or infiltrate its tissues during the inflammatory response. Both cytokines are found to be elevated in the same tissues e.g., synovial fluid, synovial membrane, cartilage, and the subchondral bone. IL-1β plays numerous roles both associated with inhibition of anabolic and stimulation of catabolic processes. IL-1β acts also in an autocrine manner stimulating its own secretion as well as the synthesis of other proinflammatory cytokines such as TNF-α, IL-6, IL-8, and CCL5 chemokine. IL-1β is suggested to decrease the chondrocytes synthesis of the extracellular matrix components e.g., type-II collagen and aggrecan. Of note, TNF-α acts synergistically with IL-1β activating the same group of intracellular signalling pathways and inhibiting the chondrocytes production of proteoglycan components, proteins binding proteoglycans, and type II collagen. Both IL-1β and TNF-α stimulate the chondrocyte synthesis of cartilage degrading enzymes mainly collagenase-1 (MMP-1), stromelysin-1 (MMP-3), and collagenase-3 (MMP-13), ADAMTS metalloproteinases.

IL-6 is a cytokine that strongly activates the immune system and enhances inflammatory responses. In OA, it could be produced by chondrocytes, osteoblasts, fibroblast-like synoviocytes, macrophages, and adipocytes stimulated in response to the action of IL-1β, TNF-α and prostaglandin E2. The effect of IL-6 on joint cartilage is not different from those of other cytokines and, in synergy with them, causes a decrease in the production of type II collagen and increases the production of MMPs. IL-6 is considered to be the key cytokine that contributes to the pathologic changes in the subchondral bone promoting bone resorption via osteoclast activation. Together with IL-β and TNF-α, it stimulates osteoblast production of MMPs by adversely affecting the cartilage located near it [3].
A positive correlation between serum levels of IL-15 and self-reported pain in knee OA has been observed [4]. Significantly higher serum levels of IL-17 have been also found in OA patients as compared with control subjects. In patients with knee OA, a correlation between IL-17 concentration in the synovial fluid and Kellgren-Lawrence grade as well as with disease severity evaluated by the Lequesne index has been observed [5].

**Transforming growth factor – β and insulin-like growth factor**

Increased expression of Transforming Growth Factor – β (TGF-β) and Insulin-like Growth Factor (IGF) has been found in human articular cartilage in OA patients with positive correlation with degree of cartilage destruction, while in healthy subjects no staining for TGF-β and IGF has been observed. In addition, an increased expression of TGF-β [6, 7] and IGF [8] was detected in the osteophytes, while in animal models of OA repeated injections of TGF-β and IGF lead to osteophyte formation [9]. Of note, the adipokine leptin is suggested to promote the expression of TGF-β and IGF [6].

**Subchondral bone in osteoarthritis**

The subchondral bone has been found to play a crucial role in the initiation and progression of OA. The subchondral bone represents the bony components located beneath the calcified cartilage and consists of the subchondral bone plate and the subchondral trabecular bone (Fig. 1). The subchondral bone plate is a thin cortical lamella adjacent to the calcified cartilage. Due to its porous structure, and via arterial, venous blood vessels and nerves that pass the connecting channels, the subchondral bone plate provides the link between the articular cartilage and the subchondral trabecular bone. The subchondral bone is considered to support the overlying articular cartilage and to distribute the mechanical loads across joint surfaces. Thus, stiffening of the subchondral bone could transmit increased loads to the articular cartilage, thus promoting cartilage damage. The subchondral bone is suggested to play a key role in the pathogenesis of OA, and subchondral sclerosis due to thickening of the subchondral bone plate and the increase of trabecular thickness is a well-recognized radiographic sign especially in the advanced stages of OA. However, in the early stages of the disease subchondral bone loss was confirmed in animal models of OA in both subchondral bone plate, and subchondral trabecular bone, which is characterized with thinning and increased porosity of the subchondral plate, deteriorated trabecular structure and decreased bone density. In the subsequent phase of radiographically confirmed subchondral sclerosis, there is an increased collagen synthesis in the subchondral bone albeit poorly mineralized and development of subchondral bone cysts (Fig. 1) [10]. Of note, Magnetic Resonance Imaging (MRI) has contributed considerably to OA research in the recent years. Subchondral Bone Marrow edema-like Lesions (BMLs) detected on MRI are frequently found in OA joints, and an association with clinical symptoms and with structural progression has been observed. On the other hand, BMLs have been observed in normal knees without clinical symptoms or articular cartilage pathology that suggests the hypothesis that early subchondral damage may precede the disease manifestation. In addition, protective effects on OA progression has been suggested for antiresorptive agents such as bisphosphonates and strontium ranelate [11].

![Fig. (1). Subchondral bone in early (A) and late osteoarthritis OA (B). (1. non-calcified cartilage; 2 calcified cartilage, divided from the non-calcified cartilage with the tide-mark; 3 – subchondral plate; 4 – subchondral trabecular bone). A. Subchondral bone loss, trabecular thinning and decreased bone density characterize changes in the subchondral in the early stage of OA. There is concomitant mild cartilage degeneration. B). Increased thickness of the subchondral plate, trabecular sclerosis due to increased collagen synthesis albeit with compromised mineralization characterize the subchondral bone in the advanced stages of OA. Subchondral bone cysts (arrows) may develop, there is advanced cartilage degeneration and joint space narrowing (modified from Li G et al., 2013 [10]).](image-url)

Vascularisation and innervation of the articular cartilage have also been noted in OA, with blood vessels and nerves originating from subchondral bone. Thus, the normally insensate articular cartilage may become an additional source of pain in OA together with periosteum, subchondral bone, synovium, ligaments and muscles [12].
Systemic factors

An increased risk of OA in obese patients was suggested to be not only a consequence of altered biomechanics in weight-bearing joints but also due to the effect of systemic mediators e.g., adipokines that are derived primarily from the dysfunctional adipose tissue and have been also associated with incidence and severity of hand OA [1, 13]. Results from in vitro studies suggest that adipokines including leptin, adiponectin, visfatin, and resistin could promote chondrolysis and inflammation [1, 14]. A higher leptin level in synovial fluid from human joints affected by OA was found in comparison with healthy controls as well as a positive correlation with the body mass index [6]. Diverse effects are reported for the role of adiponectin in OA. Filkova et al. (2009) observed increased serum adiponectin levels in patients with erosive OA compared with nonerosive form of the disease [15], suggesting that adiponectin may play a role in the pathophysiology of the erosive subtype of OA. On the other hand, there are studies that suggest the protective role for adiponectin in OA [16, 17].

Of note, estrogen receptors have been identified on human articular chondrocytes. It has been suggested that estrogens may induce both a direct effect on chondrocytes via genomic and rapid non-genomic mechanisms and may also affect the homeostasis of articular cartilage by modulating the expression/production of different molecules such as various growth factors, inflammatory cytokines, MMPs, and reactive oxygen species. In addition, potential for joint protection through inhibition of subchondral bone turnover has also been proposed similarly to other antiresorptive agents [18]. Estrogen deficiency is thought to be associated with development and progression of OA [19].

Increased expression of cyclooxygenase-2 has been found in synovial and cartilage tissue in OA patients and is associated with increased local release of lipid-derived mediators such as prostaglandin E2 (PG E2). IL-1β, IL-17, TNF-α are thought to stimulate cyclooxygenase-2 expression in the inflamed articular tissues. Martin-Pelletier et al. summarizes the results from studies that address the effects of PG E2 on articular cells that include decreased collagen synthesis, stimulated production of inflammatory mediators and MMPs, enhanced osteoclast formation and angiogenesis, abnormal chondrocytes apoptosis [20].

IMAGING IN OSTEOARTHRITIS

Bone sclerosis, subchondral cysts, osteophytes and joint space narrowing (an indirect sign of cartilage loss) in OA can be detected by radiographs. The established criteria for diagnosis and staging of OA are based on the clinical symptoms, laboratory and radiographic findings. Osteophytes and joint space narrowing on X-ray are included in the classification criteria of the American College of Rheumatology (ACR) for knee and hip OA [21, 22] (Tables 1 and 2). Currently, plain radiography is the “gold standard” for both diagnosis and staging of OA. The Kellgren-Lawrence scale evaluates joint space narrowing and osteophyte development at plain radiographs and is traditionally used both in clinical practice and in the research setting since its introduction [23] (Table 3).

Table 1. ACR classification criteria for knee OA based on clinical and laboratory criteria, clinical and radiographic signs or only on clinical findings [Altman R et al., 1986].

<table>
<thead>
<tr>
<th>Clinical and Laboratory</th>
<th>Clinical and Radiographic</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td>Knee pain+ at least 5 of 9</td>
<td>Knee pain, osteophytes + at least 1 of 3</td>
<td>Knee pain + at least 3 of 6</td>
</tr>
<tr>
<td>1. Age&gt; 50 years</td>
<td>Age &gt; 50 years</td>
<td>Age &gt; 50 years</td>
</tr>
<tr>
<td>2. Stiffness &lt; 30 minutes</td>
<td>Stiffness &lt; 30 minutes</td>
<td>Stiffness &lt;30 minutes</td>
</tr>
<tr>
<td>3. Crepitus</td>
<td>Crepitus</td>
<td>Crepitus</td>
</tr>
<tr>
<td>4. Bony tenderness</td>
<td></td>
<td>Bony tenderness</td>
</tr>
<tr>
<td>5. Bony enlargement</td>
<td></td>
<td>Bony enlargement</td>
</tr>
<tr>
<td>6. No palpable warmth</td>
<td></td>
<td>No palpable warmth</td>
</tr>
<tr>
<td>7. ESR &lt;40 mm/hour</td>
<td></td>
<td></td>
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<tr>
<td>8. Rheumatoid factor &lt; 1:40</td>
<td></td>
<td></td>
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<td>9. Synovial fluid characteristics for OA</td>
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Table 2. ACR Classification criteria for hip OA [Altman R et al., 1991].

<table>
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<tr>
<th>Hip pain and at least 2 of the following 3 features:</th>
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<tbody>
<tr>
<td>1. ESR&lt;20 mm/hour</td>
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<tr>
<td>2. Radiographic femoral or acetabular osteophytes.</td>
</tr>
<tr>
<td>3. Radiographic joint space narrowing (superior, axial, and/ or medical)</td>
</tr>
</tbody>
</table>
Table 3. Kellgren-Lawrence scale for staging of osteoarthritis OA [Kellgren JH and Lawrence JS, 1957].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0 Normal</td>
<td>No features of OA</td>
</tr>
<tr>
<td>1 Doubtful</td>
<td>Minute osteophytes, doubtful significance</td>
</tr>
<tr>
<td>2 Minimal</td>
<td>Definite osteophytes, unimpaired joint space</td>
</tr>
<tr>
<td>3 Moderate</td>
<td>Moderate narrowing of the joint space</td>
</tr>
<tr>
<td>4 Severe</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone.</td>
</tr>
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According to the pattern of bone response, hypertrophic and atrophic forms of OA have been recognized according to the number of osteophytes [24]. (Fig. 2 and 3). Significantly lower serum levels of C-propeptide that is a marker of collagen type II synthesis has been found in atrophic type of hip OA and is suggested to be associated with the absence of osteophyte formation [25].

![Fig. (2). Bilateral hip OA – hypertrophic subtype, 3rd radiographic stage of OA /Kellgren-Lawrence/ in 47-year-old female patient. Osteophytes (O) and joint space narrowing (arrows) are demonstrated.](image1)

![Fig. (3). Bilateral hip OA – atrophic subtype in 74-year-old female patient. Joint space narrowing (arrows) in the absence of osteophytes is demonstrated.](image2)

**PATHOMORPHOLOGIC CHANGES AND THE CONCEPT FOR “EARLY”, PRE-RADIOGRAPHIC OA**

The earliest pathomorphologic changes in OA include hypertrophic repair phase, softening of the articular cartilage with altered compressive resistance in the context of glycosaminoglycan loss that leads to increased water retention. Initially at this phase, the anabolic processes are enhanced with increased proliferation rate of chondrocytes that appear in clusters and production of collagen type II and proteoglycans is stimulated. Subsequently, increased synthesis and expression of inflammatory mediators and cartilage-degrading enzymes trigger catabolic processes that result in cartilage loss. Degrading fragments from collagen type II induce synovitis with synovial hyperplasia and lymphocytic infiltration that itself promotes cartilage degradation [26]. OARSI (OA Research Society International) scoring system could be applied for histological staging and includes 6 grades. Grades 1st to 3rd define the early OA when only the superficial and the middle zones of the cartilage are affected.
Grade 1 includes swelling of the articular cartilage, uneven cartilage surface with superficial fibrillation. Cell death or proliferation may present, but the middle and deep zones are preserved. Grade 2 OA is characterized by focal discontinuation of the cartilage superficial zone. Cell proliferation, increased or decreased matrix staining as well as cell death in mid zone may occur. In grade 3 OA, matrix fibrillation and vertical fissures extend into the middle zone. Grades 4 to 6 are included in the advanced stage of OA. In grade 4 of OA there is cartilage matrix loss with erosion formation. In grade 5, the unmineralized hyaline cartilage is completely eroded and the mineralized cartilage or the bone act as articular surfaces due to denudation. Finally in grade 6, the articular structure is completely rearranged with microfractures, repair and bone remodelling that change the contour of the articular surface with all these processes resulting in advanced joint deformity [27].

The increasing use of the modern instrumental techniques e.g., MRI and musculoskeletal ultrasonography provides the opportunity for visualization of joint structures that could not be visualized by radiography. They reveal changes not only in the periarticular bone but also in the cartilage, menisci, synovial membrane, ligaments and fat pad. Early detection of pre-radiographic changes could provide early diagnosis of the disease, evaluation the risk for disease progression and decision for initiation of treatment intervention [26]. MRI demonstrates cartilage damage, BMLs, meniscal pathology, synovitis that could not be visualized by radiography [28]. BMLs are features associated with OA that has only been identified since MRI is used to image joints. They are localized in the subchondral bone, which is innervated and is a potential source of pain in OA [29]. A correlation between presence of BMLs with self-reported pain as well as with structural and symptomatic progression of OA has been suggested. Therefore, they could be the new treatment target for future therapy in OA patients [29-32]. In addition, a positive correlation between the presence of synovial inflammation confirmed via both MRI and arthroscopy and OA progression has been reported [33, 34]. Sharma et al. (2015) evaluated 849 participants at high risk of development of knee OA without radiographic changes (Kellgren/Lawrence 0) via MRI for cartilage damage, BMLs and meniscal lesions at 12 and 48-month follow-up. Worsening of MRI findings e.g., cartilage damage, meniscal tear and meniscal extrusion at 12–48 month was positively associated with progression to radiographic OA for the period of observation (Kellgren-Lawrence 1-2) as compared with stable findings. Thus, these changes are suggested to be signs of early OA and in the future may serve as a target for therapeutic intervention in the process of introduction of disease-modifying drugs. Moreover, these findings support the novel hypothesis that no longer considers OA as a disorder of hyaline cartilage and guides the necessity of future trials whether targeted interventions of other joint structures could be beneficial at the early stages of the disease [35]. Future research on MRI findings in OA could provide the opportunity to understand the early pre-radiographic changes in order to prevent progression via early therapeutic intervention as well as to assess the potential disease modifying properties of future therapies [28, 30].

Even ultrasonography in contrast to conventional radiography, permits visualisation of periarticular and articular soft tissue structures. It is a non-invasive, safe, easy-to-repeat, radiation-free technique and compared to MRI differs with low cost and less time for examination. It detects both early and late changes in the hyaline cartilage, synovial membrane, meniscus, joint capsule, bursa and bony cortex. Initial findings in the hyaline cartilage are irregular edges and loss of normal sharpness. Synovial hypertrophy, joint effusion and increased vascularity could be observed using power Doppler. The musculoskeletal ultrasonography contributes to assessment of disease activity, improves differential diagnosis. Limitations of the technique are the dependency on the skills of operator and inability to evaluate deeper articular structures. Further research for evaluation the opportunities of the technique for early diagnosis of OA are needed [26].

TREATMENT OF OSTEOARTHRITIS

The therapy of OA aims to reduce pain and disability and to improve functional capacity and quality of life. Treatment of patients with OA is challenging and is based on multidisciplinary approach with non-pharmacological measures (patient education, physiotherapy, weight reduction, orthoses and surgical techniques) and drug treatment. Thus, general practitioners, rheumatologists, physiotherapists and surgeons should work in close collaboration in order to achieve better control and outcome of the disease. There is no current consensus between rheumatologists and physiotherapists about the appropriate physical and rehabilitation techniques in different stages and localizations of OA. The opportunities for patient education with the adequate use of ambulatory exercise programmes are insufficiently applied in clinical practice. The pharmacological therapy includes a classical approach for pain and inflammation control (analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, intraarticular corticosteroids) and Symptomatic Slow Acting Drugs for OsteoArthritis (SYSADOAs). SYSADOAs are supposed to slow the disease progression although currently there is no drug approved as a disease-modifying agent for OA. The group of SYSADOAs includes glucosamine sulphate, chondroitin sulphate, diacerein, unsaponifiables extract of soybean and avocado and intraarticular hyaluronic acid [36-38]. Taken into account that age is one of the most important risk factors for the development of OA, the prevalence of the radiographically and clinically manifested disease dramatically increases in the age group between 65 and 75 years. Of note, in this patient population also increases the frequency of the cardiovascular pathology such as arterial hypertension, ischemic heart disease and most of the patients receive a drug combination as supportive treatment. The administration of NSAIDs as a symptomatic treatment of OA is associated with increased risk of cardiovascular as well as gastrointestinal complications. Thus, the aim to improve the symptoms and eventually to slow the disease progression via medications with good safety profile which lead to reduction of NSAIDs consumption, is intriguing. The data regarding the therapeutic effect of SYSADOAs and their potential structure-modifying effect are contradictory. In addition, the judicious use of non-pharmacological measures especially physiotherapy also relieves complaints, reduces NSAIDs intake and improves the quality of life in OA. Promising results regarding pain relief and improvement of functional capacity are observed during treatment with biologic agents – inhibitors of nerve growth factor-β (NGF-β), e.g., fasinumab and tanezumab for intra-
venous administration and fulranumab for subcutaneous administration [39-44]. The conventional disease-modifying drugs used in inflammatory arthritides such as hydroxychloroquine and methotrexate have also been investigated in OA. They are not routinely used because of the lack of enough evidence for their efficacy in OA. The first results from a multicenter, randomized, double-blind, placebo-controlled trial focused on symptomatic hand OA were recently reported (British HERO study). It has been concluded that hydroxychloroquine was not superior to placebo as analgesic treatment or for reduction of the radiographic progression in hand OA [45]. Placebo-controlled trial evaluating the efficacy of hydroxychloroquine in inflammatory and erosive hand OA is under way [46]. Although TNF-α blockers are highly effective in inflammatory arthritides and TNF-α is involved in OA pathogenesis, the role of this class biologics as disease-modifying agents in OA is undetermined and preliminary results are negative [47]. The increased turnover of the subchondral bone is thought to play a key role in the pathogenesis of OA and is considered to be related to the progression of the cartilage loss. It is suggested that the influence of this process with antiresorptive agents such as bisphosphonates may slow bone remodeling and produce chondroprotective effect that has been proved in animal models of OA [48]. The administration of strontium ranelate has led to significant slowing of the joint space narrowing as compared with placebo in patients with symptomatic knee OA [49]. Intraarticular injections of hyaluronic acid are approved worldwide for the treatment of pain associated with OA. Hyaluronic acid administration aims to reduce pain and improve physical function by supplementing the impaired viscosity and elasticity of synovial fluid in OA [50]. Intraarticular hyaluronic acid administration is recommended by EULAR for treatment of knee OA with evidence for efficacy for pain reduction and functional improvement [51]. It is also included in the recommendations for management of hip [37] and hand OA (OA of the trapeziometacarpal joint) [38], but with lower levels of evidence that need further research. Intraarticular hyaluronate injections are conditionally recommended by ACR (2012) in patients with knee OA, who have inadequate response to the initial therapeutic options [52]. There are also data that intraarticular administration of platelet-rich plasma could be efficacious, but its use is not seen unambiguous [53, 54]. Due to recent advances in studying OA pathogenesis and new imaging modalities such as MRI, the classical view for OA has considerably changed. Thus, the traditional view has underlined the degenerative nature of the disease that manifests with cartilage loss and joint space narrowing. Nowadays, it is confirmed that inflammation is present in OA joints at earlier stages at the level of bone, synovium and cartilage. Thus, the idea for early, pre-radiographic OA has been introduced that could be a possible target for therapy but until now the benefit from such therapeutic intervention in the early and very early stage of the disease is undetermined. The opportunity for pharmacological disease-modification in OA is therefore regarded an utmost key point in the research agenda.

REFERENCES


