JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/12629

Osteoarthritis: A contemporary view of the problem, the possibilities of therapy and prospects for further research

Lina Zaripova[1], Damira Tazhibayeva[2], Natalya Kabdualieva[2], Zhaina Aitbayeva[2], Gulshakhar Beglarova[2], Lazzat Yermentayeva[2], Karlygash Niyazbekova[2]

[1]Scientific and Innovation Management Department, National Scientific Medical Center, Astana, Kazakhstan
[2]Department of Pathological Physiology named after V.G.Korpachev, Astana Medical University, Astana, Kazakhstan

Received: 2022-11-04.
Accepted: 2022-11-08

J Clin Med Kaz 2022; 19(6):6-12

Corresponding author:
Lina Zaripova.
E-mail: zaripova_lina@list.ru;
ORCID: 0000-0001-8728-0225.

Abstract

Osteoarthritis is a chronic degenerative disease characterized by the destructive changes in the articular cartilage, synovitis, subchondral bone sclerosis and osteophyte formation. Today it is the most common joint disease and one of the main causes of disability of elderly people.

This review provides an overview of advances in understanding of osteoarthritis etiology, pathogenesis, histopathology, as well as the results of up-to-date research of the molecular mechanisms underlying this heterogeneous age-related disease at the clinical and fundamental levels.

The article is devoted to a comprehensive review of the osteoarthritis problem, compiled considering the classical understanding of morphological changes, clinical picture, diagnostic methods, and current therapy protocols, supplemented by the modern trends of world research with the prospect of further development and implementation of the latest therapeutic methods, such as nerve growth factor-inhibitors, fibroblast growth factor-18 and stem cells treatments.

Key words: osteoarthritis, pathogenesis, therapy, up-to-date research, biological therapy

Introduction

Osteoarthritis (OA) is the most common chronic disease of the musculoskeletal system, characterized by defective integrity of articular cartilage, subchondral sclerosis, biochemical and biomechanical changes in the extracellular matrix, resulting in the injury of knee, hip, small joints of the hands and spine [1]. According to the generally accepted classification OA may be distinguished between primary (idiopathic) and secondary, which includes post-traumatic OA, metabolic OA (ochronosis, hemochromatosis), endocrine (acromegaly, hyperparathyroidism), neurological and others.

In the global aspect OA represents a significant public health challenge. Being a chronic joint disease OA of the hip and knee is a leading cause of disability in elderly. Moreover, it is the third most rapidly rising disease after diabetes and dementia [2]. With an aging population and an increasing prevalence of obesity worldwide, the burden of OA will continue to rise as the burden on health systems increases [3]. There is evidence of an increased risk of mortality in connection with OA, which is possibly associated with the development of hypodynamia, metabolic and psycho-emotional disorders, with the background of persistent pain syndrome and low-intensity inflammation, that increases the risk of cardiovascular catastrophes [4].

Etiology and pathogenesis

OA is a clinically heterogeneous disease with the multifactorial etiopathogenesis. The most well-known risk factors for OA include overweight, chronic micro-traumatization of the cartilage due to high physical exertion, trauma, metabolic disorders and hereditary predisposition [5]. Older age (above 65 years), woman gender, occupation with overloading of joints, intoxication (smoking, alcohol, uncontrolled medication and heavy metal salts), endocrine and congenital disorders of structure of joints play a role in OA development as the etiological factors.

The pathogenesis of OA is based on degenerative-

dystrophic damage to the articular cartilage, which develops because of imbalance between anabolic and catabolic processes in cartilage and subchondral bone [6]. Articular cartilage consists of a matrix and chondrocytes embedded in it. The extracellular matrix contains proteoglycans and collagen, the content of which decreases in OA, while the structure and biomechanical properties of cartilage are impaired [6]. An impairment of proteoglycans metabolism leads to a violation of the stability of collagen fibers, followed by dehydration and disorganization of the cartilage. The loss of glycosaminoglycans (particularly chondroitin sulphate, as well as hyaluronic acid) leads to a decrease in matrix resistance to the physical stress, and an increase in the sensitivity of the cartilage surface to damage. There is a synthesis and excessive local release of metalloproteinases by chondrocytes, which leads to a progressive slowdown in cartilage repair, an imbalance between the synthesis and degradation of collagen fibers and proteoglycans of cartilage [6]. All together these results in softening, fibrillation, ulceration, and loss of articular cartilage.

The rate of OA cases increases with the metabolic syndrome (MetS) characterised by obesity, elevated level of plasma glucose and triglycerides, reduced the high-density lipoproteins, and hypertension [7]. All these factors have been shown to implicate in the pathogenesis of OA. MetS is a low inflammatory state responsible for glucose and lipid dysregulation leading to increase in the expression of proinflammatory factors and degradative enzymes, lipid deposition in chondrocytes and ectopic inhibition of cartilage matrix synthesis. The increased level of miR-140, miR-27b and hsa-miR-148a caused by pro-inflammatory environment might affect type II collagen and proteoglycan formation [7]. Hyperglycemia contributes to oxidative stress and increase of glycation end-products leading to cartilage damage. Hypertension with the contraction of small vessels could cause insufficient blood supply compromise nutrient exchange in articular cartilage and potential activation of autophagy that leads to cartilage deterioration [7]. Hypertension probably leads to decrease in synthesis of the synovial fluid, which is necessary for cartilage metabolism. Moreover, ischemia can contribute to microstructural changes of subchondral bone leading to initiation of OA [7].

Currently, the concept of the pathogenesis of OA has undergone some changes: it is no longer considered as only a "degenerative disease", but a disease of active biomechanical and cellular processes with chronic low-intensity inflammation that acts as one of the most important factors in the progression. IL-1 and tumor necrosis factor-α (TNFα) contribute to systemic inflammation, which leads to the activation of NF-κB signaling in both synovial cells and chondrocytes [8]. A wide range of pro-inflammatory cytokines IL-1, IL-8, IL-17, IL-6, TNFα, the release of free radicals (NO), and transforming growth factor β (TGF-β) contribute to the progression of OA, synovitis and changes in the viability and function of chondrocytes [9]. Up-to-date studies have shown that systemic inflammation can reprogram chondrocytes via inflammatory mediators towards hypertrophic differentiation and catabolic reactions through the activation of NF-κB, oxidative phosphorylation, and autophagy mechanisms [10]. Inflammation usually begins in the synovial membrane of the joint; the biochemical composition of the synovial fluid is disturbed, the loss of hyaluronic acid and degenerative changes in cartilage increase. Thus, the damage of the main structural components of cartilage such as the connective tissue matrix and chondrocytes results in the initial stage to cartilage degeneration, and subsequently changes in the subchondral bone: sclerosis and eburnation of the subchondral bone, formation of osteophytes and subchondral cysts (Figure 1) [6].

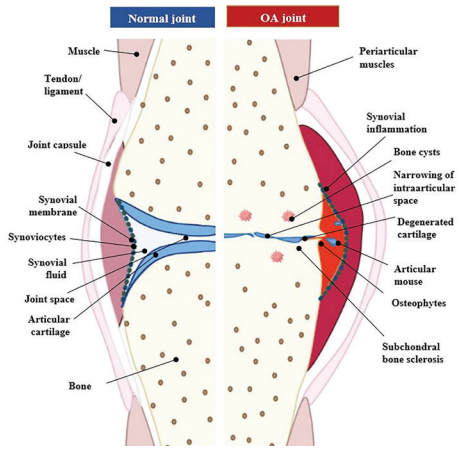

Figure 1 - Illustration of osteoarthritis features with respect to healthy joint. Morphological characteristics of OA joint include reduced joint space due to loss of articular cartilage, low-grade synovitis, hypertrophic reaction (sclerosis) in the subchondral bone following by new bone formation (osteophytes), detached fragment of the cartilage displacement to the articular cavity (articular mouse), inflammation of the synovial membrane and weakness of periarticular muscle and ligaments. Created with BioRender.com.

Morphology

Morphological changes in OA include decrease in the joint space due to loss of articular cartilage, hypertrophic reaction in the subchondral bone (sclerosis), new bone formation (osteophytes) at the joint margins, low-grade synovitis with hyperplasia of the synovial membrane, meniscal degeneration, periarticular muscles and ligaments weakness (Figure 1). In the last stage it may be seen an "articular mouse", the detached fragment of the cartilage displaced to the articular cavity. Additionally, the meniscus in OA becomes thinner and damaged.

Diagnosis

Gradual onset of pain, crepitus during movement due to a violation of the congruence of the articular surfaces, limitation of active and passive movements in the joint, atrophy of the surrounding muscles, as well as deformity of the limbs (varus deformity of the knee joints, Heberden's and Bouchard's nodules) with moderate change in laboratory parameters allow to establish the diagnosis of OA.

X-ray is the routinely used examination, golden standard for OA diagnosis that allows to reveal the narrowing of the joint spaces, osteosclerosis and marginal osteophytes (Figure 2) [11].

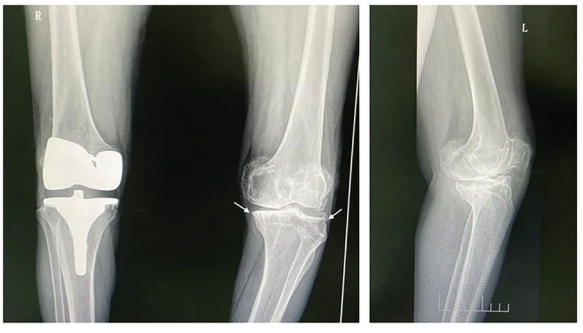

Figure 2 - Typical X-ray changes associated with osteoarthritis. Osteoarthritis of the left knee with narrowing of intraarticular space, hypertrophic reaction of subchondral bone (sclerosis) and new bone formation (osteophytes at the joint margins; labelled with white arrows), accompanied with severe systemic osteoporosis. Patellofemoral arthritis: degenerative changes underneath the kneecap. Total right knee replacement due to decompensation of osteoarthritis with severe pain syndrome and dysfunction of the joint.

Magnetic resonance imaging (MRI) scan permits visualization of a reactive bone oedema, intra-articular structures and inflammation of soft tissue, degenerated cartilage, or articular mouse in the joint. Computed tomography (CT) can be used for the evaluation of menisci and anterior cruciate ligament if needed for clinical decision [11].

There are no obvious laboratory indicators of OA in casual clinical practice, however, studies demonstrated the new molecules that may be used. Maghbooli *et al.* (2019) showed significant 23% decrease in serum levels of complement-C1q TNF-related protein 3 (CTRP3) in postmenopausal women in comparison to age-matched controls and suggested that this could be a clinical marker for osteoarthritis [12]. CTRP3 potentially play a role of anti-inflammatory mediator and may works for prevention of OA and reparation of knee cartilage [12].

The main directions of OA therapy

Classical therapy for OA is aimed at reduction of pain, improving the functional state of the joints, and preventing further destruction of cartilage. Treatment recommendations can be conditionally divided into non-pharmacological, pharmacological and surgical [13]. Among the guidelines available for the treatment of OA the most powerful are the global guidelines developed by the Osteoarthritis Research Society International (OARSI) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) updated in 2019.

Both OARSI and ESCEO recommend training, structured exercise, and weight loss as the primary treatment option [13]. The data obtained from the first international survey of OA patients the Global OA Patient Perception Survey revealed that more than 80% of OA patients have comorbidities, especially hypertension, and obesity [14].

The association between metabolic syndrome, type-2 diabetes and OA highlighted the need of low cholesterol dietary with increased consumption of long-chain omega-3 fatty-acids [15]. Benefit of patient's ability to self-manage their condition with diet and exercise was proven and included in OA recommendations. A special role is played by non-drug treatment: patient education aimed at ensuring that patients understand the disease, the need for physical exercises that support the function of the joint, and the use of special devices (kneepads, orthopedic insoles, orthoses and canes) for unloading joint [16]. It is necessary to achieve compliance between a patient and a doctor, the patient understanding that moderate physical exercises (such as swimming, cycling, walking) contribute to reducing of pain and improving the functional activity of the joints [16].

Pharmacological therapy includes the use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), the choice of which should be made individually and dictated primarily by a safety assessment. The most serious complications of this therapy are expected from the gastrointestinal tract, and COX-2 inhibitors have the lowest risk; their appointment is justified in a group of patients over 60 years of age, with concomitant diseases and a history of gastrointestinal tract pathology. According to the latest OARSI recommendations, topical NSAIDs are recommended for use in the first line of OA treatment, if ineffective - paracetamol. According to the recommendations of OARSI and ESCEO, paracetamol and NSAIDs should be used only during the period of increased pain syndrome [17]. For persons with concomitant cardiovascular diseases, the use of any oral NSAID is not recommended [13].

The OARSI guidelines for the non-surgical management of knee, hip and polyarticular osteoarthritis emphasize the appropriate use of intra-articular injections of corticosteroids and hyaluronic acid, as well as the need for aquatic exercise for the treatment of OA [17]. The OARSI and ESCEO guidelines support the use of intra-articular corticosteroid injections in patients with persistent pain unresponsive to topical and oral NSAIDs [13].

Hyaluronic acid drugs for intra-articular administration are indicated in both guidelines [13]. The use of hyaluronic acid is recommended for patients with contraindications to NSAIDs or persisting pain syndrome despite taking NSAIDs. These drugs are well tolerated and have small analgesic effect. Recent studies of the effectiveness of hyaluronic acid injections in patients with osteoarthritis of the knee joint showed a decrease in the severity of pain syndrome according to the visual analogue scale (VAS) and an improvement in joint function according to the Leken index [18].

Symptomatic slow-acting drugs for osteoarthritis (SYSADOA), including chondroitin and glucosamine sulphate, as well as their combination, avocado soybean unsaponifiables and diacerein, are well tolerated by patients and can help improve the effectiveness of treatment and reduce possible functional impairment [19]. Meta-analyses of placebo-controlled trials of SYSADOAs treatment demonstrated evidence of safety and small beneficial effects in patients with OA [19, 20]. OARSI and ESCEO recommendations are divided regarding glucosamine and chondroitin sulphate: they are recommended by ESCEO, while OARSI does not recommend their use, considering them ineffective [13].

Surgical treatment includes arthroplasty, which is prescribed for patients with severe joint dysfunction accompanied by intractable pain syndrome [21]. Lavage of the knee joints with removal of detritus and arthroscopic removal of the "articular mouse" can also reduce pain but does not stop the disease progression [21].

COVID-19 and OA

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became an important issue for healthcare in the worldwide for a few years. It affected different organs and systems and may potentiate development of a range of autoimmune disease, including arthritis, however, there is a lack of data about OA cartilage degeneration due to COVID-19 [22]. Endothelial and adipose tissue dysfunction induced by SARS-CoV-2 through its influence on angiotensin-converting enzyme 2 (ACE2), adiponectin concentration, and apoptosis lead to a meta-inflammation [22]. Acute pain is associated with the production of pro-inflammatory cytokines, including CCL2/3/4, CXCL2, IL-1, IL-6 and TNF [22]. Hypovitaminosis D, hypocalcaemia followed by demineralization and bone fragility in patients with COVID-19 point towards bone aging, while arthralgia and myalgia resemble OA aging characteristics and may be classified as early OA-like phenotype of COVID-19 [22].

COVID-19 negatively influences on patients with chronic diseases including OA. Delay of nonemergency procedures due to COVID restrictions lead to a significant number of postponed joint replacement operations or cancellations of surgical or therapeutical procedures [23]. COVID control have reduced access to healthcare services most of them became through remote working (telemedicine, telehealth, virtual consultations) [24].

OA usually going with comorbidities such as cardiovascular disease, diabetes, and obesity, that increase the risk of COVID-19 infection and its severity. Restrictions of access to exercise facilities may lead to limitations in range of motion,

hypodynamia and subsequent muscle atrophy of individuals with OA. So even in COVID quarantine patients are strongly advised to continue to exercise near or at home (walking, yoga, tai chi) and reduce weight with a healthy diet [23].

The question about routinely prescription of NSAIDs in OA was highly debatable. Research revealed no negative effect of prescribed NSAIDs on COVID-19 related deaths [24].

New therapeutic opportunities and prospects for further research

Throughout the history of OA research several therapeutic approaches have been proposed (pharmacological treatment, physiotherapy, acupuncture), but none of them leads to a complete cure or even to reliable pain relief and improvement joint function. The absence of effective disease-modifying therapy induces a vast of OA research worldwide.

Intra-articular platelet rich plasma

Intra-articular platelet rich plasma (PRP) appears to be a promising therapy in the last few decades. PRP preparations are prepared by separating autologous blood (about 100 ml) by a two-stage centrifugation method, which separates plasma and cellular elements. The concentration of platelets in this preparation is about 1 million/μl, which is about 5 times higher than the content in native blood. Platelets are activated by adding thrombin or fibrin "matrix", and then the resulting clot ("gel") is injected with a syringe into the affected area. Platelets secrete platelet growth factor, TGF-β, fibroblast growth factor, insulin-like growth factor 1 and 2, which act as tissue hormones and factors of migration and differentiation of stem cells [25]. Some authors have noted a significant reduction in pain after PRP compared with baseline in patients with knee OA, regardless of age, sex, severity and body mass index [26]. The combination of platelet-rich plasma with hyaluronic acid administered intra-articularly to patients with OA showed the same efficacy as PRP alone [27]. However, intra-articular PRP did not show a significant advantage over placebo to add this method to the recommendations for the treatment of knee OA [28, 29].

Cellular therapy

Cell therapy methods in the treatment of OA are being widely researched. Mesenchymal stem / stromal cells (MSCs) have gained significant popularity due to the enormous opportunities, lack of ethical limitations and risks usually associated with other stem cells such as embryonic stem cells. MSCs have been identified in the synovial fluid of healthy people; however, with arthritic changes, the number of MSCs increases significantly [30, 31]. Jones et al (2008) found that the level of MSCs obtained from synovial fluid is seven times higher in OA compared with the control group [32]. It was known that MSCs can play a positive role in the restoration of cartilage tissue in the pathogenesis of arthritis. De Sousa et al (2014) emphasize that these cells maintain homeostasis, involved in the restoration of joint tissue and restore the balance between catabolism and anabolism of cartilage tissue [33]. MSC studies have demonstrated cartilage remodeling in a mouse model of OA, as well as a decrease in pain due to damage to the subchondral bone when using the MSC secretome. After preclinical evaluation in experimental animal models, MSCs began to be used in single studies in patients with OA. However, according to the Canadian recommendations for intra-articular injections for osteoarthritis of the knee, there is currently insufficient evidence to recommend MSCs for the treatment of OA [29]. Thorough, well-planned clinical trials are required to establish the safety, efficacy, and cost-effectiveness of MSCs before including in the treatment protocols.

A promising method for the treatment of OA may be induced pluripotent stem cells (iPSCs). Patient-specific stem cells can be created by reprogramming a somatic cell to a pluripotent state, for example, by transferring its nucleus to an oocyte. SOX2 and OCT4 in combination with KLF4 and cMYC also promote the reprogramming of human fibroblasts into iPSCs. These studies demonstrated that pluripotency can be restored in a terminally differentiated cell, and suggest that these cells will be able to support the infinite production of functional chondrocytes [34].

Autologous chondrocyte transplantation was proposed as a variant of cell therapy for OA in the recent years and shown to be effective in restoring hyaline cartilage [35].

Monoclonal antibodies

One of the main therapeutical directions recently explored is monoclonal antibodies, such as anti-TNFα agents (adalimumab, infliximab and etanercept) and IL-1 inhibitors (anakinra, canakinumab), which are successfully used for rheumatoid arthritis, psoriatic, enthesitis-related and juvenile idiopathic arthritis treatment [36, 37]. However, they did not demonstrate statistically considerable efficacy in OA: adalimumab did not significantly decrease a pain, synovitis or bone marrow lesions in patients with erosive hand OA [38]. IL-1 targeting therapies also failed to bring remission in OA: IL-1α/β immunoglobulin had no effect on pain or imaging outcomes in patients with erosive hand osteoarthritis [39] and minimal decrease in pain score with no improvement in synovitis of knee compared to the placebo group [40]. Data about IL-6 involvement in OA pathogenesis promoted OA research with tocilizumab, an antibody against IL-6 receptor, though no efficacy was found in 83 patients with hand OA [41].

Biological therapy also includes the antibodies against nerve growth factor (NGF) [42-44]. Nerve growth factor (NGF) is the major mediator of pain, binds to tropomyosin receptor kinase A and p75 on nociceptive neurons [45]. Taking into account the key role of pain in OA and the side effects associated with long-term use of NSAIDs and opioid analgesics, anti-NGF antibodies became a promising therapeutical tool for OA treatment. Anti-NGF monoclonal antibodies currently include 3 medications (tanezumab, fasinumab and fulranumab). The drugs are currently under III phase clinical trials, but promising clinical results such as pain relief and physical function improvement have already been obtained [42, 43]. However, despite the high expectation the side effects of these drugs have to be carefully analysed before anti-NGF can enter the therapeutic arsenal for OA.

The search for the disease-modifying drugs for OA continues, and fibroblast growth factor (FGF)-18 may take this position. FGF-18 is known as a molecule that protects articular cartilage due to anti-catabolic effects mediated by tissue inhibitor of metalloproteases (TIMP)-1, stimulation of chondrocytes and maintenance of cartilage homeostasis [46]. Recombinant human FGF-18 (sprifermin) is considered a disease-modifying drug used as an intra-articular injection, and it has been shown to reduce the injury of cartilage [46]. Moreover, it was demonstrated that the intra-articular administration of 100 μg of sprifermin every 6 or 12 months resulted in significant improvement in total femorotibial joint cartilage thickness after 2 years [47].

Others: metformin

Nowadays there are conducted the range of studies dedicated to the effect of various substances that may affect the processes of destruction and formation of cartilage. For example, Li *et al.* (2020) conducted an experimental study of the effects of metformin on cartilage in a mouse model of

osteoarthritis. It is known that metformin can induce adenosine monophosphate-activated protein kinase, which is postulated as a potential therapeutic target for the treatment of OA. In vitro experiments have shown that metformin not only lowers the level of matrix metalloproteinase 13, but also increases the production of collagen type II, thereby reducing the severity of structural damage in OA and reducing pain [48].

Further directions

A number of studies have been carried out using large-scale genome-wide screening of miRNAs expressed in osteoarthritic cartilage or subchondral bone, microRNAs (miRNAs) have been identified, which play an important role in cartilage homeostasis and the OA process and can potentially be used to modify the disease [49]. miRNAs are short non-coding RNAs (18-14 nucleotides) that bind to one or more mRNAs to regulate their expression by inhibiting the translation or increasing mRNA degradation. Most of the published studies focused on one or two miRNAs and are based on the hypothesis that they target the gene that plays an important role in the pathogenesis of OA. For example, miR33a regulates cholesterol metabolism in chondrocytes via the TGF-β1/Akt/SREBP-2 pathway, while ABCA1 and ApoA1 genes associated with cholesterol efflux [50]. It was found that MiR-370 and miRNA-373 regulate the expression of SHMT-2 and MECP-2 in chondrocytes [51]. MiR-16-5p has been shown to regulate the expression SMAD5 in cartilage [52], while miRNA-26a-5p regulates the expression of inducible nitric oxide synthase (iNOS) by activating the NF-κB pathway in chondrocytes in OA [53]. The expression of osteopontin in cartilage is regulated by miR-127-5p [54], while miR-139 inhibits the proliferation and migration of chondrocytes [55]. The results of these studies may contribute to the development of radically new methods of therapy for OA in the nearest future.

Conclusion

Despite the huge amount of data of the OA the current treatment options are very limited with no effective cure that might stop or slow down the progression of this disease. The therapeutical options include NSAIDs, paracetamol, non-opioid analgesics, steroids, SYSADOAs, non-pharmacological and surgical methods. In recent years, significant progress has been achieved in understanding of the pathogenetic mechanisms of OA and promising options for biological and cell therapy have been proposed. However, further clinical studies are needed to examine their safety and efficacy.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and rheumatism.* 1998;41(5):778-799. https://doi.org/10.1002/1529-0131(199805)41:5<778::AID-ART4>3.0.CO;2-V
2. Hawker GA. Osteoarthritis is a serious disease. *Clinical and experimental rheumatology*. 2019;37(Suppl 120):3-6.
3. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK. Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. *Osteoarthritis and cartilage*. 2015;23(4):594-600. https://doi.org/10.1016/j.joca.2014.12.022
4. Veronese N, Cereda E, Maggi S, Luchini C, Solmi M, Smith T, et al. Osteoarthritis and mortality: A prospective cohort study and systematic review with meta-analysis. *Seminars in arthritis and rheumatism*. 2016;46(2):160-167. https://doi.org/10.1016/j.semarthrit.2016.04.002
5. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone research*. 2017;5:16044. https://doi.org/10.1038/boneres.2016.44
6. Man GS, Mologhianu G. Osteoarthritis pathogenesis - a complex process that involves the entire joint. *Journal of medicine and life.* 2014;7(1):37-41.
7. Tan Q, Jiang A, Li W, Song C, Leng H. Metabolic syndrome and osteoarthritis: Possible mechanisms and management strategies. *Medicine in Novel Technology and Devices.* 2021;9:100052. https://doi.org/10.1016/j.medntd.2020.100052
8. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone research.* 2017;5:16044-16044. https://doi.org/10.1038/boneres.2016.44
9. Pelletier J-P, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: Potential implication for the selection of new therapeutic targets. *Arthritis & Rheumatism*. 2001;44(6):1237-1247. https://doi.org/10.1002/1529-0131(200106)44:6<1237::AID-ART214>3.0.CO;2-F
10. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. *Nature Reviews Rheumatology.* 2015;11(1):35-44. https://doi.org/10.1038/nrrheum.2014.162
11. Teoh YX, Lai KW, Usman J, Goh SL, Mohafez H, Hasikin K, et al. Discovering Knee Osteoarthritis Imaging Features for Diagnosis and Prognosis: Review of Manual Imaging Grading and Machine Learning Approaches. *Journal of healthcare engineering*. 2022;2022:4138666. https://doi.org/10.1155/2022/4138666
12. Maghbooli Z, Hossein-Nezhad A, Khoshechin G, Niketeghad G, Moradi S, Adabi E, et al. Possible association between circulating CTRP3 and knee osteoarthritis in postmenopausal women. *Aging Clin Exp Res*. 2019;31(7):927-934. https://doi.org/10.1007/s40520-018-1035-5
13. Arden NK, Perry TA, Bannuru RR, Bruyère O, Cooper C, Haugen IK, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nature reviews Rheumatology.* 2021;17(1):59-66. https://doi.org/10.1038/s41584-020-00523-9
14. Vitaloni M, Botto-van Bemden A, Sciortino R, Carné X, Quintero M, Santos-Moreno P, et al. A patients' view of OA: the Global Osteoarthritis Patient Perception Survey (GOAPPS), a pilot study. *BMC Musculoskeletal Disorders.* 2020;21(1):727. https://doi.org/10.1186/s12891-020-03741-0

15. Thomas S, Browne H, Mobasheri A, Rayman MP. What is the evidence for a role for diet and nutrition in osteoarthritis? *Rheumatology (Oxford, England)*. 2018;57(suppl_4):iv61-iv74. https://doi.org/10.1093/rheumatology/key011
16. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis care & research*. 2020;72(2):149-162. https://doi.org/10.1002/acr.24131
17. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis and cartilage.* 2019;27(11):1578-1589. https://doi.org/10.1016/j.joca.2019.06.011
18. Abate M, Vanni D, Pantalone A, Salini V. Hyaluronic acid in knee osteoarthritis: preliminary results using a four months administration schedule. *International journal of rheumatic diseases.* 2017;20(2):199-202. https://doi.org/10.1111/1756-185X.12572
19. Honvo G, Reginster JY, Rabenda V, Geerinck A, Mkinsi O, Charles A, et al. Safety of Symptomatic Slow-Acting Drugs for Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. *Drugs & aging.* 2019;36(Suppl 1):65-99. https://doi.org/10.1007/s40266-019-00662-z
20. Eriksen P, Bartels EM, Altman RD, Bliddal H, Juhl C, Christensen R. Risk of bias and brand explain the observed inconsistency in trials on glucosamine for symptomatic relief of osteoarthritis: a meta-analysis of placebo-controlled trials. *Arthritis care & research.* 2014;66(12):1844-1855. https://doi.org/10.1002/acr.22376
21. Rönn K, Reischl N, Gautier E, Jacobi M. Current surgical treatment of knee osteoarthritis. *Arthritis*. 2011;2011:454873. https://doi.org/10.1155/2011/454873
22. Lauwers M, Au M, Yuan S, Wen C. COVID-19 in Joint Ageing and Osteoarthritis: Current Status and Perspectives. *Int J Mol Sci*. 2022;23(2). https://doi.org/10.3390/ijms23020720
23. Alhassan E, Siaton BC, Hochberg MC. Did COVID-19 impact osteoarthritis - clinical perspective? *Current opinion in rheumatology*. 2022;34(1):68-72. https://doi.org/10.1097/BOR.0000000000000851
24. Quicke JG, Conaghan PG, Corp N, Peat G. Osteoarthritis year in review 2021: epidemiology & therapy. *Osteoarthritis and cartilage.* 2022;30(2):196-206. https://doi.org/10.1016/j.joca.2021.10.003
25. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet Rich Plasma: a short overview of certain bioactive components. *Open medicine (Warsaw, Poland)*. 2016;11(1):242-247. https://doi.org/10.1515/med-2016-0048
26. 26. Hong M, Cheng C, Sun X, Yan Y, Zhang Q, Wang W, et al. Efficacy and Safety of Intra-Articular Platelet-Rich Plasma in Osteoarthritis Knee: A Systematic Review and Meta-Analysis. *BioMed Research International.* 2021;2021:2191926. https://doi.org/10.1155/2021/2191926
27. Abate M, Verna S, Schiavone C, Di Gregorio P, Salini V. Efficacy and safety profile of a compound composed of platelet-rich plasma and hyaluronic acid in the treatment for knee osteoarthritis (preliminary results). *European journal of orthopaedic surgery & traumatology : orthopedie traumatologie*. 2015;25(8):1321-1326. https://doi.org/10.1007/s00590-015-1693-3
28. Dório M, Pereira RMR, Luz AGB, Deveza LA, de Oliveira RM, Fuller R. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. *BMC Musculoskeletal Disorders*. 2021;22(1):822. https://doi.org/10.1186/s12891-021-04706-7
29. Arthroscopy Association of C, Kopka M, Sheehan B, Degen R, Wong I, Hiemstra L, et al. Arthroscopy Association of Canada Position Statement on Intra-articular Injections for Knee Osteoarthritis. *Orthop J Sports Med.* 2019;7(7):2325967119860110-2325967119860110. https://doi.org/10.1177/2325967119860110
30. Smolewska E, Cebula B, Brozik H, Stanczyk J. Relationship between impaired apoptosis of lymphocytes and distribution of dendritic cells in peripheral blood and synovial fluid of children with juvenile idiopathic arthritis. *Arch Immunol Ther Exp (Warsz)*. 2008;56(4):283-289. https://doi.org/10.1007/s00005-008-0030-5
31. Vercoulen Y, Wehrens EJ, van Teijlingen NH, de Jager W, Beekman JM, Prakken BJ. Human regulatory T cell suppressive function is independent of apoptosis induction in activated effector T cells. *PLoS One*. 2009;4(9):e7183. https://doi.org/10.1371/journal.pone.0007183
32. Jones EA, Crawford A, English A, Henshaw K, Mundy J, Corscadden D, et al. Synovial fluid mesenchymal stem cells in health and early osteoarthritis: detection and functional evaluation at the single-cell level. *Arthritis and rheumatism*. 2008;58(6):1731-1740. https://doi.org/10.1002/art.23485
33. de Sousa EB, Casado PL, Moura Neto V, Duarte ME, Aguiar DP. Synovial fluid and synovial membrane mesenchymal stem cells: latest discoveries and therapeutic perspectives. *Stem cell research & therapy.* 2014;5(5):112. https://doi.org/10.1186/scrt501
34. Huangfu D, Osafune K, Maehr R, Guo W, Eijkelenboom A, Chen S, et al. Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2. *Nature Biotechnology.* 2008;26(11):1269-1275. https://doi.org/10.1038/nbt.1502
35. Welch T, Mandelbaum B, Tom M. Autologous Chondrocyte Implantation: Past, Present, and Future. Sports medicine and arthroscopy review. 2016;24(2):85-91. https://doi.org/10.1097/JSA.0000000000000115
36. Welzel T, Winskill C, Zhang N, Woerner A, Pfister M. Biologic disease modifying antirheumatic drugs and Janus kinase inhibitors in paediatric rheumatology - what we know and what we do not know from randomized controlled trials. *Pediatric rheumatology online journal.* 2021;19(1):46. https://doi.org/10.1186/s12969-021-00514-4
37. Feist E, Baraliakos X, Behrens F, Thaçi D, Klopsch T, Plenske A, et al. Effectiveness of Etanercept in Rheumatoid Arthritis: Real-World Data from the German Non-interventional Study ADEQUATE with Focus on Treat-to-Target and Patient-Reported Outcomes. *Rheumatology and Therapy.* 2022;9(2):621-635. https://doi.org/10.1007/s40744-021-00418-5
38. Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N, et al. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis - the HUMOR trial. *Osteoarthritis and cartilage.* 2018;26(7):880-887. https://doi.org/10.1016/j.joca.2018.02.899
39. Kloppenburg M, Peterfy C, Haugen IK, Kroon F, Chen S, Wang L, et al. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann Rheum Dis.* 2019;78(3):413-420. https://doi.org/10.1136/annrheumdis-2018-213336

40. Fleischmann RM, Bliddal H, Blanco FJ, Schnitzer TJ, Peterfy C, Chen S, et al. A Phase II Trial of Lutikizumab, an Anti-Interleukin-1α/β Dual Variable Domain Immunoglobulin, in Knee Osteoarthritis Patients With Synovitis. *Arthritis & rheumatology (Hoboken, NJ)*. 2019;71(7):1056-1069. https://doi.org/10.1002/art.40840
41. Richette P, Latourte A, Sellam J, Wendling D, Piperno M, Goupille P, et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. *Annals of the Rheumatic Diseases*. 2021;80(3):349-355. https://doi.org/10.1136/annrheumdis-2020-218547
42. Schnitzer TJ, Marks JA. A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee. *Osteoarthritis and cartilage.* 2015;23:S8-S17. https://doi.org/10.1016/j.joca.2014.10.003
43. Pallav M, Zaripova L, Tazhibaeva D, Kabdualieva N. POS1126 Clinical efficacy and safety of monoclonal antibody against nerve growth factor and fibroblast growth factor-18 therapy of osteoarthritis. *Annals of the Rheumatic Diseases.* 2022;81(Suppl 1):892-892. https://doi.org/10.1136/annrheumdis-2022-eular.3584
44. Vinatier C, Merceron C, Guicheux J. Osteoarthritis: from pathogenic mechanisms and recent clinical developments to novel prospective therapeutic options. *Drug Discovery Today.* 2016;21(12):1932-1937. https://doi.org/10.1016/j.drudis.2016.08.011
45. Dakin P, DiMartino SJ, Gao H, Maloney J, Kivitz AJ, Schnitzer TJ, et al. The Efficacy, Tolerability, and Joint Safety of Fasinumab in Osteoarthritis Pain: A Phase IIb/III Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *Arthritis & rheumatology (Hoboken, NJ).* 2019;71(11):1824-1834. https://doi.org/10.1002/art.41012
46. Lohmander LS, Hellot S, Dreher D, Krantz EFW, Kruger DS, Guermazi A, et al. Intraarticular Sprifermin (Recombinant Human Fibroblast Growth Factor 18) in Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & Rheumatology.* 2014;66(7):1820-1831. https://doi.org/10.1002/art.38614
47. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis: The FORWARD Randomized Clinical Trial. *Jama.* 2019;322(14):1360-1370. https://doi.org/10.1001/jama.2019.14735
48. Li H, Ding X, Terkeltaub R, Lin H, Zhang Y, Zhou B, et al. Exploration of metformin as novel therapy for osteoarthritis: preventing cartilage degeneration and reducing pain behavior. *Arthritis Res Ther.* 2020;22(1):34. https://doi.org/10.1186/s13075-020-2129-y
49. van Meurs JB. Osteoarthritis year in review 2016: genetics, genomics and epigenetics. *Osteoarthritis and cartilage*. 2017;25(2):181-189. https://doi.org/10.1016/j.joca.2016.11.011
50. Kostopoulou F, Malizos KN, Papathanasiou I, Tsezou A. MicroRNA-33a regulates cholesterol synthesis and cholesterol efflux-related genes in osteoarthritic chondrocytes. *Arthritis Res Ther.* 2015;17(1):42. https://doi.org/10.1186/s13075-015-0556-y
51. Song J, Kim D, Chun C-H, Jin E-J. miR-370 and miR-373 regulate the pathogenesis of osteoarthritis by modulating one-carbon metabolism via SHMT-2 and MECP-2, respectively. *Aging Cell.* 2015;14(5):826-837. https://doi.org/10.1111/acel.12363
52. Li L, Jia J, Liu X, Yang S, Ye S, Yang W, et al. MicroRNA-16-5p Controls Development of Osteoarthritis by Targeting SMAD3 in Chondrocytes. *Current pharmaceutical design*. 2015;21(35):5160-5167. https://doi.org/10.2174/1381612821666150909094712
53. Rasheed Z, Al-Shobaili HA, Rasheed N, Mahmood A, Khan MI. MicroRNA-26a-5p regulates the expression of inducible nitric oxide synthase via activation of NF-κB pathway in human osteoarthritis chondrocytes. *Archives of Biochemistry and Biophysics.* 2016;594:61-67. https://doi.org/10.1016/j.abb.2016.02.003
54. Tu M, Li Y, Zeng C, Deng Z, Gao S, Xiao W, et al. MicroRNA-127-5p regulates osteopontin expression and osteopontin-mediated proliferation of human chondrocytes. *Sci Rep.* 2016;6(1):25032. https://doi.org/10.1038/srep25032
55. Hu W, Zhang W, Li F, Guo F, Chen A. miR-139 is up-regulated in osteoarthritis and inhibits chondrocyte proliferation and migration possibly via suppressing EIF4G2 and IGF1R. *Biochemical and Biophysical Research Communications.* 2016;474(2):296-302. https://doi.org/10.1016/j.bbrc.2016.03.164