# Exploring Cutting-edge Nanomedicine Strategies for the Treatment of Osteoarthritis: A Comprehensive Review

**Avinash Kumar Rao[1*], Ruchi Tiwari[1], Neeraj Sharma[2], Naveen Gupta[1], Dharmendra Rajput[1]**

*[1]Patel College of Pharmacy, [2]Faculty of Medical & Paramedical Sciences, Madhyanchal Professional University (MPU), Bhopal (MP), India*

***Corresponding author**

**Mr. Avinash Kumar Rao**

*Email: avinash66rao@gmail.com*

## Abstract

Osteoarthritis (OA), a chronic joint ailment, manifests as the gradual deterioration of cartilage, the protective tissue covering bone ends in joints. This prevalent musculoskeletal affliction stands as a leading global cause of pain and disability, predominantly impacting the elderly. Rooted in ancient Greek and Roman medical texts, the term "osteoarthritis" embodies joint and bone, with 19th-century insights shaping current understanding. Despite its historical presence, OA remains a significant public health challenge, marked by symptoms like joint pain, stiffness, and reduced mobility. Multiple factors contribute to OA, including age, joint trauma, obesity, genetic predisposition, hormonal imbalances, and metabolic disorders. While current approaches focus on symptom management, there is a growing imperative for advanced therapies given OA's chronic and complex nature and existing treatment limitations. The aging global population intensifies this need, underscoring the demand for long-term efficacy, disease progression halt, and improved quality of life. Nano medicine emerges as a promising frontier, offering precise targeting, controlled drug release, and enhanced bioavailability. Nanoparticles facilitate direct drug delivery to affected joints, minimizing systemic side effects. Various Nano carriers, including liposomes, micelles, dendrimers, polymeric nanoparticles, exosomes, and inorganic nanoparticles, are explored for OA drug delivery, each presenting distinct advantages and challenges. Despite advancements, challenges persist, such as the multifaceted nature of OA, limited regenerative capacity, and complexities in drug delivery within the joint space. However, promising perspectives arise from nanotechnology, regenerative medicine, immunomodulation, and holistic patient care. The interdisciplinary approach, combining advancements in nanotechnology, regenerative medicine, and immunomodulation, holds transformative potential, offering hope for effective and personalized OA treatment strategies.

**Keywords:** Osteoarthritis (OA); Musculoskeletal Affliction; Advanced Therapies; Nanomedicine; Interdisciplinary OA Treatment

## Introduction

Osteoarthritis (OA) is a chronic joint ailment marked by the gradual deterioration of cartilage, the protective tissue covering bone ends in joints. A prevalent musculoskeletal affliction, OA is a leading cause of pain and disability globally, predominantly affecting the elderly. The term "osteoarthritis" originates from the Greek words "osteon" (bone) and "althorn" (joint). Documented since ancient times, early descriptions date back to Greek and Roman medical texts. Substantial understanding of OA's pathology emerged in the 19th century. Characterized by joint pain, stiffness, and reduced mobility, OA poses significant public health challenges, prompting ongoing research into preventive measures and effective management strategies [1].

Numerous factors contribute to the development and progression of osteoarthritis (OA), where age stands out as a primary determinant, correlating with an increased incidence over advancing years. Joint trauma, whether from sports activities or accidents, heightens susceptibility to OA. Obesity exacerbates the risk, imposing significant stress on weight-bearing joints, particularly the knees and hips. Genetic predisposition, hormonal imbalances, and metabolic disorders also contribute to OA development. Diagnosis involves clinical evaluation, imaging such as X-rays and MRI, and, at times, joint aspiration for synovial fluid analysis. Treatment strategies aim at pain relief, improved joint function, and slowing disease progression, encompassing non-pharmacological interventions, medications, and, in severe cases, surgical options. However, the current focus is on early intervention and lifestyle modifications to prevent or delay the need for surgery [2].

The imperative for advanced therapies in osteoarthritis (OA) stems from the complex and chronic nature of the condition, coupled with the limitations of existing treatments. Conventional approaches primarily focus on symptom management and may not effectively address the underlying mechanisms driving OA progression. Advanced therapies, including innovative pharmacological interventions and emerging biotechnological solutions, offer the promise of more targeted and disease-modifying effects [3]. With an aging population and the increasing global burden of OA, there is a critical need to explore and develop therapeutic modalities that can provide long-term efficacy, halt disease progression, and enhance the overall quality of life for individuals affected by OA.

Osteoarthritis (OA) is influenced by a myriad of factors, with age emerging as a primary contributor, leading to increased susceptibility as individuals advance in years. Joint trauma from sports injuries or accidents, obesity imposing excessive stress on weight-bearing joints, genetic predisposition, hormonal imbalances, and metabolic disorders collectively contribute to OA development. The urgent need for advanced therapies in OA treatment is underscored by the limitations of current approaches. Conventional treatments often focus on symptom relief, leaving the underlying disease mechanisms unaddressed. Advanced therapies, including cutting-edge pharmacological and biotechnological interventions, are imperative to offer more targeted, disease-modifying solutions, addressing the multifaceted nature of OA and providing effective long-term outcomes for patients.

## The pivotal role of Nano medicine in Osteoarthritis (OA)

Nano medicine holds substantial promise in addressing the multifaceted challenges posed by osteoarthritis (OA). The unique properties of nanomaterials enable precise targeting, controlled drug release, and enhanced bioavailability, addressing limitations in traditional OA treatments. Nanoparticles can deliver therapeutic agents directly to affected joints, minimizing systemic side effects. Additionally, Nano carriers can encapsulate various drugs, including anti-inflammatory agents and disease-modifying agents, optimizing their efficacy. Diagnostic nanoparticles offer improved imaging for early OA detection. The role of Nano medicine extends to regenerative therapies, promoting cartilage repair. As a burgeoning field, Nano medicine presents an innovative avenue for developing tailored solutions to combat the complexities of OA, offering potential breakthroughs in treatment efficacy and patient outcomes [4].

The utilization of Nano medicine plays a crucial role in tackling the challenges associated with osteoarthritis (OA). Nanomaterials offer distinct advantages, such as precise targeting, controlled drug release, and heightened bioavailability, addressing limitations observed in conventional OA treatments. Nanoparticles enable the direct delivery of therapeutic agents to affected joints, minimizing systemic side effects. Moreover, nanocarriers can encapsulate various drugs, including anti-inflammatory and disease-modifying agents, optimizing their effectiveness. Diagnostic nanoparticles contribute to enhanced imaging for early detection of OA. The application of nanomedicine extends to regenerative therapies, fostering cartilage repair. As an evolving field, nanomedicine provides an innovative avenue for tailored solutions, potentially revolutionizing the treatment landscape for OA challenges[5].

Nanotechnology constitutes an interdisciplinary field encompassing physics, chemistry, biology, electronics, and engineering. Globally, active research and development efforts are dedicated to studying and manipulating particles at atomic, molecular, or macromolecular levels, typically within the 1 to 100 nm size range. Nanoparticles (NPs) exhibit unique properties, such as size effects, interfacial phenomena, and quantum effects, due to their scale structure, making them challenging to predict compared to microparticles. Control and manipulation of nanostructures exploit novel chemical, physical, and biological characteristics of NPs. Nanotechnology's significance lies in its high surface area-to-volume ratio, catalysis suitability, and relevance to molecular structures in the body[6].

Nanotechnology offers unique advantages for OA therapeutics, enhancing drug targeting, delivery efficiency, solubility, and stability. It prevents drug dispersion and degradation, extending circulation and retention time in the body, ultimately improving efficacy and reducing adverse reactions. Recent strides in nanotechnology's development for drug delivery systems provide innovative approaches for OA therapy. This review delves into current advancements and applications of OA-related nanoparticle-based drug delivery, encompassing liposomes, micelles, dendrimers, polymeric nanoparticles (PNPs), exosomes, and inorganic NPs[7].

## Liposomes

Liposomes, aqueous-core spherical vesicles surrounded by a phospholipid bilayer, exhibit varying sizes (50 to 5000 nm) depending on buffer and lipid composition. Morphologically, they include small unilamellar vesicles (around 100 nm), large unilamellar vesicles (200 to 800 nm), and multilamellar vesicles (500 to 5000 nm). Surface modifications, polymer coatings, or antibody attachments allow manipulation of liposomal properties, leading to the creation of immunoliposomes. Regarded as an ideal drug-delivery system, liposomes were the first nano-drug carrier approved by the FDA. Clinical formulations such as AmBisome® (anti-fungal), Doxil® (anti-cancer), and LiprostinTM (anti-thrombosis) underscore their versatility. In the clinical treatment of osteoarthritis (OA) exclusively in Germany, Lipotalon® (dexamethasone palmitate) is administered intra-articularly (IA). Liposomal formulations, widely used in OA, encapsulate hydrophilic and hydrophobic drug cargos within the phospholipid bilayer and aqueous core, ensuring good safety profiles[8].

Adenosine, crucial for cartilage homeostasis, and A2A receptor agonists encapsulated in liposomes prevented OA progression in mice and rat models. Rapamycin, an mTOR inhibitor with potential therapeutic effects in OA, delivered via liposomes, demonstrated significant anti-inflammatory effects. Gold nanoparticles (GNPs) with antioxidant and anti-inflammatory properties were encapsulated in liposomes and delivered IA, exhibiting promising anti-OA effects. Clodronate-loaded liposomes, causing macrophage depletion, reduced synovitis and cartilage degradation in obesity-associated OA mouse models. Liposomal delivery of curcumin, known for anti-inflammatory and antioxidant activities, increased bioavailability and showed potential in slowing OA progression. Despite advantages like biocompatibility and drug entrapment, liposomes face challenges, including drug leakage, physical instability, and rapid synovial fluid clearance, posing hurdles for IA drug-delivery systems[9].

## Micelles

Micelles, nanoscale amphiphilic structures with a hydrophobic core and a hydrophilic shell ranging from 5 to 100 nm, offer a versatile platform for drug delivery. Their size varies based on the amphiphile and drug entrapment properties, allowing them to carry hydrophobic drugs within the core while binding hydrophilic drugs to their shell. The critical micelle concentration (CMC), representing the minimal amphiphile concentration for micelle formation, is a pivotal parameter dictating self-assembly upon reaching the CMC in an aqueous solution. Conjugation with peptides, antibodies, or other targeting ligands facilitates preferential uptake of micelles. Polymeric micelles, composed of block copolymers with hydrophilic and hydrophobic chains, are extensively used in drug delivery systems due to their stability and prolonged circulation time resulting from a low CMC[10].

Despite being primarily employed in cancer clinical practice; polymeric micelles are rarely explored for osteoarthritis (OA) therapy. In the context of OA inflammation characterized by an acidic synovial fluid and overexpressed MMP-13, Psoralidin (PSO), a traditional Chinese medicine with anti-inflammatory effects on OA, was loaded into a theranostic nanoplatform self-assembled by a specific collagen type II targeting peptide (C-PPL) and a peptide substrate of MMP-13 enzyme (MR-PPL).

This nanoplatform (MRC-PPL) was delivered into the joint cavity of mouse models of papain-induced OA, demonstrating significant alleviation of cartilage lesions by down-regulating MMP-13 and exerting anti-OA effects via the NF-κB signaling pathway. Poly (β-amino ester) (PAE), a cationic polymer with low cytotoxicity, was utilized in the design of an acid-activatable curcumin polymer (ACP) micelle. ACP micelles demonstrated therapeutic effects in mouse models of monoidoacetic acid (MIA)-induced OA, protecting articular cartilage significantly by down-regulating TNF-α and IL-1β. Kartogenin (KGN), a compound promoting chondrogenic differentiation of human mesenchymal stem cells, was encapsulated in self-assembled PEGylated kartogenin (PEG/KGN) micelles, further incorporated into HA/PEG/KGN hydrogels. These hydrogels, injected intra-articularly in rat surgically induced OA models, significantly suppressed OA progression. Micelles present advantages such as improving solubility of highly lipophilic drugs, tunable chemical and physical properties, and controlled drug release. However, challenges include non-encapsulation of hydrophilic drugs, CMC dependency, and potential toxicity concerns, necessitating modifications to overcome these limitations[11].

## Dendrites

Dendrimers, intricate macromolecules with repetitively branched tree-like nanostructures, consist of a core, branches, and a shell. The shell, crucial for conjugation with cargo or targeting ligands, encompasses the dendrimer's outer surface, while the hydrophobic core accommodates hydrophobic cargo. The number of generations determines the size of dendrimers, which can be well-defined drug delivery systems, offering advantages such as a precise number of surface functional groups, monodispersity, controllable size, and efficient cargo payload. Polyamidoamine (PAMAM) dendrimers and polypropylene imine dendrimers are commonly used in drug delivery. VivaGelTM, a dendrimer-based commercial medical product, prevents HIV and HSV infection, showcasing the feasibility of dendrimer applications. In clinical trials, dendrimer-based products like ImDendrim for liver cancer, DEP® docetaxel, DEP® cabazitaxel for breast cancer, and OP-101 for X-linked adrenoleukodystrophy have been explored. While dendrimers have been investigated in various applications, their study in osteoarthritis (OA) treatment is limited. Addressing the catabolism exceeding anabolism imbalance in OA chondrocytes, Geiger et al. designed cationic PEGylated PAMAM conjugated with insulin-like growth factor 1 (IGF-1). In vivo studies demonstrated that PEGylated dendrimer–IGF-1 efficiently penetrated rat articular cartilage and rescued cartilage degeneration in surgically induced OA rat models [39]. Additionally, partly PEGylated PAMAM dendrimers were utilized as carriers for the anti-OA drug Kartogenin (KGN). Hu et al. conjugated KGN to PAMAM surfaces to obtain PEG-PAMAM-KGN (PPK) and KGN-PEG-PAMAM (KPP) conjugates, with KPP showing enhanced chondrogenic differentiation of mesenchymal stem cells in vitro, suggesting PEG-PAMAM as a potential nano-drug carrier for OA treatment. Another dendrimer, dendritic polyglycerol sulfate (dPGS), composed of glycerol units and sulfate groups, exhibited anti-inflammatory activity. Administered subcutaneously in surgically induced OA rat models, dPGS effectively reduced Mankin and Glasson score values after 8 weeks, indicating its potential in suppressing OA progression through chondroprotective and anti-inflammatory effects.

Despite dendrimers' advantages, including increased solubility of hydrophobic drugs and tunable physicochemical properties, challenges such as non-entrapping hydrophilic drugs and cellular toxicity persist, akin to micelles. Dendrimers' unique property of multiple functional groups positions them as promising carriers for targeted drug delivery, with modulatable cellular toxicity through surface moieties. The multifaceted nature of dendrimers opens avenues for innovative drug delivery systems, emphasizing their potential impact on diverse medical applications, including the intricate field of osteoarthritis therapy[12,13].

## Polymeric nanoparticles

Polymeric nanoparticles (PNPs), solid particles with a size range of 10–1000 nm, are composed of biocompatible and biodegradable synthetic polymers such as poly(lactide) (PLA), poly(lactide-co-glycolide) copolymers (PLGA), and natural polymers like chitosan, offering structural forms as nanospheres and nanocapsules. Synthesizing PNPs is relatively facile compared to other nanoparticles, making them widely used in nanomedicine for drug delivery, where their functions include extending drug half-life and controlling drug release. PNPs have been extensively explored in clinical trials, with examples like Copaxone® for multiple sclerosis and Abraxane® for breast cancer, but their application in osteoarthritis (OA) clinical trials is yet to be reported. In the context of OA treatment, siRNA-loaded PLGA nanoparticles targeted p66shc and p47phox, crucial contributors to reactive oxygen species (ROS) production in OA cartilage, demonstrating significant reductions in inflammatory cytokines and ROS levels in rat models. Another study utilized PLGA-PEG-PLGA triblock copolymeric nanoparticles for local delivery of the COX-2 selective NSAID etoricoxib in surgically induced OA rats, resulting in symptom alleviation through the down-regulation of OA-related factors. Furthermore, adenosine-functionalized PLA-PEG nanoparticles were employed to target the NF-κB signaling pathway in post-traumatic OA rat models, offering a potential strategy for extending OA therapeutic efficacy. Polyurethane nanoparticles, delivering Kartogenin (KGN), displayed promising results in suppressing OA progression in rat models. Incorporating KGN into poly(lactic acid) microparticles demonstrated extended drug release, protecting against osteochondral lesions in mouse OA models. Additionally, a peptide-polymer platform, binding HA-binding peptide (HABP) to PEG-COLBP conjugate, exhibited efficient localization to cartilage defects and synovium, suppressing cartilage degeneration in both young and aged mouse OA models. Chitosan nanoparticles, loaded with anti-inflammatory berberine chloride (BBR), provided extended drug release and demonstrated anti-OA efficacy in rat models. Another study employed HA/chitosan nanoparticles for curcumin delivery, achieving synergistic suppression of OA development by modulating NF-κB and MMP-13. Plasmid DNA-CrmA complexed with cationic polymers produced CrmA-HA-chitosan nanoparticles, inhibiting IL-1β formation and attenuating cartilage destruction in rat surgically induced OA models. While PNPs offer advantages such as controlled drug release and high stability, challenges like poor drug loading and potential toxicity need continued research and modification for optimal applications in OA therapy[14].

## Exospores

Exosomes, nanoscale vesicles with diameters ranging from 50 to 150 nm, originate from endosomes and consist of a membrane-bound phospholipid bilayer. Loaded with diverse cargo, including nucleic acids (DNAs, mRNAs, microRNAs, and lncRNAs), bioactive lipids, and proteins, exosomes facilitate intercellular communication by transferring these components between cells. Their ubiquitous secretion is noted across various cell types, both in normal and pathological conditions, and they are found in bodily fluids such as blood, urine, saliva, breast milk, and synovial fluids. In the context of osteoarthritis (OA), Mesenchymal Stem Cells (MSCs) have demonstrated therapeutic potential, primarily through the secretion of their secretome, which includes exosomes. Recent research underscores the importance of exosomal microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in conferring anti-OA efficacy. Despite the challenges associated with drug delivery through the dense cartilage matrix, innovative strategies have been devised, such as fusing a chondrocyte-affinity peptide (CAP) onto exosomes derived from chondrocytes. In vivo studies utilizing CAP-exosome-based miR-140 delivery via intra-articular injection showed significant alleviation of OA development in rat models. The mechanisms underlying the anti-OA effects of MSC-derived exosomes are actively under exploration. Current findings suggest that exosomal miRNAs may regulate gene expression in OA-related pathways, including NF-kB, Wnt/β-Catenin, and SIRT1/p53, thereby inhibiting the production of pro-inflammatory cytokines and proteolytic enzymes. Exosomes, beyond serving as therapeutic cargo themselves, are investigated as carriers for drug delivery. However, the limited yield of naturally occurring exosomes poses a challenge for clinical applications, prompting studies exploring approaches like hypoxic three-dimensional spheroid culture, microvesicles, and cellular-nanoporation methods to enhance exosome production. As the understanding of exosome mechanisms grows and manufacturing technologies mature, it is anticipated that exosomes will usher in a new era in the treatment of OA, providing innovative and effective therapeutic avenues[15,16].

## Inorganic nanoparticles

In the human body, peroxidase, catalase, and superoxide dismutase (SOD) serve as crucial antioxidant enzymes, acting to mitigate the damage induced by oxidative stress through the scavenging of reactive oxygen species (ROS). However, the inherent vulnerability of these natural enzymes to factors such as pH, temperature, and proteases in the microenvironment raises challenges in maintaining their activity. Consequently, research has increasingly focused on the development of nanozymes, a type of nanoparticles (NPs) endowed with natural enzyme-like activity. Among the plethora of nanozymes, inorganic NPs—such as cerium oxide (CeO2), manganese dioxide (MnO2), platinum (Pt), and others—have emerged as particularly noteworthy in the realm of biomedicine due to their multi-enzymatic capabilities. Notably, CeO2 and Pt NPs replicate the activities of SOD, catalase, and peroxidase, while MnO2 NPs emulate SOD and catalase activities. Demonstrating efficacy as potent antioxidants for cytoprotection, these inorganic NPs offer promise in addressing oxidative stress-related challenges[17].

For instance, Lin et al. harnessed cerium(III) nitrate hexahydrate and potassium carbonate to synthesize CeO2 NPs (120 nm in size) through a hydrothermal method. Their study confirmed the protective role of CeO2 NPs against H2O2-induced damage in chondrocytes by effectively scavenging ROS. Additionally, Ponnurangam et al. employed commercial CeO2 NPs (65 nm × 8 nm) to treat chondrocytes damaged by IL-1α, demonstrating conspicuous anti-inflammatory effects in an in vitro model of chronic osteoarthritis (OA). In the assessment of MnO2 NPs for their anti-OA potential, Kumar et al. synthesized these NPs through the oxidation of potassium permanganate with poly (allylamine hydrochloride), showcasing their ability to impede the development of OA in an ex vivo bovine model of IL-1β-induced chronic OA by mitigating ROS-induced oxidative stress.

While various nanozymes have proven effective in cytoprotection, traditional chemical and physical synthesis methods raise environmental and safety concerns. Therefore, the exploration of green synthesis methods has gained traction due to their eco-friendly nature and minimal adverse effects. Green synthesis, involving the use of microbes and plant extracts, offers a novel avenue for NP fabrication. Yin et al., for instance, employed chloroplatinic acid and chondroitin sulfate, heating them to biosynthesize Pt NPs (3 to 5 nm in size). Bioactivity analyses demonstrated the biocompatibility of Pt NPs with human OA chondrocytes up to a concentration of 10 ppm, suggesting their potential in OA treatment[18,19].

However, the pivotal challenge faced by inorganic NPs remains their potential toxicity, necessitating robust toxicological assessments to ensure their safety in OA treatment. The acquisition of reliable experimental data through comprehensive toxicology research is imperative to address concerns and facilitate the responsible development of these promising nanozymes.

## Challenge and Perspective in OA Therapy

Osteoarthritis (OA) therapy presents both formidable challenges and promising perspectives, reflecting the complexity of this prevalent degenerative joint disorder. One of the primary challenges lies in the multifaceted nature of OA, encompassing not only cartilage degeneration but also inflammation, synovitis, and altered subchondral bone dynamics. Addressing OA comprehensively necessitates therapies that can simultaneously target these diverse facets. Another challenge is the limited regenerative capacity of articular cartilage, hindering the natural healing process. Developing interventions that promote cartilage repair and regeneration remains a critical hurdle in OA therapy[20].

Furthermore, drug delivery to the joint space, an intricate microenvironment characterized by dense cartilage matrices, poses a significant obstacle. Overcoming this challenge requires innovative strategies to enhance drug penetration and retention within the joint, optimizing therapeutic efficacy. The inherent heterogeneity of OA, with variations in patient profiles, disease progression, and underlying molecular mechanisms, adds complexity to personalized treatment approaches. Tailoring therapies to individual needs remains an ongoing challenge in the pursuit of precision medicine for OA.

Despite these challenges, promising perspectives are emerging on various fronts. Advancements in nanotechnology offer novel avenues for drug delivery, with liposomes, micelles, dendrimers, polymeric nanoparticles, exosomes, and nanozymes demonstrating potential in OA therapy. These nanocarriers provide opportunities to enhance drug bioavailability, improve therapeutic targeting, and mitigate side effects. Moreover, the exploration of natural compounds and traditional medicines, such as curcumin and traditional Chinese medicines, presents an intriguing avenue for developing alternative and complementary OA treatments.

The rise of regenerative medicine, including stem cell-based therapies and tissue engineering, holds great promise for restoring damaged cartilage and addressing the root causes of OA. Harnessing the regenerative potential of mesenchymal stem cells (MSCs) and exploring tissue-engineered constructs offer avenues for long-term structural and functional joint restoration. Additionally, understanding the role of inflammation and the immune system in OA pathogenesis opens doors for targeted immunomodulatory therapies, potentially slowing disease progression. While challenges persist in addressing the intricate facets of OA, innovative therapeutic strategies, coupled with a personalized and interdisciplinary approach, offer promising perspectives. The evolving landscape of OA therapy encompasses advancements in nanotechnology, regenerative medicine, immunomodulation, and holistic patient care, underscoring the potential for transformative breakthroughs in the treatment of this prevalent joint disorder.

## References:

1. Zhang M, Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med. 2010;26(3):355-69.
2. Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol. 2007;213(3):626-34.
3. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. The Lancet. 2011;377(9783):2115-26.
4. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A Disease of the Joint as an Organ. Arthritis Rheum. 2012;64(6):1697-707.
5. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum. 1998;41(8):1343-55.
6. Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. The Lancet. 2015;386(9991):376-87.
7. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res. 2016;4:15040.
8. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019;393(10182):1745-59.
9. Bliddal H, Christensen R. The treatment and prevention of knee osteoarthritis: a tool for clinical decision-making. Expert Opin Pharmacother. 2009;10(11):1793-804.
10. Reginster JY. The prevalence and burden of arthritis. Rheumatology (Oxford). 2002;41 Suppl 1:3-6.
11. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther. 2009;11(3):227.

12. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.
13. Felson DT. Developments in the clinical understanding of osteoarthritis. Arthritis Res Ther. 2009;11(1):203.
14. Hunter DJ. Pharmacologic therapy for osteoarthritis—the era of disease modification. Nat Rev Rheumatol. 2011;7(1):13-22.
15. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A Disease of the Joint as an Organ. Arthritis Rheum. 2012;64(6):1697-707.
16. Goldring MB, Marcu KB. Cartilage homeostasis in health and rheumatic diseases. Arthritis Res Ther. 2009;11(3):224.
17. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. Semin Arthritis Rheum. 2014;43(6):701-12.
18. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64(4):465-74.
19. 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 Cartilage. 2019;27(11):1578-89.
20. Oo WM, Yu SP, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs. 2018;23(4):331-47.