THE ROLE OF INFLAMMATION IN OSTEOARTHRITIS: PATHOGENIC MECHANISMS AND MODERN TREATMENT STRATEGIES

Tolibova Jasmina Jo'rabekovna
Student of Samarkand State Medical University
tolibovajasmin15@gmail.com
Akbarova Munisa Sherzod qizi
Student of Samarkand State Medical University
akbarovamunesa@gmail.com
Amriyeva Marjona Azim qizi
Student of Samarkand State Medical University
marjonaamriyeva200@gmail.com
Jumabaeva Sayora Bakhitbaevna
Student of Samarkand State Medical University
zumabaevasaera783@gmail.com

Abstract: Osteoarthritis (OA) has long been regarded as a passive, "wear-and-tear" degenerative disease of articular cartilage, but contemporary evidence reframes it as a low-grade chronic inflammatory disease affecting the whole joint organ — synovium, cartilage, and subchondral bone alike. This narrative review synthesizes current evidence on the inflammatory pathogenesis of OA and modern treatment strategies, drawing on the 2019 OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis and subsequent updates through 2025. Mechanical joint stress and chondrocyte senescence release damage-associated molecular patterns (DAMPs) that engage Toll-like receptors on synoviocytes and macrophages, activating NF-κB signaling and driving secretion of interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). These cytokines induce chondrocyte expression of matrix metalloproteinase-13 (MMP-13) and ADAMTS-5, degrading type II collagen and aggrecan, while low-grade synovitis, subchondral bone remodeling, osteophyte formation, and neoangiogenesis with nerve ingrowth close a self-perpetuating whole-joint inflammatory cycle that sustains both structural progression and pain. Modern management remains predominantly symptomatic: core non-pharmacologic treatment (exercise, education, and weight management) underlies all care, topical and oral anti-inflammatory agents and intra-articular corticosteroids or hyaluronic acid provide symptom control, and emerging disease-modifying osteoarthritis drugs (DMOADs) targeting inflammatory and catabolic pathways remain investigational, with no agent yet approved for disease modification. A mechanism-based understanding of inflammation in OA, combined with individualized, comorbidity-informed non-surgical management and judicious use of surgery in advanced disease, is central to reducing pain and disability, including within the healthcare system of Uzbekistan.

Keywords: Osteoarthritis, synovitis, inflammation, cartilage degradation, interleukin-1β, matrix metalloproteinase, subchondral bone, disease-modifying osteoarthritis drug.

Methods

This work was prepared as a narrative literature review. A literature search was conducted in September 2026 using PubMed, the OARSI and ACR publication databases, and the websites of major rheumatology and orthopedic societies, with the search terms "osteoarthritis," "synovitis," "inflammation," "cartilage degradation," "disease-modifying osteoarthritis drug," and "OARSI guidelines," combined with filters for publication in English between 2016 and 2026. Priority was given to the 2019 OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis, subsequent OARSI and ACR guideline updates, systematic reviews, and peer-reviewed original research; narrative summaries from established clinical reference sources were included for foundational background. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

Introduction

Osteoarthritis is the most common joint disease worldwide and a leading cause of pain and disability, classically attributed to mechanical wear of articular cartilage with aging. This traditional view treated cartilage loss as a largely passive, degenerative process, with inflammation regarded as a late, secondary consequence of structural damage rather than a driver of disease.

Contemporary understanding has substantially revised this framework: OA is now recognized as a disease of the entire joint organ, in which low-grade, chronic inflammation of the synovium — often subclinical and undetectable on physical examination — is present from early stages and actively drives cartilage catabolism, subchondral bone remodeling, and pain. This inflammatory paradigm has reframed OA research toward mechanism-targeted disease-modifying therapies, even as current clinical management remains largely symptomatic, as reflected in the OARSI and ACR guidelines.

The aim of this review is to summarize the inflammatory mechanisms driving cartilage and subchondral bone pathology in osteoarthritis and to outline modern, evidence-based treatment strategies, with particular emphasis on updated international non-surgical management guidelines and emerging disease-modifying approaches.

Understanding the inflammatory basis of OA and its modern management is relevant across several areas of clinical practice, including:

- Rheumatology (diagnosis, disease monitoring, and pharmacologic management)
- Orthopedic surgery (timing of intra-articular therapy and joint arthroplasty)

- Sports medicine (management of post-traumatic and early-onset osteoarthritis)
- Physical medicine and rehabilitation (exercise-based core treatment and functional restoration)
- Primary care and geriatrics (weight management, comorbidity-guided drug selection)
- Pain medicine (management of nociceptive and centrally sensitized OA pain)

Pathogenesis of Inflammation in Osteoarthritis

The inflammatory cascade of OA begins with mechanical and biological stress on the joint. Repetitive loading, joint malalignment, obesity, prior injury, and age-related chondrocyte senescence together promote breakdown of the cartilage extracellular matrix. This breakdown releases damage-associated molecular patterns (DAMPs) — including fragmented fibronectin and alarmins such as S100A8/A9 — into the joint space, where they are not cleared by an adaptive autoimmune response, as in rheumatoid arthritis, but instead engage the innate immune system directly.

DAMPs bind Toll-like receptors 2 and 4 (TLR2/4) expressed on synoviocytes and resident synovial macrophages, activating the NF-κB signaling pathway. This triggers a low-grade, chronic synovitis characterized by secretion of the principal pro-inflammatory cytokines of OA: interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Unlike the florid, clinically evident synovitis of inflammatory arthritides, OA synovitis is often subtle, detectable primarily on ultrasound or MRI, yet it is present from early in the disease course and correlates with pain and structural progression.

These cytokines act directly on chondrocytes, inducing expression of matrix metalloproteinase-13 (MMP-13), the principal collagenase degrading type II collagen, and ADAMTS-5, the dominant aggrecanase responsible for proteoglycan loss, while simultaneously suppressing chondrocyte synthesis of new matrix. The combined effect of accelerated catabolism and impaired anabolic repair produces progressive cartilage thinning and fibrillation, marking the transition from subclinical joint stress to clinically apparent osteoarthritis. This stepwise inflammatory pathway is illustrated in Figure 1.

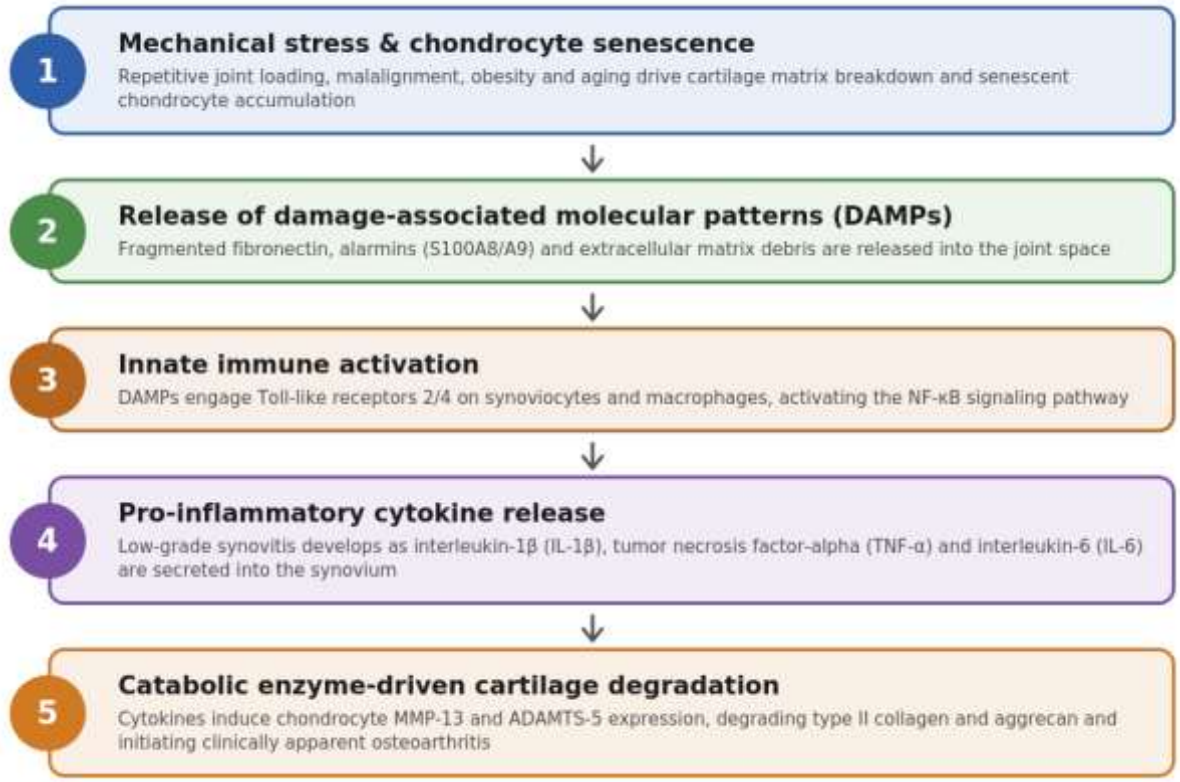

Figure 1. The stepwise inflammatory pathway in osteoarthritis: mechanical stress and chondrocyte senescence release DAMPs that activate innate immune signaling, driving pro-inflammatory cytokine release and catabolic enzyme-mediated cartilage degradation.

The Self-Perpetuating Whole-Joint Inflammatory Cycle

Inflammation and structural damage in OA are mutually reinforcing rather than sequential. Cytokine-driven cartilage catabolism does not remain confined to the cartilage: as the matrix degrades, mechanical load is transferred to the subchondral bone, which undergoes abnormal remodeling characterized by sclerosis, bone marrow lesions, and osteophyte formation at the joint margins. This subchondral bone response further compromises the mechanical environment of the overlying cartilage.

Concurrently, the inflamed synovium and remodeling subchondral bone promote neoangiogenesis and the ingrowth of sensory nerve fibers into the normally aneural osteochondral junction, a process driven substantially by nerve growth factor (NGF). This vascular and neural invasion sensitizes the joint to pain and correlates closely with OA symptom severity, often more strongly than radiographic severity. As cartilage and bone matrix continue to break down, additional DAMPs are released into the joint space, re-engaging synovial innate immune activation and closing a self-amplifying cycle that sustains both structural progression and chronic pain. This reinforcing loop is depicted in Figure 2.

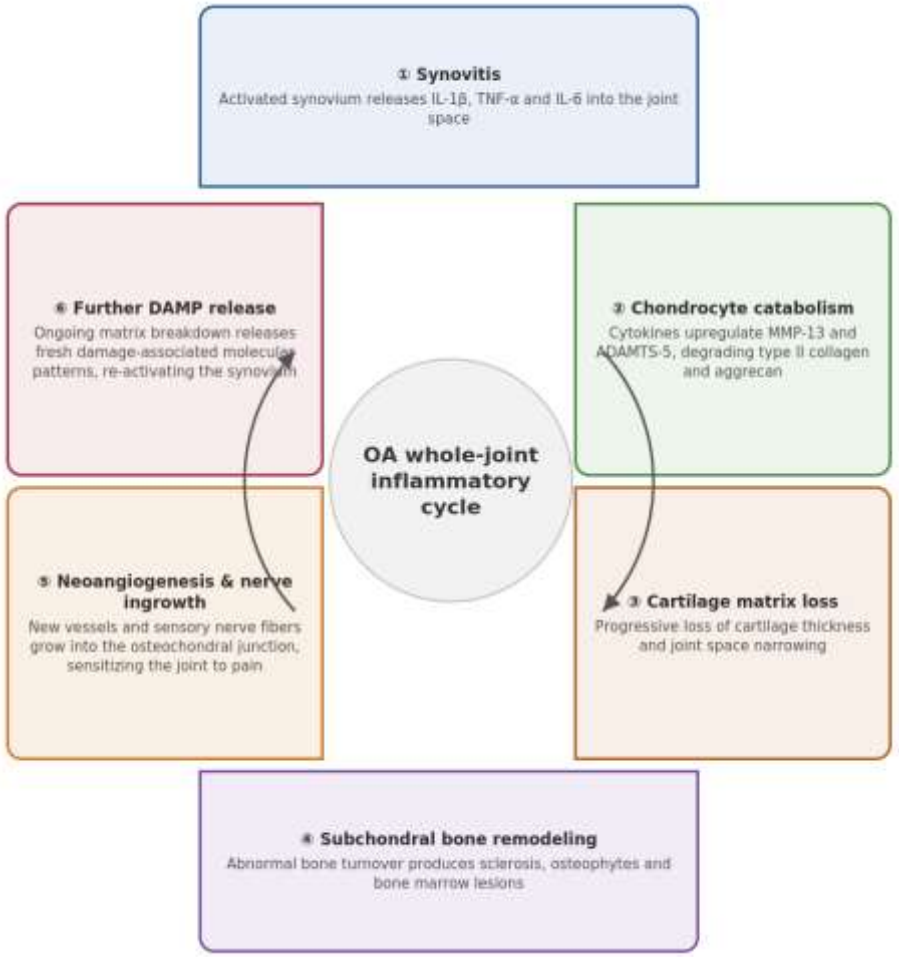

Figure 2. The self-perpetuating whole-joint inflammatory cycle in osteoarthritis: synovitis drives chondrocyte catabolism and cartilage matrix loss, subchondral bone remodeling, and neoangiogenesis with nerve ingrowth, releasing further DAMPs that re-activate the synovium.

The principal inflammatory mediators driving this cycle, and their main pathogenic effects, are summarized in Table 1.

Mediator	Principal Cellular Source	Main Pathogenic Effect
Interleukin-1β (IL-1β)	Synovial macrophages, chondrocytes	Induces MMP-13 and ADAMTS-5, suppresses collagen/aggrecan synthesis
Tumor necrosis factor-alpha (TNF-α)	Synoviocytes, macrophages	Amplifies NF-κB signaling, sustains synovial inflammation

Mediator	Principal Cellular Source	Main Pathogenic Effect
Interleukin-6 (IL-6)	Synoviocytes, chondrocytes	Promotes cartilage catabolism and systemic low-grade inflammation
MMP-13	Chondrocytes	Primary collagenase degrading type II collagen fibrils
ADAMTS-5	Chondrocytes, synoviocytes	Principal aggrecanase; degrades proteoglycan aggrecan core
Nerve growth factor (NGF)	Synoviocytes, chondrocytes, osteoblasts	Drives sensory nerve sprouting and peripheral pain sensitization

Modern Treatment Strategies

Despite the inflammatory reframing of OA pathogenesis, no disease-modifying osteoarthritis drug (DMOAD) has yet received regulatory approval, and current management according to the 2019 OARSI guidelines and subsequent updates remains predominantly symptomatic and stratified by comorbidity. Core treatment — structured exercise, patient education, and dietary weight management for overweight or obese patients — is recommended for all individuals with knee, hip, or polyarticular OA regardless of disease severity, and forms the foundation upon which pharmacologic therapy is added.

Topical NSAIDs are strongly recommended as first-line pharmacologic therapy for knee OA given their favorable systemic safety profile, with oral NSAIDs or COX-2 selective inhibitors considered for inadequate response, taking into account gastrointestinal, cardiovascular, and renal comorbidity. Intra-articular corticosteroid injections provide short-term relief by directly suppressing synovitis, while intra-articular hyaluronic acid may be offered depending on individual comorbidity profiles, though its benefit is more modest and inconsistent across trials. Current guidance recommends against routine opioid use and against intra-articular platelet-rich plasma or mesenchymal stem cell injections, reflecting persistently low-quality supporting evidence for these interventions.

The inflammatory paradigm of OA has motivated a growing pipeline of investigational DMOADs that directly target the mechanisms described above: anti-NGF monoclonal antibodies (such as tanezumab) address pain arising from neoangiogenesis and nerve

ingrowth, IL-1 pathway inhibitors aim to interrupt cytokine-driven cartilage catabolism, and fibroblast growth factor-18 analogues (such as sprifermin) attempt to stimulate cartilage anabolism directly. As of the most recent OARSI-affiliated literature reviews, however, none of these agents has demonstrated a sufficiently favorable efficacy and safety profile to achieve approval as a disease-modifying therapy, and total joint arthroplasty therefore remains the definitive intervention for advanced, symptom-limiting disease that has not responded to non-surgical management. The principal treatment categories and their current evidence base are summarized in Table 2.

Treatment Category	Modern Approach and Evidence Base
● Core (foundational)	Structured land-based exercise, patient education, and dietary weight management for overweight patients; recommended for all patients regardless of disease stage
● Topical / oral pharmacologic	Topical NSAIDs are first-line for knee OA; oral NSAIDs or COX-2 inhibitors considered with attention to gastrointestinal, cardiovascular and renal comorbidity
● Intra-articular therapy	Intra-articular corticosteroids provide short-term relief of synovitis; intra-articular hyaluronic acid may be considered depending on comorbidity profile
● Discouraged interventions	Current OARSI guidance recommends against intra-articular platelet-rich plasma and stem cell injections, and against routine opioid use, given low-quality evidence
● Emerging DMOADs	Investigational disease-modifying OA drugs targeting inflammation and pain include anti-NGF antibodies (tanezumab), IL-1 pathway inhibitors, and FGF-18 analogues (sprifermin); none are yet approved for disease modification
● Surgical management	Total joint arthroplasty is reserved for advanced, refractory disease after non-surgical options have been exhausted

Conclusion

Osteoarthritis is now understood not as a passive degenerative process but as a low-grade, chronic inflammatory disease of the whole joint, in which DAMP-driven innate immune activation, pro-inflammatory cytokine release, catabolic enzyme-mediated cartilage breakdown, subchondral bone remodeling, and neoangiogenesis with nerve ingrowth together form a self-perpetuating cycle that drives both structural progression and pain.

Current evidence-based management, guided by the OARSI and related international guidelines, remains centered on core non-pharmacologic treatment supplemented by symptom-directed pharmacologic and intra-articular therapy, while emerging disease-modifying agents targeting the inflammatory pathway remain investigational. Continued application of mechanism-based understanding, individualized comorbidity-guided treatment selection, and timely surgical referral where indicated holds the potential to reduce pain, preserve function, and improve long-term quality of life for patients with osteoarthritis, including within the healthcare system of Uzbekistan.

References

[1] Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589.

[2] Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020;72(2):220-233.

[3] Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.

[4] Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12(10):580-592.

[5] Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther. 2017;19(1):18.

[6] Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697-1707.

[7] Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. Ann N Y Acad Sci. 2010;1192:230-237.

[8] Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745-1759.

[9] Wood MJ, Miller RE, Malfait AM. The genesis of pain in osteoarthritis: inflammation as a mediator of osteoarthritis pain. Clin Geriatr Med. 2022;38(2):221-238.

[10] Miller RE, Malfait AM, Block JA. Current status of nerve growth factor antibodies for the treatment of osteoarthritis pain. Clin Exp Rheumatol. 2017;35 Suppl 107(5):85-87.

[11] Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. Osteoarthritis Cartilage. 2020;28(3):242-248.

[12] Latourte A, Kloppenburg M, Richette P. Emerging pharmaceutical therapies for osteoarthritis. Nat Rev Rheumatol. 2020;16(12):673-688.