

## OSTEOARTHRITIS REVISITED: ADVANCES IN UNDERSTANDING AND THERAPEUTIC APPROACHES

Ravindra Choudhary<sup>1\*</sup> and Dr. R. S. Tomar<sup>2</sup>

<sup>1</sup>PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur,  
Rajasthan.

<sup>2</sup>Asst. Professor, Department of Pharmacology, Bhupal Nobles' College of Pharmacy,  
Udaipur, Rajasthan.

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**\*Corresponding Author**

**Ravindra Choudhary**

PG Scholar, Department of  
Pharmacology, Bhupal  
Nobles' College of  
Pharmacy, Udaipur,  
Rajasthan.

### ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide, particularly among the aging population. Characterized by the progressive degeneration of articular cartilage, subchondral bone changes, and synovial inflammation, OA leads to chronic pain, stiffness, and functional impairment. The disease is multifactorial, influenced by aging, mechanical stress, obesity, genetics, and lifestyle factors. Despite its high prevalence, especially in weight-bearing joints like the knees and hips, the pathogenesis of OA remains complex and incompletely understood. Current treatment approaches are primarily symptomatic, focusing on pain management and improving joint function, while disease-modifying therapies are still under investigation. This review aims to provide a comprehensive overview of the epidemiology, risk factors, pathophysiology, diagnostic methods, and emerging therapeutic strategies in

osteoarthritis, with a particular emphasis on the challenges and opportunities for early diagnosis and intervention. Advancements in molecular research and imaging technologies offer promising directions for improving patient outcomes and personalizing care in OA management.

### INTRODUCTION

Osteoarthritis (OA) represents a heterogeneous group of musculoskeletal disorders that primarily affect joint integrity and functionality. It is characterized by a complex interplay of

mechanical, cellular, and biochemical processes leading to progressive degeneration of articular cartilage, subchondral bone sclerosis, osteophyte development, and joint deformities. These pathological changes result in chronic pain, reduced joint mobility, stiffness, and eventual loss of function, contributing significantly to disability and compromised quality of life (Loeser et al., 2012). The underlying pathophysiology of OA involves dysfunction of chondrocytes—specialized cells responsible for maintaining cartilage homeostasis. When these cells become imbalanced, the synthesis and degradation of extracellular matrix components become dysregulated, fostering cartilage erosion and synovial inflammation (Bobinac et al., 2003).

In recognition of its widespread health burden, the Osteoarthritis Research Society International (OARSI) officially classified OA as a serious disease in 2016. This decision was influenced by the substantial impact of OA on morbidity, increased risk of all-cause mortality, and the growing socioeconomic costs associated with long-term care and reduced productivity (March et al., 2016). OA can present in a localized form, commonly affecting large joints such as the knees and hips, or in a generalized form involving multiple joints. Post-traumatic osteoarthritis is a well-documented subset of the disease, often arising after joint injury, with symptoms manifesting approximately a decade after the trauma (Felson, 1990). Conversely, genetically predisposed or familial OA tends to emerge earlier, sometimes soon after skeletal maturity, due to structural abnormalities in the cartilage matrix. For example, mutations in the gene encoding type II collagen have been directly linked to the premature onset of OA, emphasizing the role of genetic factors in disease pathogenesis (Ala-Kokko et al., 1990).

Although the initial triggers leading to chondrocyte dysfunction and matrix imbalance remain unclear, researchers have identified several potential biomarkers that may assist in diagnosing and tracking disease progression. Notably, markers such as type II collagen degradation products and cartilage oligomeric matrix protein (COMP) are under investigation for their predictive value in OA (Pastrama et al., 2019). Clinically, OA is diagnosed through a comprehensive assessment that includes patient history, symptomatology, physical examination, and confirmatory imaging techniques. Radiological indicators—such as joint space narrowing, osteophyte formation, subchondral sclerosis, and subchondral cysts—are most prominent in joints subjected to frequent mechanical stress, such as the knees, hips, and vertebral column (Taruc-Uy & Lynch, 2013).

Despite its high global prevalence, OA currently lacks a definitive cure. Management strategies are primarily symptomatic and focus on pain relief, functional improvement, and enhancement of joint mobility. These include a multimodal approach involving pharmacologic therapy (e.g., NSAIDs, analgesics), physical rehabilitation, weight management, and, when conservative interventions fail, surgical options like total joint arthroplasty.

Recent advancements in biomedical research have shed light on the molecular basis of OA. Chronic inflammation, altered chondrocyte metabolism, and genetic susceptibility are now recognized as central contributors to disease progression. Understanding these elements opens the door for novel therapeutic strategies that move beyond symptom control and aim to arrest or even reverse joint degeneration.

This review aims to present a detailed examination of OA by addressing its epidemiological trends, molecular and cellular mechanisms, diagnostic approaches, and therapeutic innovations. In addition, it highlights laboratory techniques used to investigate protein expression in joint tissues, especially in the context of rheumatic diseases like rheumatoid arthritis (RA). Techniques such as the Bradford protein assay, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and histological staining methods are instrumental in analyzing protein changes associated with joint degeneration and inflammation.

OA is a multifactorial disease with both mechanical and biological underpinnings. Aging remains one of the primary risk factors due to the natural decline in the regenerative capacity of cartilage. However, it is now evident that OA is not an unavoidable consequence of aging alone. Factors such as obesity, joint misalignment, occupational or recreational stress on joints, metabolic syndrome, and inherited structural anomalies also play substantial roles. In particular, obesity poses a dual threat—not only increasing biomechanical stress on load-bearing joints but also promoting a pro-inflammatory state through the secretion of adipokines, which can accelerate cartilage degradation. Moreover, joint trauma, including ligamentous injuries and fractures, often leads to post-traumatic osteoarthritis, a subtype that manifests at a younger age due to accelerated wear and tear (Deshpande et al., 2016).

On a cellular level, OA is characterized by a shift in the balance between anabolic and catabolic activities within the joint environment. Chondrocytes lose their ability to maintain

matrix homeostasis and instead secrete increased amounts of matrix metalloproteinases (MMPs) and aggrecanases, which degrade the cartilage matrix. The accumulation of these enzymes, coupled with pro-inflammatory cytokines such as interleukin-1 $\beta$  and tumor necrosis factor-alpha, contributes to a self-perpetuating cycle of joint inflammation and degradation. Although OA has historically been labeled a non-inflammatory arthropathy, there is now considerable evidence suggesting that persistent, low-grade inflammation plays a central role in its pathophysiology, complicating both its clinical presentation and treatment response (Pal et al., 2016).

The clinical manifestations of OA vary widely between individuals and depend on the joints affected, the degree of structural damage, and comorbid conditions. The primary symptom is activity-related joint pain, which typically improves with rest. Additional features include stiffness—especially in the morning or after periods of inactivity—joint swelling, crepitus, and restricted range of motion. Over time, muscle atrophy and joint deformities may emerge, significantly impairing mobility and independence. Interestingly, radiological severity does not always correlate with symptom intensity; some patients with extensive joint damage remain relatively asymptomatic, while others with mild radiographic findings report severe pain and dysfunction.

Diagnostic confirmation involves clinical evaluation supplemented by imaging. While plain radiographs remain the first-line diagnostic modality due to their accessibility and cost-effectiveness, magnetic resonance imaging (MRI) offers a more detailed assessment of soft tissue structures, cartilage lesions, and early joint alterations. Additionally, biochemical markers found in serum and synovial fluid—though not yet standardized—are being explored for their potential in early detection and monitoring disease activity (Sinusas, 2012a; Emery et al., 2019).

In terms of treatment, the primary goal is to manage symptoms and slow disease progression. Non-pharmacologic interventions—such as weight reduction, exercise, and physiotherapy—form the foundation of OA management. These are often combined with medications like acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and topical agents to alleviate pain. In advanced cases, surgical options such as arthroscopy, osteotomy, or joint replacement may be indicated to restore mobility and reduce pain.

Emerging therapies rooted in regenerative medicine show promise for transforming OA treatment. Investigational strategies such as autologous stem cell transplantation, platelet-rich plasma (PRP) therapy, and gene-based therapies are being explored for their potential to promote cartilage regeneration and inhibit inflammatory cascades. Additionally, the development of disease-modifying osteoarthritis drugs (DMOADs) offers hope for altering the disease course rather than merely suppressing symptoms (Zengini et al., 2018).

As OA continues to impose a heavy burden on global health systems, ongoing research is imperative to unravel its complex etiology, identify predictive biomarkers, and develop targeted therapies. The integration of advanced molecular techniques, biomechanics, and personalized medicine may revolutionize OA management in the future. Ultimately, a deeper understanding of the disease mechanisms will pave the way for more effective and individualized interventions, enhancing patient quality of life and reducing the societal impact of this chronic, debilitating condition.

### **Current treatments**

Current treatment strategies for osteoarthritis (OA) are primarily focused on alleviating symptoms, improving joint function, and enhancing quality of life, as there is no known cure that can reverse or halt the disease completely. Management is typically multimodal, involving a combination of non-pharmacological, pharmacological, and surgical approaches depending on the severity of the disease and the individual needs of the patient. Non-pharmacological interventions form the cornerstone of OA management and include patient education, physical therapy, regular low-impact exercise, weight management, and assistive devices to reduce joint strain. Pharmacologic options commonly include acetaminophen for mild pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for more persistent symptoms, and intra-articular corticosteroid injections for acute flare-ups. Topical NSAIDs and capsaicin creams may also be beneficial for localized pain relief, particularly in patients who cannot tolerate systemic medications. In certain cases, duloxetine, a serotonin-norepinephrine reuptake inhibitor, may be used to manage chronic pain associated with OA. When conservative measures fail to provide adequate relief, surgical interventions such as arthroscopy, osteotomy, or total joint replacement may be considered, particularly in cases of advanced joint damage. Emerging therapies, including platelet-rich plasma (PRP) injections, mesenchymal stem cell therapies, and disease-modifying osteoarthritis drugs (DMOADs), are

currently under investigation and offer hope for more targeted and potentially regenerative treatment options in the near future.

### Recent advancements

Osteoarthritis (OA) management primarily focuses on alleviating symptoms, improving joint function, and enhancing the quality of life, as there is currently no definitive cure. The treatment strategies are multifaceted and tailored to individual patient needs, encompassing:

- **Non-Pharmacological interventions:** These include patient education, weight management, physical therapy, and the use of assistive devices. Regular low-impact exercises, such as swimming and walking, can help maintain joint mobility and reduce stiffness.
- **Pharmacological therapies:** Common medications involve analgesics like acetaminophen for pain relief and nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation. Intra-articular corticosteroid injections may be administered for short-term relief in cases of acute exacerbations.
- **Surgical Options:** When conservative treatments fail, surgical interventions such as arthroscopy, osteotomy, or total joint replacement may be considered, especially in advanced stages of OA.

Recent years have witnessed significant progress in OA research, leading to innovative therapies aimed at not only symptom management but also disease modification and tissue regeneration:

1. **Injectable biomaterials for cartilage regeneration:** Researchers at Northwestern University have developed an injectable "goo" composed of hyaluronic acid and peptides that promotes cartilage regeneration. In preclinical studies involving sheep, this biomaterial successfully regrew cartilage in knee joints within six months, offering a potential alternative to joint replacement surgeries.
2. **Semaglutide for pain Reduction and Weight loss:** A study involving 407 obese patients with knee OA demonstrated that semaglutide, a medication initially used for type 2 diabetes, led to significant weight loss and nearly a 50% reduction in knee pain over 68 weeks. This dual benefit addresses both mechanical stress and inflammatory aspects of OA.
3. **Genicular Artery Embolization (GAE):** GAE is a minimally invasive procedure that involves blocking specific arteries to reduce inflammation and pain in the knee joint. A

study reported that patients undergoing GAE experienced an 87% improvement in quality-of-life indices and a 71% reduction in pain scores one year post-treatment.

4. **Nasal cartilage transplantation:** Innovative techniques using cartilage harvested from the nasal septum have shown promise in repairing knee joint damage. In a study, 90% of patients receiving nasal cartilage transplants reported significant improvements in mobility and pain reduction.
5. **Liposomal dexamethasone (TLC599):** A phase 3 clinical trial introduced TLC599, a liposomal formulation of dexamethasone, which provided sustained pain relief in knee OA patients for up to 24 weeks after a single injection, outperforming traditional corticosteroid treatments.
6. **Nano-PAZII therapy:** Utilizing nanotechnology, Nano-PAZII delivers the drug pazopanib directly to affected joints, targeting specific receptors involved in OA progression. This approach has shown potential in reducing pain and slowing cartilage degeneration in preclinical models.
7. **AI-Driven diagnostic tools:** Artificial intelligence systems have been developed to analyze knee X-rays, accurately detecting OA-related changes and grading disease severity. Such tools can facilitate early diagnosis and personalized treatment planning.
8. **Stem cell therapies:** Mesenchymal stem cell (MSC) treatments, particularly those derived from adipose tissue, have demonstrated efficacy in reducing pain and improving joint function in OA patients. A meta-analysis highlighted significant improvements in cartilage status and a favorable safety profile for these therapies.
9. **Gene therapy innovations:** Emerging gene therapies aim to modify the expression of genes implicated in cartilage degradation. Techniques involving fibroblast growth factor 18 (FGF18) have shown promise in stimulating cartilage repair, potentially altering the disease course of OA.
10. **Digital twin technology:** The development of digital twins—virtual models of a patient's knee joint—leverages quantitative MRI biomarkers and machine learning to predict OA progression and optimize treatment strategies, heralding a new era in personalized medicine.

These advancements signify a paradigm shift in OA management, moving beyond symptomatic relief towards interventions that address the underlying pathophysiology of the disease. Continued research and clinical trials are essential to validate these therapies and

integrate them into standard care practices, offering hope for improved outcomes for OA patients worldwide.

## CONCLUSION

Osteoarthritis (OA) is a chronic, multifactorial joint disease that represents a leading cause of disability worldwide. Characterized by the progressive degeneration of articular cartilage, subchondral bone sclerosis, osteophyte formation, and synovial inflammation, OA significantly impairs joint function and reduces quality of life. While age-related wear and tear is a major risk factor, OA is not merely a consequence of aging. Its development is influenced by complex interactions between genetic predisposition, mechanical stress, obesity, previous joint injuries, and inflammatory processes. Recent insights reveal that low-grade inflammation and metabolic dysfunction play more prominent roles than previously recognized, highlighting OA as a disease of the whole joint rather than cartilage alone.

Current diagnostic approaches rely primarily on clinical assessment and imaging, with biomarkers emerging as potential tools for early detection and disease monitoring. Despite a wide array of treatment options—including pharmacological therapies, physical therapy, lifestyle modifications, and surgical interventions—no curative therapy exists. Most treatments aim to relieve pain, reduce inflammation, and preserve joint mobility.

Encouragingly, recent scientific and technological advancements are reshaping the landscape of OA management. Innovations such as injectable biomaterials that regenerate cartilage, semaglutide for pain reduction and weight loss, minimally invasive procedures like genicular artery embolization (GAE), and nasal cartilage transplantation have shown promising results in clinical trials. Moreover, novel approaches in gene therapy, stem cell treatment, and targeted drug delivery systems (e.g., Nano-PAZII) offer hope for disease-modifying interventions. Digital tools such as AI-based diagnostics and digital twin modeling are paving the way for personalized treatment strategies.

As OA continues to place a growing burden on healthcare systems, research aimed at understanding its molecular and cellular mechanisms is critical. Integrating traditional approaches with cutting-edge therapies may not only improve symptom control but also alter the course of the disease. With continued interdisciplinary collaboration and investment in translational research, the future holds promising potential for more effective and

individualized OA treatment strategies—ultimately improving patient outcomes and quality of life.

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