WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 16, 1386-1393. Review Article ISSN 2277–7105

EMERGING BIOMARKERS IN OSTEOARTHRITIS: CURRENT INSIGHTS AND FUTURE DIRECTIONS

Ravindra Choudhary[1]*, Dr. R. S. Tomar[2]

*[1]PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan.

[2]Asst. Professor, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan.

Article Received on
05 July 2025,

Revised on 25 July 2025,
Accepted on 15 August 2025

DOI: 10.20959/wjpr202517-38142

***Corresponding Author**
Ravindra Choudhary
PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan.

ABSTRACT

Osteoarthritis (OA) is not only a leading cause of disability but also a complex, multifactorial condition influenced by mechanical, metabolic, and inflammatory pathways. In addition to the 528 million cases reported in 2019, recent projections indicate that by 2050 over 700 million people may be living with OA globally. This makes OA a pressing global health challenge, particularly in low- and middle-income countries where early detection and treatment infrastructure remain underdeveloped. The economic burden also extends beyond direct medical costs to include lost productivity, caregiver burden, and societal impacts. Biomarkers offer the opportunity to fundamentally shift OA management from late-stage symptomatic care to proactive and personalized interventions. Osteoarthritis (OA) is the most prevalent degenerative joint disease worldwide, affecting an estimated 528 million people in 2019 and projected to rise by 2050 with aging populations and obesity epidemics. The disease accounts for 2–3% of global disability-adjusted life years (DALYs) and imposes an economic burden equivalent to 1–2.5% of GDP in high-income countries. Current diagnostic approaches, including clinical assessment and radiography, lack sensitivity for early detection and have limited ability to predict disease progression. Biomarkers represent a critical opportunity to fill this gap. They can be classified into biochemical, imaging, genetic/epigenetic, and omics-derived categories. This review provides a comprehensive overview of established and emerging OA biomarkers,

their clinical utility, challenges in validation, and future directions, including multi-biomarker panels and AI-driven integrative approaches to advance personalized medicine in OA.

1. INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disease characterized by progressive breakdown of articular cartilage, subchondral bone remodeling, osteophyte formation, and synovial inflammation. It is the leading cause of pain and disability in older adults, with knee and hip OA being the most clinically relevant forms. The disease burden is projected to increase globally due to aging populations and rising obesity rates.

Epidemiological studies demonstrate that the lifetime risk of symptomatic knee OA is approximately 45% in the general population, and up to 60% in obese individuals. Current clinical tools such as Kellgren-Lawrence radiographic grading are limited by their reliance on structural changes that often occur years after symptoms begin. Emerging diagnostic approaches incorporating biomarkers and advanced imaging techniques may allow clinicians to identify high-risk individuals well before radiographic evidence appears. Moreover, biomarkers could play a crucial role in guiding the development and approval of disease-modifying OA drugs (DMOADs), which are currently lacking.

Diagnosis and monitoring of OA currently rely on clinical evaluation and radiographic imaging (e.g., Kellgren-Lawrence grading). However, these tools are limited in detecting early disease and in predicting progression. As no disease-modifying OA drugs (DMOADs) are yet available, there is a critical need for biomarkers that can enable early detection, stratify patients, and monitor therapeutic response.

Biomarkers, as defined by the NIH and OARSI, are objectively measured indicators of normal biological processes, pathogenic processes, or responses to therapeutic intervention. This review outlines biochemical, imaging, genetic/epigenetic, and omics-derived biomarkers of OA, with emphasis on their potential clinical applications and current limitations.

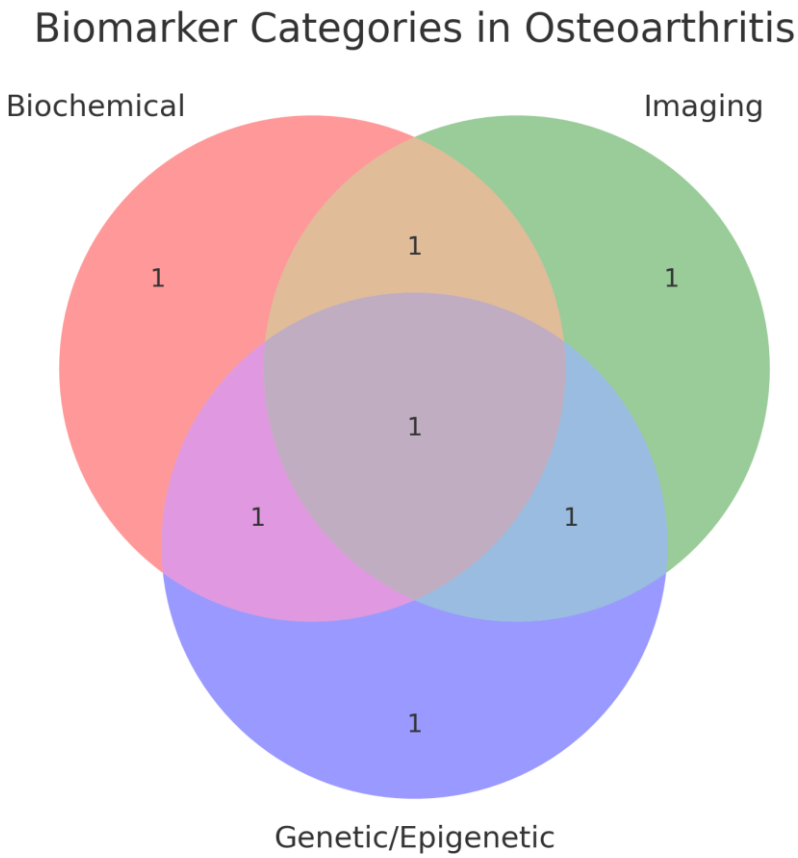

Figure 1: Categories of osteoarthritis biomarkers (biochemical, imaging, genetic/epigenetic).

2. Biochemical Biomarkers

Biochemical biomarkers not only reflect cartilage and bone metabolism but also serve as measurable indicators of systemic and local inflammation. Recent studies have highlighted neoepitope biomarkers generated by specific enzymatic cleavage events, such as Coll2-1 and Coll2-1NO2, which are linked to oxidative stress pathways in OA. Other molecules like YKL-40, a glycoprotein secreted by chondrocytes, have emerged as potential predictors of disease progression and response to therapy. Advances in multiplex assay technologies are enabling simultaneous measurement of panels of biomarkers, offering greater predictive power than single markers.

Biochemical biomarkers provide insight into cartilage, bone, and synovial tissue metabolism. Large cohort studies such as the Osteoarthritis Initiative (OAI) and the CHECK cohort have evaluated their predictive performance.

2.1 Cartilage Degradation Markers

- CTX-II: Elevated in urine/serum, reflecting type II collagen breakdown. In OAI, baseline CTX-II predicted radiographic progression with an AUC of 0.68. Meta-analyses confirm its role as a prognostic marker.
- Aggrecan fragments: Released during cartilage degradation, correlating with cartilage volume loss measured on MRI.
- COMP: Serum COMP levels are consistently elevated in progressive OA and correlate with MRI cartilage thickness loss.

2.2 Bone Metabolism Markers

- CTX-I: Marker of bone resorption; elevated in subchondral bone changes.
- PINP: Indicates bone formation; elevated PINP combined with CTX-I improves prediction of bone remodeling.
- Osteocalcin: Associated with increased bone turnover in hip and knee OA.

2.3 Inflammatory Biomarkers

- CRP: High-sensitivity CRP is weakly but significantly associated with radiographic OA progression.
- Cytokines: IL-1β, IL-6, and TNF-α levels in serum/synovial fluid are linked with synovitis and disease activity.
- Adipokines: Leptin and adiponectin link obesity with OA risk, influencing systemic low-grade inflammation.

2.4 Synovial Fluid Biomarkers

- Hyaluronic acid: Elevated in synovial fluid and serum, reflecting synovitis and cartilage degradation.
- Lubricin: Reduced in OA joints; lower levels predict worsening functional impairment.

Table 1: Biochemical biomarkers of OA.

Biomarker	Tissue/Fluid Source	Study Evidence	Clinical Utility
CTX-II	Urine/Serum	OAI cohort; AUC 0.68	Predicts progression
COMP	Serum/Synovial Fluid	Meta-analyses; MRI correlation	Cartilage turnover
CRP	Serum	Population-based cohorts	Inflammatory activity
Hyaluronic Acid	Synovial Fluid/Serum	CHECK cohort	Disease severity

3. Imaging Biomarkers

In addition to MRI, ultrasound, and PET/MRI, advanced modalities such as ultrashort echo time (UTE) MRI and quantitative susceptibility mapping (QSM) are being investigated for their ability to detect early cartilage and subchondral bone changes. AI-driven image analysis has further enhanced biomarker discovery by enabling automated cartilage segmentation, synovitis detection, and prediction of joint replacement risk. Longitudinal imaging studies such as those from the OAI cohort continue to validate imaging biomarkers as surrogate endpoints for clinical trials.

Imaging biomarkers provide non-invasive insight into structural and biochemical changes. MRI is the gold standard for soft tissue assessment, while ultrasound offers cost-effective synovitis detection. PET/MRI and AI-based imaging are emerging.

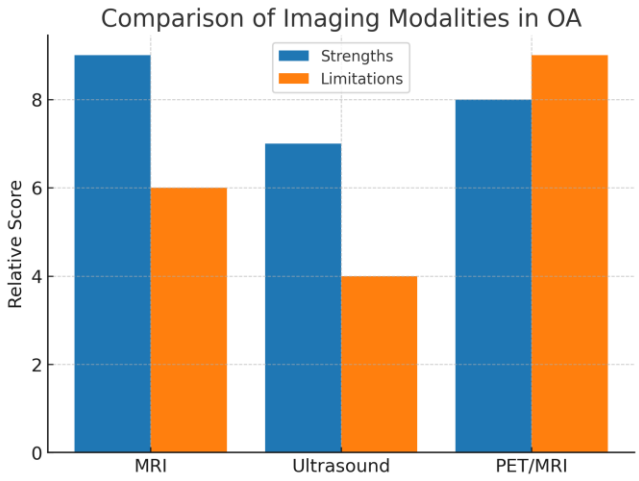

Figure 2: Comparative strengths and limitations of imaging modalities in OA.

Table 2: Imaging modalities in OA.

Modality	Strengths	Limitations
MRI	Quantitative T2, dGEMRIC; detects early biochemical changes	Expensive, long scan time
Ultrasound	Portable; synovitis detection; cartilage thickness	Operator dependent
PET/MRI	Molecular imaging of inflammation, bone activity	Experimental, costly

4. Genetic and Epigenetic Biomarkers

In addition to GWAS-identified loci like GDF5 and SMAD3, recent polygenic risk score analyses have revealed that genetic susceptibility explains approximately 20–25% of OA heritability. Epigenetic regulation, including histone modifications and non-coding RNAs, is increasingly recognized as a critical determinant of cartilage homeostasis. Circulating

exosomal miRNAs are also emerging as minimally invasive biomarkers with diagnostic and prognostic utility, offering potential for liquid biopsy approaches.

Genome-wide association studies (GWAS) have identified over 100 risk loci for OA, including GDF5, COL2A1, and SMAD3. Epigenetic studies show altered methylation in cartilage-specific genes (e.g., MMP13 promoter). Circulating miRNAs such as miR-140, miR-146a, and miR-21 have been linked to disease activity with diagnostic AUCs of 0.75–0.82.

5. Multi-omics and Systems Biology

Recent single-cell multi-omics platforms have identified specific fibroblast and immune cell subsets associated with OA progression. Integration of metabolomic and lipidomic profiles has revealed links between systemic metabolic syndrome and local joint degeneration. Machine learning algorithms are increasingly applied to combine multi-omics, imaging, and clinical features, enabling the discovery of biomarker-defined OA endotypes that could be targeted with precision therapeutics.

Proteomics has identified novel biomarkers such as clusterin and fibulin-3 in OA synovial fluid. Metabolomic studies show dysregulation of amino acid metabolism (arginine, proline) in OA plasma. Transcriptomic and single-cell RNA sequencing highlight 5 distinct chondrocyte subpopulations. Systems biology approaches integrate omics with imaging and clinical data for network-based biomarker discovery.

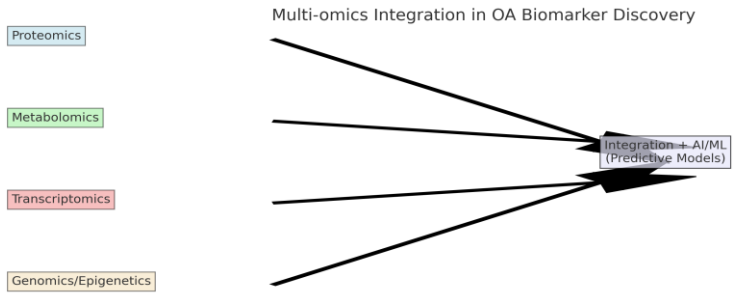

Figure 3: Multi-omics integration workflow for OA biomarker discovery and precision medicine.

Table 3: Omics-derived biomarkers in OA.

Omics Domain	Representative Biomarkers	Clinical Implication
Proteomics	Clusterin, Fibulin-3	Cartilage metabolism
Metabolomics	Arginine, Proline	Metabolic dysregulation
Transcriptomics	Inflammatory chondrocyte clusters	Disease subtyping

6. Clinical Utility of Biomarkers

Biomarkers can help stratify patients into fast versus slow progressors, guide eligibility for clinical trials, and potentially serve as surrogate endpoints for regulatory approval of new therapies. Personalized medicine approaches are beginning to incorporate biomarker signatures for tailoring exercise, pharmacological, and surgical interventions.

Applications include early diagnosis, prognosis (risk of rapid progression, joint replacement), monitoring therapy (DMOADs), and patient stratification by biomarker-defined endotypes.

7. Challenges and Limitations

A major barrier to biomarker adoption is the lack of large, harmonized, multi-ethnic validation cohorts. Additionally, variability in biospecimen collection and assay platforms leads to reproducibility challenges. Regulatory agencies such as the FDA and EMA are actively developing frameworks for biomarker qualification, but translating promising candidates into clinical-grade diagnostics remains an uphill task.

Challenges include OA heterogeneity, assay variability, lack of reproducibility across cohorts, cross-sectional study bias, and regulatory hurdles (FDA/OARSI BIPEDS framework).

8. Future Directions

Future directions will likely emphasize the development of composite indices that combine biochemical, genetic, and imaging biomarkers. Digital health tools such as wearable sensors may be integrated with biomarker data to provide continuous monitoring of OA progression. AI-based risk prediction models are expected to play an increasingly important role in personalized OA management and therapeutic development.

Future efforts should focus on multi-biomarker panels, integration of AI with omics and imaging, large longitudinal validation, biomarker-guided clinical trials, and personalized OA care.

9. CONCLUSION

Biomarkers have the potential to transform OA management. Despite advances, none have entered clinical use. Future validation, integration, and standardization will be key for translation into practice.

REFERENCES

1. S, A. 'Osteoarthrosis of the knee. A radiographic investigation', *Acta Radiol Diagn (Suppl)*, 1968; 277: 7–72. Available at: https://doi.org/10.11359/CHUBU.2010.337.
2. Safiri, S. *et al.* 'Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017', *Annals of the Rheumatic Diseases*, 2019; 78(11): 1463. Available at: https://doi.org/10.1136/annrheumdis-2019-215920.
3. Taruc-Uy, R.L. and Lynch, S.A. 'Diagnosis and Treatment of Osteoarthritis', *Primary Care: Clinics in Office Practice*, 2013; 40(4): 821–836. Available at: https://doi.org/10.1016/j.pop.2013.08.003.
4. Tsai, P.-F. *et al.* 'A pilot cluster-randomized trial of a 20-week Tai Chi program in elders with cognitive impairment and osteoarthritic knee: effects on pain and other health outcomes', *Journal of pain and symptom management*, 2013; 45(4): 660–669.
5. Vance, C.G.T. *et al.* 'Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial', *Physical therapy*, 2012; 92(7): 898–910.
6. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019; 393: 1745–1759.
7. Kraus VB, et al. Call for standardized definitions of osteoarthritis biomarkers. Osteoarthritis Cartilage. 2015.
8. Soul J, et al. Omics approaches in osteoarthritis. Nat Rev Rheumatol. 2022.
9. Deveza LA, et al. Biomarkers for osteoarthritis. RMD Open. 2018.
10. Mobasheri A, et al. Biomarkers of osteoarthritis: a review. Front Biosci. 2017.
11. Osteoarthritis Initiative (OAI) cohort publications (2008–2024).
12. IMI-APPROACH consortium biomarker validation studies (2020–2023).