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Review Article

Emerging Role of inflammatory biomarker monitoring in the Diagnosis of osteoarthritis

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Abstract

Background: Osteoarthritis has traditionally been framed as a mechanical, cartilage-wear disease, but accumulating evidence over the past two decades has established that low-grade synovial and systemic inflammation contribute meaningfully to disease onset, structural progression, and symptom burden.

Objective: This review synthesizes the published evidence on circulating and synovial inflammatory biomarkers, including C-reactive protein, interleukin-6, tumor necrosis factor-alpha, cartilage oligomeric matrix protein, matrix metalloproteinases, and emerging synovial fluid panels, as tools for diagnosing osteoarthritis, stratifying phenotypes, and monitoring progression.

Methods: We synthesized cohort studies, biomarker validation studies, and consensus statements addressing inflammatory biomarker performance in knee, hip, and hand osteoarthritis, drawing on established osteoarthritis biomarker frameworks.

Findings: High-sensitivity C-reactive protein and interleukin-6 are consistently associated with radiographic progression and pain severity, cartilage oligomeric matrix protein and matrix metalloproteinase-3 track cartilage turnover with moderate specificity, and composite panels combined with imaging outperform any single marker for identifying an inflammatory phenotype likely to progress rapidly.

Conclusions: Inflammatory biomarker monitoring is not yet ready to replace radiography or clinical criteria for osteoarthritis diagnosis, but it adds meaningful value for phenotyping, prognostication, and trial enrichment, and a layered strategy combining core biomarkers with imaging is the most defensible current approach.

Keywords: osteoarthritis; inflammatory biomarkers; C-reactive protein; interleukin-6; cartilage turnover

1. Introduction

Osteoarthritis has long been described as a disease of mechanical wear, a slow grinding away of cartilage that eventually exposes bone and produces pain. That framing shaped decades of research toward cartilage structure and joint space narrowing on plain radiographs, and it remains the basis of the most widely used diagnostic criteria. Over the past twenty years, however, synovial biology and epidemiology have forced a revision of that picture. Synovitis is detectable by imaging and histology in a majority of osteoarthritic joints, even early in disease, and synovial macrophages, fibroblast-like synoviocytes, and infiltrating lymphocytes produce a sustained low-grade cytokine milieu that both responds to and amplifies cartilage and subchondral bone damage [1]. Kraus and colleagues, summarizing the case for reframing osteoarthritis as a disease with an inflammatory component rather than a purely degenerative one, argued that this shift has direct diagnostic and therapeutic consequences, since a disease process with a measurable inflammatory signature is one for which circulating and synovial biomarkers become plausible diagnostic and prognostic tools [2].

The clinical stakes are considerable. Osteoarthritis affects an estimated 300 million people worldwide and is projected to rise with population aging and obesity, imposing a disability burden that the Global Burden of Disease collaboration ranks among the leading causes of years lived with disability globally [3]. Radiographic severity, still most commonly graded using the Kellgren-Lawrence system developed in the 1950s, correlates only weakly with reported pain and function, a disconnect confirmed in cohort analyses showing that many patients with advanced radiographic changes report little pain, while others with minimal findings report severe symptoms [4,5]. This mismatch has motivated a search for biomarkers that might explain the discrepancy, identify patients at risk of rapid progression before radiographic change is visible, and serve as objective

outcome measures in trials of disease-modifying osteoarthritis drugs, a class that has so far failed to reach approval in part because trials lack a sensitive, specific measure of ongoing joint damage [6].

This review synthesizes the evidence on inflammatory biomarker monitoring in osteoarthritis diagnosis: the biological rationale for an inflammatory phenotype, the performance characteristics of the most extensively studied circulating and synovial markers, how biomarker signatures relate to imaging and clinical phenotypes, and where the field currently stands on incorporating these markers into diagnostic and prognostic practice.

2. Inflammatory Pathophysiology of Osteoarthritis

The synovium in osteoarthritis is neither histologically normal nor uniformly inflamed; it shows a spectrum from mild lining hyperplasia to dense mononuclear infiltration resembling, at lower intensity, the synovitis of rheumatoid arthritis. Synovial biopsy and MRI studies converge on a prevalence of detectable synovitis in roughly half to two-thirds of osteoarthritic knees, with effusion-synovitis on MRI associated cross-sectionally with pain and longitudinally with faster cartilage volume loss [7]. Sellam and Berenbaum, reviewing synovitis in osteoarthritis pathophysiology, described a feed-forward loop in which cartilage breakdown products activate synovial macrophages through pattern-recognition receptors, which in turn secrete cytokines and proteases that accelerate further cartilage degradation, positioning synovial inflammation as both a consequence and a driver of structural progression [8].

Interleukin-1 beta and tumor necrosis factor-alpha are the most extensively studied upstream cytokines in this cascade; both are produced by activated synoviocytes and chondrocytes and upregulate matrix-degrading enzymes, principally matrix metalloproteinases and aggrecanases, while suppressing chondrocyte matrix synthesis [9]. Interleukin-6, downstream of this signal, is produced by synovium, cartilage, and adipose tissue and acts both

locally, amplifying catabolic signaling in chondrocytes, and systemically, driving hepatic acute-phase protein synthesis, the mechanistic basis for using circulating C-reactive protein as an indirect readout of joint-level interleukin-6 activity [10]. Adipokines add a systemic dimension particularly relevant to obesity-associated disease; leptin and other adipose-derived mediators have direct catabolic effects on chondrocytes independent of mechanical loading, explaining why hand osteoarthritis, a non-weight-bearing site, is nonetheless more common in obese individuals [11].

Subchondral bone remodeling contributes a further inflammatory dimension often underappreciated relative to synovium and cartilage. Osteoblasts and osteoclasts in the subchondral plate generate cytokine signals that cross into overlying cartilage, and bone marrow lesions on MRI, which histologically correspond to zones of remodeling, fibrosis, and low-grade inflammation, are among the strongest MRI predictors of both pain and structural progression [12].

3. C-Reactive Protein and Interleukin-6 as Systemic Markers

High-sensitivity C-reactive protein is the most widely measured circulating inflammatory marker in osteoarthritis research, chiefly because it is inexpensive, standardized, and already embedded in cardiovascular risk pathways. Spector and colleagues found that serum C-reactive protein was elevated in women with symptomatic knee osteoarthritis compared with asymptomatic controls and correlated with the number of affected joints, establishing one of the first quantitative links between systemic inflammation and osteoarthritis burden [13]. Sharif and colleagues found that baseline serum C-reactive protein predicted radiographic progression over five years, with patients in the highest tertile experiencing significantly greater joint space narrowing than those in the lowest [14]. Stannus and colleagues, using the Tasmanian Older Adult Cohort,

reported that persistently elevated C-reactive protein and interleukin-6 over time, rather than a single measurement, predicted both cartilage volume loss and increased risk of knee replacement, reinforcing a trend-over-threshold principle [15].

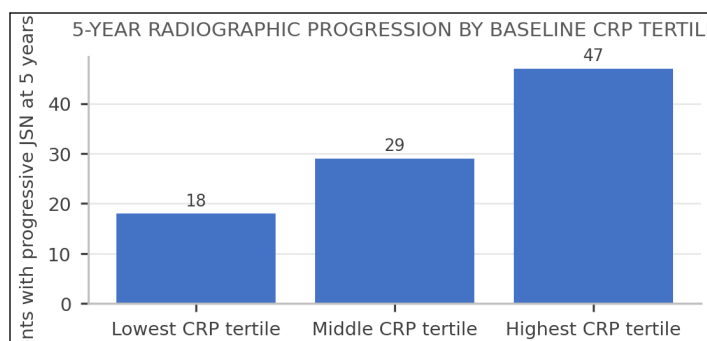


Figure 1: Five-year radiographic progression risk in knee osteoarthritis by baseline serum C-reactive protein tertile, with the highest tertile showing significantly greater joint space narrowing than the lowest, and persistently elevated C-reactive protein and interleukin-6 over time predicting both cartilage volume loss and subsequent knee replacement [14,15].

Interleukin-6 itself, measured directly rather than through its hepatic acute-phase readout, shows a similar but somewhat more specific relationship to structural outcomes. Livshits and colleagues, in a large twin cohort, found that circulating interleukin-6 predicted radiographic progression independent of body mass index and baseline severity, persisting after adjustment for C-reactive protein [16]. A meta-analysis by Jin and colleagues pooling case-control and cohort data confirmed that both markers are consistently elevated in osteoarthritis patients relative to controls, supporting a genuine, if moderate, biological signal [17]. Neither marker is specific to osteoarthritis, however; both rise with age, adiposity, smoking, and unrelated inflammatory conditions, the central limitation constraining their diagnostic, as opposed to prognostic, utility [15].

4. Cartilage- and Bone-Derived Structural Biomarkers

A separate class of biomarkers reflects direct tissue turnover rather than systemic inflammatory tone, and several are themselves modulated by the cytokine milieu

described above, blurring the line between "inflammatory" and "structural" markers in practice. Cartilage oligomeric matrix protein, a large glycoprotein component of cartilage matrix, is released into synovial fluid and serum during matrix turnover and has been the most extensively studied structural biomarker for over two decades. Sharif and colleagues found that serum cartilage oligomeric matrix protein independently predicted radiographic progression, and that combining it with C-reactive protein improved prognostic discrimination over either marker alone [18]. A systematic review by Hoch and colleagues concluded that it correlates with disease severity and progression across cohorts, though absolute concentrations vary enough between assay platforms that a universal diagnostic threshold has not been established [19].

Table 1: Principal circulating and synovial fluid biomarkers evaluated for osteoarthritis diagnosis and prognosis, by biological source and established association [18,20,21,22].			
Biomarker	Source	Biological role	Established association
High-sensitivity CRP	Serum (hepatic)	Acute-phase reactant, downstream of IL-6	Radiographic progression, pain severity
Interleukin-6	Serum, synovium, fat	Upstream catabolic and acute-phase signal	Cartilage volume loss, knee replacement risk
Cartilage oligomeric matrix protein	Serum, synovial fluid	Cartilage matrix glycoprotein turnover	Radiographic progression, improved with CRP
Matrix metalloproteinase-3	Serum, synovial fluid	Proteoglycan-degrading enzyme	Elevated with synovitis burden
Urinary coll2-1 / coll2-1NO2	Urine	Type II collagen degradation neoepitope	Radiographic severity, joint space narrowing

Matrix metalloproteinase-3, produced by synoviocytes and chondrocytes under cytokine stimulation, degrades proteoglycan core protein and has repeatedly shown elevated serum and synovial fluid concentrations in osteoarthritis, with several cohorts linking higher concentrations to greater synovitis burden on imaging [20]. Collagen degradation neoepitopes, including coll2-1, a peptide fragment released during type II collagen

degradation, have shown promise as more cartilage-specific markers; Cibere and colleagues found that urinary coll2-1 and its nitrated form were associated with radiographic severity and predicted subsequent joint space narrowing, adding a non-invasive option to the biomarker panel [21]. Bone-derived markers, including osteocalcin and C-terminal telopeptide of type I collagen, reflect the subchondral remodeling process described earlier and show associations with progression in some but not all cohorts [22].

5. Synovial Fluid and Multi-Marker Panels

Synovial fluid sampling offers a compartment-specific readout that avoids much of the systemic confounding affecting serum markers, at the cost of an invasive procedure limited to research or specialist settings. Synovial fluid interleukin-6, interleukin-8, and tumor necrosis factor-alpha concentrations correlate more tightly with local synovitis grade and effusion volume than their serum counterparts, and several studies show that synovial fluid cytokine profiles distinguish osteoarthritis from inflammatory arthritides such as rheumatoid arthritis, though overlap exists in actively inflamed joints [23]. Attur and colleagues profiled synovial fluid and plasma interleukin-1 beta, interleukin-6, and their soluble receptors and derived a composite score that predicted both symptomatic and structural progression more accurately than any single cytokine [24]. Pearle and colleagues, characterizing synovial fluid cytokine profiles across the severity spectrum, found that interleukin-1 beta and tumor necrosis factor-alpha rose progressively with radiographic grade, supporting cytokine burden as a marker of cumulative joint-level inflammatory activity rather than a feature confined to end-stage disease [25].

The recognition that no single biomarker carries sufficient diagnostic weight has driven the field toward structured multi-marker frameworks. The Osteoarthritis Biomarkers Consortium proposed the BIPED classification, categorizing candidate biomarkers as burden of disease,

investigative, prognostic, efficacy of intervention, or diagnostic, acknowledging that most inflammatory markers fit the prognostic and burden-of-disease categories rather than the diagnostic one, since none reliably distinguishes osteoarthritic from non-osteoarthritic joints at the individual level [26]. Bay-Jensen and colleagues reviewed protease-generated neoepitope biomarkers and argued that combining several complementary markers into a composite panel is more likely to achieve clinically useful discrimination than pursuing any single "master" biomarker [27].

6. Correlation with Imaging and Clinical Phenotypes

Biomarker performance improves substantially when interpreted alongside imaging, which supplies anatomic and structural context that a circulating or synovial fluid concentration alone cannot provide. Effusion-synovitis volume on MRI correlates with several of the circulating markers discussed above, and studies combining MRI synovitis scoring with serum C-reactive protein and interleukin-6 have shown improved discrimination between rapidly progressing and stable knee osteoarthritis compared with either modality alone [7]. The introduction of semiquantitative whole-organ scoring systems, including the MRI Osteoarthritis Knee Score developed by Hunter and colleagues, standardized assessment of synovitis, effusion, and bone marrow lesions across cohorts, making it possible to correlate specific imaging features with specific biomarker elevations rather than relying on global radiographic grade alone [28]. Devesa and colleagues, analyzing data-driven phenotypes, identified an inflammatory phenotype with higher circulating inflammatory markers, greater synovitis on imaging, and a distinct progression trajectory compared with a mechanical-overload phenotype driven more by malalignment and obesity [29].

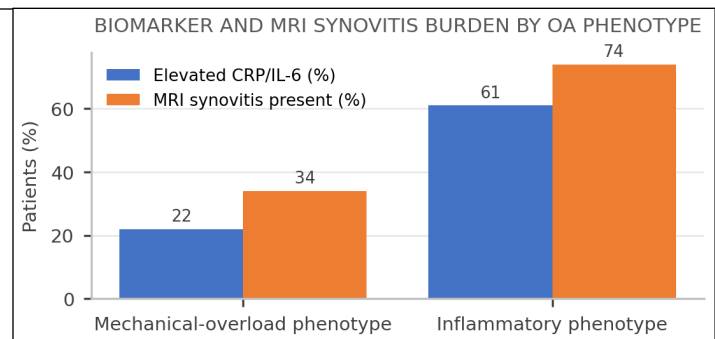


Figure 2: Distribution of inflammatory versus mechanical-overload osteoarthritis phenotypes by circulating biomarker burden and MRI synovitis score, illustrating divergent pain and structural progression trajectories between phenotypes defined by inflammatory activity rather than radiographic grade alone [29,7].

Ultrasound provides a lower-cost complement to MRI for detecting synovitis and effusion, and studies correlating grey-scale and power Doppler synovitis scores with serum inflammatory markers have generally found modest but consistent positive associations [30]. Kortekaas and colleagues found that ultrasound-detected synovitis in hand osteoarthritis was associated with local pain and, to a lesser degree, circulating inflammatory markers, indicating that the systemic inflammatory signature detectable in weight-bearing joints extends, with attenuated strength, to small non-weight-bearing joints [30]. Metabolic syndrome components are independently associated with osteoarthritis severity beyond body mass index alone, and several groups have proposed a metabolic phenotype in which systemic low-grade inflammation driven by metabolic dysfunction, rather than joint loading, is the principal driver [31].

7. Diagnostic and Prognostic Utility, and Current Limitations

Despite two decades of active investigation, no inflammatory biomarker or panel has been validated to a standard sufficient to replace clinical assessment and plain radiography in routine diagnosis, and current guidance continues to recommend clinical and radiographic criteria as the standard [26]. The reasons are consistent across the literature: individual marker elevations overlap substantially with asymptomatic

controls, particularly in older or obese populations; assay standardization across platforms remains incomplete; and most validation studies have been conducted in knee cohorts, leaving hip, hand, and multi-joint disease comparatively understudied [19]. Punzi and colleagues additionally cautioned that inflammatory markers measured before radiographic change is detectable may reflect a transient reactive synovitis rather than an early stage of a progressive inflammatory phenotype, a distinction single-timepoint studies are generally not designed to resolve [32].

Table 2: Utility and limitations of inflammatory biomarker monitoring across proposed roles in osteoarthritis care, drawn from the BIPED classification framework and subsequent composite-panel and phenotyping studies [26,24,27,6].		
Proposed role	Current evidence	Key limitation
Primary diagnosis	Not supported as a replacement for clinical/radiographic criteria	Overlap with asymptomatic controls; assay standardization incomplete
Prognosis / progression risk	Composite panels outperform single markers	Requires serial trend, not single value
Phenotyping	Distinguishes inflammatory from mechanical-overload phenotype	Best combined with MRI synovitis scoring
Trial enrichment	Proposed to select responders for anti-inflammatory DMOADs	Not yet standard in trial design; limited external validation

Where the evidence is more consistent is in prognostic, rather than purely diagnostic, application. Composite panels combining C-reactive protein or interleukin-6 with a structural marker such as cartilage oligomeric matrix protein or a collagen neoepitope, interpreted alongside MRI synovitis and bone marrow lesion scoring, have repeatedly shown better discrimination of rapid progressors than any single measure [24,29]. This prognostic value has practical implications for trial design; enriching disease-modifying osteoarthritis drug trials for an inflammatory phenotype has been proposed to increase the likelihood of detecting a treatment effect in a population biologically likely to respond to anti-cytokine intervention, addressing one commonly cited reason for

the repeated failure of such trials in unselected populations [6]. Emerging multi-omic and machine-learning-derived composite scores have shown incremental improvements in predictive accuracy over conventional few-marker panels, though external validation remains limited and this approach is not yet ready for clinical deployment [33].

8. Conclusion

Two decades of synovial biology and longitudinal cohort research have established osteoarthritis as a disease with a genuine, measurable inflammatory component rather than a purely mechanical degeneration of cartilage, producing a substantial catalog of candidate biomarkers, from C-reactive protein and interleukin-6 through cartilage oligomeric matrix protein, matrix metalloproteinase-3, and collagen degradation neoepitopes [1,2]. None of these markers, individually, achieves the sensitivity and specificity required to replace clinical assessment and radiography as the diagnostic standard, and their principal established value lies in prognostication, phenotyping, and trial enrichment rather than primary diagnosis [26,19]. The most defensible current strategy mirrors that used in other chronic inflammatory diseases where a single marker has proven insufficient: composite panels interpreted as a trend over time, combined systematically with imaging findings such as MRI synovitis and bone marrow lesion scoring, to identify the inflammatory phenotype most likely to progress rapidly and most likely to benefit from disease-modifying intervention [29,24]. As multi-omic composite scores and standardized assay platforms mature, inflammatory biomarker monitoring is likely to move from a research tool toward a genuine adjunct to imaging and clinical criteria in osteoarthritis diagnosis.

9. References

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