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Review Article

inflammatory biomarker monitoring in the Management of osteoarthritis among elderly patients with joint disease

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Abstract

Background: Osteoarthritis (OA) is increasingly understood as driven by low-grade synovial and systemic inflammation, not mechanical wear alone, renewing interest in inflammatory biomarkers for monitoring disease activity in elderly joint disease.

Objective: This review synthesizes evidence on inflammatory and joint-tissue-turnover biomarkers relevant to OA monitoring in older adults, their correlation with imaging, and confounding by aging-related inflammation and comorbidity.

Methods: We reviewed cohort studies, biomarker qualification consortia, and systematic reviews addressing C-reactive protein and interleukin-6, cartilage-degradation markers including cartilage oligomeric matrix protein and matrix metalloproteinases, and multi-marker panels in knee and hip OA.

Findings: C-reactive protein and interleukin-6 associate with radiographic presence, progression, and pain trajectory; cartilage-degradation markers track severity and treatment response; multi-marker panels outperform single analytes, though inflammation, sarcopenia, and comorbidity confound single-marker interpretation in elderly patients.

Conclusions: No single biomarker meets the bar for stand-alone monitoring in elderly osteoarthritis; its most defensible role is within a multi-marker strategy combined with imaging and clinical assessment, pending validation studies designed for older, multimorbid patients.

Keywords: osteoarthritis; inflammatory biomarkers; elderly; cytokines; disease monitoring

1. Introduction

Osteoarthritis (OA) is the most common form of joint disease among older adults and a leading global cause of pain-related disability, with the knee and hip bearing the largest share of the clinical burden [1]. For decades OA was framed as a mechanical "wear and tear" disorder of cartilage, but that view has been revised: synovial inflammation, innate immune activation, and low-grade systemic inflammation are now recognized as central features of disease onset and progression [2]. This reframing matters clinically because inflammation is measurable and can, in principle, be monitored longitudinally to track disease activity and gauge treatment response, much as it already is in rheumatoid arthritis and other rheumatic diseases.

The elderly population in whom OA is most prevalent presents a particular challenge for biomarker interpretation. Aging itself is accompanied by a chronic, low-grade elevation of circulating inflammatory mediators, termed "inflammaging," which can obscure or amplify OA-specific signals in blood-based assays [3]. Older patients also carry a heavier burden of comorbid conditions, including cardiovascular disease, diabetes, and sarcopenia, each independently influencing circulating cytokine levels and complicating use of any single biomarker as a clean surrogate for joint pathology [4]. The Johnston County Osteoarthritis Project has documented how common radiographic and symptomatic knee OA becomes with age, underscoring the scale of the population for whom a validated monitoring biomarker would have practical value [5].

This review synthesizes the evidence on inflammatory biomarkers relevant to OA monitoring in elderly patients: the pathophysiological basis for inflammation in OA, the systemic and joint-specific biomarkers studied, their correlation with imaging, the confounds aging and comorbidity introduce, and multi-marker approaches intended to improve on any single analyte. The central

question is not whether inflammation matters in OA, now well established, but whether measuring it adds clinically actionable information to how elderly patients with joint disease are followed and treated [6].

2. Inflammatory pathophysiology of osteoarthritis

The synovial membrane, subchondral bone, and articular cartilage form an interdependent unit in which inflammatory signaling propagates disease across all three tissues rather than remaining confined to one compartment [7]. Damage-associated molecular patterns released from degrading cartilage matrix activate synoviocyte and chondrocyte pattern-recognition receptors, triggering an innate immune response that is self-sustaining even without an infectious or autoimmune trigger [8]. Macrophages within the synovium polarize toward pro-inflammatory phenotypes, releasing interleukin-1beta, TNF-alpha, and IL-6, which upregulate catabolic enzymes in chondrocytes and degrade the extracellular matrix, creating a feed-forward cycle linking mechanical injury to sustained low-grade inflammation [9].

Synovitis, visible on ultrasound and MRI as synovial thickening, effusion, and Doppler signal, is present in both early and established OA joints and correlates with pain severity independent of radiographic grade, reinforcing the view of OA as an immune-mediated disease of the joint organ rather than a purely degenerative one [10].

3. Systemic inflammatory markers: CRP and interleukin-6

C-reactive protein (CRP), particularly high-sensitivity CRP (hsCRP), is the most extensively studied systemic marker in OA. Spector and colleagues found that even modest elevations in serum CRP were present in early knee OA and predicted subsequent radiographic progression, establishing CRP as a candidate prognostic marker rather than merely a marker of concurrent disease [11]. Sturmer and colleagues showed that hsCRP correlated with both

severity and extent of osteoarthritic joint involvement, suggesting systemic inflammatory burden scales with total joint disease burden rather than reflecting one affected joint [12].

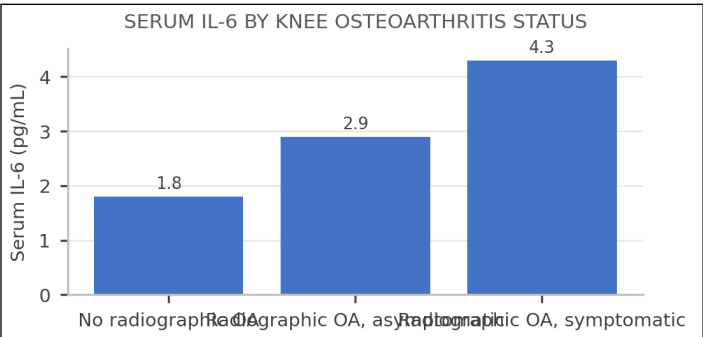


Figure 1: Serum interleukin-6 levels by radiographic knee osteoarthritis status in a community cohort of older adults, showing progressively higher circulating IL-6 across non-osteoarthritic, radiographic, and symptomatic radiographic knee categories [13,14].

Interleukin-6 has emerged as an equally, and in some cohorts more consistently, informative marker. The Chingford study found circulating IL-6 was a significant predictor of radiographic knee OA in a large community cohort, persisting after adjustment for body mass index and age [13]. Stannus and colleagues, in a longitudinal cohort of older adults, reported IL-6 and TNF-alpha were both associated with radiographic knee OA and cartilage volume loss over time [14]; a follow-up analysis found these markers also tracked with change in knee pain over five years [15]. In an elderly cohort with symptomatic knee OA, Penninx and colleagues showed elevated inflammatory markers were associated with poorer physical function, an outcome that often matters most to older patients [16]. Attur and colleagues combined inflammatory plasma lipid and leukocyte gene expression biomarkers and found this composite signature carried prognostic value for pain and structural progression, an early demonstration that multi-analyte panels can outperform any single marker [17].

4. Cartilage- and joint-specific degradation biomarkers

Beyond systemic inflammatory markers, a distinct family

of biomarkers reflects turnover of cartilage and other joint tissue, several modulated by inflammatory cytokine signaling. Cartilage oligomeric matrix protein (COMP), a glycoprotein released during cartilage matrix breakdown, shows the most consistent association with OA presence and severity among structural biomarkers; the Johnston County Osteoarthritis Project found serum COMP tracked disease severity, and Sharif and colleagues showed serial COMP measurements predicted radiographic progression in an inception cohort [18,19]. Because COMP release is amplified by inflammatory cytokine exposure in cartilage explant models, its signal likely reflects both mechanical turnover and inflammation-driven catabolism [20].

Table 1: Principal inflammatory and joint-tissue-turnover biomarkers studied in osteoarthritis, their tissue source, and their reported clinical associations [11,18,20,21].

Biomarker	Tissue source	Primary biological signal	Reported clinical association
hsCRP	Liver (acute-phase)	Systemic low-grade inflammation	Early disease presence; radiographic progression
Interleukin-6	Synovium, adipose, muscle	Pro-inflammatory cytokine signaling	Radiographic OA; cartilage volume loss; pain change
COMP	Articular cartilage matrix	Cartilage matrix turnover/breakdown	Disease severity; predicts radiographic progression
MMP-3	Chondrocytes, synoviocytes	Matrix-degrading enzyme activity	Falling levels predict structural treatment response
CTX-II	Type II collagen fragments	Collagen degradation	Detects early, pre-radiographic cartilage lesions

Type II collagen degradation fragments (CTX-II) and matrix metalloproteinase (MMP) activity, particularly MMP-3, have also been studied. Pelletier and colleagues found decreasing serum MMP levels during treatment predicted the disease-modifying effect assessed by quantitative MRI, linking a blood-based biomarker to a structural treatment-response endpoint [21]. Karsdal and

colleagues emphasized that cartilage and subchondral bone turnover are biologically coupled in OA, so a comprehensive biomarker strategy should capture bone remodeling markers alongside cartilage-specific ones [22]. Kraus and colleagues proposed combining several biochemical markers reflecting different joint tissues into a composite index of total body OA burden, anticipating later multi-marker consortium efforts [23].

5. Correlation with imaging and structural progression

Because inflammatory and degradation biomarkers are proxies for joint tissue processes that can also be visualized directly, their validity depends substantially on correlation with imaging. MRI-detected synovitis and joint effusion independently increase the risk of subsequent cartilage loss, including in knees not yet meeting radiographic OA criteria at baseline, in the Multicenter Osteoarthritis Study (MOST) cohort [24]. This demonstrates that inflammatory change precedes, rather than merely accompanies, structural progression, supporting inflammatory markers as early or predictive signals rather than only concurrent disease indicators.

Structural imaging also correlates, imperfectly, with the symptom burden that matters most to elderly patients. Hunter and colleagues found bone marrow lesions and synovitis, both inflammation-adjacent findings, associated more consistently with pain than cartilage loss itself, explaining why radiographic severity alone correlates poorly with reported symptoms and why inflammatory activity helps identify elderly patients most likely to need escalation of care [25].

6. Multi-marker panels and the BIPED framework

No single biomarker studied to date has demonstrated the sensitivity and specificity required to serve, alone, as a validated tool for diagnosing OA, predicting its course, or monitoring treatment response, driving the field toward composite approaches. van Spil and colleagues applied the consensus Burden of disease, Investigative,

Prognostic, Efficacy of intervention, and Diagnostic (BIPED) classification to serum and urinary biochemical markers in knee and hip OA, concluding that while numerous candidates show significant associations, none met the full evidentiary bar for routine clinical use in isolation [26]. The FNIH OA Biomarkers Consortium evaluated a panel of biochemical markers in a large, well-characterized knee OA cohort and found combinations of markers, rather than any single analyte, carried meaningful predictive validity for radiographic and pain progression, the most rigorous qualification effort in the field to date [27].

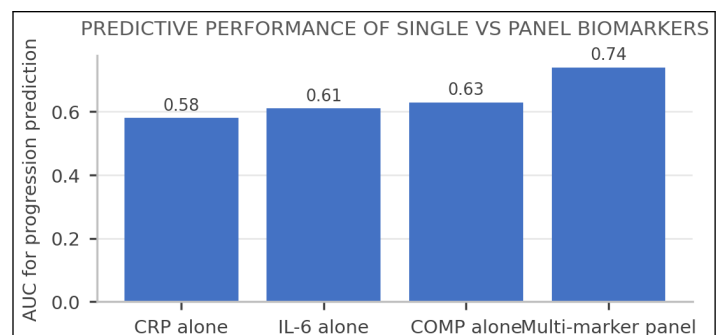


Figure 2: Reported predictive performance (area under the curve) for progression of knee osteoarthritis using single systemic markers compared with combined multi-marker panels drawn from FNIH OA Biomarkers Consortium and related biochemical marker analyses, illustrating the incremental gain from panel-based over single-analyte approaches [27,17,26].

The practical implication for elderly patients is that inflammatory biomarker monitoring is most defensible as one input among several, combined with imaging and clinical judgment, rather than a stand-alone test, given how easily an isolated elevated CRP or IL-6 value in an older, comorbid patient could be over-interpreted as joint-specific activity.

7. Inflammaging, sarcopenia, and comorbidity in the elderly

Interpreting inflammatory biomarkers in elderly OA patients requires accounting for the background inflammatory physiology of aging itself. Inflammaging describes a chronic, low-grade, sterile inflammatory state that accompanies normal aging and is implicated in

conditions well beyond joint disease, including cardiovascular disease and frailty, meaning elevated CRP or IL-6 cannot automatically be attributed to OA activity without considering this shared, upstream immune-metabolic background [4].

Table 2: Age-related and comorbid factors that confound interpretation of inflammatory biomarkers in elderly patients with joint disease [4,3,28,16].			
Confounding factor	Mechanism	Effect on inflammatory markers	Implication for monitoring
Inflammaging	Chronic sterile immune activation with age	Raises baseline CRP, IL-6 independent of joint status	Requires age-adjusted or trend-based interpretation
Sarcopenic obesity	Adipose tissue as endocrine/inflammatory organ	Elevates circulating cytokines	Body composition should be recorded alongside markers
Cardiometabolic comorbidity	Shared low-grade inflammatory pathways	Confounds marker specificity for joint disease	Multi-marker panels favored over single analytes
Reduced physical function	Deconditioning, disuse	Associated with higher inflammatory marker levels	Functional status monitored jointly with biomarkers

Sarcopenia and sarcopenic obesity compound this challenge. Misra and colleagues found sarcopenic obesity carried a distinct, often elevated risk profile for knee OA compared with obesity or sarcopenia alone, with adipose tissue acting as an endocrine and inflammatory organ contributing cytokines independent of joint pathology [28]. Because muscle loss, weight gain, and reduced activity frequently co-occur in elderly patients with joint disease, biomarker monitoring in geriatric OA populations should account for body composition and comorbidity as covariates rather than treat a single inflammatory value as a clean signal. The substantial, rising lifetime cost of knee OA management, driven by the aging population and extending indications for joint replacement, underscores the stakes of accurate risk stratification in this age group [29].

8. Clinical application: monitoring disease activity

and treatment response

The most immediately actionable use of inflammatory biomarkers in elderly OA patients is not diagnosis, since imaging and clinical criteria remain the standard, but monitoring of disease activity and treatment response over time. Current management guidelines for knee OA, including the ESCO algorithm, integrate pharmacological and non-pharmacological interventions stepwise, and inflammatory biomarker trajectories offer a plausible adjunct for judging whether an intervention is dampening the underlying inflammatory drive rather than only masking symptoms [30]. Pelletier and colleagues' demonstration that falling serum MMP levels predicted a favorable structural response to treatment is the clearest existing example of a biomarker used prospectively as a treatment-response signal [21].

Not every biomarker application has borne out. A re-analysis adjusting for trial quality found no clear comparative-effectiveness advantage of glucosamine and chondroitin, agents once hypothesized to work partly through anti-inflammatory mechanisms, over placebo for knee OA symptoms, a reminder that biomarker plausibility does not guarantee clinical efficacy [31]. This caution is particularly relevant in elderly patients, for whom polypharmacy and comorbidity make it important that any biomarker-guided treatment decision be corroborated by clinical response.

9. Limitations and future directions

Several limitations constrain the current evidence base. Most cohort studies of inflammatory biomarkers in OA are observational, with modest effect sizes and heterogeneity in assay methods, cutoff values, and adjustment for confounders such as body mass index, comorbidity, and medication use, all especially prevalent in elderly populations. Few studies have been designed specifically to test whether biomarker-guided monitoring changes outcomes in geriatric patients with joint disease, as opposed to demonstrating statistical association in

mixed-age cohorts. The pathophysiological literature is more mature than the applied monitoring literature: inflammation is well established as a mechanistic driver of cartilage and synovial pathology [8,7], but translating that into a validated, elderly-specific monitoring protocol remains incomplete.

Future work should prioritize prospective, elderly-focused cohorts modeling inflammaging and comorbidity as covariates, multi-marker panels validated against structural and patient-reported outcomes specifically in patients over 65, and pragmatic trials testing whether biomarker-informed treatment adjustment improves outcomes over standard monitoring alone. Panels combining systemic cytokines, cartilage-degradation fragments, and bone-turnover markers, in the spirit of the coupled-tissue framework proposed by Karsdal and colleagues, appear more promising than continued single-marker studies, given how consistently single analytes have underperformed against the BIPED evidentiary standard [22,26].

10. Conclusion

Inflammation is now firmly established as a mechanistic driver, rather than a bystander, of osteoarthritis in the aging joint, and a substantial body of evidence links systemic and joint-specific inflammatory biomarkers, from CRP and IL-6 to COMP, MMPs, and collagen degradation fragments, to disease presence, structural progression, symptom burden, and treatment response [2,14,18]. In elderly patients, these biomarkers must be interpreted against a background of inflammaging, sarcopenia, and multimorbidity that can independently elevate circulating markers, meaning no single analyte is likely to serve as a reliable stand-alone monitoring tool in this population [4,28]. The most defensible current role for inflammatory biomarker monitoring in elderly OA care is as one component of a multi-marker strategy combined with imaging and clinical assessment, pending the prospective, elderly-specific validation studies the field

still needs [27,26].

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