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Prognostic biomarkers in osteoarthritis

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Abstract

Purpose of review—Identification of patients at risk for incident disease or disease progression in osteoarthritis remains challenging, as radiography is an insensitive reflection of molecular changes that presage cartilage and bone abnormalities. Thus there is a widely appreciated need for biochemical and imaging biomarkers. We describe recent developments with such biomarkers to identify osteoarthritis patients who are at risk for disease progression.

Recent findings—The biochemical markers currently under evaluation include anabolic, catabolic, and inflammatory molecules representing diverse biological pathways. A few promising cartilage and bone degradation and synthesis biomarkers are in various stages of development, awaiting further validation in larger populations. A number of studies have shown elevated expression levels of inflammatory biomarkers, both locally (synovial fluid) and systemically (serum and plasma). These chemical biomarkers are under evaluation in combination with imaging biomarkers to predict early onset and the burden of disease.

Summary—Prognostic biomarkers may be used in clinical knee osteoarthritis to identify subgroups in whom the disease progresses at different rates. This could facilitate our understanding of the pathogenesis and allow us to differentiate phenotypes within a heterogeneous knee osteoarthritis population. Ultimately, such findings may help facilitate the development of disease-modifying osteoarthritis drugs (DMOADs).

Keywords

biomarkers; inflammation; osteoarthritis; progression

INTRODUCTION

Osteoarthritis is the most common adult joint disease, and is increasing in frequency and severity, with an estimated US prevalence of more than 25 million affected adults. Disease progression is associated with cartilage degradation, joint space narrowing (JSN), and bony changes including osteophytes, subchondral sclerosis, and bone marrow lesions. However, identification of patients at risk for either incident disease or disease progression remains a challenge, particularly since routine radiography is an insensitive measure of molecular changes that presage cartilage and bone abnormalities. Therefore, there is a need for the validation of biochemical and imaging bio-markers that identify patients at risk for

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Conflicts of interest

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progressive disease; identify molecular events that detect early disease; and act as clinical surrogates that could respond to candidate disease-modifying osteoarthritis drug (DMOAD) intervention [1[■]]. Various disease-modifying treatments have been studied for osteoarthritis and, to date, none has achieved US Food and Drug Administration (FDA) approval as DMOADs. At present, DMOAD development must demonstrate slowing of radiographic JSN that is 'clinically meaningful' – that is, will be associated with improvement in symptoms or function. Given the high cost and recent failed attempts at DMOAD development, a significant international effort is underway to identify prognostic biomarkers that identify patients at increased risk for progression.

PROGNOSTIC BIOMARKERS OF SYNTHESIS AND DEGRADATION

An important classification of biomarkers was proposed by the Osteoarthritis Biomarkers Network, a consortium of five sites designated by the National Institutes of Health (NIH) [2]. The six categories (captured in the acronym BIPEDS) proposed to facilitate the development of osteoarthritis bio-markers include: Burden of disease, Investigative, Prognostic, Efficacy of intervention, Diagnostic, and Safety. Of particular importance for DMOAD development are prognostic biomarkers, which predict progression and/or future incidence of osteoarthritis. Validation of prognostic biomarkers requires longitudinal studies that demonstrate an association with development of osteoarthritis documented by radiography, or osteoarthritis progression as defined by JSN or change in cartilage volume by MRI. Additional outcomes of importance, but which are typically secondary endpoints in current studies, would include other measures of MRI worsening (e.g. bone marrow lesions), symptoms documented by patient questionnaires [e.g. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS)], and total joint replacement.

The validation of prognostic biomarkers is of particular importance for clinical trial design, since the rate of progression in a non-selected osteoarthritis population may be as low as 6–20% of patients over a study period of 24 months, and as many as 50% of patients show no progression at all based on JSN or change in Kellgren–Lawrence score, making it difficult to show differences between placebo and an active comparator [1[■]]. Using prognostic biomarkers to identify patients at high risk for progression, and to select this subset for clinical trials, could reduce the number of patients and also the length of time required to observe a DMOAD effect. A focus of this article will be to review potential prognostic biomarkers of osteoarthritis, with an emphasis on reports since 2011.

Recently, the Biomarkers Working Group, representing experts in the field of osteoarthritis biomarker research from both academia and industry, developed a consensus document under the auspices of the Osteoarthritis Research Society International (OARSI) US FDA initiative [3]. The comprehensive article summarizes definitions and classification systems for biomarkers, the current outcome measures used in osteoarthritis clinical trials, and the potential utility of biomarkers for DMOAD development. The authors also propose a research agenda for osteoarthritis-related bio-markers. One recommendation was to focus significant future efforts across studies on selected commercially available osteoarthritis-related bio-markers, including urinary C-terminal telopeptides of type II collagen (uCTX-II); serum cartilage oligomeric matrix protein (COMP); serum hyaluronan; serum and urine C1, 2C; serum and urine C2C; serum and urine Coll2–1 and Coll2–1NO2; serum CPII; serum Procollagen type II N-terminal propeptide (PIIANP); urine/serum NTX-1; urine/serum CTX-1; serum CS846; and serum matrix metalloproteinase 3 (MMP-3). This panel was suggested as a starting point in a field that will rapidly evolve.

As is apparent, the biomarkers chosen include markers of collagen synthesis and degradation indicative of cartilage breakdown, and markers of bone and synovium breakdown. Excellent reviews of these biomarkers have been published in the past year [4[■]–6[■],7[■]].

Serum COMP, uCTX-II, and serum hyaluronan are elevated in populations of patients with hip or knee osteoarthritis, and are among the list of candidate prognostic markers [8]. A recent meta-analysis by Hoch *et al.* [9[■]] found that serum COMP is elevated in patients with knee osteoarthritis and is sensitive to osteoarthritis disease severity. The potential of COMP as a prognostic marker has been previously reported in patients with symptomatic knee osteoarthritis (SKOA) [10,11]. Recently, Golightly *et al.* [12[■]] reported that higher baseline COMP and hyaluronic acid serum levels predicted incident JSN, and higher COMP levels predicted incident knee osteophytes. Led by Hunter, the Boston Osteoarthritis Knee Study group examined the relationship between knee MRI changes and a number of markers of cartilage turnover, including COMP [13]. They found a six-fold increase in the likelihood of cartilage loss for each unit increase in COMP, after adjustment for age, sex, and BMI. In contrast, in a study of 75 patients, Eckstein *et al.* [14[■]] found that none of the 16 molecular markers (including uCTX-II, uTIINE, sCOMP, sPIINP, etc.) investigated was associated with longitudinal MRI-based cartilage thinning in radiographic knee osteoarthritis.

The complexity of biomarkers as predictors of disease progression is further underscored by a study by Pelletier *et al.* [15] showing that higher baseline values of interleukin (IL)-6, C-reactive protein (CRP), and COMP predicted greater risk of cartilage loss in osteoarthritis. However, over time a reduction in MMP-1 and MMP-3 levels correlated best with reduction in cartilage volume loss [15]. Moreover Kumm *et al.* [16[■]] showed, in a population-based longitudinal study of 128 patients with knee osteoarthritis, that elevations of COMP and uCTX-II predicted subsequent progressive osteophytosis in multiple knee compartments and, in the case of uCTX-II, progressive JSN. Over the first 3 years (2002–2005), significant associations were observed between COMP and progressive osteophytosis, whereas 3 years later (2005–2008) uCTX-II associated with progressive JSN.

An interesting study by Erhart-Hledik *et al.* [17[■]] showed that mechanical stress (30-min walk) produced a change in serum concentrations of COMP that was associated with cartilage thickness changes on MRI. In this study, increases in COMP levels 3.5 and 5.5 h after activity were correlated with changes in cartilage thickness in the medial femur and tibia at 5-year follow-up. A newly established COMP fragment ELISA showed greater sensitivity than the commercial kit in detecting differences between osteoarthritis and control patients [18[■]]. In addition, serum COMP fragment levels were well correlated with radiographic severity in osteoarthritis patients and progression of surgically induced osteoarthritis in murine models.

Like COMP, uCTX-II is among the well studied osteoarthritis biomarkers. Early studies by Garnero *et al.* [19] showed that elevated uCTX-II levels, particularly if associated with low serum levels of PIIANP (a marker of collagen 2 synthesis), conferred relative risks of progression of 2.9 by radiography and 9.3 by arthroscopy. In the Rotterdam study [20] of 1235 osteoarthritis patients, radiographic progression (mean duration 6.6 years) in both knees and hips was significantly associated with high baseline uCTX-II concentration. Elevated levels of CTX-II have also been found to predict progression of JSN in hip osteoarthritis [21,22]. In addition, bone marrow abnormalities on MRI significantly correlated with uCTX-II and patients with highest baseline uCTX-II levels were more likely to have worsening bone marrow abnormalities at 3 months [23]. It should be noted, however, that the predictive value of uCTX-II in clinical trials remains uncertain. For example, Bingham *et al.* [24] showed that decreases of uCTX-II within several weeks of

instituting therapy with risedronate did not predict improvement in symptoms or JSN at 24 months.

A recent study by Conrozier *et al.* [25[■]] assessed the effect of intra-articular injections of hyaluronic acid in patients with knee osteoarthritis. Fifty-one patients with unilateral SKOA received Intra-articular (IA) injections of 2 ml hyaluronic acid on days 1, 7, and 14, and were followed for 3 months. The authors found that uCTX-II and serum hyaluronic acid at baseline were independently predictive of clinical response; moreover, 90 days after hyaluronic acid IA injections, uCTX-II levels were significantly decreased compared with baseline [25[■]].

Using proteomics and bioinformatics technologies to identify novel disease biomarkers, van Spil *et al.* [26[■]] assessed 14 biomarkers (uCTX-II, urinary C-terminal telopeptides of type I collagen, urinary N-Telopeptide Of Type I Collagen, sCOMP, sPIIANP, sCS846, sC1,2C, sOC, sPINP, sHA, sPIIINP, pLeptin, pAdiponectin, pResistin) in CHECK (Cohort Hip and Cohort Knee), a 10-year prospective cohort of 1002 individuals with early knee and/or hip osteoarthritis. Principal component analysis identified five clusters, designated as 'bone-CTX-II,' 'inflammation,' 'synovium,' 'C1,2C-adipokines,' and 'cartilage synthesis' clusters. Notably, uCTX-II clustered with biomarkers of bone metabolism, whereas sCOMP clustered with biomarkers of synovial activity.

Novel candidate biomarkers have also been identified during the past year. Using a quantitative proteomic approach that included tandem mass spectrometry (MS) analysis, Blanco and associates identified 349 different proteins in sera of osteoarthritis patients that differentiated patients from controls, including complement components, lipoproteins, von Willebrand factor, tetranectin, and lumican [27[■]]. Fukuda *et al.* [28[■]] followed 68 patients with primary knee osteoarthritis for 18 months; N-glycoproteomic Two dimensional-Liquid chromatography–Matrix-assisted laser desorption/ionization (2D-LC-MALDI) analysis of plasma and serum samples identified four MS peaks that exhibited significantly different intensities between progressors and non-progressors, representing clusterin, hemopexin, alpha-1 acid glycoprotein-2, and macrophage-stimulating protein. An interesting novel biomarker was recently reported by Henrotin *et al.* [29[■]], who identified elevated fibulin peptides in urine and sera from SKOA patients using proteomic analyses. Fibulins are associated with basement membranes and the extracellular matrix protein (ECM); their aminoterminal regions resemble those of the complement component anaphylatoxins C3a, C4a, and C5a. Serum Fib3–1 and Fib3–2 levels discriminated between osteoarthritis and normal populations; immunostaining revealed the presence of Fib3–1 and Fib3–2 in the superficial layer of chondrocytes of fibrillated cartilage.

Finally, Wang *et al.* [30[■]] reported that follistatin-like protein 1 (FSTL1) mRNA and protein levels were substantially elevated in synovial fluids and sera from osteoarthritis patients compared with control trauma patients. FSTL1, a secreted glycoprotein, has been implicated in arthritis pathogenesis in a mouse model. As a potential serum biomarker that may reflect the severity of joint damage, FSTL1 merits study in monitoring of osteoarthritis progression and efficacy of osteoarthritis therapies [30[■]].

INFLAMMATORY PROGNOSTIC BIOMARKERS

Although numerous subsets of inflammatory bio-markers are under evaluation in osteoarthritis, we will describe three key groups (Table 1) [14[■],31[■], 32[■],33[■],34,35,36[■], 37[■],38[■],39,40[■],41,42[■],43[■],44, 45[■],46[■]].

Cytokines/chemokines, complement, and lipid mediators

Whereas degradation and synthesis of cartilage, bone, and synovium had dominated osteoarthritis biomarker research, a significant amount of work has also focused on evidence from serum or plasma of inflammatory processes occurring within affected osteoarthritis joint tissues. Although traditionally considered a non-inflammatory joint disease, it is now appreciated that inflammatory mediators are produced by articular tissues in osteoarthritis and are implicated in disease pathogenesis. Cytokines and prostaglandins produced by cartilage promote cartilage degeneration, whereas synovitis has been associated with greater risk of cartilage loss in patients with knee osteoarthritis [47[■],48[■],49]. Among the many biochemical pathways activated within joint tissues during the course of osteoarthritis are mediators classically associated with inflammation, notably IL-1 β , TNF- α , nitric oxide, prostaglandins, and complement [45[■],50–52]. Denoble *et al.* [34] further demonstrated the importance of low-grade inflammation within osteoarthritis joints, reporting that synovial fluid uric acid strongly correlated with synovial fluid IL-18 and IL-1 β in a cohort of patients with knee osteoarthritis. All three biomarkers associated with osteoarthritis severity as measured by radiograph and/or bone scintigraphy. Synovial fluid IL-18 was associated with radiographic progression at 3 years. The authors concluded that correlation of synovial fluid uric acid with IL-18 and IL-1 β suggested activation by uric acid of inflammasomes, supporting the potential involvement of the innate immune system in osteoarthritis pathology and progression.

Emerging literature indicates that the local inflammation within osteoarthritis joint tissues described above can be reflected in serum bio-markers, suggesting that in subsets of osteoarthritis patients there is evidence for systemic inflammation. One of the earliest studies was by Fraenkel *et al.* [35], who reported associations of IL-1 β production with the presence of knee osteophytes as well as JSN in women; these women also had higher rates of knee osteoarthritis, but lower rates of hand osteoarthritis. More recently, using a proteomic approach, serum proteins such as MIP-1 α , IL-1 α , IL-2, IL-15, and MMP-7 were shown by Ling *et al.* [53] to differentiate early osteoarthritis from controls.

Our lab has demonstrated elevations of prostaglandin E2 (PGE2), IL-1 receptor antagonist (IL-1Ra), and MMP-9 in SKOA patients [36[■]]. Plasma PGE2 levels in SKOA patients studied at baseline were twofold higher than in healthy controls and associated with disease severity. Among the plasma proteins studied, IL-1Ra predicted radiographic severity (KL1/2 vs. KL3/4). Elevated plasma levels of MMP-9 and IL-1Ra predicted JSN at 24 months. Nemirovskiy *et al.* [44] also reported elevations of plasma PGE2 as well as the lipoxygenase product, 15-HETE, in SKOA patients.

Baker *et al.* [54[■]] recently examined the association of fasting plasma phospholipid n-6 and n-3 polyunsaturated fatty acids (PUFAs) with synovitis (as measured by synovial thickening on contrast-enhanced knee MRI) and cartilage damage among 472 patients in the Multicenter Osteoarthritis Study (MOST), finding an inverse relation between total n-3 PUFAs and the specific n-3, docosahexaenoic acid with patellofemoral cartilage loss. A positive association was observed between plasma levels of the pro-inflammatory n-6 PUFA, arachidonic acid, and synovitis [54[■]]. Cohen *et al.* [31[■]] reported that patients treated with an anti-IL-1R1 monoclonal antibody showed statistically insignificant but numerically greater improvements in pain; minimal, if any, clinical benefit was observed. Of note, reductions of highly sensitive C-reactive protein (CRP) (hsCRP) levels (1.9 vs. 0.7 mg/l; $P < 0.001$) in treated patients occurred within 2 weeks of therapy and were sustained through week 16 of follow-up (8 weeks after last injection).

Elevated circulating levels of IL-6 and TNF- α in knee osteoarthritis have been reported by Stannus *et al.* [39] in 172 patients assessed at baseline and approximately 3 years' follow-up.

T1-weighted fat-suppressed MRI of the right knee was performed at baseline and follow-up to determine cartilage loss over 2.9 years in older adults. At baseline, quartiles of IL-6 and TNF- α were associated with increased prevalence of medial tibiofemoral JSN (OARSI grade 1). Longitudinally, baseline IL-6 predicted loss of both medial and lateral tibial cartilage volume, independently of TNF- α . Change in IL-6 was associated with increased loss of medial and lateral tibial cartilage volume; change in TNF- α was also negatively associated with change in medial cartilage volume. In a subsequent study of osteoarthritis pain, Stannus *et al.* [32[■]] also found that baseline hsCRP was positively associated with worsening in total knee pain, as well as change in the pain at night in bed and while sitting/lying, over 2.7 years. Baseline TNF- α and IL-6 were associated with change in pain while standing, and change in TNF- α was positively associated with worsening of total knee and pain while standing.

In contrast, Vlad *et al.* [40[■]] reported no association between markers of inflammation and osteoarthritis of the hands and knees in the community-based Framingham Offspring cohort. In 1998–2001 patients provided blood specimens that were tested for 17 markers of systemic inflammation; in 2002–2005 patients had radiographs of knees and hands. Analysis indicated no association between any marker and the presence of radiographic osteoarthritis in any joint. It is difficult to compare this community cohort to the other populations in which positive associations have been reported, particularly as those were typically studies of patients with symptomatic osteoarthritis. In addition, the radiographic assessment in the Framingham cohort was separated from the prior blood sampling by a range of 3–7 years.

In interesting novel studies, Robinson and associates used proteomic and transcriptomic analyses of synovial fluids and membranes from patients with osteoarthritis, and determined that expression and activation of complement are abnormally high in human osteoarthritis joints [45[■]]. Using mice genetically deficient in C5, C6, or CD59a, and pharmacological inhibitors of complement in wild-type mice, the authors showed that complement, and specifically the membrane attack complex (MAC), is critical to development of osteoarthritis. The authors provide evidence that MAC acts, in part, via the activation of chondrocytes and release of MMPs, including MMP-13. Recent work from this laboratory utilized MS and multiplex bead-based immunoassay to survey proteins present in synovial fluid and sera of patients with SKOA compared to patients with rheumatoid arthritis (RA), as well as to sera from healthy individuals [38[■]]. Multiplex cytokine analysis revealed increased inflammatory proteins in sera of osteoarthritis patients compared to controls, including IL-1 β , IL-1Ra, IL-6, MCP-1, Monokine induced by interferon gamma (CXCL9) (MIG), Vascular endothelial growth factor (VEGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The levels of these cytokines were higher in osteoarthritis synovial fluid than sera, consistent with their origin from joint tissues. In this regard, the abnormal production and ‘leakage’ of inflammatory proteins into sera are analogous to that observed for more conventional biomarkers of joint tissue synthesis and degradation. In addition, the authors found that a large proportion of the proteins present in osteoarthritis synovial fluid activated cultured macrophages via TLR4 to induce the production of an array of inflammatory cytokines. They suggest that proteins present in osteoarthritis synovial fluid may contribute to low-grade inflammation in osteoarthritis by functioning as damage-associated molecular pattern (DAMP), that is, ligands of TLR4.

A recent study by Rbenhagen *et al.* [42[■]] demonstrated increased IL-7 levels in synovial fluid of osteoarthritis patients. IL-7 is a cytokine produced by osteoarthritis chondrocytes (among other cell types; IL-7-stimulated chondrocytes respond with proteoglycan release from cartilage [55]). The authors also observed that MMP-1 levels decrease with radiographic severity of osteoarthritis, attributed to progressive loss of cartilage, the

presumptive origin of the MMP production. Other cytokines, including IL-1Ra, were highly correlated with synovial levels of MMP-9, MIP-1a, and IL-8 [42[■]].

The findings that osteoarthritis is characterized by both local and systemic inflammatory conditions have been similarly observed in Inbred strain of mice (STR/ort) mice, a model for spontaneous osteoarthritis [43[■]]. Serum analysis showed higher concentrations of IL1 β , IL12p70, MIP1 β , and IL5, correlated with worsened joint morphology and local expression of inflammatory mediators.

Obesity-related inflammatory biomarkers

Obesity is one of the primary risk factors for developing both knee and hand osteoarthritis [56]. It is postulated that in addition to the biomechanical impact of obesity, which would not account for the increased incidence of hand osteoarthritis, some pro-inflammatory adipokines produced by adipose tissue contribute to development and progression of osteoarthritis [57]. Leptin, resistin, and adiponectin may contribute to obesity-associated osteoarthritis via actions on cartilage metabolism. A detailed review of the mechanism by which obesity contributes to osteoarthritis is provided by Berenbaum in this issue.

Koskinen *et al.* [46[■]] investigated adiponectin as a plasma biomarker in male osteoarthritis patients undergoing total knee replacement surgery. Plasma adiponectin levels were higher in patients with more radiologically severe osteoarthritis, and positively correlated with plasma levels of COMP and MMP-3. Richette *et al.* [33[■]] demonstrated the beneficial effect of bariatric surgery on knee osteoarthritis symptoms and systemic inflammatory biomarkers. Preoperatively, serum IL-6 levels were elevated and correlated with levels of hsCRP. Six months after surgery, knee pain decreased, as did serum levels of IL-6, hsCRP, COMP, and fibrinogen, whereas levels of N-terminal pro-peptide of type IIA collagen levels (a biomarker of cartilage synthesis) increased. Our group examined the effects of bariatric surgery on osteoarthritis symptoms, and similarly demonstrated significant decreases in knee pain [41].

Transcriptomic biomarkers

We have recently reported that increased IL-1 β gene expression in peripheral blood leukocytes (PBLs) is associated with increased pain and predicts risk for progression of SKOA [37[■]]. Inflammatory gene expression in PBL was assessed using microarray and further validated using qPCR. Radiographic progression at 2 years was assessed in 86 patients. Patients with the inflammatory 'IL-1 β PBL signature' had higher pain scores, decreased function, and higher risk of radiographic progression. Since that publication additional patients have completed the 24-month study [36[■]], in whom PBL mRNA overexpression of IL-1 β , TNF- α , and COX-2 at baseline predicted higher risk for radiographic progression, as measured by change in minimal medial joint space width. Similar observations have been made in a dog model of spontaneous osteoarthritis: inflammatory response genes, including TNF- α , were differentially expressed in PBLs (determined by microarray) [58[■]].

These data indicate that, in subsets of osteoarthritis patients at higher risk for radiographic progression, PBLs are activated by repeated circulation through diseased synovium and subchondral bone of affected joints. An alternative explanation was suggested by Hirohata *et al.* [59], who demonstrated enhanced expression of mRNA for IL-6 and TNF- α by CD34+ hematopoietic precursor cells in bone marrow of both osteoarthritis and RA patients compared with normal individuals. This raises the intriguing possibility that activated peripheral mononuclear cells originate from a pool of activated precursor cells in the bone marrow of osteoarthritis joints. The above studies suggest that inflammatory biomarkers

may identify subgroups among osteoarthritis patients in whom disease progresses at different rates. This may facilitate our understanding of osteoarthritis pathogenesis and allow us to differentiate disease phenotypes within a heterogeneous knee osteoarthritis population.

CONCLUSION

During the past decade, there have been significant developments in the scientific understanding of osteoarthritis. Aided by advances in imaging technology, we have come to appreciate that osteoarthritis is a disease of the ‘whole joint’ involving a complex series of molecular changes at the cell, matrix, and tissue levels, and complex interactions between the tissues that make up the joint. We are beginning to understand better the mechanisms by which genetic, mechanical, and metabolic risk factors initiate and perpetuate the biochemical changes that lead to progressive failure of the joint. However, DMOAD drug development has been hampered by the absence of validated and qualified biomarkers, particularly those that may predict disease incidence or progression. As described in this review, extensive work over the past decade has identified a significant number of candidate bio-markers that can now be focused upon in well characterized population studies and clinical trials. There is little doubt, given international effort in this area and a common focus on high-value candidate biomarkers, that the next several years will see major breakthroughs that may lead to effective therapies to reduce the symptoms and slow the progression of osteoarthritis.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 155–156).

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KEY POINTS

- Osteoarthritis is a disease of the whole joint affecting cartilage, synovium, bone, ligament, and muscles, leading to deterioration or loss of joint function.
- On the basis of US Food and Drug Administration (FDA) recommendations, a biomarker can be defined as that which is 'objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.'
- Studies have identified many candidate molecular biomarkers from the various joint tissues, some involved in synthesis and degradation, whereas others are more inflammatory in nature.
- The cause of osteoarthritis varies among individuals; therefore development of biomarkers will allow differentiation of phenotypes, prognoses and rates of disease progression within a heterogeneous knee osteoarthritis population, and ultimately may facilitate the development of disease-modifying osteoarthritis drugs (DMOADs).

Table 1

Candidate inflammatory prognostic biomarkers in knee osteoarthritis

Inflammatory biomarker subgroup	Candidate biomarkers	Presumed source: C =cartilage, S =synovium, B =bone	Selected recent citations
Cytokine/chemokines, complement and lipid mediators	hsCRP	Liver	[14 [■] ,31 [■] ,32 [■] ,33 [■]]
	IL-1 β	C,S,B	[34,35,36 [■] ,37 [■]]
	IL-1Ra	C,S,B	[36 [■] ,38 [■]]
	TNF- α	C,S,B	[32 [■] ,38 [■] ,39,40 [■]]
	IL-6	C,S,B	[32 [■] ,39,40 [■] ,41]
	IL-7	C,S	[42 [■]]
	IL-15	C,S	[38 [■] ,43 [■]]
	15-HETE	C,S	[44]
	PGE2	C,S,B	[36 [■] ,44]
	Complement	C,S	[45 [■]]
Obesity-related inflammatory biomarkers	Leptin	Adipose tissue	[33 [■] ,46 [■]]
	Adiponectin	Adipose tissue	[33 [■] ,46 [■]]
	Resistin	Adipose tissue	[33 [■] ,46 [■]]
Transcriptomic biomarkers	PBL expression of IL-1 β / TNF α	PBL	[37 [■] ,58 [■]]

15-HETE, 15-hydroxy eicosatetraenoic acid; hsCRP, highly sensitive C-reactive protein; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; PBL, peripheral blood leukocytes; PGE2, prostaglandin E2; TNF, tumor necrosis factor (Note: Table is original).