Review Article

Inflammatory biomarkers and state of the tibiofemoral joint in the osteoarthritic knee: a narrative review

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Background: The healing process is initiated by injurious stimuli in response to cellular damage. Upon recruiting proinflammatory biomarkers to the tissue site of injury, the release of additional biomarkers occurs, including the likes of cytokines, matrix molecules, macrophages, neutrophils, and others. This influx of immune system mediators can occur for chronic periods, and though its intention is for healing the original injurious stimuli, it is also suspected of causing long term cartilage impairment following internal structure damage. The objective of this narrative review is to identify which inflammatory factors have the leading roles in the progression of osteoarthritis (OA) following knee injuries and how they fluctuate throughout the healing process, both acutely and chronically.

Methods: This narrative review was performed following a computerized search of the electronic database on PubMed in May 2023. Abstracts related to the inflammatory biomarkers of the post-traumatic knee were included for review.

Key Content and Findings: The chronic low-level inflammation that leads to OA leads to the destruction of the cartilage extracellular matrix, which new and developing orthopedic research is still attempting to find resolve for. Some of this damage is attributed to the biomechanical alterations that occurs following injury, though with most procedures capable of joint biomechanical restoration, focus has rather been shifted toward the environment of inflammatory biomarkers.

Conclusions: Future studies will be aiming to improve the diagnostics of OA, focusing on a consistent correlation of inflammatory biomarkers with imaging. Additionally, biochemical treatments will need to focus on validating reproducible modulation of signaling molecules, in attempts to lessen the chronic elevations of destructive biomarkers.

Keywords: Inflammatory modulators; post-operative inflammation; knee trauma

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Introduction

The slow progression of osteoarthritis (OA) is believed to occur from chronic inflammatory responses that alter the joint through bone remodeling and degradation of cartilage (1). As a response to cellular damage, injurious stimuli initiate the healing process by recruiting proinflammatory biomarkers to the tissue site of injury. This is followed by an influx and release of numerous mediators by the immune system, in order to reach the origin of disruption. The effects of these mediators range from occurring for acute periods or lasting

into chronic stages, and they may be targeted directly to the site of injurious stimuli origin or they may occur systemically. In recent years, a greater focus has been placed on the potentially destructive role this pro-inflammatory state has played in the progression of OA (1-3). It has drawn more attention with the recent literature shifting the focus of OA toward being a disease predominantly affected by the biochemical-, as opposed to its biomechanical-origin (2,3). This is due to the inability of reconstructive procedures to significantly decrease the occurrence of articular degenerative changes, even after succeeding in restoring knee stability to injured knees.

This postulate derives from the potential for low level inflammation progressing to chronic inflammation, with numerous inflammatory factors contributing to subclinical OA progression (4-7). Some of the factors include synovial macrophages, which induce destructive inflammatory responses via the stimulation of aggrecanases and matrix metalloproteinases (MMPs) (8). The complement system, part of the innate immune system, is activated by many components of the cartilage extracellular matrix (ECM) (9) that leads to tissue destruction. This activation is observed through increasing levels of C3A and C5B-9, and decreasing levels of factor H, C4-binding protein, C1 inhibitor, and clusterin, which were more evident in the synovial fluid of patients enduring OA (10). Even in obese patients, who frequently endure OA as a result of increased joint forces and the subsequent amplified degradation of cartilage, synovial fluid has been shown to exhibit increased levels of interleukin (IL)-6 and soluble IL-6 receptor released from the infrapatellar fat pad (11).

Studying these biomarkers is challenging and frequently varies study by study, with subtle adjustments to the time of day or period from injury to collection subtly influencing the significance of biomarker elevations and depressions. Furthermore, not all of the correlations found in differing levels of these inflammatory biomarkers between healthy and OA patients has been directly linked to cartilage destruction. None the less, variations such as these emphasize the elevated risk these patients have with regards to the susceptibility of cartilage and its inability to self-repair following traumatic events within the knee joint (12). Understanding which biomarkers are associated with these types of biochemical events are relatively cost-effective and easy to collect by serum or urine, as well as being an accurate source for identification of early OA changes; the relative concentration of these biomarkers enable formulation of diagnoses through the assessment of general and post-traumatic OA (13,14).

With OA being one of the leading causes of disability (15), and a significantly high risk of developing symptomatic OA within 10 to 20 years post knee injury repairs (16), there is a dire need to identify which inflammatory factors have the leading roles in the progression of OA following knee injuries and how they fluctuate throughout the healing process, both acutely and chronically. These biomarkers represent a wide range of molecules within serum and synovial fluid, and they may ultimately enable future modifications across treatment protocols for lessening the degradative effects so commonly seen following injury. Prior to being capable of developing these modification and treatment protocols, we first must understand the various classes of biomarkers that are most associated with inflammation following soft tissue injuries of the knee and interpret their quantifiable changes with regards to elevation and depression of their respective levels in post-traumatic states. We present this article in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-23-59/rc).

Methods

This narrative review was performed following a computerized search of the electronic database on PubMed in May, 2023. The initial search included the following terms: ((Inflammatory biomarkers) AND (osteoarthritis)) AND (tibiofemoral) AND (trauma)). The specific form of trauma causing injury was not restricted to soft tissue or fracture, but rather all-inclusive of knee injuries. Published studies were only included if completed in English. Abstracts were originally screened for inclusion to assess their contents for applicability, and further publications were pulled from referenced material within these initial inclusions (*Table 1*).

Post-traumatic inflammatory state

The structural elements of the human body are all organized by a set of molecules that are regulated by an assembly process. Chondrocytes are surrounded by an ECM, consisting of both collagenous and non-collagenous components, and they comprise the articular cartilage of joints. Of the five main types of collagen, the majority of the fibrillar collagen network of chondrocytes consist of type II collagen (17). Aggrecan is a contributor to the tensile properties of collagen fibers due to its extreme anionic charge density and influence on water retention.

Table 1 The search strategy summary

Items	Specification
Date of search	05/25/2023
Databases and other sources searched	PubMed
Search terms used	((Inflammatory biomarkers) AND (osteoarthritis)) AND (tibiofemoral) AND (trauma))
Timeframe	1980 to present
Exclusion criteria	Exclusion criteria: animal studies, non-English language publications
Selection process	Independent review by two authors for selection of publications, additional publications pulled from articles included from original database query

The process of collagen turnover is a normal metabolic process associated with collagen and proteoglycan synthesis and degradation. It can be induced by the biomechanical forces of movement or by various biochemical mediators in response to injury, with a balance between the two being carefully leveled as to prevent any overproduction or inadequate protection of connective tissue.

Biomechanical induced inflammation

The incidence and progression of knee OA is significantly increased from disruption by mechanically induced traumatic knee joint injuries (16,18,19), with preinjury biomechanical profiles having an important role as an effect-modifying factor in post-traumatic osteoarthritis (PTOA) following anterior cruciate ligament (ACL) injury. A method for evaluating the inflammatory status following injuries has commonly been in using serum biomarkers, and when assessing the effects of ambulation on the environment of the knee, lower extremity loading has been linked with cartilage oligomeric matrix protein (COMP) concentrations (20).

Associations like these have led many to support research toward enhancing our understanding of the relationship between the biological response of collagen metabolism biomarkers from altered joint loading, and the difference in these biomarker levels from the presence or absence of acute knee injuries (21). With there being differences in preinjury serum biomarker levels from cartilage turnover, this may suggest that ACL tears are occurring at higher rates in individuals with altered bone and collagen metabolism relative to those lacking any history of joint injury (22). Structural alterations and breakdown of collagen and its metabolism have been linked with mechanical loading shifts (21), which leads some to question whether individuals with altered gait and biomechanics are placed at a higher risk for incident ACL injuries in being predisposed to biomechanically induced biochemical alterations in the synovial environment of the knee.

Even slight changes in motion have been linked with similar increased risk for OA given the alteration of force distribution and biomechanical patterns, like adjusted valgus knee movement or knee abduction angle (14,23), which both are similar alterations in gait commonly seen in osteoarthritic knee biomechanics (14,24,25). These altered biomechanics are also observed to cross over and present in contralateral non-injured knees following severe knee injuries. Dahlberg *et al.* (26) showed that in the contralateral knee of ACL injured patients, some evidence suggests that concentrations of aggrecan, COMP, and MMP-3, are elevated in the uninjured contralateral knee as a result of altered joint loading following injury.

Understanding the effects upon the biochemical environment as a direct cause of biomechanical alterations is still unclear when comparing studies in the literature. Jørgensen *et al.* (27) ultimately concluded that loading had no influence on cartilage collagen synthesis of the tibial plateaus in patients with OA, but was able to see significant improvements in pain and physical function. When OA had reached late stages, they also didn't appear to observe differences in collagen turnover relative to the cartilage of the medial tibial plateau and its exposure to greater forces centrally or peripherally under the meniscus (27).

Pro-inflammatory cytokines

Since the shift in focus to biochemical influences has occurred, the development of OA is more likely attributed

to an origin of an inflammatory nature, which is then perpetuated from the prolonged presence and exacerbation of these modulators in the synovium of the knee joint following injurious events. Even from the early stages of the disease, the pro-inflammatory cytokines secreted into this synovium disturbs the metabolism and ultimately leads to increased catabolism of the cartilage tissue, like type II collagen. Being a major component of cartilage ECM, the highly cross-linked triple helical type II collagen has been shown to be highly responsive to signaling between cytokines, like IL-1β. While there are many inflammatory modulators involved in this process, the major players linked with OA are IL-1β and tumor necrosis factor (TNF) (3,28). Though IL-1β is believed to have a role in the homeostasis maintaining cartilage (29), it is more widely accepted for its consistent role as a pro-inflammatory cytokine. Compared to normal cells, osteoarthritic chondrocytes have shown increased expression of TNF receptor I (TNFRI) (30) and IL-1 receptor type 1 (IL-1RI) (30,31), the receptors responsible for activating TNF and IL-1β, respectively.

Activation of these receptors leads to distinct intracellular protein cascades, which enables IL-1β and TNF to act either independently or in concert with other cytokines that are associated with cartilage destruction and perpetuation of the inflammatory cascade. They are mediated by the activation of signaling pathways like c-Jun N-terminal kinas, p38 mitogen activated protein kinase, and nuclear factor κB (NFκB). Following activation, the induction and production of numerous other pro-inflammatory and catabolic factors in inflammatory environment occurs, especially in patients with OA, with both events typically observed at significantly elevated levels throughout the synovial fluid, synovial membrane, cartilage, and subchondral bone.

As soon as two days following acute knee injury, initial alterations in joint remodeling are observed with degradation potentially lasting a decade (3,32). The initial wound healing process following acute trauma is accompanied by a flare of cytokines, including IL-1, IL-1β, IL-6, IL-8, and IL-10, along with IL receptor antagonist (IL-1Ra) and TNFα (33). Cartilage damage from acute knee injury is observed through the resultant massive release of proteoglycan and collagen fragments in the synovial fluid during in the first few weeks following injury (34,35), but continued damage may occur from the persistence of these significantly elevated concentrations for decades following injury (34,36-40). In an *in vitro* experiment of cartilage explants stimulated with proinflammatory cytokines, Cawston *et al.* (41) observed a rapid release and loss of proteoglycans and collagen fragments, ultimately followed by collagen loss. This experiment simulates the wave of proteoglycan and non-collagenous protein loss that occurs initially as a response of the injured joint to acute injury. Similarly, Catterall *et al.* (42) found that after acute injury, collagen damage occurred alongside a rise of synovial fluid collagen biomarkers and a decline in the concentration of small cartilage molecules and proteoglycans.

Following ACL injury, OA is heavily influenced by the significant increases in some of these aforementioned proinflammatory cytokines, along with others like interferon-γ (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), in order for the tissue to begin the repair process following injury. Increased signaling of these proinflammatory cytokines is required for the healing process, but the drawback of this repair process is the damage occurring to surrounding synovial tissue, subchondral bone, and cartilage (43). Any loss of proteoglycans has been shown to be reversible in earlier animal studies (44,45), but the loss of collagen appears to cause the greatest damage to cartilage, as it is irreversible (46); occurring within days to weeks following severe knee injury. Both proteoglycans and type II collagen, along with glycosaminoglycans, compose the ECM of cartilage and are what provide its integrity and capability in resisting compressive loads (47). The increase in proinflammatory cytokines induces inflammation, ultimately ending in the breakdown of collagen once the production of MMPs are stimulated (48).

Matrix molecules

Chondrocytes are stimulated by the aforementioned IL-1β and TNF cytokines, leading to the secretion of several proteolytic enzymes. These enzymes, secreted in their inactive proenzyme form and activated at the tissue level, comprise a group of at least 28, and are referred to as MMPs. They have an essential role in the repair and remodeling of tissue after inflammation, and they are also key regulators to the destruction of cartilage through their induction of ECM catabolism, including components of collagen, fibronectin, and proteoglycans. Increased stimulation and release of MMPs occurs following the downregulation of extracellular synthesis (49) and the subsequent increase in chondrocyte induced ECM breakdown (50).

MMP-1 is the most widely recognized of the MMP molecules, as it is highly versatile and efficient in cleaving

multiple collagen chains at different points, sequentially along collagen fibers. Its overproduction in osteoarthritic chondrocytes is thought to play one of the largest roles in the irreversible destruction of joint tissue during OA (51). But MMP-induced damage isn't limited to cartilage breakdown, and may extend to affecting the surrounding subchondral bone and synovial tissue (52). One of particularly importance being MMP-3. In addition to its degradative influences on collagen, proteoglycans, fibronectin, and elastin, MMP-3 is also able to activate other proteinases such as MMP-1, MMP-7, MMP-9, and MMP-13 (53). There are many others that are expressed and associated with various articular cartilage conditions, but among these, there are three that are exclusively characteristic of pathological conditions, being MMP-3, MMP-8, and MMP-9. These chondrocyte derived MMP's are considered the major catabolic enzymes associated with articular cartilage degradation (54).

With the level of these enzymes drastically increasing under the influence of cytokines and growth factors (55), there is a important balance maintained for these MMPs by their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). There is a persistently elevated concentration of matrix molecules in synovial fluid, like tissue inhibitor of metalloproteinase (TIMP)-1 and COMP, for a period of time following ACL injury (40,56). In even longer periods, MMP-1 (38) and MMP-3 (38,40,57) can remain elevated for up to twelve years post-injury. This leads to an offset in the balance of degradation and synthesis, given an increased ratio between MMPs and TIMP-1 following injury (38).

These elevations are not always associated with greater cartilage degradation. Jørgensen *et al.* (27) showed that despite having higher MMP-3 expression submeniscally, collagen turnover under the meniscus from exercise in late-stage OA patients is the same (not matched by increasing synthesis of collagen). They postulated that in combination with lower lubricin expression in the submeniscal area, there could be an increased loss of cartilage matrix. Higher MMP3 has also been shown to be associated with undamaged knee cartilage in the medial tibial plateau (58) as well as in the femur condyles (59).

MMP3 also contributes to the breakdown of cartilage through the generation of damage-associated molecular patterns (DAMPs) (52,60). The DAMPs produced from this collagen degrading protease (45) directly induces synovial inflammation through toll-like receptor signaling (52,60) and activation of macrophages and neutrophils (61) signaling. Studies have also shown that the increased expression and signaling of these MMP molecules isn't limited to the tissue adjacent to the injury, as patients with OA have been seen to have increased levels of MMP expression in all joint tissues (62).

Macrophages and neutrophils

Pro-inflammatory cytokines, along with MMP-induced DAMPs, vascular cellular adhesion molecule-1 (VCAM-1), and vascular endothelial growth factor (VEGF), can lead to the development of OA via the activation of macrophages via chemotactic functions. Macrophages and neutrophils are guided to the joint to by the chemotactic stimuli role of DAMPs and monocyte chemotactic protein (MCP)-1 (38), ultimately resulting in the promotion of cartilage degradation. Following activation, macrophages regulate the environment of growth factors, cytokines, and MMPs (63,64). Another chemotactic stimulus for macrophages is soluble VCAM-1 (65) through its ability to bind leukocytes (66) and is expressed in all cell types of the joint organ serves as a chemotactic stimulus for macrophages.

Neutrophils respond to similar signaling by secreting proteinases and propagating local inflammation, one of particular importance being elastase (67). Elastase is able to degrade the components of cartilage, including proteoglycans, elastin, and collagens (68) which along with synovitis, may further compound the loss of cartilage due to elastase activation and upregulation of proteinase-activated receptors (PARs) (69-71).

VEGF

An important signal protein of angiogenesis, VEGF, causes the creation of blood vessels, which then recruit leukocytes and lead to increased inflammation (72,73). VEGF is even capable of activating of macrophages, acting as a chemoattractant (74), which becomes amplified upon macrophage arrival to the joint. Joint inflammation become exacerbated to a point where an increased production of VEGF leads to more significant symptoms of synovitis and angiogenesis (75), which recruits macrophages for further inflammation and damage to the joint (1). In an attempt to understand how important VEGF is in the is correlation with OA disease severity, Nagao *et al.* (76) surgically induced knee OA into mice (modeling PTOA of humans). They found not only that by inducing VEGF, an increase in catabolic processes occurred in both synovial cells and chondrocytes, but when knocking down VEGF via anti-

VEGF antibodies they contrarily found an attenuation of OA given its effect in phosphorylation of VEGFR2 in articular chondrocytes and synovial cells.

One feature of OA that is provides a significant contribution to its symptoms is the development of osteophytes. These bony outgrowths are covered by fibro-cartilage (77), and in OA knees there seems to be a high turnover, evident by a 10 fold increase in deuterium incorporation (indicates rapid tissue growth) (27). While proteinase activated receptor 2 (PAR2) plays a critical role in subchondral bone changes and the development of osteophytes (69), alongside PAR2, during all phases of osteophyte development, are hypertrophic chondrocytes expressing VEGF. VEGF promotes the vascular invasion of cartilage which ultimately results in the formation of osteophytes (78) in these settings. While VEGF is well documented for its purposes during development as a chondrocyte survival factor, studies like this highlight the importance of studying this biomarker and any effects from monitoring or regulating its levels during periods of post-traumatic injuries. Future studies will mostly likely be focusing on the correlation of VEGF with OA severity outcomes, but specifically given its association of fluctuation levels in the synovial fluid as opposed to serum. This is due to the literature supporting the local disease-related phenomena of these biomarkers and their relevance with analytes of OA (79).

Anti-inflammatory cytokines

As mentioned earlier, the post-traumatic state of the knee joint is believed to undergo a wave of proteoglycan and collagen loss accompanied by an initial flare of proinflammatory cytokines. This elevation of proinflammatory cytokines is then met with an increase in its counterpart, the anti-inflammatory cytokines of IL-1Ra (80) and IFN-γ (81). IL-1Ra is a natural inhibitor of IL-1 activity, and it is produced by chondrocytes and synovial fibroblasts for the purpose of anti-inflammatory regulation of the increasing level of pro-inflammatory cytokines.

This temporary buffer is effective during the subacute phases of this inflammation, and though both types of cytokines eventually subside, some proinflammatory cytokines may persist for chronic periods without adjacent increased in its anti-inflammatory counterpart. This balance of destructive and protective cytokines is critical for the maintenance of cartilage in these post traumatic states. In the chronic ACL-deficient knees, Cameron *et al.* (80) observed a drastic decrease in IL-1Ra over time. When considering the persistence of destructive cytokines and tapering of IL-1Ra, a chondrodestructive response may be occurring, being driven by low-grade inflammation from subtle elevations of IL-1 throughout the chronic healing phase. For up to twelve years after acute knee injury, proteoglycans (38,40,57) and glycosaminoglycans (82) can be overwhelmed by the proinflammatory biomarkers leading to inadequate protection of cartilage leading to degradation.

GM-CSF is another cytokine that was observed as elevated for a similar time period following injury (80). As a contributor to the anabolic cytokine response, GM-CSF, along with IL-7 and granulocyte colony-stimulating factor (G-CSF), promotes the synthesis of cartilage ECM components which opposes degradation of cartilage, though generally they aren't seen to be significantly different when compared to controls participants (81).

Although for the most part, the signaling molecules have a specific role in the destruction or protection of cartilage following injury, there are two cytokines that are capable of acting as either anti- or pro-inflammatory signaling molecules following ACL injuries, IL-6 (80,81) and IL-8 (80,83). The mechanism of this dual effect by IL-6 is thought to be attributed to its primary regulation of immunosuppression and anti-inflammation during the acute phase response (84). Studies have been inconsistent in identifying whether IL-6 is more protective or destructive to cartilage. In the subchondral bone of OA, rather than observing the features of bone resorption and osteoclast stimulation, bone accretion and sclerosis is commonly seen late in the disease process, which may be explained by an initial phase of bone resorption which is later followed by a period of increased bone formation as the disease progresses.

Future directions

The current means for diagnosis of knee OA have yet to successfully implement a biochemical component to track the progression or even identify the presence of OA. Many studies are currently attempting to correlate these biomarkers alongside imaging methods, but some limitations that have arisen is the usage of these cartilage degradation biomarkers relative to the stages of OA (85). While measuring levels of matrix synthesis may be informative in understanding the direct healing response, it is advised that interpretation of these levels be supplemented with matrix degradation in order to better differentiate these

OA stages, as links between type II collagen degradation and synthesis markers is well documented with regards to the progression of radiographically defined OA (86,87). Combining these biochemical and imaging observations would ideally provide greater accuracy and support for correlating OA developments given the more direct visualization of cartilage and synovial tissue, yielding more representative correlations between data. For instance, Pan *et al.* recently found associations with lateral compartment-specific cartilage volume loss (but not medial) in addition to worsening pain trajectories, suggesting an implication of cartilage loss from inflammatory factors from factors like IL-6, with no association with TNF-α (88).

Molecular validity regarding the origin and metabolism has been an issue in many biomarker studies. The correlation between components of OA with biomarker metabolism has been questioned from unexpected concentration changes and the absent mechanism of action for such outcomes (52,89,90). Biochemical markers for bone metabolism haven't performed well across the literature, as concentrations are potentially obscured by turnover levels by the complete skeleton (52). Biochemical markers of matrix degradation commonly perform superior to matrix synthesis markers of bone metabolism, and are often investigated more frequently, making them a much more promising field of detection values for future analysis. Nieboer *et al.* (2) looked into the inflammatory response for traumatic knee injuries, but found that after six weeks there was an absence of inflammatory proteins in the SF, which poses the question about the specific time frame studies should be using in the future for more consistent standardization of biomarkers levels following injury.

In a review by Khella *et al.* (3), although the models discussed in their review were matched the knee, joint trauma of patience and their clinical presentations for investigating the mechanisms of inflammation and post injuries effects, they also found laboratory studies, applied market higher concentrations of biomarkers than those relative to the synovial fluid of the knee joint following traumatic knee injuries. Therefore, authors suggest that future prospective studies evaluate the effects of these biomarkers in a closer approximation of the levels that appear in synovial fluid following injury.

Future studies for improving diagnostics of OA will need to focus on a consistent correlation of these biomarkers with imaging, but in order to effectively test biochemical treatments, there will also need to be a focus on validating reproducible modulation of signaling molecules via lessening the chronic elevations of destructive biomarkers or elevating protective biomarkers that seem to taper off and become overwhelmed. It will also be crucial for studies to include the exact time frame of biomarker fluctuations relative to the original injurious stimuli as most biomarkers are levels are transiently increased following injuries. Lastly, sample collection standardization would most likely improve biochemical markers consistency in performance, eliminating any confounding variables like exercise and diurnal rhythm discrepancies (91-94).

Conclusions

With the global healthcare and financial burden of OA likely to amplify in the coming years, given the high prevalence of OA in the growing elderly population, treatments need to be better anticipated and diagnostic improvements must be approached for newer means to achieve greater accuracy and prediction of cartilage changes. This review provides a background for refining our understanding of the key regulators involved in OA progression that will help in identifying the individual roles of pro inflammatory modulators, the degradation of cartilage tissue that ensues, and the future directions for OA biomarkers analysis studies in order to further control the effects of each biomarker relative to their contributing role to the development of OA following knee injuries. Compounds that may be able to regulate the activity of cytokines, or by lessening their synthesis, may be achieved by increasing the level of inhibitory cytokines that antagonize the catabolic activities of OA developments. These will need to be performed alongside advancing imaging and drug delivery models, so that we may better identify OA and understand its pathophysiology throughout the course of the disease.

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Footnote

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References

1. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6:625-35.
2. Nieboer MF, Reijman M, Wesdorp MA, et al. Improved Understanding of the Inflammatory Response in Synovial Fluid and Serum after Traumatic Knee Injury, Excluding Fractures of the Knee: A Systematic Review. Cartilage 2023;14:198-209.
3. Khella CM, Asgarian R, Horvath JM, et al. An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications. Int J Mol Sci 2021;22:1996.
4. Roemer FW, Guermazi A, Felson DT, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804-9.
5. Daghestani HN, Pieper CF, Kraus VB. Soluble macrophage biomarkers indicate inflammatory phenotypes in patients with knee osteoarthritis. Arthritis Rheumatol 2015;67:956-65.
6. Kraus VB, McDaniel G, Huebner JL, et al. Direct in vivo evidence of activated macrophages in human osteoarthritis. Osteoarthritis Cartilage 2016;24:1613-21.
7. Ayral X, Pickering EH, Woodworth TG, et al. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage 2005;13:361-7.
8. Bondeson J, Wainwright SD, Lauder S, et al. The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis. Arthritis Res Ther 2006;8:R187.
9. Hsueh MF, Önnerfjord P, Kraus VB. Biomarkers and proteomic analysis of osteoarthritis. Matrix Biol 2014;39:56-66.
10. Wang Q, Rozelle AL, Lepus CM, et al. Identification of a central role for complement in osteoarthritis. Nat Med 2011;17:1674-9.
11. Pearson MJ, Herndler-Brandstetter D, Tariq MA, et al. IL-6 secretion in osteoarthritis patients is mediated by chondrocyte-synovial fibroblast cross-talk and is enhanced by obesity. Sci Rep 2017;7:3451.
12. Hashimoto S, Rai MF, Janiszak KL, et al. Cartilage and bone changes during development of post-traumatic osteoarthritis in selected LGXSM recombinant inbred mice. Osteoarthritis Cartilage 2012;20:562-71.
13. Bauer DC, Hunter DJ, Abramson SB, et al. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage 2006;14:723-7.
14. Boden BP, Sheehan FT, Torg JS, et al. Noncontact anterior cruciate ligament injuries: mechanisms and risk factors. J

Am Acad Orthop Surg 2010;18:520-7.
15. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91-7.
16. Lohmander LS, Englund PM, Dahl LL, et al. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007;35:1756-69.
17. Heinegård D. Fell-Muir Lecture: Proteoglycans and more--from molecules to biology. Int J Exp Pathol 2009;90:575-86.
18. Lohmander LS, Ostenberg A, Englund M, et al. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 2004;50:3145-52.
19. Roos EM. Joint injury causes knee osteoarthritis in young adults. Curr Opin Rheumatol 2005;17:195-200.
20. Mündermann A, Dyrby CO, Andriacchi TP, et al. Serum concentration of cartilage oligomeric matrix protein (COMP) is sensitive to physiological cyclic loading in healthy adults. Osteoarthritis Cartilage 2005;13:34-8.
21. Andriacchi TP, Mündermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006;18:514-8.
22. Svoboda SJ, Owens BD, Harvey TM, et al. The Association Between Serum Biomarkers of Collagen Turnover and Subsequent Anterior Cruciate Ligament Rupture. Am J Sports Med 2016;44:1687-93.
23. Chaudhari AM, Andriacchi TP. The mechanical consequences of dynamic frontal plane limb alignment for non-contact ACL injury. J Biomech 2006;39:330-8.
24. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum 2005;52:2835-44.
25. Boden BP, Torg JS, Knowles SB, et al. Video analysis of anterior cruciate ligament injury: abnormalities in hip and ankle kinematics. Am J Sports Med 2009;37:252-9.
26. Dahlberg L, Roos H, Saxne T, et al. Cartilage metabolism in the injured and uninjured knee of the same patient. Ann Rheum Dis 1994;53:823-7.
27. Jørgensen AEM, Agergaard J, Schjerling P, et al. The regional turnover of cartilage collagen matrix in late-stage human knee osteoarthritis. Osteoarthritis Cartilage 2022;30:886-95.
28. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011;7:33-42.
29. Clements KM, Price JS, Chambers MG, et al. Gene deletion of either interleukin-1beta, interleukin-1beta-converting enzyme, inducible nitric oxide synthase, or stromelysin 1 accelerates the development of knee osteoarthritis in mice after surgical transection of the medial collateral ligament and partial medial meniscectomy. Arthritis Rheum 2003;48:3452-63.
30. Sadouk MB, Pelletier JP, Tardif G, et al. Human synovial fibroblasts coexpress IL-1 receptor type I and type II mRNA. The increased level of the IL-1 receptor in osteoarthritic cells is related to an increased level of the type I receptor. Lab Invest 1995;73:347-55.
31. Martel-Pelletier J, McCollum R, DiBattista J, et al. The interleukin-1 receptor in normal and osteoarthritic human articular chondrocytes. Identification as the type I receptor and analysis of binding kinetics and biologic function. Arthritis Rheum 1992;35:530-40.
32. Harkey MS, Luc BA, Golightly YM, et al. Osteoarthritis-related biomarkers following anterior cruciate ligament injury and reconstruction: a systematic review. Osteoarthritis Cartilage 2015;23:1-12.
33. Irie K, Uchiyama E, Iwaso H. Intraarticular inflammatory cytokines in acute anterior cruciate ligament injured knee. Knee 2003;10:93-6.
34. Lohmander LS, Dahlberg L, Ryd L, et al. Increased levels of proteoglycan fragments in knee joint fluid after injury. Arthritis Rheum 1989;32:1434-42.
35. Lohmander LS, Atley LM, Pietka TA, et al. The release of crosslinked peptides from type II collagen into human synovial fluid is increased soon after joint injury and in osteoarthritis. Arthritis Rheum 2003;48:3130-9.
36. Lohmander LS. The release of aggrecan fragments into synovial fluid after joint injury and in osteoarthritis. J Rheumatol Suppl 1995;43:75-7.
37. Lohmander LS, Hoerrner LA, Dahlberg L, et al. Stromelysin, tissue inhibitor of metalloproteinases and proteoglycan fragments in human knee joint fluid after injury. J Rheumatol 1993;20:1362-8.
38. Lohmander LS, Hoerrner LA, Lark MW. Metalloproteinases, tissue inhibitor, and proteoglycan fragments in knee synovial fluid in human osteoarthritis. Arthritis Rheum 1993;36:181-9.
39. Lohmander LS, Neame PJ, Sandy JD. The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. Arthritis Rheum 1993;36:1214-22.

40. Lohmander LS, Roos H, Dahlberg L, et al. Temporal patterns of stromelysin-1, tissue inhibitor, and proteoglycan fragments in human knee joint fluid after injury to the cruciate ligament or meniscus. J Orthop Res 1994;12:21-8.
41. Cawston TE, Ellis AJ, Humm G, et al. Interleukin-1 and oncostatin M in combination promote the release of collagen fragments from bovine nasal cartilage in culture. Biochem Biophys Res Commun 1995;215:377-85.
42. Catterall JB, Stabler TV, Flannery CR, et al. Changes in serum and synovial fluid biomarkers after acute injury (NCT00332254). Arthritis Res Ther 2010;12:R229.
43. Olson SA, Furman BD, Kraus VB, et al. Therapeutic opportunities to prevent post-traumatic arthritis: Lessons from the natural history of arthritis after articular fracture. J Orthop Res 2015;33:1266-77.
44. Page Thomas DP, King B, Stephens T, et al. In vivo studies of cartilage regeneration after damage induced by catabolin/interleukin-1. Ann Rheum Dis 1991;50:75-80.
45. THOMAS L. Reversible collapse of rabbit ears after intravenous papain, and prevention of recovery by cortisone. J Exp Med 1956;104:245-52.
46. Jubb RW, Fell HB. The breakdown of collagen by chondrocytes. J Pathol 1980;130:159-67.
47. Gentili C, Cancedda R. Cartilage and bone extracellular matrix. Curr Pharm Des 2009;15:1334-48.
48. Cameron ML, Fu FH, Paessler HH, et al. Synovial fluid cytokine concentrations as possible prognostic indicators in the ACL-deficient knee. Knee Surg Sports Traumatol Arthrosc 1994;2:38-44.
49. Nietfeld JJ, Wilbrink B, Den Otter W, et al. The effect of human interleukin 1 on proteoglycan metabolism in human and porcine cartilage explants. J Rheumatol 1990;17:818-26.
50. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol 2011;23:471-8.
51. Zeng GQ, Chen AB, Li W, et al. High MMP-1, MMP-2, and MMP-9 protein levels in osteoarthritis. Genet Mol Res 2015;14:14811-22.
52. van Spil WE, DeGroot J, Lems WF, et al. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage 2010;18:605-12.
53. Manka SW, Bihan D, Farndale RW. Structural studies of the MMP-3 interaction with triple-helical collagen introduce new roles for the enzyme in tissue remodelling. Sci Rep 2019;9:18785.
54. Burrage PS, Mix KS, Brinckerhoff CE. Matrix metalloproteinases: role in arthritis. Front Biosci 2006;11:529-43.
55. Löffek S, Schilling O, Franzke CW. Series "matrix metalloproteinases in lung health and disease": Biological role of matrix metalloproteinases: a critical balance. Eur Respir J 2011;38:191-208.
56. Lohmander LS, Saxne T, Heinegård DK. Release of cartilage oligomeric matrix protein (COMP) into joint fluid after knee injury and in osteoarthritis. Ann Rheum Dis 1994;53:8-13.
57. Dahlberg L, Fridén T, Roos H, et al. A longitudinal study of cartilage matrix metabolism in patients with cruciate ligament rupture--synovial fluid concentrations of aggrecan fragments, stromelysin-1 and tissue inhibitor of metalloproteinase-1. Br J Rheumatol 1994;33:1107-11.
58. Snelling S, Rout R, Davidson R, et al. A gene expression study of normal and damaged cartilage in anteromedial gonarthrosis, a phenotype of osteoarthritis. Osteoarthritis Cartilage 2014;22:334-43.
59. Dunn SL, Soul J, Anand S, et al. Gene expression changes in damaged osteoarthritic cartilage identify a signature of non-chondrogenic and mechanical responses. Osteoarthritis Cartilage 2016;24:1431-40.
60. Catterall JB, Cawston TE. Drugs in development: bisphosphonates and metalloproteinase inhibitors. Arthritis Res Ther 2003;5:12-24.
61. Hui W, Litherland GJ, Jefferson M, et al. Lithium protects cartilage from cytokine-mediated degradation by reducing collagen-degrading MMP production via inhibition of the P38 mitogen-activated protein kinase pathway. Rheumatology (Oxford) 2010;49:2043-53.
62. Davidson RK, Waters JG, Kevorkian L, et al. Expression profiling of metalloproteinases and their inhibitors in synovium and cartilage. Arthritis Res Ther 2006;8:R124.
63. Blom AB, van Lent PL, Holthuysen AE, et al. Synovial lining macrophages mediate osteophyte formation during experimental osteoarthritis. Osteoarthritis Cartilage 2004;12:627-35.
64. Huang WC, Sala-Newby GB, Susana A, et al. Classical macrophage activation up-regulates several matrix metalloproteinases through mitogen activated protein kinases and nuclear factor-κB. PLoS One 2012;7:e42507.
65. Cook-Mills JM, Marchese ME, Abdala-Valencia H. Vascular cell adhesion molecule-1 expression and signaling during disease: regulation by reactive oxygen species and antioxidants. Antioxid Redox Signal 2011;15:1607-38.
66. Oertli B, Beck-Schimmer B, Fan X, et al. Mechanisms of hyaluronan-induced up-regulation of ICAM-1 and

VCAM-1 expression by murine kidney tubular epithelial cells: hyaluronan triggers cell adhesion molecule expression through a mechanism involving activation of nuclear factor-kappa B and activating protein-1. J Immunol 1998;161:3431-7.
67. Korkmaz B, Horwitz MS, Jenne DE, et al. Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human diseases. Pharmacol Rev 2010;62:726-59.
68. Muley MM, Krustev E, Reid AR, et al. Prophylactic inhibition of neutrophil elastase prevents the development of chronic neuropathic pain in osteoarthritic mice. J Neuroinflammation 2017;14:168.
69. Huesa C, Ortiz AC, Dunning L, et al. Proteinase-activated receptor 2 modulates OA-related pain, cartilage and bone pathology. Ann Rheum Dis 2016;75:1989-97.
70. Russell FA, McDougall JJ. Proteinase activated receptor (PAR) involvement in mediating arthritis pain and inflammation. Inflamm Res 2009;58:119-26.
71. Zhou J, Perelman JM, Kolosov VP, et al. Neutrophil elastase induces MUC5AC secretion via protease-activated receptor 2. Mol Cell Biochem 2013;377:75-85.
72. Pfander D, Körtje D, Zimmermann R, et al. Vascular endothelial growth factor in articular cartilage of healthy and osteoarthritic human knee joints. Ann Rheum Dis 2001;60:1070-3.
73. Pufe T, Petersen W, Tillmann B, et al. The splice variants VEGF121 and VEGF189 of the angiogenic peptide vascular endothelial growth factor are expressed in osteoarthritic cartilage. Arthritis Rheum 2001;44:1082-8.
74. Barleon B, Sozzani S, Zhou D, et al. Migration of human monocytes in response to vascular endothelial growth factor (VEGF) is mediated via the VEGF receptor flt-1. Blood 1996;87:3336-43.
75. Haywood L, McWilliams DF, Pearson CI, et al. Inflammation and angiogenesis in osteoarthritis. Arthritis Rheum 2003;48:2173-7.
76. Nagao M, Hamilton JL, Kc R, et al. Vascular Endothelial Growth Factor in Cartilage Development and Osteoarthritis. Sci Rep 2017;7:13027.
77. van der Kraan PM, van den Berg WB. Osteophytes: relevance and biology. Osteoarthritis Cartilage 2007;15:237-44.
78. Hashimoto S, Creighton-Achermann L, Takahashi K, et al. Development and regulation of osteophyte formation during experimental osteoarthritis. Osteoarthritis Cartilage 2002;10:180-7.
79. Zhang W, Likhodii S, Aref-Eshghi E, et al. Relationship between blood plasma and synovial fluid metabolite concentrations in patients with osteoarthritis. J Rheumatol 2015;42:859-65.
80. Cameron M, Buchgraber A, Passler H, et al. The natural history of the anterior cruciate ligament-deficient knee. Changes in synovial fluid cytokine and keratan sulfate concentrations. Am J Sports Med 1997;25:751-4.
81. Cuellar VG, Cuellar JM, Golish SR, et al. Cytokine profiling in acute anterior cruciate ligament injury. Arthroscopy 2010;26:1296-301.
82. Pruksakorn D, Rojanasthien S, Pothacharoen P, et al. Chondroitin sulfate epitope (WF6) and hyaluronic acid as serum markers of cartilage degeneration in patients following anterior cruciate ligament injury. J Sci Med Sport 2009;12:445-8.
83. Goldring MB. Osteoarthritis and cartilage: the role of cytokines. Curr Rheumatol Rep 2000;2:459-65.
84. de Hooge AS, van de Loo FA, Bennink MB, et al. Male IL-6 gene knock out mice developed more advanced osteoarthritis upon aging. Osteoarthritis Cartilage 2005;13:66-73.
85. Cibere J, Zhang H, Garnero P, et al. Association of biomarkers with pre-radiographically defined and radiographically defined knee osteoarthritis in a population-based study. Arthritis Rheum 2009;60:1372-80.
86. Garnero P, Ayral X, Rousseau JC, et al. Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. Arthritis Rheum 2002;46:2613-24.
87. Cahue S, Sharma L, Dunlop D, et al. The ratio of type II collagen breakdown to synthesis and its relationship with the progression of knee osteoarthritis. Osteoarthritis Cartilage 2007;15:819-23.
88. Pan F, Tian J, Cicuttini F, et al. Prospective Association Between Inflammatory Markers and Knee Cartilage Volume Loss and Pain Trajectory. Pain Ther 2022;11:107-19.
89. Otterness IG, Brandt KD, Le Graverand MP, et al. Urinary TIINE concentrations in a randomized controlled trial of doxycycline in knee osteoarthritis: implications of the lack of association between TIINE levels and joint space narrowing. Arthritis Rheum 2007;56:3644-9.
90. Eyre DR, Weis MA. The Helix-II epitope: a cautionary tale from a cartilage biomarker based on an invalid collagen sequence. Osteoarthritis Cartilage 2009;17:423-6.
91. Gordon CD, Stabler TV, Kraus VB. Variation in osteoarthritis biomarkers from activity not food consumption. Clin Chim Acta 2008;398:21-6.
92. Andersson ML, Thorstensson CA, Roos EM, et al. Serum

levels of cartilage oligomeric matrix protein (COMP) increase temporarily after physical exercise in patients with knee osteoarthritis. BMC Musculoskelet Disord 2006;7:98.
93. Quintana DJ, Garnero P, Huebner JL, et al. PIIANP and HELIXII diurnal variation. Osteoarthritis Cartilage 2008;16:1192-5.
94. Kong SY, Stabler TV, Criscione LG, et al. Diurnal variation of serum and urine biomarkers in patients with radiographic knee osteoarthritis. Arthritis Rheum 2006;54:2496-504.

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