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Commentary

Cartilage-derived biomarkers in osteoarthritis

Osteoarthritis (OA) is a chronic joint disease and a leading cause of disability worldwide. It is characterized by a metabolic imbalance between anabolic and catabolic factors produced by chondrocytes, which leads to cartilage degradation and destruction. A large body of evidence supports the role of inflammation in OA and the involvement of the synovium, subchondral bone and other joint structures in the disease[1]. There is no effective pharmacological treatment for OA despite its high impact and the growing global burden. While non-steroidal anti-inflammatory drugs aim to reduce symptoms, symptomatic slow-acting drugs for OA are recommended to delay structural joint changes. However, no drugs have shown to stop the progression of the disease so far, and prevention remains the best strategy to hinder OA development.

The lack of validated biomarkers that can accurately predict the evolution of the disease makes the identification of new pharmacological targets more difficult[2]. This is further aggravated by the presence of multiple OA phenotypes which may potentially be treated and targeted differently[3].

In the last decades, there has been a progressive growing interest in identifying diagnostic and prognostic biomarkers in OA. With the development and the expansion of new proteomic methodology mainly focused on extracellular matrix (ECM) components[4], a large number of molecules have been proposed as useful biomarkers. However, given the heterogeneous nature of the disease, the lack of clinical validation and the lack of reproducible and internationally validated techniques, none of these have, until now, found a routine application in identifying disease state or to orient to a specific cure in OA.

ECM components and structural proteins of the cartilage are among the most investigated and studied molecules associated with OA progression. Their concentrations are linked to tissue metabolism and, therefore, can directly reflect the degree of tissue damage. Type II collagen epitopes, such as urinary C-terminal telopeptide of type II collagen (uCTX-II) and collagen degradation products, serum cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA) and proteoglicans (PGs), are some of the cartilage-derived biomarkers which have demonstrated potential applications in assessing disease severity[2].

Small leucine-rich proteoglycans (SLRPs), in particular, have been shown to be involved in OA pathogenesis[5]. These have been demonstrated to act as endogenous danger signal thus activating innate immune receptors and trigger catabolic responses in chondrocytes[6]. Moreover, SLRPs possess different regulatory functions such as complement activation[7], which has been shown to be abnormally high in human osteoarthritic joints and supposed to have a role in OA pathogenesis[8].

Among SLRPs, decorin consists of a protein core containing leucine repeats with a glycosaminoglycan chain which binds to collagen fibrils and plays a role in matrix assembly. Released from cartilage matrix as a result of tissue injury, decorin has attracted potential interest as OA biomarker. The study by Ozler *et al*[9] published in this issue investigated the levels of decorin in serum and synovial fluid (SF) samples collected from patients with knee OA and their relationship with clinical indices. The authors found significantly higher levels of decorin in serum of OA patients with respect to a control group. Although higher in OA, SF decorin did not show a significant difference with respect to controls. Comparing the concentration of the proteoglycan in the two biological fluids, OA patients showed significantly higher decorin levels in serum with respect to SF[9]. Investigating the association between decorin and clinical indices, a positive correlation was found between serum decorin levels

and the WOMAC (Western Ontario and McMaster University) score, a composite index of pain, structural and functional features, which defines disease severity in OA[10]. Cut-off levels of serum decorin and WOMAC score for the prediction of OA evaluated with receiver operating characteristic analysis were also reported by the authors. Finally, a multivariate logistic regression analysis showed that increased decorin was an independent risk factor for OA.

Overall, the results reported by Ozler *et al*[9] support a role for decorin as a marker of disease state in OA. The association of this molecule with early tissue damage may warrant of further investigation involving a larger number of patients.

Although in this study neither SF decorin level nor its SF/serum ratio was associated with the disease, SF represents a valuable biological substrate in the search for biomarkers in both OA and other arthropathies, in particular regarding cartilage-derived components. Indeed, SF composition reflects the metabolic status of synovial tissue and, with respect to serum and urine, offers a unique opportunity to study specific molecular patterns at the site of inflammation. The identification of calcium crystals in SF, for instance, allows to classify a subset of OA patients with higher WOMAC, algo-functional and severity indexes[11].

Studies investigating the ability of SF biomarkers in predicting radiographic progression in knee OA showed a role for aggrecan fragments[12] and pro-inflammatory cytokines[13]. By contrast, a more recent study found an association between SF cartilage-derived biomarkers and joint injury but failed to demonstrate their useful prognostic role[14]. A drawback concerning SF pertains the presence of a joint effusion as well as the discomfort that arthrocentesis might cause to some patients. A routine SF sampling might therefore, be useful for diagnostic reasons but not feasible in terms of the evaluation of disease progression due to the necessity of multiple injections over the course of the disease.

Owing to its intimate relationship with all joint tissues, SF has been largely utilized in proteomic studies on OA pathogenesis and biomarker search. In particular, the metabolomic profiling of the SF in OA has identified some metabolites as potential biomarkers of OA and has confirmed the existence of metabolically different OA phenotypes[15].

As far as serum is concerned, blood is frequently sampled in patients affected with rheumatic diseases, principally due to the need of controlling systemic inflammatory indices and lipoprotein and lipid profiles linked to the increased risk of these patients to develop cardiovascular comorbidities. As a consequence, serum represents the most used biological fluid for biomarker research in OA. The most common molecules investigated in serum are those indicative of collagen II degradation (*e.g*., CTX-II Coll2-1, C2C and C2M) and synthesis (*e.g*., PIIANP, PIIBNP and CPII). Others include COMP and proteoglycan epitopes[16].

The expression pattern of new molecules such as miRNA has shown to change in the serum of OA patients through upregulation or downregulation[17]. Some of these have demonstrated to be independent risk factors for OA, while others to have a diagnostic value.

Contrary to serum and SF, urine can be obtained through a non-invasive method. Urine is widely used in OA biomarker research mainly to investigate the significance of collagen II fragments such as the c-telopeptide of type II collagen (uCTX-II)[18]. Cleaved by metalloproteinases, collagen fragment uCTX-II has been demonstrated to be higher at baseline in patients developing OA with respect to non-progressors[19]. It has also been suggested to be independently associated with the incidence and progression of OA, in particular, when associated to imaging markers of the disease[20].

Identifying early articular degradation is the most important challenge in OA research and clinical care. Currently, OA is diagnosed by radiographs when clinical signs of pain and loss of function have already appeared. At this point, intervening successfully on disease progression is much difficult. The challenge is to detect those molecular and metabolic changes which precede by many years the onset of structural alterations, hence the early disease detection. Another challenge is to identify markers capable of predicting patient's long-term progression. This might allow to tailor a more aggressive treatment to each patient.

In conclusion, cartilage-derived components and metabolites have demonstrated promising application as diagnostic and prognostic markers in OA. A better definition of their role in predicting disease severity and progression will allow to improve patients' management and to find new targets in this disease.

***Conflicts of Interest*:** None.

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References

1. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, *et al*. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016; *12* : 580-92.
2. Mobasheri A, Bay-Jensen AC, van Spil WE, Larkin J, Levesque MC. Osteoarthritis Year in Review 2016: Biomarkers (biochemical markers). *Osteoarthritis Cartilage* 2017; *25* : 199-208.
3. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics. *Osteoarthritis Cartilage* 2014; *22* : 609-21.
4. Hsueh MF, Khabut A, Kjellström S, Önnerfjord P, Kraus VB. Elucidating the molecular composition of cartilage by proteomics. *J Proteome Res* 2016; *15* : 374-88.
5. Ni GX, Li Z, Zhou YZ. The role of small leucine-rich proteoglycans in osteoarthritis pathogenesis. *Osteoarthritis Cartilage* 2014; *22* : 896-903.
6. Barreto G, Soininen A, Ylinen P, Sandelin J, Konttinen YT, Nordström DC, *et al*. Soluble biglycan: A potential mediator of cartilage degradation in osteoarthritis. *Arthritis Res Ther* 2015; *17* : 379.
7. Sjöberg AP, Manderson GA, Mörgelin M, Day AJ, Heinegård D, Blom AM. Short leucine-rich glycoproteins of the extracellular matrix display diverse patterns of complement interaction and activation. *Mol Immunol* 2009; *46* : 830-9.
8. Wang Q, Rozelle AL, Lepus CM, Scanzello CR, Song JJ, Larsen DM, *et al*. Identification of a central role for complement in osteoarthritis. *Nat Med* 2011; *17* : 1674-9.
9. Ozler K. Relationship between increased serum & synovial fluid decorin levels & knee osteoarthritis. *Indian J Med Res* 2020; *152* : 453-8.
10. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; *15* : 1833-40.
11. Frallonardo P, Ramonda R, Peruzzo L, Scanu A, Galozzi P, Tauro L, *et al*. Basic calcium phosphate and pyrophosphate crystals in early and late osteoarthritis: Relationship with clinical indices and inflammation. *Clin Rheumatol* 2018; *37* : 2847-53.
12. Larsson S, Englund M, Struglics A, Lohmander LS. Association between synovial fluid levels of aggrecan ARGS fragments and radiographic progression in knee osteoarthritis. *Arthritis Res Ther* 2010; *12* : R230.
13. Orita S, Koshi T, Mitsuka T, Miyagi M, Inoue G, Arai G, *et al*. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. *BMC Musculoskelet Disord* 2011; *12* : 144.
14. Neuman P, Dahlberg LE, Englund M, Struglics A. Concentrations of synovial fluid biomarkers and the prediction of knee osteoarthritis 16 years after anterior cruciate ligament injury. *Osteoarthritis Cartilage* 2017; *25* : 492-8.
15. Vicenti G, Bizzoca D, Carrozzo M, Solarino G, Moretti B. Multi-omics analysis of synovial fluid: A promising approach in the study of osteoarthritis. *J Biol Regul Homeost Agents* 2018; *32* : 9-13.
16. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: A systematic review applying the consensus BIPED criteria. *Osteoarthritis Cartilage* 2010; *18* : 605-12.
17. Kong R, Gao J, Si Y, Zhao D. Combination of circulating miR-19b-3p, miR-122-5p and miR-486-5p expressions correlates with risk and disease severity of knee osteoarthritis. *Am J Transl Res* 2017; *9* : 2852-64.
18. Munjal A, Bapat S, Hubbard D, Hunter M, Kolhe R, Fulzele S. Advances in Molecular biomarker for early diagnosis of Osteoarthritis. *Biomol Concepts* 2019; *10* : 111-9.
19. Poole AR, Ha N, Bourdon S, Sayre EC, Guermazi A, Cibere J. Ability of a urine assay of type II collagen cleavage by collagenases to detect early onset and progression of articular cartilage degeneration: results from a population-based cohort study. *J Rheumatol* 2016; *43* : 1864-70.
20. Saberi Hosnijeh F, Kavousi M, Boer CG, Uitterlinden AG, Hofman A, Reijman M, *et al*. Development of a prediction model for future risk of radiographic hip osteoarthritis. *Osteoarthritis Cartilage* 2018; *26* : 540-6.