Review / Derleme

Biochemical Markers for Osteoarthritis: Is There any Promising Candidate?

Osteoartritte Biyokimyasal Belirteçler: Umut Vadeden Bir Aday Var mı?

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Abstract

Osteoarthritis (OA) is the most common degenerative joint disease. OA affects millions of individuals each year and becoming the most important cause of pain in geriatric population. Progressive destruction of articular cartilage is one of the prominent features of the disease. The diagnosis of OA is generally based on clinical and radiographical findings, which are insufficient to determine early-stage OA and predict disease course. There is a need for biomarkers that help clinicians early diagnose, assess disease activity, predict prognosis and monitor response to therapy. There are a growing number of publications regarding candidate markers in this field. The aim of this paper was to review recent studies on biochemical markers that reflect cartilage, synovial and bone turnover and their clinical use in patients with OA.

Keywords
Osteoarthritis, biomarkers, bone, cartilage, synovium

Öz

Osteoartrit (OA) en sık rastlanan dejeneratif eklem hastalığıdır. OA her yıl milyonlarca kişiyi etkileyerek, geriatrik yaş grubunun en önemli ağrı sebebi haline gelmektedir. Eklem kıkırdağının ilerleyici hasarı hastalığın en belirgin özelliklerinden biridir. Hastalığın tanısı daha çok klinik ve radyolojik olarak konmaktadır, ancak bu yöntemler erken dönemdeki olguları saptamada ve hastalık son durumunu tahmin etmede yetersiz kalmaktadır. OA hastalarında erken tanı konabilmesi, hastalık aktivitesinin değerlendirilmesi ve tedaviye yanıtın izlenebilmesi için biyokimyasal belirteçlere ihtiyaç vardır. Bu alanda aday biyokimyasal belirteçlerin saptanabilmesi için son dönemde birçok çalışma yayınlanmıştır. Bu yazının amacı kıkırdak, sinovyum ve kemik döngüsünü yansıtan bu biyokimyasal belirteçlerin klinik kullanımları ile ilgili yapılan son dönem çalışmaların derlenmesidir.

Anahtar Kelimeler
Osteoartrit, biyobelirteçler, kemik, kıkırdak, sinovyum

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Introduction

Osteoarthritis (OA) is the most common joint disorder characterized by progressive cartilage destruction, pain and loss of function. OA affects millions of individuals and becoming the most important cause of pain in geriatric population. Changes in articular cartilage, synovium and bone contribute to the pathogenesis of the disease. The diagnosis of OA is mainly based on clinical observation and radiological findings. Bone sclerosis, osteophyte formation and joint space narrowing are well known radiological features of OA. Progression of cartilage

destruction is evaluated with the measurement of joint space width by radiography. However, radiologic evaluation is insufficient to determine early cases when no significant joint damage has occurred yet. In addition, it is not possible to evaluate minor changes in cartilage by conventional radiography.

Therefore, there is an urgent need for new assessment tools with high sensitivity. In this respect, laboratory markers have drawn great interest in recent years. Such molecular markers are promising for improving diagnosis, assessment of disease activity, prognosis, and monitoring response to therapy in patients with OA. This report reviews recent studies of biochemical markers that reflect cartilage, synovial and bone turnover and their clinical use in patients with OA.

Biochemical Markers

A biochemical marker, released from connective tissue matrices, refers to an characteristic that objectively measured in biological fluids. An appropriate marker should be disease-specific. In addition, a good marker should be able to reflect actual disease activity, monitor changes with therapy and can predict the prognosis. Recently, numerous markers have been suggested for identifying and monitoring OA. They can reflect cartilage and synovial breakdown and synthesis, bone turnover and inflammation (Table 1) (1-3). These products can easily be obtainable from body fluids, such as blood, urine or synovial fluids.

Cartilage Oligomeric *Matrix Protein*

Cartilage oligomeric matrix protein (COMP) is a non-collagenous biochemical marker for cartilage degradation. It is primarily isolated from the extracellular matrix of cartilage (4). High serum and synovial fluid levels have been detected in various diseases, such as rheumatoid arthritis (RA), OA, juvenile idiopathic arthritis, and psoriatic arthritis (5-7). Studies suggest that serum COMP levels can be used as a marker for cartilage destruction associated with OA. A meta-analysis by Hoch et al. (8) concluded that serum COMP levels are elevated in patients with radiographic knee OA and higher levels of serum COMP are associated with radiographic OA severity. In a study investigating the relationship between cartilage markers and cartilage loss on magnetic resonance imaging in patients with knee OA, only COMP was found to be a predictor of cartilage loss (9). In another survey, femoral cartilage thickness detected by ultrasound was found to be inversely related with serum COMP levels in patients with early stage knee OA (10). The authors have also reported that for every unit increase in COMP level, there was 33% higher risk for tibiofemoral osteophyte progression (11). In a study including 272 patients with knee OA, high serum COMP levels were associated with non-symptomatic narrowing of the articular space (12). Similarly, Conroizer et al. (13) found that a high serum COMP level had a positive correlation with joint space narrowing in hip OA. In a recent study, Golightly et al. (14) investigated the ability of COMP, hyaluronic acid (HA), keratan sulphate (KS) and high sensitivity C-reactive protein (CRP) to predict radiographic knee OA. The authors have suggested that high levels of COMP and HA might predict incident radiographic knee OA. According to the results of another survey, serum COMP levels were found to be correlated with the risk of rapidly progressing OA and to be remained significantly high in first 3 years of disease duration (15). All these findings suggest that serum COMP levels

Table 1. Biochemical markers for osteoarthritis (1-3)

	Synthesis	Degradation
Bone	PICP, PINP, OC, ALP^{bone}	PYD, DPD, CTX-1, NTX-1, ICTP, TRAP, BSP, Cathepsin K, Helical peptide
Cartilage	PIICP, PIIANP, PIIBNP, YKL-40, CS, CD-RAP	PYD, CTX-II, C_2C, C_1-$_2C$,TIINE, Helix-II, Coll 2-1, COMP, KS, Aggrecanase neopeptides, Coreprotein MMPs
Synovium	YKL-40, COMP, MMPs, HA, PIINP	PYD, CTX-I, NTX-I, Glc-Gal-PYD
Systemic inflammation	CRP, hsCRP, TGF-β1, TNF-α, IL-6, IL-1, RAGE, ECP	

RAGE: Receptor for advanced glycation endproducts, TNF-α: Tumor necrosis factor-alpha, OC: Osteocalcin, ALP: Alkaline phosphatase, PIICP: Procollagen II C-terminal propeptides, PIIANP: N propeptide of type IIA procollagen, RAGE: Receptor for advanced glycation endproducts, OC: Osteocalcin, CTX: C terminal crosslinking telopeptides, NTX: N-terminal telopeptide, HA: Hyaluronic asid, CS: Chondroitin sulphate, MMPs: Matrix metalloproteinases, COMP: Cartilage matrix protein, Glc-Gal-PYD: Glucosyl-galactosyl-pyridinoline, CRP: C-reactive protein, TGF-β1: Transforming growth factor-beta 1, TNF-α: Tumor necrosis factor-alpha, ILX: Interleukin, KS: Keratan sulphate

may be a useful assessment tool for OA. On the other hand, COMP is an abundant protein particularly in tendons, ligament and meniscus. Therefore, increased concentrations can be related to injuries to these structures (16,17). In addition, serum concentrations vary by ethnicity, gender, age and exercise (18-20).

Type II Collagen Biomarkers

Type II collagen is the most important protein in human cartilage and it is relatively specific for hyaline cartilage. Since alteration in articular cartilage turnover is the main pathology in OA, type II collagen has been investigated as a potential marker of cartilage remodelling in OA (21). Type II collagen is a triple helix composed of three identical alpha chains. It is firstly synthesized as a procollagen which is constituted by the collagen molecule itself that forms the framework of cartilage matrix and the procollagen II N-terminal propeptides (PIINP) and C-terminal (PIICP) propeptides at each end. These propeptides are cleaved-off during the subsequent maturation stage and released into the biological fluids. Additionally, there are alternative forms of procollagen that differ by the presence of a 69-amino acid sequence in the N-propeptide. During the degradation process of type II collagen, different molecules are released in biological fluids. These include fragments of triple helix, collagenase neo-epitopes and c-terminal cross-linking telopeptides. Type II collagen biomarkers are summarized in Table 2.

C-terminal crosslinking telopeptides (CTX-II) and Helix II are markers of collagen degradation. These two markers are believed to reflect different but complementary parts of cartilage degradation. While CTX-II is a fragment of C-telopeptides region, Helix-II is the fragment of the helical domain of type II collagen. Recent studies have shown that urinary levels of CTX-II and Helix-II were significantly higher in patients with OA compared with healthy controls (22-24). CTX-II were found to be associated with radiological progression in patients with knee and hip OA and this association was stronger in participants with joint pain (11,25). Contrarily, in another trial, CTX concentrations were found to be correlated with radiologic progression but not with clinical status (26). High levels of urinary CTX-II are associated with rapidly progressive disease (27,28). Urinary levels of CTX-II have also been reported to be linked to the efficacy of treatment in OA (29). Levels of CTX-II and Helix-II are influenced by body mass index (23,30), but there are conflicting data about the relationship between age and urinary CTX levels (23,30).

Table 2. Type II collagen biomarkers (21)

Cleavage neoepitopes	C_2C, $C_{1\text{-}2}C$, TIINE, Coll2-1/4N1, Coll2-1/4N2
Denaturation epitopes	Coll 2-1, Coll2-1/NO2, Helix-II, CB-11 (COL2-3/4 m), AH8, AH9, AH12
Telopeptide epitopes	Col2CTx, CTX-II
Propeptide epitopes	CPII, PIIANP

PIIANP: N propeptide of type IIA procollagen, CTX: C terminal crosslinking telopeptides

N-propeptide of type IIA procollagen (PIIANP) is one of the two splice forms of type-II procollagen. It is mainly expressed in embryonic cartilage and believed to re-expressed in osteoarthritic cartilage (27,31). Recent studies have shown that its combination with CTX-II could be useful in identifying patients with OA at high risk for rapid progression of joint damage, since these two markers represent imbalance between cartilage synthesis (PIIANP) and degradation (CTX-II) (27,28). Rousseau et al. (32) found decreased levels of PIIANP in patients with knee OA and RA suggesting that type IIA collagen synthesis may be altered in these arthritic diseases. In their 5-year longitudinal study, Sharif et al. (28) assessed serum concentration of PIIANP and urinary concentration of CTX-II in patients with mild-to-moderate knee OA. The authors observed that over the 5-year study period, average PIIANP and CTX-II levels were higher in patients with progressive disease than in those with nonprogressive disease. The risk of progression was highest in patients with 5 year levels of PIIANP in the highest quartile and/or CTX-II in the two highest quartiles. Kumm et al. (10) have stated that tendon calcification was associated with higher levels of PIIANP in men with early-stage knee OA. The investigators have reported that tendon calcification was related to cartilage synthesis in males and to cartilage degradation in females during early stages of the disease.

There are also promising type II collagen biochemical markers, such as type II collagenase neoepitopes (C_2C, $C_{1\text{-}2}C$, TIINE), Coll 2-1, Coll 2-1 NO_2, CPII, CPIII which need further human studies. In a recent study, Ishijima et al. (33) suggested that

cartilage turnover markers, such as CTX-II, C_2C, CPIII, bone resorption marker N-terminal telopeptide and HA were all significantly increased in subjects with knee pain independent of grade. Deberg et al. (34) concluded in their study that increase in Coll 2-1 and Coll 2-1 NO_2 was predictive of radiological progression of OA. They have demonstrated that Coll 2-1 levels were decreased after total hip or knee arthroplasty, however, Coll 2-1 NO_2 levels remained elevated. This finding suggests that Coll 2-1 can be a useful disease-specific marker for monitoring structural changes in a single joint (35). In a study by Lohmander et al. (16), CPII levels in synovial fluid was elevated in patients with OA compared with healthy subjects. Additionally, CPII levels have been suggested to be predictive of radiographic progression in early-stage OA (36).

Glucosyl-Galactosyl-Pyridinoline (Glc-Gal-PYD)

Urinary glucosyl-galactosyl-pyridinoline (Glc-Gal-PYD) is a marker of synovial tissue turnover and reflects synovial matrix degradation. It has been shown to be associated with cartilage loss and radiographic knee OA (26-37). Gineyts et al. (38) observed in their study evaluating the effect of ibuprofen on CTX-II and Glc-Gal-PYD levels in knee OA that at baseline, urinary levels of CTX-II and Glc-Gal-PYD were higher in patients with knee swelling than in subjects without. After 4-6 weeks of treatment, placebo group patients with knee effusion had significantly higher urinary CTX-II and Glc-Gal-PYD concentrations compared with ibuprofen group. A trial on the relationship between markers and disease activity in patients with knee OA concluded that Gly-Gal-PYD and CTX-II were the most important predictors of the Western Ontario and McMaster Universities Osteoarthritis Index score and joint damage, respectively (26).

Hydroxyproline and Lysylpridinoline

Hydroxyproline (HP) and lysylpridinoline (LP) are components of collagen. They are both derived from bone. HP is also derived from cartilage. Otterness et al. (39) carried out a study in 39 patients with knee or hip OA. They investigated 14 molecular markers used to monitor OA. There was a strong correlation between urinary HP levels and baseline clinical status of the patients. However HP levels did not reflect the clinical changes after one year follow-up. Thompson et al. (40) have reported a correlation between x-ray grade and collagen crosslinks. Astbury and colleagues have found higher urinary levels of collagen crosslinks in patients with OA compared with healthy controls, but no associations with radiological grades (41). Overall, collagen crosslinks may be useful for understanding cartilage and bone destruction in OA.

Aggrecan Biomarkers

Aggrecan is the major proteoglycan in the articular cartilage. Aggrecan markers are also studied as potential molecular markers of cartilage turnover. There are variable reports about KS depending on the antibodies used (42,43). Interestingly, Nakajima et al. (44) have reported a significant reduction in KS levels after arthroscopic surgery in patients with knee OA. Epitope 846 of chondroitin sulphate (CS) reflects proteoglycan synthesis. It has been found that serum levels of epitope 846 decreased in patients with OA (31). Serum HA is also considered as a potential biomarker for OA. HA levels have been shown to be increased in serum of patients with knee and hip OA and suggested to have a predictive value for further radiographic progression (26,45-48). Matrix metalloproteinases (MMPs) are endopeptides that are capable of cartilage matrix degradation. MMPs levels reflect inflammation and predict joint erosion in RA. Similarly, serum levels of MMP3 in patients with OA have been shown to be increased (49). In a randomized prospective study, nimesulid treatment reduced serum levels of MMP-3 and MMP-13 in patients with OA flare-up (50). In this study, the decrease in levels of MMP-13 significantly correlated with the decrease in levels of CTX-II and HA. Endogenous inhibitors of MMPs are called as tissue inhibitors of matrix proteinases (TIMPs). Among entire types of TIMPs, TIMP-1 has the highest affinity for MMP-3 and MMP-13 (51). Chevalier et al. (52) investigated serum levels of TIMP-1 and HA in hip OA. The authors found that serum levels of TIMP-1 was beneficial in discriminating slowly progressive disease from rapidly progressive one.

YKL-40

YKL-40 (human cartilage glycoprotein-39) is a recently discovered human glycoprotein which is related to histopathological changes in synovium and

cartilage. High levels of YKL-40 have been measured in serum and synovial fluid of patients with OA, especially in later stages (53). Zivanović et al. (54) have reported that YKL-40 concentration was correlated with the level of cartilage destruction and could be used for assessment of destruction.

Osteocalcin

There have been a number of studies considering osteocalcin (OC) as a biomarker for OA. Joint space narrowing has been reported to be significantly associated with serum OC level in patients with hand OA (55). Higher OC levels were significantly correlated with decreased rates of cartilage loss and radiologic progression of knee OA (56,57). In contrast, Naito et al. (58) have demonstrated that OC levels were not elevated in patients with OA. Similarly, Jung et al. (59) found no relationship between serum OC concentrations and ultrasonographic findings of knee OA.

Inflammatory Biomarkers

Although OA is commonly known as a non-inflammatory disease, markers that reflect inflammatory process also have been studied. Otterness et al. (39) analyzed 14 serum and urine markers in an attempt to find an association with particular clinical end-points. Swelling of the joint was correlated with inflammatory markers; CRP was found to have the highest correlation. Elevated levels of high sensitivity CRP predict cartilage loss in OA and poorer outcomes in knee arthroplasty (60,61). Transforming growth factor-beta 1 (TGF-β1) was also found related with patient self assessment, pain on weight bearing and stiffness in OA (39). Also, in an animal study, it was concluded that higher levels of synovial TGF-β1 predict the later development of more severe OA changes (62). Tumor necrosis factor-alpha, receptor for advanced glycation endproducts, interleukin-6 (IL-6), and IL-1 are other assessed markers for inflammation for OA.

Adipokines

Adipokines (adiponectin, leptin and nesfatin-1) are cytokines released from adipose tissue. They are also secreted from osteoblasts, synoviocytes and chondrocytes and, therefore, thought to be linked to OA. Elevated levels of adiponectin leptin and nesfatin-1 have been shown in synovial fluids of patients with OA. In addition, they have been found to be correlated with disease progression (63-66).

Conclusion

There is an increasing interest in the use of biochemical markers in patients with OA, especially in order to predict disease progression and monitoring treatment. Besides, new markers have been investigated to identify healthy individuals at high risk for the development of OA. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis working group has identified avenues for future research in this field. According to their recommendation, further studies must be performed in order to reveal underlying mechanisms of OA and to explore new biomarkers to predict prognosis and patients at risk for OA. Although there are promising candidate markers, none of them have been specifically recommended for clinical usage yet.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Elif Aydın, Yasemin Turan, Design: Elif Aydın, Yasemin Turan, Data Collection or Processing: Elif Aydın, Yasemin Turan, Analysis or Interpretation: Elif Aydın, Yasemin Turan, Literature Search: Elif Aydın, Yasemin Turan, Writing: Elif Aydın, Yasemin Turan.

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