DOI: 10.53469/jcmp.2025.07(02).03

Research Progress of Laboratory Diagnostic Indexes of Osteoarthritis

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Abstract: ***Osteoarthritis (OA) is a common joint degenerative disease. The current diagnosis of OA is mainly through imaging and physical examination. Once such diagnosis is established, it means that the lesion is often advanced, resulting in poor treatment effect. The laboratory diagnostic indicators of OA can be used as a way to diagnose OA early, and promote the early detection, diagnosis and treatment of osteoarthritis. In this paper, we selected some representative clinical candidate biomarkers and auxiliary diagnostic indicators of OA to review its clinical significance, diagnostic value and research progress.***

Keywords: Osteoarthritis, Laboratory diagnostic indicator, Biomarker, Vitamin D.

1. Introduction

Osteoarthritis (OA) is one of the most common joint diseases, characterized primarily by the gradual degeneration of cartilage, accompanied by changes in joint structure such as synovitis and subchondral bone sclerosis [1]. OA typically leads to joint pain, stiffness, deformity, impaired mobility, and even disability. According to a survey by the World Health Organization, the global prevalence of OA among individuals aged 65 and above is 9.6% in men and 18% in postmenopausal women, with the latter being significantly higher than the former [2].With the continuous development of modern medicine and clinical diagnostic techniques, the diagnosis of OA has evolved to include a variety of methods such as imaging studies, arthroscopy, gait analysis, bone mineral density testing, and the detection of OA biomarkers. Currently, the diagnosis of OA mainly relies on imaging and physical examination. Cartilage loss is primarily observed through X-ray imaging. The main scale for assessing the severity of osteoarthritis is the Kellgren-Lawrence (KL) scale, which rates the severity of OA from 0 to 4 based on radiographic joint space narrowing [3,4]. Physical examination can be used to determine the degree of pain and the extent of impaired mobility [5].

These methods are reactive rather than predictive. Once such a diagnosis is established, it often means that the disease has already progressed to an advanced stage, with irreversible cartilage damage. This results in the loss of the “golden” period for early diagnosis and treatment, leading to suboptimal therapeutic outcomes. Many patients eventually have to consider surgery, including total knee replacement, which severely reduces their quality of life and creates significant economic pressure. The research goal for laboratory diagnostic indicators of OA is to develop predictive rather than reactive tests. With the widespread adoption of the concept of “early detection, early diagnosis, and early treatment” and the continuous updating of diagnostic techniques, laboratory diagnostic indicators are increasingly valued by clinical researchers as a means for early diagnosis, assessment, and prediction of disease progression in OA. Currently, the main categories of laboratory diagnostic indicators for osteoarthritis that have attracted attention are as follows.

2. Biomarkers

A characteristic of OA is the progressive degradation of the extracellular matrix (ECM) of articular cartilage. Despite increased biosynthetic activity of chondrocytes, the normal balance between ECM anabolism and catabolism has been disrupted. The ECM is primarily composed of type II collagen and aggrecan [6]. As OA progresses, the overexpression of matrix-degrading enzymes (MMPs, ADAMTS) leads to the gradual degradation of collagen, aggrecan, and other components of the cartilage matrix, with subsequent release of fragments into the synovial fluid, serum, and urine [7]. Detection of OA biomarkers reflects whether chondrocytes and the ECM are damaged and the extent of the damage. OA biomarkers are defined as large molecules originating from joint structures, the levels of which in synovial fluid, blood, or urine reflect metabolic events occurring locally in the joint [8]. The main biological fluids used to identify biomarkers of OA pathophysiology are urine, synovial fluid, and blood. Blood is easily obtained from the body and mediates many of the body's immune and inflammatory pathways. Urine is readily accessible. Synovial fluid is the first fluid to change during the OA disease process, but it is more difficult to assess, and biomarker detection in OA tends to focus on blood. These biomarkers can be used for diagnostic and prognostic purposes as well as to estimate treatment effectiveness. Currently, clinical candidate biomarkers are mainly divided into two types: one related to collagen metabolism (e.g., CTx-II) and aggrecan metabolism (e.g., CS); the other related to non-collagen proteins (e.g., COMP) or inflammatory cytokines (e.g., IL-17) [9-14].

2.1 Cartilage Oligomeric Matrix Protein (COMP)

COMP is an extracellular glycoprotein that belongs to the thrombospondin family [15]. As a major non-collagenous component of the ECM, COMP has distinct tissue specificity and plays an important role in maintaining the integrity of the cartilage matrix. It is currently the most widely studied and applied biomarker for joint diseases [16, 17]. Existing studies have shown that during OA lesions, the synthesis or degradation of ECM can cause changes in the expression of COMP in serum, and its expression level is positively correlated with radiographic progression of OA [15, 18]. In addition, Fernandes et al. [19] studied the serum COMP levels

in patients with subclinical OA who had clinical symptoms of OA but no radiographic changes. The results showed that the serum COMP levels in this group of patients were significantly higher than those in the normal group, suggesting that serum COMP levels may be an effective early diagnostic marker for patients with subclinical OA. The results of Li Heng et al. [20] showed that even in patients with subclinical OA who had no radiographic changes, significant increases in serum COMP levels could be detected 2 years before diagnosis, and it could effectively distinguish them from patients with subclinical forms of other related diseases. This further indicates that serum COMP can serve as a potential biomarker and diagnostic indicator for early detection of OA.

Y. Lai et al. [21] prepared a set of monoclonal antibodies targeting COMP fragments and developed a capture enzyme-linked immunosorbent assay (ELISA) that can reproducibly detect COMP fragments in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). The study results showed that the newly established ELISA kit detected a significant increase in COMP fragments in the serum of OA patients. Additionally, in mouse models, serum COMP fragment levels were closely related to the severity of OA in patients and the progression of surgically induced OA. The most significant issue with using COMP as an OA biomarker is the elevated COMP levels in the serum of RA patients; however, RA is associated with other markers, including rheumatoid factor and anti-citrullinated antibodies [22]. The above studies provide important evidence for serum COMP as a biomarker and diagnostic indicator for detecting OA.

2.2 Interleukin-17 (IL-17)

In the process of osteoarthritis (OA), the inflammatory response plays a key role in the development of OA. During the inflammatory response in OA, the catabolic process of chondrocytes is accelerated, leading to an increased degradation of the extracellular matrix (ECM) of chondrocytes. Inflammatory cytokines are involved in the metabolism of bone and joints and play an important role in maintaining the homeostasis of the internal environment of the joints. In OA patients with severe inflammatory responses in the knee joint (such as redness, swelling, heat, and pain), many inflammatory cytokines can be detected. Common pro-inflammatory cytokines include tumor necrosis factor (TNF)-α and interleukin (IL) IL-17, IL-15, IL-6, IL-1β, IL-18, etc. [23]. Interleukin (IL) IL-17 is a recently proposed inflammatory signaling factor that has a key position in the inflammatory response of osteoarthritis. IL-17 is an inflammatory cytokine produced by Th cells, which can induce various pro-inflammatory and chemotactic factors and mediate inflammatory responses. To date, six members of the IL-17 family have been identified (IL-17A, 17B, 17C, 17D, 17E, and 17F). IL-17A was the first member of the family to be discovered by researchers and was formerly named CTLA-8. IL-17 exerts its immunological functions by binding to its corresponding receptors.

Current research has confirmed that IL-17 is associated with the occurrence of various inflammatory diseases, including psoriasis [24], autoimmune encephalomyelitis, rheumatoid arthritis (RA) [25], and osteoarthritis (OA) [26]. IL-17 has potent inflammatory effects, and during inflammation, it exerts its own recruiting ability and has synergistic effects with other cytokines. IL-17 can induce fibroblasts, osteoblasts, and chondrocytes to express important inflammatory cytokines, including TNF-α, IL-1β, IL-6, G-CSF, GM-CSF, etc., which exacerbate the occurrence of knee joint inflammation, leading to cartilage destruction and further damage [27]. Additionally, IL-17 can upregulate the expression of metalloproteinases (MMPs) in the extracellular matrix (ECM), including MMP-1, MMP-3, MMP-9, MMP-12, and MMP-13 [28, 29], further degrading components such as proteoglycans, osteopontin, and type II collagen, accelerating ECM degradation, and inhibiting ECM synthesis, thereby damaging chondrocytes and tissues. Researchers have demonstrated that in collagen-induced arthritis in rodent models, overexpression of IL-17B in arthritic cartilage induces the production of IL-8, which recruits a large number of neutrophils to the cartilage. Subsequent neutralization antibody treatment targeting IL-17B helps to alleviate arthritis in animals [30]. This shows that IL-17B plays a significant role in arthritis. Moreover, IL-17 can also activate the production of chemokines in chondrocytes (such as IL-8, CXCL1, CXCL2, CXCL12, etc.), exacerbating the inflammatory response.

Yamaguchi Y et al. co-cultured normal primary lung fibroblasts with recombinant IL-17A in mice at different densities. They measured the mRNA levels of type I collagen and the chemokine CXCL12 in the cultured lung fibroblasts using real-time reverse transcription PCR and ELISA techniques, respectively. They found that both levels were significantly elevated, indicating that IL-17 plays a key role in the progression of osteoarthritis (OA) [31]. Wang Guoliang et al. compared patients with knee osteoarthritis (KOA) and those with other joint diseases (non-KOA group). They used the non-KOA group as a control and detected IL-17 levels in synovial fluid and serum using ELISA, and IL-17 levels in synovial tissue using immunohistochemistry [32]. The results showed that IL-17 levels in synovial fluid and synovial tissue were significantly higher in the KOA group than in the non-KOA group. Moreover, IL-17 levels in synovial fluid and synovial tissue of the KOA group were positively correlated with serum high-sensitivity C-reactive protein (HS-CRP) levels. Additionally, Y. H. Lee et al. conducted a systematic review of 2214 studies, including 2474 OA patients and 17 controls, to evaluate the evidence linking interleukin-17 (IL-17) gene polymorphisms to OA susceptibility and the relationship between circulating IL-17 levels and OA [33]. Their analysis revealed that IL-17 levels in the blood of OA patients were elevated, suggesting that IL-17 may play a crucial role in the pathogenesis of OA. Blocking the IL-17 signaling pathway could be a novel therapeutic approach to control OA symptoms and prevent joint destruction. These studies collectively demonstrate that IL-17, as an inflammatory signaling factor, is of significant importance in the progression of OA. It not only provides new therapeutic insights for OA but also offers important evidence for future detection and diagnosis of OA.

2.3 C-terminal Cross-linking Telopeptide of Type II Collagen (CTX-II)

Normal adult cartilage is composed of chondrocytes and ECM,

with type II collagen being the main component of the ECM. CTX-II is a C-terminal peptide of type II collagen in the ECM, which is degraded by matrix metalloproteinases (MMPs) during the development of osteoarthritis. It is a high molecular weight protein rich in hydroxyproline and plays an important role in cartilage repair. In the body, CTX-II is mainly found in blood, synovial fluid, and urine. Researchers have found that CTX-II originates from mature structural collagen and enters the urine in the form of small peptides [34]. Urinary CTX-II is well correlated with the presence of osteophytes on radiographs of most OA joints and may serve as a sensitive quantitative biomarker for the severity of osteoarthritis [35, 36].

In a Rotterdam study involving 1, 235 men and women with an average follow-up period of 6.6 years, individuals in the highest quartile of urinary CTX-II levels had a sixfold increased risk of radiographic progression of knee osteoarthritis (OA) and more than an eightfold increased risk of hip OA progression. These results were independent of known clinical risk factors for OA, such as age, gender, and body mass index. The study concluded that elevated urinary CTX-II levels are associated with the progression of radiographic OA [37]. Dam et al. supported the potential of urinary CTX-II as a diagnostic marker for OA in a study of 142 OA patients and 145 healthy controls [38]. They also reported that CTX-II, in combination with radiographic parameters, has better potential for diagnosing cartilage loss. CTX-II and COMP (cartilage oligomeric matrix protein) levels reflect the degradation of type II collagen and non-collagenous proteins, respectively. Spil et al. conducted a systematic review of commercially available OA biochemical markers using the "BIPED" (Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic) classification. Urinary CTX-II and serum COMP were found to be the best-performing markers among all commercially available biomarkers [39]. The BIPED classification, specifically designed for OA, aims to provide information at an early stage of disease progression to inform future clinical trials and research designs. These studies indicate that urinary CTX-II levels can reflect the degree of cartilage degradation and destruction, serving as a reference indicator for OA diagnosis and disease assessment. It can detect early-stage OA and dynamically reflect radiographic progression.

2.4 Chondroitin Sulfate 846 (CS-846)

Patients with OA experience varying degrees of ECM damage, which may lead to increased synthesis of aggrecan. Chondroitin sulfate 846 (CS-846) is a marker of chondroitin sulfate synthesis (effective or ineffective), located on the epitope of the chondroitin sulfate chain of proteoglycan. Elevated serum levels of CS-846 can reflect the synthesis of new aggrecan [40]. Initially discovered by proteomics, it was found to be increased in the urine of OA patients. Later studies revealed that CS-846 expression levels are elevated in both OA cartilage and synovial fluid [41]. Elevated serum CS-846 levels are positively correlated with radiographic findings, clinical pain VAS scores, and joint space narrowing in OA patients, and have certain reference value for early diagnosis of OA [40, 42, 43].

The research results of Xiaojie Dou et al. showed that patients with knee osteoarthritis (KOA) had higher serum levels of COMP and CS-846 compared to the control group. Both serum COMP and CS-846 levels were positively correlated with pain VAS scores and the degree of joint space narrowing, indicating that COMP and CS-846 can serve as independent biomarkers for KOA patients [40]. Additionally, using ROC analysis, the combined use of COMP and CS-846 demonstrated higher diagnostic value for OA, with an AUC of 0.896, which is higher than the AUC values when either is used independently for OA diagnosis. Furthermore, Zhang et al. detected the expression levels of cartilage markers, including urinary CTX-II, serum CS-846, and serum COMP, in 100 OA patients and 100 controls. Based on the combination index of biomarkers selected by stepwise linear regression analysis, they found the best correlation between urinary CTX-II, serum CS-846, serum COMP, and early diagnostic indicators of OA [43]. Other studies have also shown that serum CS-846 levels in KOA patients are positively correlated with serum IL-17 levels [44]. These studies indicate that serum CS-846, derived from the proteoglycan of the ECM, has certain reference value for early OA diagnosis on its own. It has good correlation with serum COMP, urinary CTX-II, and IL-17. The combined use of these markers provides higher diagnostic value for OA.

3. Vitamin D

Vitamin D (Vitamin D), as a steroidal hormone, exerts a variety of biological effects on multiple tissues [45]. Its primary function is to maintain normal calcium levels and skeletal development by regulating phosphorus and calcium metabolism. Therefore, abnormalities in vitamin D may impede the growth and remodeling of subchondral bone, which plays a key role in the pathogenesis of OA [46]. Vitamin D is also believed to affect inflammation and muscle strength, both of which are associated with the progression of OA [45]. Because of its potential effects on bones, inflammation, and muscles, vitamin D has attracted widespread attention for its role in the pathogenesis of osteoarthritis [47]. However, the specific impact of vitamin D on the onset and development of OA remains unclear, and consensus has not yet been reached in previous studies.

Some cross-sectional and longitudinal studies have shown that vitamin D deficiency is associated with osteoarthritis [48-50], but other studies have indicated no such relationship [51, 52]. These differences may be caused by many variables in the research process, including differences in baseline vitamin D levels, geographical and ethnic differences, population characteristics, and sample size [53]. A cross-sectional study involving 2, 756 participants (1, 654 women) found that the prevalence of osteoarthritis was higher in the lowest quartile of vitamin D levels. However, the individuals in the study were relatively old (mean age 79.04 ± 7.75 years), and the serum vitamin D levels in women (23.09 ± 9.15 nmol/L) were relatively low [48]. Age and gender may be confounding factors related to low serum vitamin D levels, which could influence the study results. Recent studies have suggested that low serum vitamin D may simply be a marker and not the cause of poor health in many cases [54].

In the elderly, vitamin D deficiency may be a result of inflammatory processes and reduced sun exposure due to low

activity levels associated with osteoarthritis, rather than a cause of the disease. Laslett et al. demonstrated that moderate vitamin D deficiency (<25 nmol/L) can independently predict the occurrence or worsening of knee pain within 5 years and hip pain within 2.4 years [49]. However, due to the association between vitamin D deficiency and chronic widespread pain, these findings cannot prove that vitamin D deficiency independently indicates the onset or progression of osteoarthritis [55].Guo et al. conducted a cross-sectional study to assess the correlation between serum vitamin D and osteoarthritis, using a nationally representative large sample from the National Health and Nutrition Examination Survey (NHANES) between 2001 and 2018, with numerous potential confounding factors excluded to ensure validity [56]. The results indicated that higher serum vitamin D levels were associated with an increased risk of osteoarthritis, with a positive correlation independent of other factors. Additionally, obesity was found to be a potential moderator of the relationship between serum vitamin D and osteoarthritis, with a combination of higher BMI and serum vitamin D levels possibly accelerating the progression of subchondral sclerosis. This study highlights the potential adverse effects of high serum vitamin D levels on osteoarthritis, particularly in obese individuals. Currently, the mechanisms by which vitamin D influences the development and progression of OA are not fully understood, and more research is needed in the future. Therefore, vitamin D is currently mostly used as an auxiliary diagnostic tool for OA.

4. Summary and Prospects

Laboratory diagnostic indicators for OA are gradually gaining clinical attention due to their predictive diagnostic value. These indicators are mainly divided into two categories: candidate biomarkers and auxiliary diagnostic indicators. Among them, clinical candidate biomarkers are further categorized into two types: one related to collagen and aggrecan metabolism, and the other related to non-collagen proteins or inflammatory factors. In this article, representative clinical candidate biomarkers from each category are selected to discuss their individual value in the early diagnosis of OA, while also highlighting that the combined use of these biomarkers offers higher clinical value for OA diagnosis. Currently, vitamin D is mostly used as an auxiliary diagnostic tool for OA, primarily for regulating bone metabolism and calcium homeostasis. However, the specific impact of vitamin D levels on the occurrence and progression of OA has not yet reached a consensus, and further exploration is needed. With the increasing popularity of the concept of "early diagnosis" and the advancement of diagnostic techniques, various laboratory diagnostic indicators are expected to play a greater role in the diagnosis of osteoarthritis.

References

[1] Xu Xin. Daphnoretin delays articular cartilage degeneration by negatively regulating the NF-κB and MAPK signaling pathways [D]. Anhui Medical University, 2022.

[2] Zhang Xu, Zheng Jie, Zhao Liping, et al. The role of IL-17 in the pathogenesis of osteoarthritis and research progress. Journal of Cellular and Molecular Immunology, 2021, 37(12): 1138-1142.

[3] McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014; 22(25): 363-388.

[4] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957; 16(4): 494-502.

[5] Iversen M, Lyn Price L, von Heideken J, Harvey W, Wang Ch. Physical examination findings and their relationship with performance-based function in adults with knee osteoarthritis. BioMed Central Musculoskeletal Disorders. 2016; 17(273): 12.

[6] Choi M, Jo J, Park J, et al. NF-κB signaling pathways in osteoarthritic cartilage destruction. Cells (Basel, Switzerland), 2019, 8(7): 734.

[7] Mueller MB, Tuan RS. Anabolic/catabolic balance in pathogenesis of osteoarthritis: identifying molecular targets. PM & R: the journal of injury, function, and rehabilitation 2011; 3(6 Suppl 1): S3-11.

[8] Piscoya JL, Fermor B, Kraus VB, Stabler TV, et al. The influence of mechanical compression on the induction of osteoarthritis-related biomarkers in articular cartilage explants. Osteoarthritis & Cartilage, 2006, 13(12): 1092-1099.

[9] Bauer DC, Hunter DJ, Abramson SB, et al. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage 2006; 14(8): 723-727.

[10] Hunter DJ, Nevitt M, Losina E, et al. Biomarkers for osteoarthritis: current position and steps towards further validation. Best practice & research Clinical rheumatology 2014; 28(1): 61-71.

[11] Ahmed U, Anwar A, Savage RS, et al. Biomarkers of early stage osteoarthritis, rheumatoid arthritis and musculoskeletal health. Scientific reports 2015; 5: 9259.

[12] Hsueh MF, Onnerfjord P, Kraus VB. Biomarkers and proteomic analysis of osteoarthritis. Matrix biology: journal of the International Society for Matrix Biology 2014; 39: 56-66.

[13] Hunt MA, Pollock CL, Kraus VB, et al. Relationships amongst osteoarthritis biomarkers, dynamic knee joint load, and exercise: results from a randomized controlled pilot study. BMC musculoskeletal disorders 2013; 14: 115.

[14] Saberi Hosnijeh F, Runhaar J, van Meurs JB, et al. Biomarkers for osteoarthritis: Can they be used for risk assessment? A systematic review. Maturitas 2015.

[15] Vilím V, Olejarova M, Machacek S, et al. Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. Osteoarthritis Cartilage, 2002, 10(9): 707-713.

[16] Henrotin Y, Sanchez C, Bay-Jensen AC, et al. Osteoarthritis biomarkers derived from cartilage extracellular matrix: current status and future perspectives. Annals of physical and rehabilitation medicine, 2016, 59: 145-148.

[17] Acharya C, Yik JHN, Kishore A, et al. Cartilage oligomeric matrix protein and its binding partners in the cartilage extracellular matrix: interaction, regulation and role in chondrogenesis. Matrix Biology, 2014, 37: 102-111.

[18] Zhu Taihang, Cai Chunyuan, Zhang Lei. Research progress of osteoarthritis biomarker COMP. Chinese Journal of Orthopedics, 2010, 23(12): 959-961.
[19] Fernandes FA, Pucinelli ML, da Silva NP, et al. Serum cartilage oligomeric matrix protein (COMP) levels in knee osteoarthritis in a Brazilian population: clinical and radiological correlation. Scand J Rheumatol, 2007, 36(3): 211-215.
[20] Li Heng, Wang Dan, Wu Zhongqing, Zhong Jianming, Yuan Yongjian. The role of serum COMP in the early diagnosis of osteoarthritis. Chinese Journal of Orthopedics, 2012, 25(05): 380-383.
[21] Lai Y, Yu XP, Zhang Y, et al. Enhanced COMP catabolism detected in serum of patients with arthritis and animal disease models through a novel capture ELISA. Osteoarthritis Cartilage. 2012; 20(8): 854-862.
[22] Staikova ND, Kuzmanova SI, Solakov PT. Serologic markers of early rheumatoid arthritis. Folia Medica. 2003; 45(3): 35-42.
[23] Kim JR, Yoo JJ, Kim HA. Therapeutics in Osteoarthritis Based on an Understanding of Its Molecular Pathogenesis. Int J Mol Sci. 2018; 19(3): 674. Published 2018 Feb 27.
[24] Steel KJA, Srenathan U, Ridley M, et al. Polyfunctional, proinflammatory, tissue-resident memory phenotype and function of synovial interleukin-17A+ CD8+ T cells in psoriatic arthritis. Arthritis Rheumatol. 2020; 72(3): 435-447.
[25] Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: A review. JAMA. 2020; 323(19): 1945-1960.
[26] Na HS, Park JS, Cho KH, et al. Interleukin-1-interleukin-17 signaling axis induces cartilage destruction and promotes experimental osteoarthritis. Front Immunol. 2020; 11: 730.
[27] Veldhoen M. Interleukin 17 is a chief orchestrator of immunity. Nat Immunol. 2017; 18(6): 612-621.
[28] Xu Qiang, Li Haiyan, Jin Gang. Screening and identification of potential anti-osteoarthritis targets of luteolin. Journal of Zhejiang Chinese Medical University. 2020; 44(4): 381-386.
[29] Xu Q, Li H, Jing G. Optimization and identification of anti-osteoarthritis potential targets of luteolin. Zhejiang Zhong Yi Yao Da Xue Xue Bao. 2020; 44(4): 381-386.
[30] Li Z, Yuan B, Pei Z, et al. circ_0136474 and MMP-13 suppressed cell proliferation by competitive binding to miR-127-5p in osteoarthritis. Cell Mol Med. 2019; 23(10): 6554-6564.
[31] Yamaguchi Y, Fujio K, Shoda H, et al. IL-17B and IL-17C are associated with TNF-alpha production and contribute to the exacerbation of inflammatory arthritis. J Immunol. 2007; 179(10): 7128-7136.
[32] Wang Guoliang. Expression of IL-17 and mechanisms of inflammatory response in osteoarthritis [D]. Shandong University, 2018.
[33] Lee YH, Song GG. Association between IL-17 gene polymorphisms and circulating IL-17 levels in osteoarthritis: a meta-analysis. Zusammenhang zwischen IL-17-Genpolymorphismen und zirkulierendem IL-17 bei Osteoarthrose: eine Metaanalyse. Z Rheumatol. 2020; 79(5): 482-490. doi: 10.1007/s00393-019-00720-2
[34] Vos LM, Kuijer R, Huddleston Slater JJ, et al. Alteration of cartilage degeneration and inflammation markers in temporomandibular joint osteoarthritis occurs proportionally. J Oral Maxillofacial Surg. 2013; 71(10): 1659-1664.
[35] Meulenbelt I, Kloppenburg M, Kroon HM, et al. Urinary CTX-II levels are associated with radiographic subtypes of osteoarthritis in hip, knee, hand, and facet joints in subjects with familial osteoarthritis at multiple sites: the GARP study. Ann Rheum Dis. 2006; 65: 360-365.
[36] Kraus VB, Kepler TB, Stabler T, et al. First qualification study of serum biomarkers as indicators of total body burden of osteoarthritis. PLoS ONE. 2010; 5: e9739.
[37] Reijman M, Hazes JM, Bierma-Zeinstra SM, et al. A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum. 2004; 50: 2471-2478.
[38] Dam EB, Loog M, Christiansen C, et al. Identification of progressors in osteoarthritis by combining biochemical and MRI-based markers. Arthritis Res Ther. 2009; 11: R115.
[39] 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.
[40] Dou X, Zhang Z, Wang S, Zhou X. Combined use of Serum miR-338-3p, Cartilage Oligomeric Matrix Protein, and Chondroitin Sulfate-846 in the Early Diagnosis of Knee Osteoarthritis. Clin Lab. 2019; 65(3): 10.7754/Clin.Lab.2018.180803.
[41] Jansen NW, Roosendaal G, Lundin B, et al. The combination of the biomarkers urinary C-terminal telopeptide of type II collagen, serum cartilage oligomeric matrix protein, and serum chondroitin sulfate 846 reflects cartilage damage in hemophilic arthropathy. Arthritis Rheum. 2009; 60(1): 290-298.
[42] Wang Teng, Ding Hong, Zhao Zhengming, et al. Expression of S100A8/A9, CS-846, and MMP3 in knee osteoarthritis and their clinical significance. International Journal of Laboratory Medicine. 2020; 41(19): 2337-2340.
[43] Zhang Junfeng, Song Linghua, Dong Haiyuan, et al. Combined detection of urinary C-terminal type II collagen, serum cartilage oligomeric matrix protein, and chondroitin sulfate 846 in the early diagnosis of osteoarthritis. Chinese Journal of Drugs and Clinical Therapeutics. 2014; 14(7): 861-864.
[44] Zhou Tao, Zhang Bing, Zhu Peng. Detection of serum glucose-6-phosphate isomerase, chondroitin sulfate 846, and thrombospondin-1 levels in patients with knee osteoarthritis and their clinical significance. Laboratory Medicine and Clinical. 2022; 19(13): 1750-1753.
[45] Bouillon R, Marcocci C, Carmeliet G, Bikle D, White J, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev. 2019; 40: 1109-1151.
[46] Martel-Pelletier J, Barr A, Cicuttini F, Conaghan P, Cooper C, Goldring M, et al. Osteoarthritis. Nat Rev Dis Primers. 2016; 2: 16072.
[47] Mabey T, Honsawek S. Role of vitamin D in osteoarthritis: molecular, cellular, and clinical perspectives. Int J Endocrinol. 2015; 2015: 383918.

[48] Veronese N, Maggi S, Noale M, De Rui M, Bolzetta F, Zambon S, et al. Serum 25-hydroxyvitamin D and osteoarthritis in older people: the Progetto Veneto Anziani study. Rejuvenation Res. 2015; 18: 543-553.
[49] Laslett L, Quinn S, Burgess J, Parameswaran V, Winzenberg T, Jones G, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. Ann Rheum Dis. 2014; 73: 697-703.
[50] McAlindon T, Felson D, Zhang Y, Hannan M, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med. 1996; 125: 353-359.
[51] Felson D, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis Rheum. 2007; 56: 129-136.
[52] Konstari S, Paananen M, Heliövaara M, Knekt P, Marniemi J, Impivaara O, et al. Association of 25-hydroxyvitamin D with the incidence of knee and hip osteoarthritis: a 22-year follow-up study. Scand J Rheumatol. 2012; 41: 124-131.
[53] Bergink A, Zillikens M, van Leeuwen J, Hofman A, Uitterlinden A, van Meurs J, et al. 25-hydroxyvitamin D and osteoarthritis: a meta-analysis including new data. Semin Arthritis Rheum. 2016; 45: 539-546.
[54] Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014; 2: 76-89.
[55] Shipton E, Shipton E. Vitamin D deficiency and pain: clinical evidence of low levels of vitamin D and supplementation in chronic pain states. Pain Ther. 2015; 4: 67-87.
[56] Yu G, Lin Y, Dai H, Xu J, Liu J. Association between serum 25-hydroxyvitamin D and osteoarthritis: A national population-based analysis of NHANES 2001-2018. Front Nutr. 2023; 10: 1016809. Published 2023 Feb 28.