Bone and Arthrosurgery Science, 2025, Volume 3, Issue 4
http://ojs.bbwpublisher.com/index.php/BAS
Online ISSN: 2981-8222
Print ISSN: 3083-4856

Research on Serum Biomarkers in Knee Joint Diseases of the Elderly

Jikui Guan, Li Zhao*

The First People's Hospital of Wuhu, Wuhu 241000, Anhui, China

**Corresponding author: Li Zhao, ok1858@163.com*

Abstract: *Background*: Knee osteoarthritis (KOA) is characterized by chronic degeneration or wear of the articular cartilage, cartilage degeneration, fragmentation, and hardening, as well as bone spur formation and synovial inflammation. Over time, these changes occur slowly, and bone wear becomes more severe. This in turn causes pain, stiffness and swelling. It has an impact on normal work and life. To understand the mechanism and monitoring index of cartilage injury in the elderly population and prevent osteoarthritis. The purpose of this study was to compare the changes of serum cytokine biomarker levels in elderly patients with knee injury and osteoarthritis, and explore the correlation with the severity of lesions, which is conducive to early diagnosis and prevention of knee diseases. *Objective:* To investigate the differences in serum concentrations of matrix metalloproteinase-3 (MMP-3) and cartilage oligomeric matrix protein (COMP) in elderly patients with osteoarthritis, knee fracture or ligament injury. *Methods:* A total of 36 elderly KOA patients who underwent knee replacement in our hospital from July 2021 to May 2023 were selected as the observation group, and 36 elderly patients with knee fractures, patellar fractures, ligament or meniscus injuries who were treated during the same period were selected as the control group for the study. The age, gender, weight and other data of the patients were compared. The anteroposterior and lateral radiographs of the knee joints were examined for the first time, and the Kellgren and Lawrence (KL) score was used to compare the severity of KOA. The levels of serum MMP-3 and COMP in the two groups of patients were tested by enzyme-linked immunosorbent assay, and the changes and sensitivity of the two biomarkers in elderly knee diseases were compared and analyzed. *Results*: (1) Among the 72 knee joints included in the study, 36 cases were assigned to each group. No significant differences were observed in gender, age, or weight between the two groups ($P > 0.05$). (2) The concentrations of serum MMP-3 and COMP in the observation group were significantly higher than those in the control group. *Conclusion*:The elevated levels of COMP and MMP-3 in patients with knee osteoarthritis (KOA) suggest a potential correlation with disease progression, as their concentrations increased with worsening severity. These biomarkers may hold significant value for early detection, diagnosis, and prevention of KOA in elderly populations, warranting further investigation.

Keywords: Matrix metalloproteinases; Cartilage oligomeric matrix proteins; Biomarkers; Cartilage injury; Knee osteoarthritis

Online publication: September 4, 2025

1. Introduction

Knee osteoarthritis (KOA) is the most common arthritis of the knee in the elderly. It poses a huge burden on the affected elderly, healthcare providers and society. Current treatments focus on symptomatic relief, the use of non-steroidal painkillers and advanced arthroplasty. It is characterized by degeneration, erosion, wear and tear, injury, loss of articular cartilage, narrowing of the joint space, bone redundancy, subchondral sclerosis and synovial inflammation. In the pathogenesis of osteoarthritis of the knee, inflammation has been shown to underlie the pathogenesis. The inflammatory response promoted by inflammatory cytokines is a major factor and an important cause of chronic pain [1].

There are several high-risk factors for osteoarthritis of the knee, including age, trauma, and obesity. Current methods of clinical evaluation of disease severity often utilize imaging (radiographs and magnetic resonance imaging) and are assessed using the Kellgren and Lawrence scale, known as the KL grading system (grades 0-4). However, radiographs only show changes in bone and cartilage, which often occur late in the disease. In the clinical setting, when clinical signs of pain and reduced mobility have already appeared, the bone and cartilage lesions have become irreversible. Therefore, there is a need to find sensitive and predictive tests that could eventually replace current imaging methods and facilitate punctual, more targeted and personalized treatment [2]. Biomarkers (inflammatory cytokines) will likely be a better choice to reflect the severity of the lesion. Their concentrations can be measured in body fluids such as blood, urine or synovial fluid [3].

2. Data and methods

2.1. General information

36 elderly patients with KOA who underwent knee replacement admitted to our hospital during July 2021-May 2023 were selected as the observation group, and 36 elderly patients with knee fracture, patella fracture, ligament injury or meniscus injury who were hospitalized and received treatment at the same time were selected as the control group for the sexual study. Differences in age, gender, and weight between the two groups were compared. All of them took the frontal and lateral radiographs of the knee joint, and the severity of KOA was assessed by the Kellgren and Lawrence (K-L) grading system score. ELISA kits were used to detect the concentrations of serum MMP-3 and COMP in both groups. The correlation between the two biomarkers and the severity of knee disease was comparatively analyzed. The study was approved by the Ethics Committee of the First People's Hospital of Wuhu City under the informed consent of the patients.

2.2. Inclusion and exclusion criteria

Test group: (1) age ≥ 55 years old; (2) K-L grade 3-4; (3) X-ray frontal and lateral radiographs and MRI; (4) intermittent pain and activity limitation in the last month; (5) in line with the guidelines for the diagnosis and treatment of osteoarthritis [4].

Blank group: (1) age ≥ 55 years old; (2) K-L grade 0-1; (3) X-ray frontal and lateral radiographs and MRI; (4) patella fracture, femoral condyle fracture, tibial plateau fracture, meniscus injury or ligament injury.

Exclusion criteria: (1) medical diseases (respiratory, digestive, endocrine, cardiovascular and cerebrovascular and other systemic diseases); (2) rheumatism, autoimmune diseases or infectious diseases, etc.; (3) cognitive disorders, psychiatric disorders, and so on.

2.3. Research methods

2.3.1. Clinical data collection

On the day of admission, patients in both groups were measured for height, weight, blood pressure, etc., and asked about history, family history, clinical symptoms and other clinical data. On the next day, 5ml of fasting venous blood was collected, within 4h after collection, centrifuged at 2500 rpm for 10 minutes, and the serum was stored in the refrigerator at -20 ℃. An ELISA kit was used to detect the concentration of MMP-3 and COMP in the serum; the COMP kit was provided by Shanghai Research Biotechnology Co., Ltd, and the MMP-3 kit was provided by the American Abcam Company.

2.3.2. Observation indexes

Compare the relationship between the MMP-3 and COMP levels of the two groups and the K-L classification and clinical symptoms of the patients.

2.3.3. Statistical methods

The data were analyzed using SPSS 25.0 statistical software. Continuous variables were presented as mean ± standard deviation (SD), with between-group comparisons conducted using independent samples t-tests and analysis of variance (ANOVA). Categorical data were expressed as percentages, and group comparisons were performed using the chi-square (χ^2) test. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Comparison of cohort characteristics

In the 72 enrolled patients, there was no statistically significant difference in age, gender and weight ($P > 0.05$) (**Table 1**).

Table 1. Comparison of clinical data between the two groups

Groups (n = 36)	Age (years old)	BMI (kg/m^2)	Male/female	Left/right
Test group	67.3 ± 8.3	28.73 ± 3.69	11/25	17/19
Blank group	61.7 ± 6.6	29.89 ± 4.59	22/14	20/16
P	> 0.05	> 0.05	> 0.05	> 0.05

3.2. Comparison of MMP-3 and COMP

The serum MMP-3 and COMP levels of the observation group were higher than those of the control group, and the difference was statistically significant ($P < 0.05$) (**Table 2**).

Table 2. Comparison of MMP-3 and COMP levels between the two groups (ug/l,`mean ± SD)

Groups (*n* = 36)	MMP-3	COMP
Test group	4.38 ± 0.78	5.62 ± 1.65
Blank group	1.22 ± 0.40	1.34 ± 0.47
t	23.7034	25.7493
P	< 0.05	< 0.05

4. Discussion

KOA is characterized by chronic nonspecific inflammation with predominantly articular cartilage damage. The pathological mechanism is characterized by chondrocytopenia and extracellular matrix degradation. It includes degenerative changes in all tissue structures of the joint (bone, cartilage, synovium, ligaments and joint space) [5]. Clinical manifestations are swelling, pain, stiffness, deformity, and consequently limited mobility and disability of the knee joint. The inflammatory process involves anabolic and catabolic metabolism with the involvement of multiple factors such as chemokines, cytokines, matrix metalloproteinases and their inhibitors. The current routine clinical adjuncts for knee disease are radiographs and other imaging tests, the positive manifestations of imaging examinations are often detected late in the development of the disease, indicating poor sensitivity in disease detection. Disruption of the metabolic balance of intra-articular cartilage is associated with the pathomechanism of osteoarthritis of the knee [6]. Haraden *et al.* [7] found in their study that six biomarkers in joint fluid, (including VEGF, MMP-3, TIMP-1, sICAM-1, sVCAM-1, and MCP-1), were associated with the severity of knee osteoarthritis. They also observed the association between these biomarkers and activated macrophages and neutrophils. Therefore, detecting the metabolic products of cartilage may be a method for early diagnosis, detection, and early warning of KOA.

Cartilage oligomeric matrix protein (COMP) is an extracellular matrix non-collagenous glycoprotein present in cartilage [8]. It belongs to the thrombospondin family, also known as TSP-5, and is found mainly in human bone (articular cartilage, menisci, ligaments, tendons, and synovium) [9–11]. COMP can interact with many other cartilage extracellular matrix (ECM) components, including type I, II, IX, IX, and XIV collagens, fibronectin, and proteoglycans [12]. It promotes the secretion and assembly of collagen and maintains the stability of the extracellular matrix. It has obvious tissue specificity due to its high expression in cartilage. As one of the by-products of cartilage metabolism, it is now gaining increasing attention and research as a possible biomarker for early detection of osteoarthritis in the knee [13].

Georgiev *et al.* [14] observed that serum COMP levels were higher in patients with KOA than in controls, and that COMP was positively correlated with knee MRI scores, which suggests that COMP may reflect knee joint structural damage. In KOA, COMP expression is regulated by tumor necrosis factor (TNF-α). In this study, it was found that a portion of patients with knee joint trauma had elevated serum COMP. This research evidences indicate that COMP is involved in the molecular processes related to cartilage metabolism. Detecting COMP will pave the way for early prevention and treatment of synovitis and eventual cartilage degeneration in KOA patients [15].

Matrix metalloproteinase 3 (MMP-3) is widely used as a serum biomarker.MMP-3 is the major enzyme involved in cartilage degradation.MMP-3 is thought to be a more specific indicator of a protein originally secreted by synovial fibroblasts. MMP-3 degrades a variety of extracellular substrates, including proteoglycans, fibronectin, laminin, and collagen type IV, and in addition initiates the MMP-3 can degrade various extracellular substrates, including proteoglycans, fibronectin, laminin, and collagen type IV, in addition to other matrix metalloproteinase family members. Therefore, MMP-3 is a degradation enzyme that plays a major role in cartilage destruction, and is the enzyme with the highest prevalence of KOA. However, serum MMP-3 is also significantly elevated in diseases involving synovitis. The biomechanical alterations of KOA stimulate the production of inflammatory mediators by chondrocytes, such as in interleukin-1 and tumor necrosis factor. These inflammatory mediators' response also triggers an increase in the synthesis of MMP-3, which, when activated, directly degrades proteoglycans in the extracellular matrix, while also activating other zymogens, leading to extracellular matrix degradation, and the products of the MMP-3 degradation are released into the joints, causing arthritis. The products of MMP-

3 degradation are simultaneously released into the joints, causing joint inflammation. Serum MMP-3 levels reflect the degree of inflammation and correlate with the level of disease activity.MMP-3 has a dominant role in joint disease damage. At the site of cartilage destruction, the level of MMP-3 in cartilage tissue increases. The expression of MMP-3 in the KOA group was significantly higher than that in the control group. Heard *et al.* [16] investigated the protein expression levels of MMP and TIMP in the synovial fluid of normal and early KOA joints. It showed that there was a significant difference in MMP-3 expression between normal and early KOA samples; the level of MMP-3 expression was significantly higher in advanced KOA. More importantly, MMP-3 can activate MMP-1, MMP-9, MMP-13 and other zymogens to produce a cascade amplification effect and accelerate cartilage destruction. The mRNA of MMP-3 is more strongly expressed in cartilage, showing different patterns in early and advanced disease, and more significantly in advanced disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated efficacy in alleviating symptoms and mitigating inflammation. Intra-articular injections of corticosteroids (CS), platelet-rich plasma (PRP), mesenchymal stem cells, and hyaluronic acid have been reported to relieve symptoms. However, the duration of action of these drugs and local side effects remain questionable.

The diagnostic criteria of clinical symptoms and imaging criteria are clinically relevant in the diagnosis of advanced stages. In clinical studies, diagnostic criteria for early osteoarthritis of the knee have good predictive power for individuals with knee pain, although more validation is needed [17]. Because when there is clear imaging evidence in clinical practice, the articular cartilage has already undergone irreversible degenerative damage, irreversible disease progression and joint degeneration have already occurred, thus delaying the optimal time for early treatment [18]. In addition, the onset of clinical symptoms of KOA (e.g., pain) is often delayed due to the patient's usually advanced age and pain tolerance, resulting in delayed diagnosis and treatment. Identifying reliable biochemical markers for early diagnosis of KOA and predicting disease progression is a top priority for KOA [19]. This is important for individuals at risk of OA (e.g., trauma) who may present with knee pain without observing obvious signs or radiographic evidence of KOA. This helps to identify patients with early KOA and monitor treatment at the individual level [20]. Studies have been conducted to analyze the correlation of various biomarkers and to identify the factors that are most easily and accurately used for early clinical diagnosis to provide a basis for early diagnosis of KOA.

The study analyzed serum levels of the biomarkers MMP-3 and COMP in elderly patients with patellar fractures, meniscus and ligament injuries, and knee osteoarthritis (KOA) to assess their variations in knee-related disorders and KOA. The findings revealed significantly higher MMP-3 and COMP levels in the observation group compared to the control group ($P < 0.05$), suggesting that these biomarkers are particularly elevated in KOA patients. Furthermore, patients with more severe disease exhibited even greater increases in MMP-3 and COMP levels, with these differences also being statistically significant ($P < 0.05$).

5. Conclusion

In conclusion, the serum biomarker COMP, MMP-3 levels were significantly elevated in elderly patients with KOA and gradually increased with the aggravation of the disease, which has a certain reference value for early warning, diagnosis, prevention and treatment of chronic cartilage damage in knee diseases.

Funding

The Fifth Batch of National Outstanding Clinical Talent Training Program in Traditional Chinese Medicine (Letter No. [2022]1 from the National Administration of Traditional Chinese Medicine); Yan'an City Special Project for Prevention and Control of COVID-19, 2020 (Project No.: 2020ZCYS-007); Yan'an University Emergency Scientific Research Guiding Fund for COVID-19 Prevention and Treatment (Project No.: YDKYYJ03).

Disclosure statement

The authors declare no conflict of interest.

References

[1] Berenbaum J, 2013, Osteoarthritis as an Inflammatory Disease (Osteoarthritis Is Not Osteoarthritis!). Osteoarthritis Chondroitin, 21: 16–21.

[2] Mobasheri A, Bay-Jensen A, Spil W, et al., 2017, Osteoarthritis Year in Review 2016: Biomarkers (Biochemical Markers). Osteoarthritis Cartilage, 25(2): 199–208.

[3] Glyn-Jones S, Palmer A, Agricola R, et al., 2015, Osteoarthritis. Lancet, 386(9991): 376–387.

[4] Joint Surgery Group of Chinese Orthopaedic Association, 2018, Guidelines for the Diagnosis and Treatment of Osteoarthritis (2018 Edition). Chinese Journal of Orthopaedics, 38(12): 705–715.

[5] Geurts J, Jurić D, Müller M, et al., 2018, Novel Ex Vivo Human Osteochondral Explant Model of Knee and Spine Osteoarthritis Enables Assessment of Inflammatory and Drug Treatment Responses. International Journal of Molecular Sciences, 19(5): 1314.

[6] Fujii Y, Liu L, Yagasaki L, et al., 2022, Cartilage Homeostasis and Osteoarthritis. International Journal of Molecular Sciences, 23(11): 6316.

[7] Haraden C, Huebner J, Hsueh M, et al., 2019, Synovial Fluid Biomarkers Associated with Osteoarthritis Severity Reflect Macrophage and Neutrophil Related Inflammation. Arthritis Research & Therapy, 21(1): 146.

[8] Tseng S, Reddi A, Cesare P, 2009, Cartilage Oligomeric Matrix Protein (COMP): A Biomarker of Arthritis. Biomarkers Insights, 4: 33–44.

[9] Posey K, Coustry F, Hecht J, 2018, Cartilage Oligomeric Matrix Protein: COMPopathies and Beyond. Matrix Biology, 71–72: 161–173.

[10] Lopez-Franco M, Lopez-Franco O, Murciano-Anton M, et al., 2016, Meniscal Degeneration in Human Knee Osteoarthritis: In Situ Hybridization and Immunohistochemistry Study. Archives of Orthopaedic and Trauma Surgery, 136: 175–183.

[11] Kobayashi M, Kawabata K, Kusaka-Kikushima Aet al., 2016, Cartilage Oligomeric Matrix Protein Increases in Photodamaged Skin. Journal of Investigative Dermatology, 136: 1143–1149.

[12] Schulz J, Nuchel J, Niehoff A, et al., 2016, COMP-Assisted Collagen Secretion—A Novel Intracellular Function Required for Fibrosis. Journal of Cell Science, 129: 706–716.

[13] Schulze K, Nuchel K, Niehof K, et al., 2016, Complex-Assisted Collagen Secretion: An Intracellular Function Required for Fibrosis. Journal of Cell Science, 129(4): 706–716.

[14] Georgiev T, Ivanova M, Kopchev A, et al., 2018, Cartilage Oligomeric Protein, Matrix Metalloproteinase-3, and Coll2-1 as Serum Biomarkers in Knee Osteoarthritis: A Cross-Sectional Study. Rheumatology International, 38: 1–10.

[15] Wanvisa U, Natcha M, Thanyalak T, et al., 2024, Cartilage Oligomeric Matrix Protein (COMP): A Biomarker of

Arthritis. Bone & Joint Research, 13(6): 261–271.

[16] Heard B, Martin L, Rattner J, et al., 2012, Matrix Metalloproteinase Protein Expression Profiles Cannot Distinguish Between Normal and Early Osteoarthritic Synovial Fluid. BMC Musculoskeletal Disorders, 23(13): 126.

[17] Runhaar J, Kloppenburg M, Boers M, et al., 2021, Towards Developing Diagnostic Criteria for Early Knee Osteoarthritis: Data from the CHECK Study. Rheumatology, 60: 2448–2455.

[18] Hao H, Zhang J, He Q, et al., 2019, Cartilage Oligomeric Matrix Protein, C-Terminal Cross-Linking Telopeptide of Type II Collagen, and Matrix Metalloproteinase-3 as Biomarkers for Knee and Hip Osteoarthritis (OA) Diagnosis: A Systematic Review and Meta-Analysis. Osteoarthritis and Cartilage, 27: 726–736.

[19] Riegger J, Rehm M, Buchele G, et al., 2020, Serum Cartilage Oligomeric Matrix Protein in Late-Stage Osteoarthritis: Association with Clinical Features, Renal Function, and Cardiovascular Biomarkers. Journal of Clinical Medicine, 9: 268.

[20] Henrotin Y, 2022, Osteoarthritis in Year 2021: Biochemical Markers. Osteoarthritis and Cartilage, 30: 237–248.