Review Article

# Cartilage Oligomeric Matrix Protein: A Biomarker for Diagnostic and Monitoring Osteoarthritis

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## Abstract

Osteoarthritis (OA) is a painful, chronic, and widespread disease. Early treatment for disease is very important to prevent the progression of the disease. Currently, X-ray and clinical history are still the most dependable ways to diagnose OA and estimate the severity of disease. However, the joint damage by OA disease begins before it is diagnosed by radiographic changes. Hence, further practices for early diagnosis are required. Biomarkers and particles that are released into fluids during the disease have received many research interests for early diagnosis of OA. Therefore, in order for the biomarker to be beneficial in diagnosing of OA preradiography, it must have a strong and direct association with the disease. Hence, a good approach to detect and follow-up this disease is cartilage oligomeric matrix protein (COMP). COMP is one of the important biomarkers, which is closely related to the breakdown of the articular cartilage and the loss of function. Many studies have suggested that the COMP level is an indicator of the diagnosis and severity of the disease. In this review article, we highlighted the importance's role of COMP in OA.

**Keywords:** Cartilage oligomeric matrix protein, joint, osteoarthritis, serum, synovial fluid

## Introduction

Osteoarthritis (OA) is the most common form of joint disease.[1-3] It can cause pain and disability in the elderly.[4-7] OA and rheumatoid arthritis (RA) are the most common arthritis.[1,8] Knee and hip are the most common causes of OA, causing pain and mobility disabilities worldwide.[9] Late-stage joint replacement is the preferred option for effective treatment to relieve pain and improve quality of life.[9,10] Approximately 10%–20% of patients do not benefit from this surgical approach, and this aspect is still not understood.[11,12] The increased prevalence of OA over the past years underscores the importance of preventive strategies or more effective treatment based on the reliable indicators.[9]

Cartilage oligomeric matrix protein (COMP) has an important role in initiating and progressing with OA.[13,14] Furthermore, the high level of COMP has a clear impact on the severity of the disease.[15,16] Therefore, the focus on the importance of COMP in OA increased, especially in knee arthritis patients.

## Osteoarthritis Affected the Synovial Joint

Joint is a place where two bones or more connect.[17] The end of the bones is covered with cartilage.[18,19] Each joint is protected by a capsule, which provides support and protection toward external shocks.[20] The capsule is lined with the synovial membrane (synovium). It is a type of tissue that secretes the synovial fluid (SF) to soften and nourish the joint tissues.[21-23] In normal physiological condition, the layer of synovium is thin.[24]

SF is a biofluid in contact with the synovial membrane and the meniscus.[25,26] It plays a significant function in the mechanical metabolism of articular cartilage tissue.[27,28] The major difference between SF and other fluids in the body is that it contains a high amount of hyaluronic acid,[20,26,29] which is characterized by lubrication.[30] SF is excreted in small amounts by synovium and occasionally by synovial tendon sheaths.[26,31] Until large joints, a small drop of SF occurs on the joint surface to the lip on each other.[32] Therefore, isolation

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and analysis are onerous. The effusion continually illustrates articular syndrome.[28,29,33] A alteration in the structure and functions of the normal joint has been associated with many forms of arthritis.[21]

Arthritis means inflammatory of the joint, where *arthr* indicates joint and *itis* indicates inflammation.[31,34,35] There are many types of arthritis that may affect other body parts, such as the internal organs and skin.[31,34] The most common prevalent types of arthritis are OA and RA.[8]

OA is a common of arthritis; its prevalence in both developing and development countries.[36-39] Thus, in the United States, more than 25 million of population has been diagnosed with OA.[40-42] Further, about 9.3 million of people aged over 45 years affected with OA, causing a clear cost-effective load and an influence on the quality of life.[17,43] The incidence of OA disease increases with age.[44,45] Nearly 80% of the population at the age of 65 are infected with the disease.[46,47] The women are more infected than men, especially after the age of postmenopausal.[37,48-50]

Articular cartilage is broken due to the imbalance between the construction and destruction of cartilage cells that may cause weakening of the articular cartilage.[51] OA is characterized by many signs, namely advanced damage to the articular cartilage, narrowness of the joint area, formation of osteophyte, significant deformities in both the bones under the cartilage, synovial membrane, cartilage purse, tendons, and joint muscle, resulting in loss of joint functions.[43,44,47,49,52-56]

Unluckily, the risk factors that reason of OA are not completely understood.[7,57] Nevertheless, there are numerous factors that are supposed to show a role in the incidence and improvement of the disease, such as elderly and female sex.[17,58,59] In addition, smoking and history of family as it is recognized.[17] Synovial inflammation might happen in the early period of OA improvement; hence, it comes to be a possible aim for the management of knee OA. Unfortunately, the risk factors for a synovium in the knee OA are not fully understood.[57]

## Biomarkers and Their Correlation with Osteoarthritis

Currently, X-ray and clinical history are still the most dependable ways to diagnose OA and estimate the severity of disease.[57,60] However, the destruction of the joint caused with OA begins before it is diagnosed by radiographic changes.[43] Hence, further practices for early diagnosis are required. Biomarkers and particles that are released into fluids during the turnover the matrix have received many research interests for early diagnosis of OA. There are many biomarkers that can be applied to OA diagnosis, such as catabolic enzymes, cytokines, anti-inflammatory markers, and marks of cartilage and bone metabolism.[44] Biological factors are classified into one or more of the following totals: disease burden, intervention and investigation activity, prognosis, and diagnosis.[44] Identifying the sensitive diagnostic method for the purpose of identifying OA disease before radiographic is important to prevent irreversible articular cartilage damage.[61] Numerous biomarkers have been recognized in the serum or SF or both for diagnosing preradiographic OA.[15,43,57,62-68]

Therefore, in order for the biomarker to be useful in diagnosing of OA preradiography, it must have a strong and direct correlation with the disease, as well as a clear change in its level between the patients and the healthy people.[15,53,69] Hence, a good approach is to detect and follow-up on one of these important biomarkers that have a close relationship with the breakdown of the cartilage joint is COMP.

## Cartilage Oligomeric Matrix Protein

Cartilage oligomeric matrix protein (COMP) is a glycoprotein, non collagen homopentrameric. also, known thromposidne-5. Its an extracellular matrix (ECM), has molecular weight 524- kDa.[70-76] COMP presents major in the cartilage; further, later, it was found in smaller quantities in a variety of tissues, such as tendons, fibroblasts, synovium, ligaments, vascular smooth cells, activated platelets, breast cancer cells, and cardiomyocytes.[7,9,43,44,67,77,78] When cartilage is damaged, it releases from the cartilage to the SF and thus into the blood circulation.[77]

### Function of cartilage oligomeric matrix protein

Function of COMP is still unclear, but there are suggestions that COMP has an important role in the endochondral ossification and the interaction with collagen fibrils by each C-terminal globule, for the purpose of stabilizing the ECM.[79,80] Furthermore, COMP has an important role in stimulating the formation of fibril for Type I and II collagen, as well as the acceleration of fibril genesis and binding to aggrecan.[7,43,44,67,78,81]

### Association of cartilage oligomeric matrix protein with osteoarthritis

Table 1 reveals that many studies showed the estimation of COMP level either in the serum, SFs, or both in patients with OA. Previous studies have shown that the level of serum COMP can be used to diagnose and distinguish between OA and healthy people, where the serum COMP level for OA patients was found to be higher than healthy people.[14,16,44,57] In addition, several studies have found that the high level of COMP has been detected in the serum and SF and that its concentration in the SF is higher than in the serum, which means that the COMP is released from the affected joint.[16,43] Some studies have indicated that patients who have the most crashing joint have a higher COMP level than patients who have a less crashing joint.[63,82]

Sharif *et al*., 1995 in detailed study on patients with knee OA found that high COMP levels have a close relationship with the progression of the disease.[48,82] Besides, Neidhart *et al*., 1997 also found that the level of COMP serum is high in patients with OA compared to healthy people[83] and concluded that the changes in the serum COMP can reflect changes in the cartilage breakdown.[83]

**Table 1: Studies on cartilage oligomeric matrix protein either in serum, synovial fluids, or both, in patients with rheumatoid arthritis**

| Author | Years | Type of OA | Type of fluid | Outcomes |
|---|---|---|---|---|
| Sharif *et al*.[82] | 1995 | KOA | Serum | Sharif *et al*., 1995 in detailed studies on patients with KOA found that high COMP levels have a close relationship with the progression of the disease |
| Neidhart *et al*.[83] | 1997 | OA | Serum | Also found that the level of COMP serum is high in patients with OA compared to healthy people. And concluded that changes in serum COMP can reflect changes in cartilage breakdown |
| Conrozier *et al*.[84] | 1998 | Hip OA | Serum | Observed a high level of serum COMP when predicting the development of hip OA symptoms. And concluded that the level of serum COMP as an indicator of OA and possible benefit in using COMP to determine the risk of rapid progression of hip arthritis disease |
| Clark *et al*.[15] | 1999 | KOA, hip OA | Serum | Found that the presence of radiographic KOA and hip OA associated with the high level of serum COMP |
| Vilím *et al*.[85] | 2001 | OA | Serum | Revealed correlation between synovitis and level of serum COMP |
| Jordan *et al*.[86] | 2003 | OA | Serum | Found an increase in the level of COMP serum |
| Murphy *et al*.[87] | 2002 | Chondromalacia patellae | Serum | Found an increase level of serum COMP for patients caused with chondromalacia patellae |
| Andersson *et al*.[88] | 2006 | KOA | Serum | Showed that the level of COMP does not change during rest. However, the level of serum COMP increases after of exercise, and then decreases after of rest. And concluded that the level of serum COMP increases in KOA while the serum COMP level is lower during rest |
| Andersson *et al*. 2006[89] | 2006 | KOA | Serum | Showed that there was no difference in the level of serum COMP between 8 and 21 h. However, Anderson *et al*. showed that there is a significant decrease in the level of serum COMP during the night or bed rest, and that the lowest level of COMP is between 4 and 5 h[54] |
| Bijlsma *et al*[90] | 2011 | OA | Serum | Found a rise in the level of COMP for OA patients |
| Hoch *et al*.[61] | 2011 | KOA | Serum | Noted that serum COMP level was constantly elevated in patients who radiographically diagnosed with knee OA when compared to controls. And concluded that these results point out serum COMP is raised in patients with KOA and is subtle to KOA disease development |
| Zivanović *et al*.[55] | 2011 | OA | Serum | Showed a significant difference in the level of serum COMP between patients who get the presence of joint effusion and patients who do not have no joint effusion. As well as a significant difference between patients who have synovitis and patients who do not have synovitis |
| Gheita *et al*.[16] | 2015 | OA | Serum, SF | Showed that the COMP level of OA patients in the synovial fluid is higher than in their serum. And the level of serum COMP for OA patients increases with age and severity. Positive correlation between serum COMP level with each of SF COMP level and the severity of disease. Gheita *et al*., concluded that COMP level in serum or SF reveal a degree of joint destruction in OA patients. Further, COMP level has potentially reliable diagnostic markers in early diagnosis of joint damage and can be monitored for predicting rapid treatment starting with early-stage patients and monitoring the response to various therapeutic methods. COMP levels in serum or synovial fluid reflect the severity of disease |
| Arellano *et al*.[43] | 2017 | KOA | Serum, SF | Showed that KOA patients have a positive correlation between the level of COMP synovial fluid and the level of COMP serum, age, and sampling daytime, also, the high level of COMP is only in the female synovial fluid of patients. Arellano *et al*. concluded that these results may propose a promising role for serum and synovial fluid COMP as a measure for primary knee osteoarthritis |
| Martadiani *et al*.[57] | 2017 | OA | Serum | Showed that the level of serum COMP for OA patients higher than health about 5.5 times. And concluded that elevated the level of COMP might reveal progression of joint matrix turnover or damage |
| Zhang[91] | 2018 | KOA | Serum | Found that the high level of COMP in the serum of KOA patients is associated with the incidence of KOA disease, and concluded that patients with a higher level of COMP serum have a greater chance of developing KOA |

*Contd...*

**Table 1: Contd...**

| Author | Years | Type of OA | Type of fluid | Outcomes |
|---|---|---|---|---|
| Hamodat and Al-Ashou[92] | 2020 | OA | Serum, SF | Showed a higher level of serum COMP for OA patients in compression with level of serum COMP; the COMP level in the synovial fluid of OA patients is also higher than the COMP level in their serum. Furthermore, the high level of COMP is in the synovial fluid of female OA patients; and the level of serum COMP increases with age and severity of the disease. They concluded that the COMP level could be a biomarker of the extent of damage to the cartilage joint, which could be used as a diagnostic tool to determine the degree of the disease as well as monitor the effect of treatment |

COMP: Cartilage oligomeric matrix protein, SF: Synovial fluid, OA: Osteoarthritis, KOA: Knee osteoarthritis

Furthermore, another study by Conrozier *et al*.[84] observed a high level of serum COMP when predicting the development of hip OA symptoms. Conrziier *et al*. concluded that the level of serum COMP as an indicator of OA and possible benefit in using COMP to determine the risk of rapid progression of hip arthritis disease.

In addition, Clark *et al*. found the presence of radiographic knee OA and hip OA associated with the high level of serum COMP.[15] Moreover, Vilim *et al*. revealed correlation between synovitis and level of serum COMP.[85] Further, Jordan *et al*.[86] found an increase in the level of serum COMP for OA patients.

In addition, Murphy *et al*. found increase levels of serum COMP for patients caused with chondromalacia patellae.[87]

Moreover, Andersson *et al*., 2006 showed that the level of COMP does not change during rest. However, the level of serum COMP increases after of exercise and then decreases after of rest. They concluded that the level of serum COMP increases in knee OA while the serum COMP level is lower during rest.[88]

Other study by Andersson *et al*., 2006 showed that there was no difference in the level of serum COMP between 8 and 21 h. However, Anderson *et al*. showed that there is a significant decrease in the level of serum COMP during night or bed rest and that the lowest level of COMP is between 4 and 5 h.[89]

In addition, Bijlsma *et al*. also found a rise in the level of COMP.[90] Further, Hoch *et al*.[61] noted that serum COMP level was constantly elevated in patients who radiographically diagnosed with knee OA when compared to controls and concluded that these results point out that serum COMP is raised in patients with knee osteoarthritis (KOA) and is subtle to KOA disease development.[61]

The results of Zivanović *et al*. showed a significant difference in the level of COMP serum between patients who get the presence of joint effusion and patients who do not have no joint effusion, as well as a significant difference between patients who have synovitis and patients who do not have synovitis.[55]

Moreover, Verma and Dalal have observed that the level of COMP serum in OA patients is higher than the control group. Verma and Dalal's results also showed that the level of serum COMP for patients is associated with a negative correlation with the duration of the disease and a positive correlation with age. In addition, they observed that the difference of sex has an effect on the level of serum COMP for OA patients. Moreover, they found that males have a higher level of COMP than females and concluded that the level of serum COMP could be used as a diagnostic indicator and its value could measure the risk of progression.[93]

Besides, Singh *et al*., 2015 showed that the level of serum COMP for patients in conditions with mild was lower than moderate, and in severe condition, it was higher than moderate. Singh *et al*.[94] concluded that the value of serum COMP can distinguish between patients and health, as well as the value of COP can reflect the severity of the disease.

In addition, Gheita *et al*., 2015 also showed that the COMP level of OA patients in the SF is higher than in their serum. The level of serum COMP for OA patients increases with age and severity. Positive correlation between serum COMP level with each of SF COMP level and the severity of disease.

Gheita *et al*., 2015 concluded that COMP level in the serum or SF reveals a degree of joint destruction in OA patients. Furthermore, COMP level has potentially reliable diagnostic markers in early diagnosis of joint damage and can be monitored for predicting rapid treatment starting with early-stage patients and monitoring the response to various therapeutic methods. COMP levels in the serum or SF reflect the severity of disease.[16]

Moreover, Arellano *et al*., 2017 showed that KOA patients have a positive correlation between the levels of COMP SF and the levels of COMP serum, age, and sampling daytime; further, the high level of COMP is only in the female SF of patients. Arellano *et al*. concluded that these results may propose a promising role for serum and SF COMP as a measure for primary knee OA.[43]

Martadiani *et al*., 2017 showed that the level of serum COMP for OA patients higher than health about 5.5 times and concluded that elevated the level of COMP might reveal progression of joint matrix turnover or damage.[57]

Zhang, 2018 also found that the high level of COMP in the serum of OA patients is associated with the incidence of KOA disease and concluded that patients with a higher level of COMP serum have a greater chance of developing KOA.[91]

Hamodat and AL-Ashou[92] showed a higher level of serum COMP for OA patients in compression with the level of serum COMP; the COMP level in the SF of OA patients is also higher than the COMP level in their serum. Furthermore, the high level of COMP is in the SF of female OA patients, and the level of serum COMP increases with age and severity of the disease. They concluded that the COMP level could be a biomarker of the extent of damage to the cartilage joint, which could be used as a diagnostic tool to determine the degree of the disease as well as monitor the effect of treatment.[92]

Differences in findings could be the majority of these studies performed with a size sample and did not detail the patient's appearance and medication. However, despite many studies, it remains unclear whether the COMP level is sufficient to diagnose OA patients?

## Conclusion

Through our reviewer, we could draw a conclusion; it was possible to say that COMP could be considered as a biomarker for the diagnosis and monitoring of OA patients. Further, it is possible to adopt the COMP level as a diagnostic biomarker preradiography as well as possible to adopt the level of COMP as indication of the diagnosis of the severity of the disease.

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### Conflicts of interest

There are no conflicts of interest.

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