Chapter 1

Cartilage Oligomeric Matrix Protein (COMP) As a Candidate Biomarker in Osteoarthritis

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Abstract

Biomarker research aims to provide better diagnostic and prognostic tools, potentially leading to improved treatments for the condition. Biomarker research in osteoarthritis is a field of study focused on identifying and understanding specific molecules, genes, or other measurable indicators that can help diagnose, predict, and monitor the progression of osteoarthritis. These biomarkers can be found in blood, synovial fluid or urine. Osteoarthritis is a degenerative joint condition that causes pain, stiffness, and limited movement due to the breakdown of cartilage in the joints. There are a significant number of studies investigating possible biomarkers which may be useful in the diagnosis and prognosis of osteoarthritis. These biomarkers are included in the groups of synthesis and degradation of bone/cargilage/synovium, inflammation, metabolic parameters and microRNAs. In this book chapter, we aim to focus the current status of studies about cartilage oligomeric matrix protein, which is an indicator of cartilage degradation. When we evaluate the current literature findings, we can say that cartilage oligomeric matrix protein may be a promosing biomarker for the diagnosis of osteoarthritis, but there is not sufficient data for the role of cartilage oligomeric matrix protein in the prognosis of osteoarthritis.

1. Osteoarthritis

Osteoarthritis (OA) is a very common type of age-related, injury-related joint degenerative disorder [1]. The most prevalent type of arthritis worldwide is OA, frequently seen in the elderly population, leading to erosion

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in the joint cartilage, osteophyte formations, and subchondral sclerosis [2]. Epidemiological studies conducted in various parts of the world have reported that symptomatic knee OA is seen in 10-30% of people who are over 65 years old [2].The prevalence of symptomatic knee OA in adults over the age of 55 was found to be 13% [3]. Data from the Framingham OA study shows that the prevalence is 11% in women and 7% in men. In a prevalence study conducted in Turkey, the prevalence of symptomatic knee OA in the population aged 50 and over was 14.8%, and it was reported as 22.5% in women and 8% in men [3].

OA may be associated with obesity, type 2 diabetes, insulin resistance, dyslipidemia, hypertension and metabolic syndrome, either together or separately [4]. Today, we understand that osteoarthritis is more than just a condition where the illness is brought on by mechanical stress-induced cartilage loss, but also a pathological process that affects all tissues in the joints and causes discernible alterations in tissue structure, metabolism, and function. All these changes are mediated by the complex and as yet incompletely investigated interplay of pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, and adipokines; all of these can be measured in serum, synovial fluid, and histological samples and potentially evaluated as biomarker candidates for disease staging and prognosis [5-11].

Obesity refers to the condition of body weight being higher than normal. Excessive weight on the joint surfaces can put excessive stress on the joints, which can cause wear of the joint cartilage. The risk of osteoarthritis increases significantly in obese individuals, especially in large joints such as the knee and hip joints. Additionally, obesity can lead to arthritis, which can trigger osteoarthritis. On the other hand, patients with osteoarthritis may limit their physical activities due to movement restrictions. This can promote weight gain and increase the risk of obesity. Additionally, patients who have difficulty maintaining an active lifestyle due to pain and stiffness engage in less physical activity, which may promote obesity [12].

Traditionally, radiological imaging techniques that corroborate clinical symptoms are used to diagnose OA. However, primary OA, which develops without any macro trauma attack, begins years before radiological findings become apparent, and pathology often cannot be detected early. The course of the disease is usually slow and spreads over many years [13].

2. The Role of Biochemical Markers in Osteoarthritis

Early diagnosis of osteoarthritis (OA) remains a diagnostic challenge due to the limited signs and symptoms presented in the early stage of the disease. The use of magnetic resonance imaging (MRI) for diagnosis is limited due to cost and accessibility issues. The joint is a complex structure composed of bone, cartilage and synovial tissue. Therefore, it would be useful to use markers of these three structures when assessing how much the joint has degenerated [13]. No single biomarker has been recognized that is sufficiently validated for systematic use that can be used to aid early diagnosis. Standard laboratory procedures, such as the extremely sensitive CRP test, are unable to conclusively determine the level of disease activity in OA. Despite the fact that the quantitative CRP values may show slight increases in a patient with synovitis showing signs of inflammation, normal values are usually found. Similarly, serum levels of anti-nuclear antibodies, rheumatoid factor and complement components are normal [13].

We now understand that osteoarthritis is a condition marked not just by cartilage loss due to mechanical loading, but also a pathological process that affects all tissues in the joint and causes detectable changes in tissue architecture, metabolism and function. All these changes are mediated by the complex and as yet incompletely investigated interplay of pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, and adipokines; all of these can be measured in serum, synovial fluid, and histological samples and potentially evaluated as biomarker candidates for disease staging and prognosis [14].

A "biomarker" is a characteristic that may be tested and assessed objectively to determine if it represents diseased or normal biological processes or the pharmacological reactions to therapeutic intervention and may be represented by radiographic, histological, physiological, or molecular features. [15]. An ideal biomarker should have following features: It shouldn't be impacted by illnesses that aren't related to the system it belongs to; analysis shouldn't require pricey equipment, and interpreting the biomarker's results should be simple, its quantity shouldn't vary significantly among the broader population. Unfortunately, there is currently no osteoarthritis biomarker that has all of these features.

The Osteoarthritis Biomarkers Network developed a five-point classification scheme called BIPED (burden of disease, investigative, prognostic, efficacy of intervention, and diagnostic) to help provide a common framework for communication amongst researchers in the field of osteoarthritis biomarkers [5]. As a result, an individual with and without

osteoarthritis can be distinguished using a "diagnostic" biomarker that has good positive and negative likelihood ratios (sensitivity and specificity) as well as an area under the curve in the receiving operator curve. Whereas a "prognostic" biomarker forecasts the development of osteoarthritis in those who already have the condition or its advancement in those who do not, a "burden of disease" biomarker evaluates the severity of the disease in people who already have osteoarthritis. In order to assess risk in people without obvious illness, predictive biomarkers may be utilized.

Currently investigated biomarkers of osteoarthritis can be summarized in the following groups [16]:

- Biomarkers of synthesis and degradation of bone
- Biomarkers of synthesis and degradation of cartilage
- Biomarkers of synthesis and degradation of synovium
- Biomarkers of systemic inflammation
- Biomarkers related with obesity and metabolism
- microRNAs related to osteoarthritis

In this book chapter we will focus on one of the degradation biomarkers of cartilage, namely Cartilage Oligomeric Matrix Protein (COMP).

3. Cartilage Oligomeric Matrix Protein (COMP)

Cartilage oligomeric matrix protein (COMP) is a non-collagenous extracellular matrix glycoprotein that is mostly present in the human skeleton system, including articular cartilage, meniscus, ligaments, tendons, and synovium [17, 18]. It is a member of the thrombospondins (TSPs) family, commonly referred to as TSP-5. Additionally, vascular smooth muscle cells, the heart, and the eye's vitreous all express COMP [19]. Moreover, bodily fluids may include COMP and its particles. In the typical population, serum and synovial COMP levels are roughly 5.93 ± 1.95 μg/mL [20] and 33 ± 10 μg/mL [21], respectively.

Apart from osteoarthritis, the role of COMP in other diseases including skeleton diseases, rheumatoid arthritis, malignancies, cardiovascular diseases, fibrosis and some other diseases is a current research topic and there are promising results [22].

COMP is the most well-known cartilage degradation marker and the closest to being a biomarker in osteoarthritis. Although the main source of COMP is cartilage, COMP can also be synthesized by synovial cells, tendon

fibroblasts and osteoblasts. Therefore, an increase in COMP levels may indicate cartilage degradation as well as synovial inflammation. Increased COMP levels are associated with osteoarthritis, as both conditions have a role in the etiopathogenesis of osteoarthritis. Here, we will summarize the recent literature findings of COMP related to osteoarthritis. We can say that although most of the studies have reported higher levels of COMP in osteoarthritis patients, serum COMP measurement was not a reliable indicator of the prognosis for osteoarthritis, according to some research.

3.1. Studies reporting a relationship between COMP levels and osteoarthritis

The clinical usefulness of COMP has been suggested and evaluated in a few studies because of its roles in inflammation and cartilage deterioration. In a study conducted on 56 patients with primary osteoarthritis and 31 healthy controls it was reported that COMP levels were higher in patients with osteoarthritis and the researchers have concluded that COMP levels may reflect structural damage of the knee [23].

Measuring serum COMP levels has the potential to be useful in both OA diagnosis and disease progression prediction [24].

A study by Sharif et al. included 115 participants who had osteoarthritis (OA) of the knee. At the conclusion of the study, serum COMP levels were assessed at baseline and every six months, along with radiographic cartilage loss at 0, 24, 36, and 60 months. It was discovered that the COMP level was linked to progressive joint degradation [25].

Individuals suffering from primary knee OA symptoms (KL stages I–III) and met ACR criteria were included in a study and blood COMP levels were tested at the onset of the trial and three years afterwards. It was discovered that the COMP assessment might function as a possible predictor of the course of the disease [26].

Investigating COMP levels related with exercise in osteoarthritis patients is a current research topic. One study has reported that walking for thirty minutes can raise serum COMP levels in both knee OA patients and healthy age-matched controls [27].

Regardless of age or BMI, high serum COMP values were linked to an increased risk of incident knee OA [28]. Radiographic knee OA development has been linked to high concentration of COMP [29].

Due to the conflicting results of some studies and the concern about whether COMP is a valid biochemical measure, the first meta-analysis

(2019) was conducted thoroughly on 35 human research [30]. According to this meta-analysis, COMP performed moderately well in predicting the course of OA and differentiating between patients with knee or hip OA and control subjects. The study's size and diagnostic criteria had no discernible impact on the performance. Additionally, subgroup analysis revealed that serum COMP was more effective in males than in females, and that synovial fluid performed better for COMP than serum [30]. Obtaining synovial fluid in early OA may be challenging, despite the meta-analysis's conclusion that COMP performs best in synovial fluid.

Another meta-analysis was conducted to investigate the usage of serum COMP as a biomarker for knee OA and its correlation with the severity of the disease. Meta-analysis was performed on selected 9 controlled studies which had been used Kellgren-Lawrence (K-L) classification for knee OA and included data of serum COMP in OA patients and healthy controls. Nine studies were pooled, and the results showed that patients with knee OA had significantly higher serum COMP levels than controls (SMD 0.81, [95% CI, 0.36, 1.25], P = 0.0004). All three categories, with the exception of K-L grade 1 versus control, showed noticeably increased serum COMP when compared to K-L 1-4 and controls. Patients with more critical illness stages had considerably greater serum COMP levels than those with less serious disease stages, according to comparisons between K-L grades 1-4. When compared to K-L grade 1 patients, the elevation in patients with K-L grade 3 did not, however, reach statistical significance. Overall analysis revealed that knee OA patients had considerably greater blood COMP than controls, suggesting that serum COMP may be useful in distinguishing knee OA patients from healthy individuals. The statistic of the meta-analysis demonstrated that serum COMP levels were useful in differentiating between patients with K-L $\geq$ 2 [31].

For early OA, COMP might be a promising biomarker. Results have shown that there exists a possibility for COMP to function as a diagnostic and prognostic indicator, as well as an indicator for the effectiveness of interventions in knee OA [32].

3.2. Studies reporting no relationship between COMP levels and osteoarthritis

In a study conducted by Yıldız et al. the relationship of COMP levels with radiographic and clinical findings of knee osteoarthritis was investigated. Researchers have found that serum COMP and MMP-3 (levels did not significantly change across groups with varying radiographic stages of knee

osteoarthritis, nor did they differ in clinical criteria such as pain intensity and functional status in daily activities [33]. However, we have to mention that this study has a limitation that the lack of a control group.

A specific group of biochemical biomarkers (18 biomarkers) was studied by Kraus et al. as potential indicators of the clinically significant development of osteoarthritis (OA). According to the findings, researchers have reported that measuring serum COMP does not serve as a reliable predictor of deteriorating knee OA [34].

Teirlinck et al. conducted a literature review in order to determine the variables which may be predictive of hip OA patients' eventual progression. Researchers have found that there was no evidence of a relationship between the marker COMP and radiographic advancement [35].

4. Conclusion

Currently available biomarkers do not perform consistently enough to be used in clinical studies as a supplementary or supporting endpoint, as a surrogate result, nor do they discriminate well enough to help diagnose osteoarthritis or predict the prognosis of individuals with or without the disease. There is growing evidence that the most effective approach would involve combining tissue biomarkers with other measures (such radiography or MRI) into a single diagnostic test, or alternatively, a panel of biomarkers that cover the spectrum of physiological effects [36].

When evaluating different results in the literature, it is necessary to consider the strengths and limitations of the studies such as sample sizes of groups, standardization of analyse method, existence of a control group, evaluation of radiographic data. Again, it should be considered that BMI levels, sampling time, exercise status, ethnicity and gender may affect results. We have to mention that COMP levels may decrease in advanced stages of OA, most likely as a result of its depletion in severely deteriorated tissue.

Among the candidate biomarkers, COMP is one of the promising biomarkers for OA. COMP is a cartilage-resident glycoprotein and connective tissues that has been associated with osteoarthritis. Elevated levels of COMP in synovial fluid and serum can be indicative of cartilage degradation and may serve as a potential biomarker for this degenerative joint condition.

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