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RESEARCH ARTICLE

Correlation between Body Mass Index and Cartilage Oligomeric Matrix Protein Levels in Woman with Postmenopausal Symptomatic Osteoarthritis

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Abstract

Background: Measurement of serum cartilage oligomeric matrix protein (sCOMP) concentration is expected to be new approach for osteoarthritis early detection. Osteoarthritis has been linked to obesity as its risk factor. This study aimed to determine relationship between BMI and sCOMP in woman with symptomatic osteoarthritis. Methods: : A cross-sectional study was done using consecutive sampling. The study population comprised of female patients age 50-70 y.o who had menopause since last 1 year and symptomatic knee arthritis. Osteoarthiris were comfirmed by genu imaging. sCOMP concentration were determined in Clinical Phatology Laboratorium of Sanglah Hospital using ELISA technique. The body mass index was calculated using the standarized formula. Correlation test was used to determine the correlation between body mass indexes with sCOMP level. Results: From total of 68 participants, the mean age was 73.66 (SD 9.356), the mean BMI was 21.97 (SD 4.66), and the mean sCOMP concentration was 7.935 (SD 10.11). Significant correlations ($p < 0.01$) occured for this sample. However, Spearman's rho was quite low ($r = -0.382$), indicating only weak correlations. A higher BMI was associated with lower sCOMP concentration. Conclusion: The results prove the relationship between BMI and sCOMP concentration. Further research is needed to reveal causality between both variables.

Keywords: *Osteoarthitis, Women, BMI, sCOMP concentration.*

Introduction

Osteoarthritis is a chronic inflammatory joint disease that is often overlooked in the early stage of the disease but may present potentially severe morbidity in later stages. The early development of the disease is often asymptomatic; thus, early diagnosis is difficult for most patients. Various methods for early detection have been developed to prevent severe morbidities; one of them is measurement of serum cartilage oligomeric matrix protein (sCOMP) concentration.

Osteoarthritis (OA) results from permanent joint damage, which manifests pathologically by cartilage destruction, osteophyte formation, and joint space narrowing [1]. This condition is a major source of chronic disabling pain of older individuals, which is much more prevalent than rheumatoid arthritis or any other form of arthritis [2]. The incidence of OA in general population reaches 10% of the female population. In Spain, approximately 46% of women aged 45 years or more reported OA complaint, which costs around 4.7 million Euro each year [3]. As the older population increases, the incidence of OA rises accordingly. Early detection is needed to prevent severe degeneration and decrease the need for more expensive management. Until now, no definite method can be used to detect OA at the preclinical or subclinical stage.

Bone and cartilage biomarkers, such as sCOMP have been reported by many researchers to show changes, even before clinical or radiologic manifestations can be noted [4]. Obesity has been linked to OA as one of its risk factor. It was reported that individuals with obesity had an OA risk of 1.5 to 2 times higher than non-obese. Every 5 kg/m^2 increase in body mass index (BMI) is associated with an increased risk of OA by 32% [5].

Until now, not much has been known about the relationship between BMI and sCOMP level in women with symptomatic OA.

Materials and Methods

This cross-sectional study was approved by the Ethics Committee of the Medical Faculty Udayana University/Sanglah Hospital before the study was conducted. Written informed consentobtainment preceeded the enrollment of participants. We included female patients age 50-70 years old from our outpatient clinic who has symptomatic osteoarthritis in knee. Those female that enrolled in our study had menopause since last 1 year. Osteoarthritis were confirmed by x-ray examination of genu.

Exclusion criteria for the study were as follows: (a) patients who had hormonal therapy, (b) had history of knee sugery, (c) on going corticosteroid treatment, (d) history of bilateral ovariectomy, (e) had malignancy disease, and (f) had osteoarthritis in other part but knee. All participants went through a standardized examination to obtain their weight, height, and sCOMP concentration. The objective measurements were taken from the participants by weighting them on a calibrated personal scale, measuring their height with a stadiometer and sCOMP concentration were determined in Clinical Phatology Laboratorium of Sanglah Hospital using ELISA technique. The body mass index was calculated using standardized formula from participant' height and weight. Kolmogorov Smirnof test were used to determain data distribution and Spearman correlation test were used for corelation analysis. We evaluated correlation coefficient with 95% confidence intervals (CI), and the *p* values. The data was then analyzed statistically using the SPSS software, version 20.0. *p* values (*p*) of <0.05 were considered significant.

Results

A total of 68 participants with knee osteoarthritis were recruited and eligible for study inclusion. The mean age of the sample was 73.66 (SD 9.356) and ranged from 50 to 90 years. The mean BMI was 21.97 (SD 4.66) and ranged from 14.20 to 37.20. The mean sCOMP concentration was 7.935 (SD 10.11) and ranged from 1.70 to 81.68. The median of age at menopause was 51 years and ranged from 41-53 years.

Table 1: Subject characteristics

Characteristics	
Age (Mean ± SD)	73.66 ± 9.35
Body Mass Index (Kg/m2) (Mean ± SD)	21.97 ± 4.66
sCOMP consentration (Mean ± SD)	7.93 ± 10.11
Age at menopause (years) (Median-IQR)	51 (44-53)

Table 2: Correlation between sCOMP with body mass index

Variable	sCOMP
Body Mass Index	
r (coefficient correlation)	-0.382
p	0.001
n	68

To assess the significance of correlations, Spearman's rho was calculated for bivariate correlation between BMI and sCOMP concentration. Results are displayed in Table 2. Significant correlations (p<0.01) occured for this sample. However, Spearman's rho was quite low (-0.382), indicating only weak negative correlations. The correlation between BMI and sCOMP concentration was notable negative, means higher BMI will contribute to lower sCOMP concentration and vice versa.

Discussion

Beside spine and hip, knee osteoarthritis is the most common disease affecting aging adult's joint [4].

Increasing number of ageing population has resulted in exponential increase in number of patients with symptomatic knee OA, which number was estimated to be more than 25 million in the United States and 8 million in Japan [5]. OA diminishes quality of life related to health and is one of the top five sources of nonfatal health burden, responsible for disability on 3% of total living years [6, 7]. The Osteoarthritis Research Society International (OARSI) has published new definition of OA:

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that

activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness". Numbers of factors have been accounted for the progression and pathogenesis of OA, some of which are bone shape and joint dysplasia, obesity, synovitis, complement proteins, inflammatory mediators, aging, innate immunity, low-grade inflammation induced by metabolic syndrome and diabetes mellitus [2].

Clinical presentation is usually used as the basis of diagnosis of this disease, along with radiographic examination, but without the need of laboratory examination. Previous study has shown there are only few clinical correlations between knee pain on osteoarthritis and the degree of osteoarthritis severity on radiological examination, thus showing no correlation between them [4]. Also in another research, it is shown that radiographic severity doesn't correlate with molecular changes in OA, resulting in difficulties on prediction of disease progression, in aspects such as cartilage degradation, joint space narrowing, subchondral sclerosis, osteophyte formation, and abnormalities on bone marrow [4]. Early pathological changes occur in OA which take place periarticularly are not well captured using conventional radiography, however can only be captured by the costly MRI.

This resulted in the need of biomarkers, which can be used in place of MRI, to diagnose the progression of OA, to decide the management plan, to measure the therapy effectiveness, and to understand more on the disease pathogenesis. Development of markers measured from serum to be used to determine OA status would exponentially increase the ease on diagnosing the disease with less economic burden compared to the radiographic method [8]. A biomarker is an objectively measured compound that can be used to as an indicator of normal biologic, pathologic, or pharmacologic processes and responses to therapeutic interventions. It is essential on understanding the pathological pathways and diagnosing a disease, including predicting its prognosis and length of follow up [9]. Turnover process of cartilage matrix resulted in fragments of extracellular matrix molecules and other degradation products of cartilage metabolism being released into synovial fluid and then entered into blood serum in either normal and pathological joints. COMP is one of the biomarker used to detect these changes, which is degradation product of articular cartilage that can be promising to be a diagnostic modality and a prognostic marker in serum to diagnose knee OA [8]. COMP is a 524-kd pentameric glycoprotein, and part of thrombospondin family. This protein is found mostly in cartilage, beside on tendon and synovium [10].

COMP pentamer is able to bind up to five collagen molecules and retain them in close proximity. This process facilitates interaction between collagen and the formation of microfibryl. COMP production has been studied and was shown to be produced by articular chondrocyte and agreed that its level in synovial fluid is related with cartilage damage [8]. Particular cartilage and proliferative and hypertrophic chondrocytes of endochondral ossification process in growth plate abundantly express COMP, showing its correlation with the ossification process and articular cartilage development. This molecule's interaction with ECM proteins, such as collagens, chondroitin sulfate, aggrecan, matrillin, and fibronectin, will produce a bridge-like structure between these molecules reflected by its multidomain modular structure.

Its interaction with various ECM molecules has formed an integral part of ECM with cartilage; therefore, its increase is correlated with type IX collagen reduction, matrilin-3 deposition, and matrix formation reduction as well as chondrocyte death [11]. Increased serum COMP level is correlated with population who suffers from knee osteoarthritis, accompanied with insignificant gender bias, and its increase is proportional with the increase of disease severity [4]. High sCOMP level also reflects synovial inflammation in OA patients' knees, as demonstrated by one study in Bali. They found high sCOMP in 66% patients with synovial inflammation, as compared to 33% in control group. High sCOMP was proven to be a remarkable risk factor for the inflammation process of the synovium

(adjusted-OR=3, $p < 0.05$), comparable to knee OA severity (adjusted-OR=2.37, $p < 0.05$) and body mass index (adjusted OR=1.16, $p < 0.05$). High sCOMP level is correlated with increased knee OA radiographic abnormalities in middle aged woman population (OR: 1.97; 95% CI: 1.33–2.91) over 20 years [12]. African American women tend to have higher serum COMP level compared to Caucasian women (P=0.003), whereas Caucasian men tend to have higher serum COMP level compared to Caucasian women ($P = 0.0001$). Therefore, it can be assumed that the levels of serum COMP may vary depending on one's gender and ethnicity. This is possibly caused by the difference in bone density, body composition, metabolism, the size of joints, bones, cartilage, meniscus, and tendon between them.

COMP found in osteoblasts also result in the difference of osteoblastic activity and COMP expression, supporting this hypothesis [13]. Two of the most common chronic conditions affecting people aged 50-84 years old are obesity and knee osteoarthritis [7]. Obesity has been long known as one of the risk factors in osteoarthritis development, ant the correlation between them has been well-documented. However, speculations have been raised whether obesity gives the greatest impact for the development of knee osteoarthritis. Grotle et al reported that a high BMI (> 30) was significantly associated with knee (OR 2.81; 95%CI 1.32–5.96) and hand OA (OR 2.59; 1.08–6.19) in a dose-response relationship [14]. High BMI also increases the likelihood of having more severe activity-limiting OA (RR 2.3; 95% CI, 1.68-315) in Norwegian population [15].

Meta-analysis shows that the risk of knee OA increase with BMI and a dose-response relationship exist. A 5-unit increase in BMI is significantly associated with an increased risk of developing knee OA (RR: 1.35; 95% CI: 1.21, 1.51). That is, every 5-unit increase in BMI is associated with a 35% increased risk of knee OA [16]. One study involving a very large cohort found that overweight and (grade I, II) obesity increased knee OA risk by a factor of 2, 3.1 and 4.7-fold respectively [17]. Body weight reduction decreases the risk of OA by 5% in China and by 50% in United States, depending on the prevalence of obesity and overweight [18].

Although obesity has been repeatedly confirmed as a risk factor for knee osteoarthritis, there was no overall association between obesity and the actual progression of knee osteoarthritis [19]. Grotle et al reported that a high BMI (> 30) was statistically significant in association with knee (OR 2.81; 95%CI 1.32–5.96) and hand OA (OR 2.59; 1.08–6.19) in a dose-response relationship [14]. High BMI also increases the likelihood of having more severe activity-limiting OA (RR 2.3; 95% CI, 1.68-315) in Norwegian population.[15] Meta-analysis study shows knee OA risk is increasing accordingly with BMI and a dose-response relationship does exist.

It is found that a 5-unit increase in BMI is significantly associated with an increased risk of developing knee OA (RR: 1.35; 95%CI: 1.21, 1.51). In other words, every 5-unit increase in BMI is associated with a 35% increased risk of knee OA [16]. One study involving a very large cohort found that overweight and obesity (grade I, II) was increasing the risk of knee OA as much as 2, 3.1 and 4.7-times respectively [17]. Body weight reduction decreases the risk of OA by 5% in China and by 50% in United States, based on the prevalence of obesity and overweight [18]. Although obesity has been repeatedly proven and widely accepted as a risk factor for knee osteoarthritis, there is still no precise association between obesity and the factual progression of knee osteoarthritis [19]. Our study shows low correlation between BMI and sCOMP but in contrary trend. To our knowledge, there is no other study in concordance with our result.

However, previous studies failed to show persistent result with regard to this relation. In prior study by Jordan et al, 17-C10 COMP levels, measured with inhibition ELISA using single monoclonal antibody, were proven to have no correlation with obesity, which was defined as BMI > 30 kg/m^2, and with BMI itself. But in their recent work, there are a statistically significant association of BMI with sCOMP levels [13]. Another study found that age (r=0.35; P<0.0001) is positively correlated with sCOMP, while no identified correlation with BMI (r=0.03; P=0.691) or gender (P=0.326), and these relationships are shown in all multivariable models [20]. Both sCOMP level and BMI have been studied as risk factors or predictive marker for subclinical or radiographic OA, but their

relationship has not been studied much in studies [21].Although, some studies relate high sCOMP with higher BMI in positive fashion [22]. Previous study has shown that gait and joint biomechanics are altered in obesity with significant evidence, but without necessarily increasing joint loads or torques magnitude. Mechanical factors such as altered loading of joints are one of the most critical risk factor of joint degeneration. Other than that, low-grade chronic systemic inflammation has also been linked with obesity [23].

Mechanical attrition in osteoarthritis (OA) is supported by the focal nature of the joint pathology, slowly progressive changes, and time dependency. When joint disease is associated with imperfect anatomy or malalignment, these geometric aberrations generate locally high stresses and promote subluxation [24]. However, we were not matched our sample for this mechanical factors.

Further study should evaluate this mechanical factors and establish better multivariate analysis in order to make preventive approach for obesity population [25]. Potensial limitations of this study are its cross-sectional design rather than longitudinal follow up and relatively small number of participants who included in this study.

The revealed relationship cannot confirmed as predictors over time. Moreover we used only composite BMI that do not adequately reflect correlation between extreme BMI score with sCOMP concentration. In addition knee osteoarthritis were not further classified, so we were not able to asses both variables contribution to the severity of osteoarthritis. The samples also taken only at one centre. This limit the comparison with data collected in hospital settings or majority population. Thus, generalization of these results need to carefully looked.

Conclusions

Our results confirm that BMI and sCOMP concentration were related in one and another way. More research with larger sample and further longitudinal research is needed to identify this relationship while confirmed consistency of previous studies.

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