LITERATURE REVIEW

Relationship between the Serum Cartilage Oligomeric Matrix Protein Concentration and Degree of Knee Osteoarthritis Pain in Elderly Patients at the Public Health Service Clinic

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ABSTRACT

Background: Elderly population in Indonesia is increasing in every year, affecting the prevalence of knee osteoarthritis (OA). OA is a major health problem for elderly, exerting a profound socio-economic impact and quality of life. This condition can result in lower productivity and higher health cost in both developing and developed countries. Therefore, we sought to investigate the relationship between the serum concentration of Cartilage Oligomeric Matrix Protein (COMP) and the degree of osteoarthritis pain in elderly patients.

Methods: A cross-sectional sampling technique was employed, involving 146 respondents (40 males and 106 females) aged >60 years with knee OA. The Western Ontario and Mcmaster University Osteoarthritis Index (WOMAC) scale was used to assess the dependent variable, i.e., degree of osteoarthritis pain. The independent variable was the COMP serum value on a numerical scale. This study utilized secondary data obtained from research conducted from January 2017- January 2018 at KPKM Reni Jaya UIN Syarif Hidayatullah Jakarta.

Results: There is a significant relationship in the increase in COMP serum concentrations in individuals aged 65-85 years compared to those aged 45-64 years (p=0.0001). However, no significant changes in COMP concentration within gender (p=0.4) was found. The result indicates no significant relationship between pain degree and age (p=0.110) or pain degree and gender (p=0.585).

Conclusion: There is significant relationship between the concentration of COMP and the degree of knee OA pain in the elderly

Keywords: cartilage olligomeric matrix protein (comp), osteoarthritis (oa).

ABSTRAK

Latar belakang: Populasi lanjut usia di Indonesia semakin meningkat setiap tahunnya sehingga mempengaruhi prevalensi penyakit Osteoartritis lutut (OA). OA adalah masalah kesehatan utama bagi populasi lanjut usia, yang memberikan dampak sosial-ekonomi dan kualitas hidup yang besar. Kondisi ini dapat mengakibatkan rendahnya produktivitas dan tingginya biaya kesehatan baik di negara berkembang maupun maju. Studi ini bertujuan untuk menyelidiki hubungan antara konsentrasi serum Protein Matriks Oligomerik Tulang Rawan (COMP) dan derajat nyeri osteoartritis pada pasien usia lanjut.

Metode: Metode pengambilan sampel adalah metode potong lintang atau *cross-sectional,* melibatkan 146 responden (40 laki-laki dan 106 perempuan) berusia >60 tahun yang menderita OA lutut. Skala Western Ontario dan Mcmaster University Osteoarthritis Index (WOMAC) digunakan untuk menilai variabel terikat, yaitu derajat nyeri osteoartritis. Variabel independennya adalah nilai serum COMP pada skala numerik. Penelitian ini menggunakan data sekunder yang diperoleh dari penelitian yang dilakukan pada bulan Januari 2017-Januari 2018 di KPKM Reni Jaya UIN Syarif Hidayatullah Jakarta.

Hasil: Terdapat hubungan yang signifikan terhadap peningkatan konsentrasi COMP serum pada individu usia 65-85 tahun dibandingkan dengan usia 45-64 tahun (p=0,0001). Namun, tidak ditemukan perubahan signifikan pada konsentrasi COMP berdasarkan jenis kelamin (p=0,4). Hasil penelitian menunjukkan tidak ada hubungan yang signifikan antara derajat nyeri dengan usia (p=0,110) atau derajat nyeri dengan jenis kelamin (p=0,585).

Simpulan: Terdapat hubungan yang bermakna antara konsentrasi COMP dengan derajat nyeri OA lutut pada lansia

Kata kunci: cartilage olligomeric matrix protein (comp), osteoarthritis (oa).

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INTRODUCTION

Population aging is increasing every year in Indonesia. According to the World Health Organization (WHO), there is a projected 414 percent increase in the number the number of older adults b 2025 compared to 1990.[1] This demographic shift potentially affects the prevalence of radiologically visible knee osteoarthritis (OA). The prevalence rates stand at 15.5 percent for men and 12.7 percent for women aged 40-60.[2] Due to its high prevalence and chronic-progressive nature, OA exerts a significant socio- economic impact, both in developing and developed countries.[3-4] Literature

states that OA affects the productivity of human resources and the entails substantial costs of the affected individuals. Patients with OA experience lower productivity and higher health costs.[5-8] A study conducted at the Rheumatology clinic of Hasan Sadikin Hospital in Bandung revealed that out of 1297 patient cases, 74.78 percent were attributed to OA cases. The lifetime risk of developing OA symptoms is reported to be 40 percent for men and 7 percent of women around the age 50 and after age 70. The number of patients with OA tends to increase every year due to the increase in the population's average age.[9] The Massachusetts Health Care Organization states that approximately 100 out of 100,000 person-years suffer from OA. The radiological prevalence of knee OA in the United States, among adults aged ≥45 years, was 19.2% in the Framingham study and 27.8% in the Johnston County OA study. The National Health and Nutrition Examination Survey (NHANES III) study reported that 37.4 percent of respondents aged ≥60 years were identified to have radiological knee OA.[10]

Osteoarthritis (OA) is a joint disease that attacks millions of people globally and affects elderly patients, with approximately 13 percent of men and 15 percent of women aged ≥60 years affected.[11] There is currently no disease-modifying therapy for OA, and existing drugs to treat OA symptoms have demonstrated limited efficacy in the modern era. The multifactorial nature of OA, coupled with the absence of validated animal models, poses considerable challenges for scientists to develop new drugs. Common treatments for OA patients include acetaminophen, non-steroidal anti-inflammatory agents, cyclooxygenase 2 (COX2) inhibitors, and intra-articular hyaluronic acid steroid injections.[12] However, the long-term use of these drugs may lead to gastrointestinal side effects in chronic patients.[13]

For decades, serum Cartilage Oligomeric Matrix Protein (COMP) has been used as a marker of cartilage degradation and a diagnostic biomarker for knee OA.[14] The literature suggests that COMP serum protein concentrations reflect joint tissue metabolism, providing insight into knee deterioration. Furthermore, research findings suggest that a Moreover, research findings indicate that a 1-unit increase in serum COMP levels elevates the likelihood of radiographic progression by 15 percent.[15] Previous studies have characterized COMP levels based on age and sex, exploring the potential utility of COMP as a diagnostic biomarker for knee OA disease. COMP levels were measured by immunosorbent assay with a 17-C10 monoclonal antibody. Studies show no significant difference in COMP serum levels based on gender.[16] Other findings indicate that serum COMP has an effect on OA in elderly patients.[17-19] Against this backdrop, we sought to assess the relationship between the COMP serum concentration and the degree of OA pain in elderly patients.

LITERATURE REVIEW

Cartilage Oligomeric Matrix Protein (COMP)

The turnover or damage to the joint cartilage will release the cartilage matrix fragments and the degradation products of another cartilage metabolism into the the synovial fluid and blood serum.[20] One of the macromolecules, the Cartilage Oligomeric Matrix Protein (COMP) is an important degradation product of joint

cartilage, serving as a diagnostic marker and prognosis in the serum for the diagnosis of knee OA.[14]

Cartilage Oligomeric Matrix Protein (COMP), as a biomarker, can identify progressive joint destruction in OA resulting in joint pain.[21] Proposed COMP serum cut off point proposed by Singh et al. is divided into 3 groups, indicating that higher values correspond to more severe clinical presentation and radiological findings: Normal (up to 652.5 ng/mL), Grade 1 (up to 801.5 ng/mL), Grade 2 (up to 1100.5 ng/mL) and Grade 3 (over 1100.5 ng/mL). Several studies have found that serum COMP concentrations can serve as a prognostic marker of OA disease. Serum Cartilage Oligomeric It is an important degreasing product of joint cartilage and diagnostic marker for knee OA. The initial symptom in OA patients is often manifested in pain during activities, especially those involving loading on the affected joint. Immediate pain is commonly reported during weightlifting or activities that require significant joint movements, such as climbing stairs and sports.[15]

Cartilage Oligomeric Matrix Protein (COMP) is part of the thrombospondin family, an extracellular calcium-binding protein originally isolated from cartilage. It is a non-collagen glycoprotein with a substantial molecular weight (> 500kDa). COMP has a significant role in the normal growth and function of cartilage. Its function is believed to contribute to the stability of the extracellular matrix of cartilage by binding to collagen and other extracellular matrix components. In patients with knee OA, the serological concentration of COMP increases with disease progression. COMP levels correlate with rates of synovial proliferation and osteophyte length. A high baseline COMP value indicates a progressive course of disease in OA patients and serves as a predictor of joint damage.[16]

Osteoarthritis (OA)

In etiology, Osteoarthritis (OA) is classified into two types: primary and secondary OA. The former occurs indiscriminately with age, without a clear cause (idiopathic), and is not associated with systemic disease or local joints' changes.[13] In some cases, only a few joints (oligoarticular) are affected. This disease not only debilitates the patient's condition but also affects the patient's psychosocial well-being. OA's occurrence is influenced by risk factors, namely age, genetics, obesity, joint injury, work, exercise, anatomical anomalies, metabolic diseases, and inflammatory joint disease. The impact is also significant on comorbid conditions such as hypertension and kidney disorders.[9,22]

OA is a heterogeneous condition that causes signs and symptoms in joints related to damage to the joints' cartilage integrity and changes in the bones and joint edges. Osteoarthritis (OA) is a joint pain disease with a degenerative condition resulting in a person's physical inactivity.[10] This degeneration results from the loss of a focal area in the synovial joint articular cartilage. The patient's condition is also associated with osteophytes, subchondral sclerosis, and thickening of the joint capsule. The multifactorial causes of OA include age, mechanical, genetic, humoral, and cultural factors.[3] The main abnormality in OA is damage to joint cartilage, which can be followed by subchondral bone thickening, osteophyte growth, ligament damage, and mild synovial

inflammation, resulting in joint effusion. Despite the significant health impacts, OA remains a perplexing condition for epidemiologists due to difficult detection of main causes and the absence of cure.[11,13]

Pain is an unpleasant sensory and emotional experience and is associated with actual and potential tissue damage.[23] Pain in body parts, especially joints, along with six other criteria, indicates the occurrence of OA. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is commonly used to measure the functional activity in patients with knee OA.[24] It is an index that can be used to assess a patient's state of knee OA. It encompasses 24 parameters, including pain, stiffness, physical and social functions. Anatomical analysis can be seen in Figure 2. Histopathology and radiology of OA are not abnormalities exclusively in the articular cartilage. Multiple components are damaged in the occurrence of OA, including the peri-articular bone, synovial layer, and other supporting connective tissue. Typical structural changes associated with OA include a progressive reduction in the articular cartilage volume, an increase in the thickness of the subchondral plate, the formation of new bone at the joint margins (osteophytes), and the formation of subchondral bone cysts.[25]

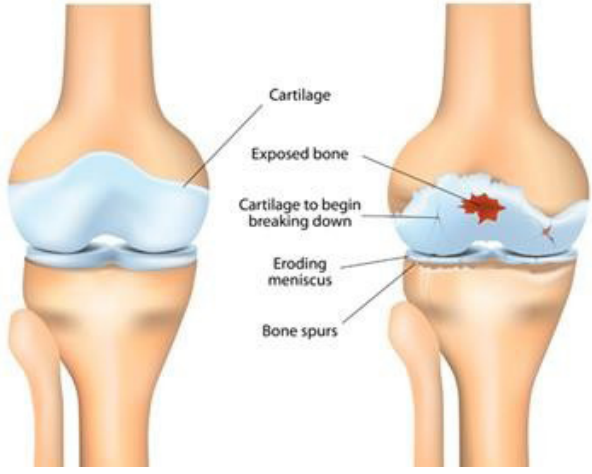

Figure 1. Differences between Normal Knee Joints and Joints with OA
Source: Netter[25]

Osteoarthritis (OA) primarily affects weight-bearing joints, such as the knees, hips, vertebrae, lumbar, and cervical joints. Among these, knee joint (Articulation Genue), is most frequently involved in OA due to its frequent use in various activities. The knee joint is referred to as the modified hinge joint because its main motion is the uniaxial hinge motion. Comprising three main components within a single synovial cavity, the knee joint plays a crucial role in supporting body weight. First, the lateral side is the tibiofemoral joint, which lies between the lateral condyles femurs, lateral meniscus, and lateral condyles of the tibia. Its function is to hold the weight on the legs. Second, the medial side is the tibiofemoral joint located between the medial condyles of the femurs of the medial meniscus and the condyles of the medial tibia. The third component is the intermediate patellofemoral joint that lies between the patella and the surface of the patella femur.[25]

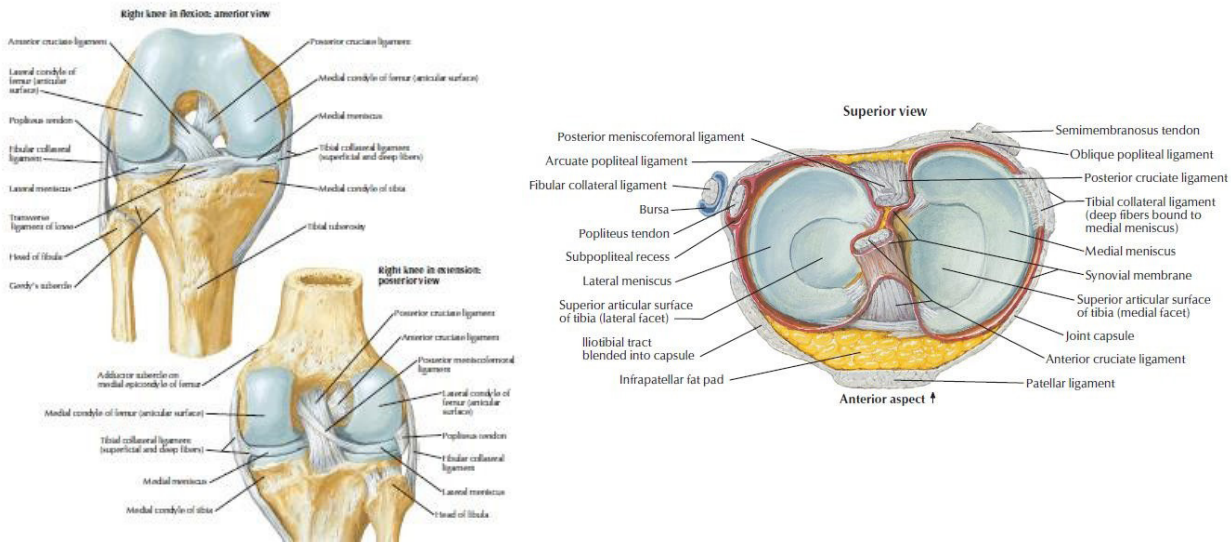

Figure 2. Anatomical Components of the Articulation Genue (Knee Joint)
Source: Kniegelenks[25]; Netter[26]

As shown in Figure 2, knee joint comprises nine components, namely: 1) the joint capsule, i.e., the outer part that connects the joint and bone; 2) the medial and lateral patellar retinaculae, i.e., tendons combined with the insertion of the M. Quadriceps femoris and the fascia lata tendons that strengthen the anterior portion of the joint; 3) the patellar ligament, which strengthens the anterior part of the joint; 4) oblique popliteal ligament, which serves to strengthen the posterior part of the joint; 5) arcuate popliteal ligament, which serves to strengthen the posterior lower portion of the joint; 6) the collateral tibial ligament that is firmly attached to the medial meniscus, repeated tearing can cause meniscus damage and anterior cruciate ligament injury; 7) the collateral fibular ligament that surrounds the lateral part of the joint serves to strengthen the lateral part of the joint; 8) The meniscus joint, which is two fibrocartilaginous discs located between the condyles of the tibia and femur, compensating for bone irregularities and the circulation of synovial fluid; 9) intracapsular ligament that connects the os tibia and the femur, consisting of two ligaments: namely the anterior cruciate ligament (ACL), which prevents knee hyperextension, and the posterior cruciate ligament (PCL), which prevents posterior sliding of the tibia during the knee flexion.[26,25]

The severity of symptoms can depend on the joint's damage, but in principle, it also varies among individuals and across different joints. Pain is the first symptom that prompts patients to seek medical examination. Pain can be felt to spread or transferred to a location far from the actual predilection location (knee pain due to OA that occurs in the hip). The onset of pain is gradual and exacerbates by activities.

Although rest initially provide relief, over time, it is not sufficient to alleviate pain. The severity of knee OA can affect the scale of the escalation of pain, supported by the theory that the presence of osteophytes causes periosteal reactions and pressure on the nerves, causing pain. Then the femorotibial joint space decreases from its normal size, increasing intramedullary pressure, which results in pain. Subchondral fractures of the joints can also cause pain.[3]

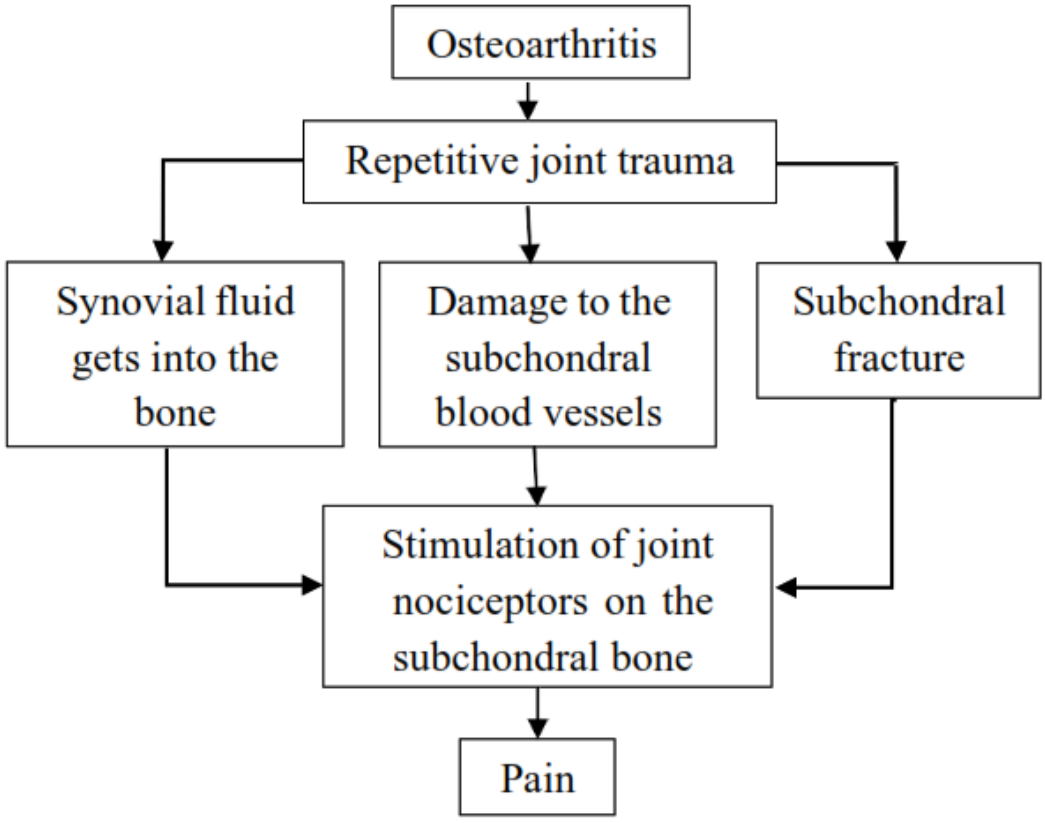

Figure 3. Pathophysiology of Pain in Osteoarthritis
Source: Antony et al.[27]; Mora, Przkora, & Cruz-almeida[28]

In patients with osteoarthritis, the pain is exacerbated by increased fibrinogenic activity and decreased fibrinolytic activity. This process causes a buildup of thrombus and lipid complexes in the subchondral blood vessels, causing ischemia and tissue necrosis. This results in the release of chemical mediators such as prostaglandins and interleukins, which can cause pain. Pain is also a result of the release of kinins, which can cause stretching of the tendons, ligaments, and muscle spasms. Pain is also caused by osteophytes pressing the periosteum and nerve roots originating from the spinal cord and increasing intramedullary venous pressure due to venous static in the trabecular and subchondral remodeling processes.[27,29]

The second symptom is stiffness, typically occurring after the patient do not engage in any activity. However, over time, this stiffness becomes persistent and progressive. In some patients, joint stiffness may develop after immobility, such as sitting in a chair or car for a long time or even after waking up. The third symptom is swelling, which can occur continuously (due to capsular thickening or large osteophytes) or intermittently (due to an effusion). The fourth symptom, the deformity, can occur due to capsular contracture or joint instability. It important to note that that the deformity may predate these conditions and may even be a risk factor for osteoarthritis in certain patients. The fifth symptom, loss of function, is the symptom most patients complain about. Usually, patients complain of imperfect gait and

tend to limp, difficulty climbing stairs, walking long distances, and a limited movement, especially in full extension.

The sixth symptom is crepitus, a sensation of something being broken or crushed reported by the patient or the examining doctor. As the disease progresses, crepitus may be audible over a distance. This symptom results from the friction between two joint surfaces when the joint is moved or passively manipulated.[30,31]

The most frequently used classification system for OA is based on radiological images of the patients' joints. Observable sign on the radiological images include the formation of osteophytes, sclerosis, and cysts.[32] The severity of OA, as viewed radiologically, can be described using the Kellgren-Lawrance scale, which is classified into four degrees (0 - 4). By comparing the patient's radiological results to radiological images of normal joints on the radiographic atlas, the degree of severity can be determined.[33] Based on the radiological image, OA can be classified in Figure 4 below:

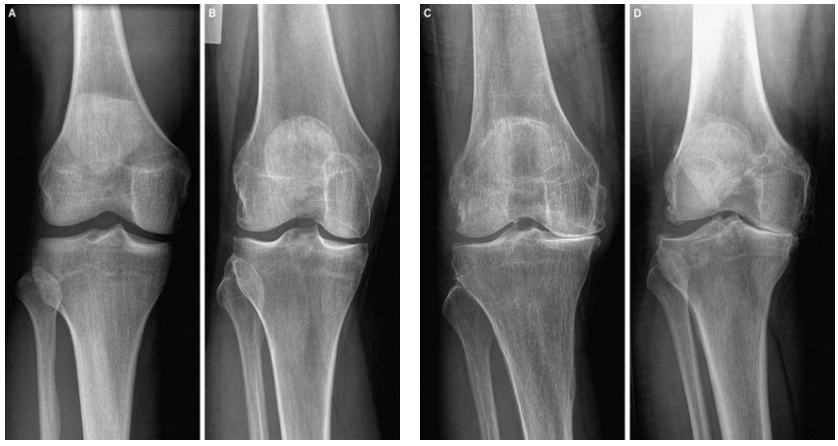

Figure 4. Radiological Features of OA Severity
Source: Kohn et al.[33]

From figure 4, a brief description is explained in table 1 below;

Table 1. The severity of OA Genu Based on Kellgren Lawrance's Radiological Overview

Rankings	Description
Level 0	There is no description of OA
Level 1	It is doubtful that there is a narrowing of the joint space, and there may be a lipping osteophyte
Level 2	There are osteophytes and possibly joint space narrowing on anteroposterior weight-bearing radiographs
Level 3	Characterized by multiple osteophytes, definite joint space narrowing, sclerosis, possibly a bone deformity
Level 4	There are many osteophytes, no joint gaps, sclerosis, severe and definite bone deformity

Source: Symmons[34]

The risk factors that contribute to OA can be divided into two broad groups: General predisposing factors and mechanical factors. The former includes age, gender, excess BMI (obesity), heredity, smoking, bone mass density, hormonal, joint weakness, and other chronic rheumatic diseases, while the latter includes trauma, joint shape, strenuous activity.[35] Individual cases may involve a combination of these factors, each potentially reinforcing the impact of the others. Notably, early risk factors for the onset of OA may differ from those influencing its progression.[9,34,36]

Joint Functional Activity using WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)

Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC) is an index used to assess the state of patients with osteoarthritis of the knee.[37]4 months and 1 year after TKA. Our hypothesis was that there is a significant influence of psychological factors on clinical outcome scores before and after TKA. Methods: A prospective, longitudinal, single-cohort study investigating the correlation of depression, control beliefs, anxiety and a variety of other psychological factors with outcomes of patients undergoing TKA was performed. A total of 104 consecutive patients were investigated preoperatively using the Beck's depression inventory, the State-Trait Anxiety Index, the questionnaire for assessment of control beliefs and the SCL-90R inventory. The Knee Society Clinical Rating System (KSS In comparison to Lequesne's index, all subscales and the total WOMAC exhibit more satisfactory internal consistency and validity. The validity of WOMAC ranges from 0.79 to 0.94, with reliability between 0.80-0.98 for knee OA. Therefore, WOMAC can be used as a research measurement tool.[38]

WOMAC assesses 24 parameters, including pain, stiffness, and physical and social functioning.[24] The obtained values indicate the patient's functional limitations, with higher values reflecting greater limitations and lower values indicating improved functional ability. WOMAC parameters include the presence of pain when walking, climbing stairs, doing activities, at night, at rest and support; the presence of clumsiness in the morning and stiffness throughout the day; and the state of the patient's physical function includes difficulties. Getting downstairs, difficulty climbing stairs, difficulty from sitting to standing, difficulty standing, difficulty sitting on the floor, difficulty walking on flat surfaces, difficulty getting in and out of vehicles, difficulty shopping, difficulty wearing socks, difficulty lying in bed, difficulty removing socks, difficulty sitting, difficulty doing heavy tasks and difficulty doing light tasks.[24]

WOMAC employs functional algorithm values obtained from questionnaires to measure pain and disability in knee osteoarthritis patients.[39] Responses are scored on a scale of 0 to 4, representing the patient's perceived state. The total score is calculated by dividing the sum of the 24 questions by 96 and multiplying the result by 100%, categorizing patients into mild (0-40%), moderate (40%-70%), and severe (70%-100%) based on their scores. A higher score indicates more significant pain and disability in knee osteoarthritis patients.[38]

METHOD

Research Design

This study employed an analytic cross-sectional design to investigate the correlation between serum concentration and the degree of knee osteoarthritis (OA) pain in elderly individuals, utilizing the WOMAC scale. The dependent variable was the degree of osteoarthritis pain, determined by the WOMAC Index. In contrast, the independent variable was the numerical scale representation of Serum Cartilage Oligomeric Matrix Protein Value.

This study was carried out in five stages: preparing for research at the Faculty of Medicine, Syarif Hidayatullah State Islamic University; conducting research licensing arrangements at the KPKM FK UIN Reni Jaya, South Tangerang; tracing patient secondary data results; Performing data collection and data analysis using SPSS, and concluding the results of data analysis. The research was carried out from March to August 2020.

Data and Samples

The data utilized in this study were secondary data derived from research conducted at KPKM Reni Jaya UIN Syarif Hidayatullah Jakarta between January 2017 and January 2018. The research focused on elderly patients aged ≥60 years, encompassing the entire eligible population of elderly individuals aged ≥60 who sought services at the public health service clinic of the Faculty of Medicine, Syarif Hidayatullah State Islamic University (UIN) Jakarta, Indonesia. A total of 146 elderly patients were selected as the sample. The sample criteria included: 1) Age ≥ 60 years; 2) symptomatic knee OA patients meeting clinical and radiological criteria; and 3) those who visited KPKM FK UIN Syarif Hidayatullah Jakarta and underwent assessment for COMP serum levels and the degree of pain based on the WOMAC index.

Table 2. Characteristics of Age and Gender of Respondents

Characteristics Respondents	Category	Frequency (n)	Percentage (%)
Age	60-69 year	107	73.3
	70-79 year	39	26.7
Gender	Male	40	27.4
	Female	106	72.6

Source: (Processed data, 2020)

The study comprised 146 respondents aged ≥60 years. Among these, 107 individuals (73.3%) fell into the category of young elderly (60-69 years), while 39 individuals (26.7%) were classified as middle elderly (70-79 years). The age distribution of the respondents ranged from 60 to 79 years, with a median age of 66 years.

Data Analysis Technique

The data were processed in four stages. Firstly, the Cleaning stage involved the removal of unnecessary data. Secondly, during the Editing stage, the data underwent scrutiny for completeness and correction of any unclear

information. Thirdly, in the Coding stage, codes were assigned to facilitate the grouping and entry of data. Finally, in the Entry stage, the grouped and coded data were compiled. This compilation process could be executed manually or through computerized data entry. Subsequently, data analysis was performed. The data were analyzed using SPSS version 25 application. The Pearson or Spearman correlation test was applied to determine the relationship between the serum concentration of COMP and the degree of WOMAC pain in elderly patients with knee OA. This test was chosen because the variables under examination are numeric in nature.

RESULT AND DISCUSSION

The results of the sample testing indicate that the majority of respondents were female, with 40 respondents (27.4%) being male and 106 respondents (72.6%) being female. Women have a higher risk of developing OA, particularly those who have entered menopause. This association is linked to the hormone estrogen, which diminishes with age. One of the functions of estrogen is to aid in synthesizing chondrocytes in the bone matrix. As estrogen levels decrease, chondrocyte synthesis decreases, leading to a reduction in proteoglycan and collagen synthesis, and an increase in lysosome activity. This is the underlying cause of osteoarthritis occurring more frequently in women. At Prof. Dr. W. Z. Johannes Kupang, the prevalence of OA was 81.8% in females and 18.2% in males. The intensity of pain is correlated with the quality of life in OA patients, where higher pain intensity corresponds to lower quality of life.[40]

The study by Kharini[41and (2 at Raden Matther Hospital Jambi revealed that the largest percentage, 48.6%, of knee OA patients were aged over 60 years. Additionally, age was found to be significantly related ($p = 0.021$) to the incidence of OA. This finding aligns with Tarigan et al.[40] research, which reported that 47.7% of OA patients at Prof. Dr. W. Z. Johannes Kupang were aged 51-60 years, while 52.3% were aged 61-70 years. Consequently, it can be concluded that age is a significant risk factor for OA, with a higher prevalence as age increases. In PKU Muhammadiyah Gamping Hospital, the incidence of OA was 78.8% in women and 21.2% in men. However, this study did not provide information regarding the relationship between sex and OA. The causes of OA are more prevalent in women than in men and are multifactorial, encompassing anatomical differences, previous trauma history, and hormonal influences.[42] The results of the Serum COMP concentration data analysis can be seen in Table 3 below;

Table 3. An Overview of the Results of the Degree of Pain Based on the WOMAC Index

	N	Maximum	Minimum	Median
COMP	146	2160.00	355.30	684.50

Source: Processed data, SPSS 25

The COMP serum concentration was assessed using ELISA in ng/ml units. In this study, the lowest concentration recorded was 355.30 ng/ml, while the highest concentration reached 2160.00 ng/ml. The mean serum concentration of COMP was 743.90 ng/ml, with a median of 684.50 ng/ml. Subsequently, a normality test was conducted utilizing the Kolmogorov-Smirnov test, revealing that the data did not follow a normal distribution (p = 0.000).

A study by Ahmed, Anuntiyo, Malemud, & Haqqi[43] established a COMP cut-off point of 1097.5 ng/ml for distinguishing OA-free patients from those with OA, demonstrating an 80% sensitivity. Additionally, a cut-off point of 1290 ng/ml was identified, providing 100% specificity for diagnosing OA in patients with radiological findings. The results of the WOMAC degree of pain analysis can be seen in table 4 below;

Table 4. An Overview of the Results of the Degree of Pain Based on the WOMAC Index

	N	Maximum	Minimum	Median
Degree of pain	146	15.00	5.00	7.00

Source: Processed data, SPSS 25

The degree of pain was assessed using a 5-point Likert scale, specifically the WOMAC Index for pain, measured in the Numeric Rating Scale (NRS) unit. The total WOMAC pain score ranges from 0 to 20 when utilizing the LK3 series.44 In this study, respondents had an average WOMAC pain index score of 7.9 NRS, with a median value of 7. The observed pain levels ranged from a minimum of 5 to a maximum of 15. Subsequently, a normality test was conducted using the Kolmogorov-Smirnov test, revealing that the data did not exhibit a normal distribution (p = 0.000).

Similarly, the normality test utilizing the Kolmogorov-Smirnov test indicated that the data for both the serum concentration of COMP (p = 0.000) and the degree of WOMAC pain (p = 0.000) were not normally distributed. Consequently, the parametric test assumptions were not met. Therefore, correlation measurement in this study utilized the Spearman test.

The data obtained highlights the relationship between COMP serum concentration and the degree of pain in osteoarthritis patients. Correlation analysis was conducted with COMP serum concentration as the independent variable and the degree of pain in osteoarthritis patients as the dependent variable. The Spearman correlation test was chosen for analysis due to the non-normal distribution of the data and the nature of the two variables-numerical ratio for COMP serum concentration and interval numeric for the degree of pain.

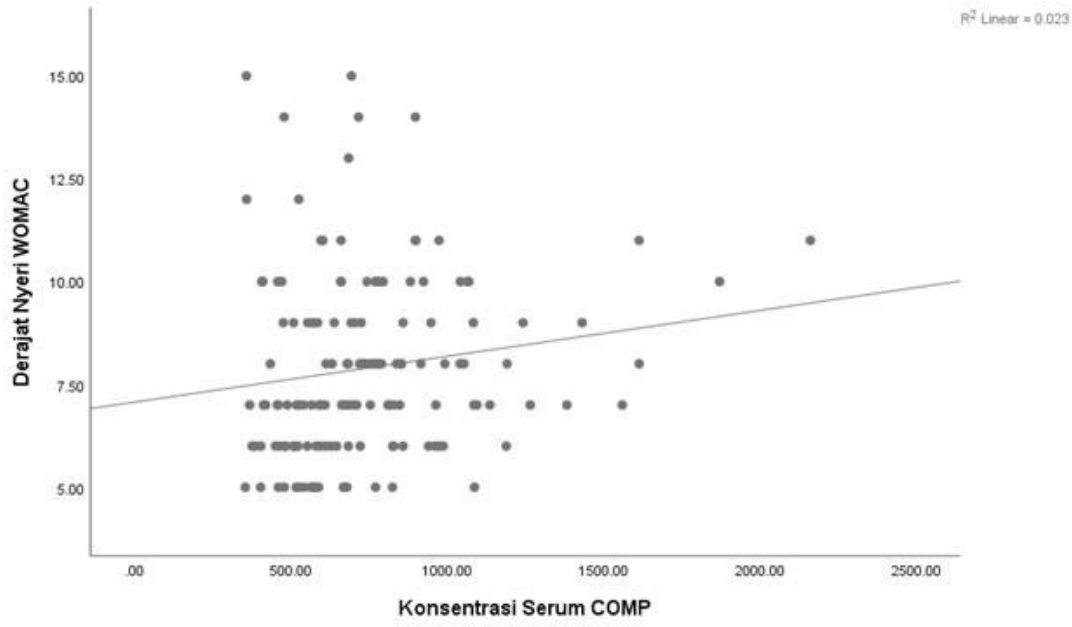

Figure 5. Correlation of the COMP Derum Concentration with the Degree of WOMAC Pain
Source: Processed data, SPSS 25

After subjecting the data to the Spearman hypothesis test, a significant association was observed with $p = 0.012$. This result indicates that the COMP serum concentration is significantly linked to the degree of WOMAC pain in patients with knee OA. To quantify the correlation between the serum concentration of COMP and the degree of WOMAC pain in OA patients, the authors employed the Spearman correlation test, yielding a correlation coefficient value of $r = 0.208$. This value signifies a weak relationship between the two variables, suggesting a direct proportional relationship-where a higher serum concentration of COMP corresponds to a higher degree of OA pain experienced by the respondent.

The findings of this study are in line with earlier research conducted by Wisłowska & Jabłońska[44], who reported a correlation between the serum concentration of COMP and the degree of pain in the Western Ontario and McMaster Universities (WOMAC) index in the lower limbs ($p < 0.005$) and the T-score of the examination densitometry ($p < 0.036$) in osteoarthritis patients. The observed relationship indicates a pathway between the serum concentration of Cartilage Oligomeric Matrix Protein (COMP) and the degree of osteoarthritis pain affecting physical function in elderly patients. An elevated level of serum COMP may trigger inflammatory mediators, leading to joint effusion as a consequence of the inflammation process in the synovium, triggered by the presence of cartilage degradation product (in this case, COMP) in the joint space.

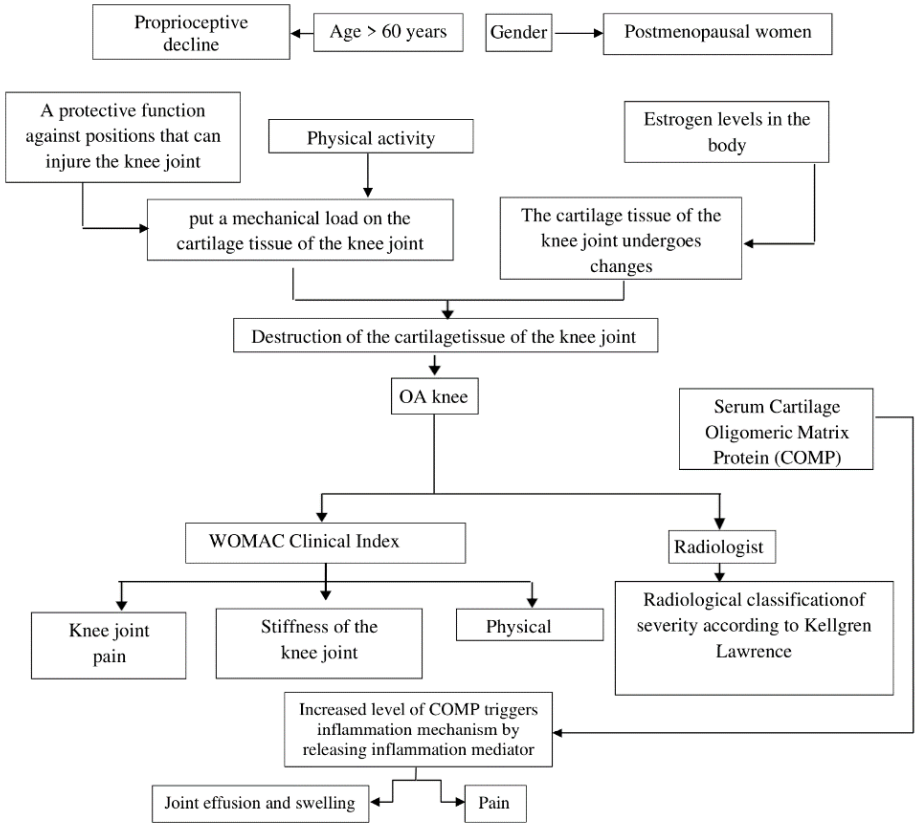

Figure 6. Relationship of COMP Affecting Pain

Researchers employed a comparative hypothesis test to further explore the relationship between various variables that may influence the serum concentration of COMP and the degree of pain. This test was specifically utilized to determine whether there were significant differences in serum COMP concentration and the degree of pain within different age and sex groups. The aim was to assess the associations between age and sex with both COMP serum concentrations and the degree of WOMAC osteoarthritis pain.

Table 5. COMP Characteristics Based on Age and Gender

COMP	Age		Gender	
	Young Elderly	Middle Aged	Male	Female
Average	698.80	867.62	772.16	733.23
Maximum	2160.00	1870.00	1870.00	2160.00
Minimum	355.30	359.00	355.30	358.50

Source: Processed data, SPSS 25

From the results of the Mann-Whitney comparative test with the tested variables, namely numerical variables and unpaired categorical variables of 2 groups with data results that were not normally distributed.

Table 6. Comp serum COMP and WOMAC pain degree by Age and Gender

Comparison	P VALUE
COMP by Age	0.003
COMP with Gender	0.400
WOMAC Pain Degree with Age	0.110
WOMAC Pain Degree by Gender	0.585

Source: Processed data, SPSS 25

Mann-Whitney hypothesis test results indicate statistically significant differences in serum COMP concentrations between the young and middle elderly groups ($p = 0.003$). This finding aligns with a study by Clark et al.[16], which reported a significant relationship indicating an increase in serum concentrations of COMP in individuals aged 65-85 years compared to those aged 45-64 years ($p = 0.0001$). Specifically, the median serum COMP was elevated in the control group of women aged ≥65 years (1249.0 ng/ml) compared to the control group of women aged <65 years (889.4 ng/ml). These results highlight a demonstrated increase in COMP serum concentrations with age. However, the hypothesis test results assessing the relationship between COMP and gender ($p = 0.4$), the relationship between WOMAC pain degree and age ($p = 0.11$), and the relationship between WOMAC pain degree and gender ($p = 0.585$) indicated no statistically significant differences.

The findings highlight a relationship between the serum concentration of Cartilage Oligomeric Matrix Protein (COMP) and the degree of osteoarthritis pain in elderly patients. However, the utility of serum COMP is confined to being a diagnostic biomarker for knee OA, as indicated by Verma & Dalal.[19] Notwithstanding, it falls short of consistently offering an effective cure for OA. Consequently, a more efficacious approach would be the early prevention of this disease.

In the public health service clinic of the Faculty of Medicine at the Syarif Hidayatullah State Islamic University (UIN) Jakarta, Indonesia, a significant proportion of patients exhibit a history of joint injuries. Some also lead unhealthy lifestyles and engage in activities that impose excessive loads on their joints. The prevalence of risk factors for depression[45] compromised health status[1], and low quality of life among the elderly population in Indonesia is notably high.[46] Consequently, it becomes imperative to implement comprehensive health management and maintenance strategies, especially considering that with age, individuals become more susceptible to various diseases. Also, advances in imaging and biochemical markers in the modernization era offer a great deal of potential for diagnosis and new treatment measures. One of them is joint maintenance interventions that include individual lifestyle modifications and pharmaceutical modalities, and surgical advice and infrastructure.[3] While some of these interventions have demonstrated progress, not all have proven effective in preventing or delaying the progression of OA.

CONCLUSION

Based on research conducted by researchers through cross-sectional analytic studies, conclusions can be drawn. First, there is a significant relationship between the serum concentration of COMP and the degree of knee OA pain in the elderly with a p-value of 0.012 and a value of r = 0.208. Second, there was a statistically significant relationship between serum COMP concentrations between the young and middle elderly groups (p = 0.003). Older adults diagnosed with OA and who have high serum concentrations of COMP are advised to continue taking medication and have a healthy and balanced lifestyle, such as eating a balanced nutritious diet and exercising diligently. Adults approaching old age are advised to actively exercise and control their weight to avoid overweight (obesity), one of the risk factors for osteoarthritis.

Given that osteoarthritis can affect the quality of life of the elderly, researchers suggest that the government develop a special health program as a prevention and management of osteoarthritis in the elderly. Despite its potential in describing OA progression, COMP serum concentration test in Indonesia is still sporadic. Therefore, it is suggested to incorporate COMP tests in all hospitals in Indonesia.

The cross-sectional analytic method employed in this study may fail to capture the long-term effects of COMP and actual pain degree on OA over time, considering that COMP serum concentrations and pain degrees may be fluctuating and the measurement was taken only once. The absence of reference values and standardization for COMP serum concentrations leads to reliance on previous studies. Pain is subjective in nature, so sometimes there is a bias between the answers given and the real situation. Additionally, pain being subjective introduces potential bias between responses and the actual situation. Subjects aged ≥60 years may experience reduced memory recall, affecting responses to WOMAC questionnaire interviews. To further investigate the relationship between COMP serum concentration and the degree of pain in OA patients, future studies are recommended to employ a cohort method.

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