Original Research Article

Degrees of Pain, Levels of Cartilaginous Oligomeric Matrix Protein, and Degrees of Kellgren-Lawrence of Symptomatic Knee Osteoarthritis in Post-Menopausal Women with Osteoporosis are Higher than Post-Menopausal Women without Osteoporosis

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ABSTRACT

Introduction: Osteoarthritis (OA) and osteoporosis (OP) belong to major health problems affecting the overall well-being and quality of life of the patient, both can occur simultaneously. Loss of subchondral bone characterizes OP and early phase of OA. Biological markers, including cartilage oligomeric matrix protein (COMP), describe this pathological process. We aim to evaluate the role of OP on OA through pain level (VAS), COMP level and Kellgren-Lawrence degree in post-menopausal women with OA.

Methods: This is a case-control study conducted in Sanglah General Hospital during March-August 2021. Consecutive sampling was performed, with study subjects being post-menopausal women aged 50-70 years old suffering from OA with or without OP. Data analysis included descriptive analysis, normality test, and hypothesis testing using independent T-test or Mann-Whitney Test.

Results: 33 subjects were involved in this study, with 11 belonged to case and 22 patients to control group. Mean age was 69,12 ± 9,103. Kellgren-Lawrence I, II, III and IV were observed in 3 (9.1%), 7 (21.2%), 14 (42.4%) and 9 (27.3%) patients, respectively. Mild VAS was observed in 17 patients (51.5%), meanwhile moderate VAS was observed in 16 patients (48.5%). High COMP level was found in 17 (51.5%) patients. Hypothesis testing revealed significantly higher COMP level in case group (p=0.042). Degree of pain and Kellgren-Lawrence degree were also significantly higher in control group, with p-value of 0.012 and 0.001, respectively.

Conclusion: Pain level, serum COMP level and Kellgren-Lawrence degree were significantly higher in post-menopausal women suffering from OA with OP compared to patients without OP.

Keywords: Osteoarthritis, osteoporosis, VAS, COMP, Kellgren-Lawrence

INTRODUCTION

Osteoarthritis (OA) is a common disease and is a chronic disease that affects all joint tissues, causes irreversible progressive damage and, eventually leads to joint failure. Pathological changes in OA include not only degeneration of joint cartilage but also thickening of subchondral bone, osteophyte formation and synovial inflammation, all of which are associated with capsule weakening and muscle strength. OA can develop in any joint, but most often hits the knees, hips, hands, and feet. In the early 1990s, more than 7 million

Americans had limitations to participate in their major daily activities, such as going to work or maintaining independence simply because of OA. In 2005, it was estimated that more than 26 million people in the U.S. had OA in various joints. The prevalence of OA varies greatly depending on the age, gender and geographic region studied. The incidence of OA in women is higher than in men, especially after age 50. Incidence rate in Massachusetts (US) 240/100,000/year for OA in the knee Joint pain is the main complaint of OA patients.[1] Over a one-year period, 25% of people over the age of 55 experience persistent episodes of knee pain. About 50% of these people turn out to have radiographic knee OA.[2] Activity-related pain in OA is common, but rest pain and nighttime pain sometimes occur, and various pain patterns are described differently by patients, from dull pain to sharp, stabbing pain.[3]

Both diseases are major public health problems that affect overall health and quality of life, especially in the elderly. Clinical experience suggests that osteoporosis and OA can occur simultaneously. The relationship between the two remains unclear, although studies have proven a common genetic link. OA and OP have a considerable link to morbidity. In the past, we only focused on the inverse relationship between OA and OP. Because both health problems often hit elderly people. However, recent research has revealed several factors that contribute to the pathogenesis of both disorders. Increased subcondral bone loss is characteristic of OP and the early phases of OA, and these findings are the rationale for the study of the drug's effects of antiosteoporosis on OA. In addition, inflammation and poor body composition are said to be factors that cause both disorders. Less weight is a risk factor for OP, while obesity stimulates the development of OA, with excessive mechanical load on weight-bearing joints.[2] Other studies on dual-energy x-ray absorptiometry (DXA) have shown that patients with OA experience increased BMD and bone mineral content.[5]

It has been observed that during the turnover of the cartilage matrix in normal joints and with abnormalities, extracellular matrix molecular fragments, and other degradation products of cartilage metabolism are released into synovial fluid and then into blood serum. One of the most widely studied biological markers to date for predicting the development of knee OA is the cartillage oligomeric matrix protein (COMP). COMP is an important degradation product of articular cartilage and can prove to be a promising diagnostic and prognostic marker. Early pathological changes in OA occur periarticly, so this condition is not well described by radiographic examination, but is seen on magnetic resonance imaging (MRI) examination. Therefore, biological markers are needed that can demonstrate OA prediction, OA management, and understanding of OA pathogenesis. If the status of OA disease can be objectively determined through serum examination, it will significantly improve the ability of early detection of the disease rather than radiographic methods.[1]

Osteoporosis (OP) is a systemic disease characterized by low bone mineral density (BMD) and microarchitecture disorders of bone tissue that result in bone fragility and the risk of fractures. (Roman-Blas, 2009). The prevalence of osteoporosis has increased significantly and will continue in the future, resulting in the prevalence and incidence of fractures will also increase. In 1990 it was projected that by 2050, the incidence of hip fractures worldwide in men would increase by 310% and 240% in women. In 2010, there were an estimated 158 million individuals with a high risk of fractures; by 2040 it is estimated that this figure will double due to demographic shifts. [4]

In accordance with the background above, research on osteoporosis and osteoarthritis has not been widely studied. Therefore, the authors wanted to know the

role of osteoporosis on the degree of pain, COMP levels, and KL degrees among post-menopouse women in knee osteoarthritis patients. This is expected to be used as a method of predicting the severity of the disease, determinants of governance, and prognosis of OA patients.

METHODS

This is a case-control study conducted in Sanglah General Hospital during March-August 2021 to determine the relationship between osteoporosis and VAS pain scores, KL degrees, and COMP levels. The population that met the inclusion criteria was then measured against serum COMP levels. The population in this study were female patients who came to the Orthopedic polyclinic at Sanglah Central General Hospital with knee OA who complained of post-menopausal pain with or without OP. The sample selection used a consecutive sampling technique where every subject who came to the polyclinic and met the selection criteria was sampled until the number of samples was met, inclusion criteria for this study is 1) patients with knee OA confirmed by plain x-ray examination of Genu AP / Lateral aged 50 - 70 years who complain of pain or women who have not menstruated for the last 10 years accompanied by Osteoporosis, 2) patients with knee OA confirmed by plain x-ray examination of Genu AP / Lateral aged 50 - 70 years who complain of pain or women who have not menstruated for the last 10 years without osteoporosis, 3) Women with Normal BMI, 4) willing to take part in research. For the exclusion criteria included are: 1) women receiving hormonal drug therapy, 2) history of knee surgery, 3) currently on corticosteroid treatment, 4) history of surgical removal of both ovaries, 5) suffering from malignancy, 6) suffering from osteoarthritis in a region other than the knee.

The data obtained in this study will be analyzed using Descriptive Analysis in order to determine the standard deviation, mean and median. Frequency distribution to describe general characteristics and variations between groups. Afterward, the research variables in the case and control groups were tested for normality with the Shapiro-Wilk test because the number of samples was less than 50 and the aim was to determine whether the research data were normally distributed or not. For numerical variables, a significance test was conducted for the data of two unpaired groups, namely the Independent T-Test for normally distributed data and the Mann-Whitney Test for data that were not normally distributed.

RESULT

This samples of this study were OA knee patients with osteoporosis. Meanwhile in the control group were OA patients without osteoporosis. VAS scoring, KL degrees, and COMP levels were checked on both groups. The distribution of the characteristics of research subjects can be seen in table 1.

Table 1. Characteristic

Variable	Total (%)	Mean ± SD
Umur		69,12 ± 9,103
VAS Score		
• 0-3 (mild)	17 (51,5%)	
• 4-7 (moderate)	16 (48,5%)	
• 8-10 (severe)	0 (0%)	
Kellgren-Lawrence Degree		
• Grade I	3 (9,1%)	
• Grade II	7 (21,2%)	850.91±349.167
• Grade III	14 (42,4%)	1121.10±375.011
• Grade IV	9 (27,3%)	
COMP		
• Without osteoporosis	15 (48,5%)	
• With osteoporosis	18 (51,5%)	

From the Shapiro-Wilk normality test, it was found that the data were normally distributed ($p = 0.123$) on the COMP level variable and VAS score variable. Meanwhile KL score variable was found that the data was not normally distributed ($p = 0.012$). T-test was used to test the significance for the data of two unpaired groups for normally distributed data. The p value at the limit of significance was 0.05. The hypothesis test used in this study is an independent t-test for the mean difference in COMP level which can be assessed (Table 2)

Table 2. Independent T-test results for the mean difference in COMP level and Vas Score

No	Variable		Group		P Value	IK 95%
			Sample	Control		
1	COMP Level	Mean ± SD	1121,10 ± 375,01	850,91 ± 349,17	0,042	-529,42 - -10,96
2	VAS Score	Mean ± SD	3,89 ± 0,96	2,87 ± 1,25	0,012	-1,8066 - -0,2379

Based on the independent t-test on the COMP level variable, significant results were found (p=0.042) which indicated that the serum COMP level in patients with postmenopausal knee OA with OP was higher than in patients with postmenopausal knee OA without OP. Significant results were also found on VAS score variable (p = 0.012) which indicated that the degree of pain in patients with postmenopausal knee OA with OP was higher than in patients with postmenopausal knee OA without OP.

Based on the Mann-Whitney test on the KL score variable, significant results were found (p = 0.001) which indicated that the KL score in patients with postmenopausal knee OA with OP was higher than patients with postmenopausal knee OA without OP. Table 3

Table 3

No	Variable		Group		P Value
			Sample	Control	
1	KL Score	Mean ± SD	3,39 ± 0,50	2,27 ± 0,96	0,001

DISCUSSION

In this study, it was found that the degree of pain in post-menopouse knee OA patients with osteoporosis was higher compared to patients with post-menopouse knee OA without osteoporosis, this was proven statistically meaningfully.

The results of our study are in line with research conducted by Takuo et al. (2010) which proves that the visual value rating scale on knee loading increased (97 + 39) in patients with post-menopouse knee OA with osteoporosis. Judging from the aspect of pain degrees with different assessments, research by Patricia G et al. (2020) also showed that there was an increase in the degree of pain in patients with OA. The parameters in this study are seen from the Pain Scale on the WOMAC index with a score of 8.29+4.88. In addition, our study also corresponds to findings in metaanalysis from 11 journals by De Rooij

et al. (2016) that found that high levels of pain were found in knees with OA (p value < 0.01). In principle, knees that experience OA will have a higher degree of pain compared to knees without OA (p value < 0.05) [6,7].

Related to the degree of pain in osteoporosis, research by Scharla et al. (2006) explained that there is an increase in pain in postmenopouse patients with osteoporosis where estrogen levels have an effect on this condition. A similar study looking for pain expression in female patients with osteoporosis explained that at the end of the study there was an increase in pain levels in every female patient with osteoporosis. This is reinforced by Peterson, in his study, that osteoporosis is a painful condition, especially if there is a pathological fracture [8,9].

Although studies explaining the direct link between the degree of pain in post-OA and osteoporosis are still few, previous studies have explained that post-menopouse patients with OA and post-menopouse conditions with osteoporosis will have a higher degree of pain compared to normal people. Therefore, from the results of our study and studies of previous literature, researchers concluded that there was an increase in the degree of pain in patients with post-menopouse and osteoporosis knee OA compared to patients with post-menopouse knee OA without osteoporosis. According to Blas et al, there is a link between estrogen and the knee joint. But at that time it could not be proven the exact role of estrogen from OA. Neogi et al found that OA will be more common in post-menopausal patients due to estrogen deficiency. Therefore, there are many studies that examine the use of estrogen replacement therapy (ERT) for the implementation of OA. One of them is xiao et al, finding quite promising results with

the administration of estrogen and selective estrogen receptor modulators. [10-12]

Cartilage oligomeric matrix protein (COMP) is commonly found in joint cartilage, and in recent studies it was found that comp expression levels can come from other structures such as ligaments, tendons, meniscus, and synovial membranes, so comp examination rates are often performed for diagnosis in the course of cases of osteoarthritis (OA). In the study by Bi, there was a significant difference in serum COMP between patients with KL grades 2-4 with healthy control (KL 2: SMD = 0.86, 95% CI, 0.09, 1.62, P = 0.03; KL 3: SMD = 1.05, 95% CI, 0.01, 2.08, P = 0.05; KL 4: SMD = 0.99, 95% CI, 0.33, 1.65, P = 0.003).[13]

A meta-analysis conducted by Bi (2018) reviewed 9 studies that provided knee KL OA degree data and had serum COMP level data in both OA and control patients. In the study conducted a subgroup evaluation to find out the relationship between serum COMP levels and the severity of OA. The results of the analysis showed a significant increase in serum COMP levels in knee OA patients compared to the control group (SMD 0.81, IK 95%, 0.36 – 1.25, p=0.0004). When compared further by kl degrees 1-4 and control groups, there were higher serum COMP levels in all three subgroups except in the KL group of 1-1 degrees versus control. Comparisons between kl degree groups showed significantly higher COMP levels in patients with more severe manifestations of OA. However, it was also observed that in OA patients OA degrees KL 3 there was no significant difference when compared to the group of OA KL patients' degree 1. Bi based on his meta-analysis concluded that measurement of serum COMP levels can effectively distinguish OA from KL degrees ≥2.[13]

Another study conducted by Kelman et al, examined COMP levels in female patients with post-menopause pelvic OA. COMP levels were found to be 13% higher compared to the group of patients who did not suffer from pelvic OA. There is a 30%

increase in the incidence of post-menopause OA in each 1 SD increase of serum COMP. However, the study found that COMP levels were only related to the development of new OA, not to the progression of OA in the study population. It is thought this is due to the condition of the release of COMP into the blood in the cartilage damage phase, which is a pre radiologic period where changes that appear in the joints have not been seen on plain photo examination.[14]

In this study researchers found significantly higher serum COMP levels in postmenopausal knee OA patients with OP than in postmenopausal knee OA patients without OP (p=0.042). COMP is a major component in the extracellular matrix of cartilage. Based on previous studies, COMP levels were observed to be significantly higher in knee OA patients with synovitis than in patients without synovitis. In addition, COMP also observed higher levels in post-menopouse female patients who received hormone replacement therapy.

The causes of osteoporosis and osteoarthritis tend to be multifactorial and have their own etiologies. Both are constitutional, influenced by the environment, mechanical trauma, and endocrine and metabolic status. In this study specifically discussed hormonal etiology, namely menopause. In this study, patients' association with post-menopause knee OA with osteoporosis was shown to be higher levels of Kellgren Lawrence. Based on studies conducted by Im et al, the radiography picture of OA which in this case is indicated by kl degrees will be higher in patients with post-menopause knee OA which is also accompanied by osteoporosis. This is in line with the hypothesis in this study. Im said osteoporosis is associated with higher degrees of OA but does not affect the acceleration of progression from the onset of OA. This is due to the dynamic balance between bone formation and bone resorption due to hormonal influences. Calciotropic hormone levels in OA patients with osteoporosis were found to be higher

than in OA patients without osteoporosis. In addition, high leptin levels in OA patients accompanied by osteoporosis in postmenopause patients are also one of the causes of the severity of knee OA.[15]

But contrary to the studies mentioned above, research conducted by Dequeker et al said that the degree of KL in postmenopause knee OA patients is no higher than that of post-menopause knee OA patients without osteoporosis. As we age, bone mass lost in OA patients tends to be lower due to lower turnover. Therefore, osteoporosis can be said to be protective against OA progression.[16]

Although the KL system has limitations, it remains widely used in clinical practice and research. Like other radiography classification tools, the KL system is ideally used with a thorough clinical examination. In addition, the application of KL on the development of the disease is still debated and less sensitive to changes.[4]

CONCLUSION

From this study the author concludes that the degree of pain in post-menopause knee OA patients with OP is higher than with post-menopause knee OA patients without OP, also KL degrees in post-menopause knee OA patients with OP are higher than in post-menopause knee OA patients without OP and Serum COMP levels in post-menopause knee OA patients with OP were higher compared to patients with post-menopause knee OA without OP.

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