THE RELATIONSHIP BETWEEN DIABETES MELLITUS AND THE SEVERITY OF KNEE OSTEOARTHRITIS BASED ON X-RAY IMAGING AT HAJI ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract

Background: Osteoarthritis (OA) is a degenerative joint disease resulting from the destruction of joint cartilage to the formation of subchondral bone and osteophytes that cause pain in the joints. According to WHO, the prevalence of OA in Southeast Asia in 2004 reached 27.4 million people. One of the metabolic disorders that is thought to be a risk factor for OA progressivity is Diabetes Mellitus (DM). Indonesia has the fourth largest number of DM patients with a prevalence of 8.6% of the total population. Current evaluation of OA is based on clinical and radiographic examinations such as X-ray, MRI, CT etc. The Kellgren-Lawrence (KL) system is a validated method to classify the severity of OA into 5 levels. Objective: To determine the relationship between DM and the severity of genu OA based on X-ray photographs at Haji Adam Malik Hospital Medan. Methods: This study used a cross sectional design. The data obtained will then be processed and analyzed with the Chi-Square test, Fisher Exact test, or Kruskal-Wallis test using a data processing program. Results: It was found that DM patients with right genu OA location amounted to 29 people (39.7%), left amounted to 13 people (17.8%), and both amounted to 31 people (42.5%). DM patients with grade 1 severity amounted to 6 people (8.2%), grade 2 amounted to 18 people (24.7%), grade 3 amounted to 25 people (34.2%), and grade 4 amounted to 24 people (32.9%). The results of the Chi-Square test found that there was a significant relationship between DM and the severity of genu OA (p<0.001). Based on Kruskal-Wallis test, there was no significant relationship between DM comorbidity and genu OA severity (p=0.636) and there was no significant relationship between OA severity and HbA1c (p=0.408). Conclusion: There is a significant relationship between DM and the severity of genu OA based on X-ray photos at Haji Adam Malik Hospital Medan.

*Keywords: **Diabetes Mellitus, Kellgren-Lawrence, Osteoarthritis, X-Ray.***

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by damage to the joint cartilage and subchondral bone, or the formation of new bone on the subchondral bone, as well as the formation of new cartilage and bone at the joint edges (osteophytes), which subsequently causes joint pain. OA is the most commonly found form of arthritis in the community, is chronic, and has a significant impact on public health issues1. OA is known to affect one-third of the population over the age of 65 and is one of the five leading causes of disability in the elderly population in the United States. According to the World Health Organization (WHO), the global prevalence of OA in 2004 reached 151.4 million people, with 27.4 million in Southeast Asia. According to WHO reports, Indonesia ranks fourth in the number of diabetes mellitus (DM) cases, with a prevalence of 8.6% of the total population, following India, China, and the United States. In Indonesia, OA is the most frequently encountered rheumatic disease. The radiologically visible prevalence of knee OA in Indonesia is 15.5% in men and 12.7% in the total population of 255 million people1-4. Various risk factors have been identified in the initiation and progression of OA, including age, gender, traumatic injury, obesity, metabolic dysfunction, as well as genetic and environmental factors.

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One metabolic disorder suspected to be a risk factor for the progression of OA is diabetes mellitus (DM). The diagnosis of DM is based on increased blood glucose levels. Currently, there are many therapeutic modalities, both pharmacological and non-pharmacological, for the management of OA, necessitating effective management recommendations for OA in Indonesia based on the latest scientific evidence1-4. The evaluation of OA is currently based on clinical examination, symptoms, and simple radiographic assessment techniques (X-ray), MRI, CT, etc. The Kellgren-Lawrence (KL) system is a validated method for classifying the severity of each joint into five levels. This classification was proposed by Kellgren and Lawrence in 1957 and was later accepted by the World Health Organization (WHO) in 1961 as the radiological definition of OA for epidemiological studies2,5,6. Based on a study conducted by Hery (2002) on musculoskeletal disorders in diabetic patients at Dr. Kariadi General Hospital, Semarang, it was found that there was a significant relationship between connective tissue disorders (extra-articular rheumatism) in DM patients and blood glucose control (HbA1c) (p = 0.037)7.

In a study conducted by Merryawan (2020) on the correlation between type 2 DM and the incidence of knee OA, it was found that there was a significant correlation between type 2 DM and the incidence of OA (p = 0.002). The study also mentioned that type 2 DM increases the risk of OA fourfold (OR = 4.32; CI 1.791-10.425)3. Based on a study conducted by Georg (2012) on diabetes as an independent predictor for OA, it was found that type II DM is a predictive risk factor for arthroplasty with HR 3.8 (2.1-6.8) (95%CI) (p < 0.001) in unadjusted analysis and HR 2.1 (1.1-3.8) (p = 0.023) after adjusting for age and Body Mass Index (BMI). In a study conducted by Maruf (2021) on the relationship between type 2 DM and the severity of knee OA, it was found that there was no significant relationship between type II DM and the severity of knee OA with a p-value of 0.828 (p > 0.05). The study indicated that there was no significant relationship between type II DM and the severity of knee OA. Based on the above explanation, it is still uncertain whether there is a relationship between DM and the severity of OA because previous studies have shown varying results. Therefore, the researchers aim to determine whether there is a relationship between DM and the severity of knee OA using X-ray with the Kellgren-Lawrence classification at Haji Adam Malik General Hospital, Medan.

METHOD

This study is an analytical research using a cross-sectional design comparing DM with the severity of knee OA based on X-ray imaging at Haji Adam Malik General Hospital, Medan. Data collection has obtained permission from the Ethics Committee for the Implementation of Health Research, Faculty of Medicine, University of North Sumatra, with the letter number 135/KOMET/FKUSU/2020. The population of this study consists of knee OA patients who have undergone X-ray examinations, with the X-ray results stored in the database. The research subjects are a portion of the population that meets the inclusion and exclusion criteria. The minimum number of research subjects required is 55 people for each group. The total number of research subjects is 110. Inclusion criteria include knee OA patients who have undergone X-ray examinations and have documented expertise.

Patients with medical records indicating a history of DM or no DM. DM patients with a BMI of 18.5-24.9. DM patients with and without comorbidities. DM patients aged 17-64 years. Exclusion criteria include patients with a history of trauma or knee joint trauma. Patients with a history of surgery on the knee joint. Patients with incomplete, lost, or inaccessible medical records. The data is secondary data from 2019-2020. The data consisted of dependent variable data (Diabetes Mellitus) and independent variables (Severity of Knee OA). After obtaining approval from the Ethics Committee of the Faculty of Medicine, University of North Sumatra, a search and data collection of knee X-ray results were conducted in the radiology database at the Radiology Department of Haji Adam Malik General Hospital, Medan. After recording the knee X-ray results, patient data and expertise results were retrieved based on the medical record numbers obtained from the previous data collection. Patients were then sorted based on the inclusion and exclusion

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criteria from the obtained medical records. Patients meeting the inclusion and exclusion criteria were included in the study subjects, and their age, gender, weight, body mass index, HbA1c levels, comorbidities, and the degree of knee OA were recorded. All obtained data were processed and statistically analyzed. Data analysis was performed using statistical software. The clinical and demographic data of the subjects, including age, gender, body mass index, OA severity, and DM history, were presented as percentages and displayed in tables. Inferential analysis was then conducted to analyze the relationship between DM and the severity of knee OA using the Chi-Square test. If the requirements for the Chi-Square test were not met, the Fisher Exact test was used as an alternative analysis.

RESULTS AND DISCUSSION

RESULTS

The research subjects were selected based on medical records from the period 2021-2022 at H. Adam Malik General Hospital, Medan. There were 258 data subjects that met the inclusion and exclusion criteria. This study aims to compare DM with the severity of knee OA based on X-ray imaging.

Table 1. Demographic Data Characteristics

Data Demografi	N	%
Age		
18-30	17	6,6
31-40	11	4,3
41-50	26	10,1
51-60	88	34,1
>60	116	45
Gender		
Male	104	40,3
Female	154	59,7
Location of Knee OA		
Right	94	36,4
Left	61	23,6
Both	103	39,9
Severity of Knee OA		
Grade 1	67	26
Grade 2	73	28,3
Grade 3	82	31,8
Grade 4	36	14
Diabetes mellitus		
Yes	73	28,3
No	185	71,7
Comorbidities		
Yes	157	60,9
No	101	39,1

In Table 1, it is observed that patients aged 18-30 years numbered 17 (6.6%). Patients aged 31-40 years numbered 11 (4.3%). Patients aged 41-50 years numbered 26 (10.1%). Patients aged 51-60 years numbered 88 (34.1%). Patients aged >60 years numbered 116 (45%). Additionally, it is noted that the number of male patients was 104 (40.3%) and female patients was 154 (59.7%). Furthermore, it is observed that the prevalence of right knee OA was 94 (36.4%), left knee OA was 61 (23.6%), and both knees OA was 103 (39.9%). It is also noted that the prevalence of knee OA

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severity was as follows: Grade 1 - 67 (26%), Grade 2 - 73 (28.3%), Grade 3 - 82 (31.8%), and Grade 4 - 36 (14%). Moreover, it is known that the number of patients with DM was 73 (28.3%) and without DM was 185 (71.7%). It is also noted that patients with comorbidities other than DM numbered 157 (60.9%) and patients without comorbidities numbered 101 (39.1%).).

Tabel 2. Demographic Characteristics of Patients with Diabetes Mellitus (DM)

Data Demografi	N	%
Age		
18-30	2	2,7
31-40	1	1,4
41-50	6	8,2
51-60	29	39,7
>60	35	47,9
Gender		
Male	21	28,8
Female	52	71,2
Location of Knee OA		
Right	29	39,7
Left	13	17,8
Both	31	42,5
Severity of Knee OA		
Grade 1	6	8,2
Grade 2	18	24,7
Grade 3	25	34,2
Grade 4	24	32,9
Comorbidities		
Yes	64	87,7
No	9	12,3

In Table 4.2, it is noted that patients with DM aged 18-30 years numbered 2 (2.7%). Patients aged 31-40 years numbered 1 (1.4%). Patients aged 41-50 years numbered 6 (8.2%). Patients aged 51-60 years numbered 29 (39.7%). Patients aged >60 years numbered 35 (47.9%). Additionally, it is observed that the number of male patients with DM was 21 (28.8%) and female patients with DM was 52 (71.2%). It is also noted that the prevalence of patients with DM and right knee OA was 29 (39.7%), left knee OA was 13 (17.8%), and both knees OA was 31 (42.5%). The prevalence of knee OA severity among patients with DM was as follows: Grade 1 - 6 (8.2%), Grade 2 - 18 (24.7%), Grade 3 – 25 (34.2%), and Grade 4 - 24 (32.9%). Additionally, it is known that the number of patients with DM and comorbidities was 64 (87.7%) and patients with DM without comorbidities was 9 (12.3%).

Tabel 3 Distribusi Data Demografi Pasien DM

Data Type	Mean	+SD	Median	P value
Pasien DM				
Age	61,54	11,16	61	0.117[a]
HbA1c	8,46	1,89	8	<0,001[a]

[a]Uji Kolmogorov-Smirnov

Based on the normality test results above, it is known that the age data in patients with DM is normally distributed, while the HbA1c data is not normally distributed. Data is considered normally distributed if the p-value of the normality test is >0.05 and considered not normally

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distributed if the p-value of the normality test is <0.05. In this study, the average (standard deviation) age data is 61.54 (11.16) years and the HbA1c data is 8.46 (1.89)%.

Tabel 4. Results of the Test for the Relationship Between Diabetes Mellitus (DM) and the Severity of Knee Osteoarthritis (OA)

Diabetes Mellitus	Derajat								Total		p-value
	1		2		3		4				
	f	%	f	%	f	%	f	%	f	%	
Ya	6	2,33	18	6,98	25	9,69	24	9,3	73	28,29	
Tidak	61	23,64	55	21,32	57	22,09	12	4,65	185	71,71	<0,001[b]
Total	67	25,97	73	28,29	82	31,78	36	13,95	258	100	

[b]Uji Chi-Square

Based on Table 4, it is evident that the proportion of respondents experiencing DM is lower (28.29%) compared to non-DM patients (71.71%), with the most common severity being Grade 3 (31.78%) and the least common being Grade 4 (13.95%). Furthermore, there is a significant association between DM and the severity of knee OA (p < 0.001).

Tabel 5. Results of the Test for the Relationship Between DM Comorbidity and the Severity of Knee OA

Jenis Data	P-value
DM Comorbidities Severity of Knee OA	0,636[c]

[c]Uji Kruskal-Wallis

Tabel 6. Results of the Test for the Relationship Between the Severity of Knee OA and HbA1c Levels

Jenis Data	P-value
Derajat Keparahan OA Genu HbA1c	0,408[c]

[c]Uji Kruskal-Wallis

Based on Table 6, the Kruskal-Wallis test was conducted because the HbA1c data was not normally distributed. The analysis revealed that there is no significant relationship between the severity of OA and HbA1c, as the p-value is greater than 0.05 (p = 0.408).

DISCUSSION

Knee OA accounts for over 80% of the total disease burden and affects at least 19% of American adults aged 45 and older. The prevalence of OA increases with age. In the United States, OA affects one-third of the population over 65 years old and is one of the top five causes of disability among the elderly. According to the World Health Organization (WHO), the global prevalence of OA in 2004 reached 151.4 million people, with 27.4 million in Southeast Asia. In Indonesia, OA is the most frequently encountered rheumatic disease. Radiographic studies conducted in Indonesia indicate that the incidence of knee OA is 15.5% in men and 12.7% of the total Indonesian population of 255 million people1,8. Determining the degree of OA radiologically is useful for assessing the severity of OA and not for diagnosis. Diagnosing OA is based on clinical symptoms, as there are no specific diagnostic tests for OA. Supportive examinations are primarily conducted for monitoring and ruling out differential diagnoses. Radiological examinations can determine the severity but are not directly related to clinical symptoms1.

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In this study, the most common location of knee OA was bilateral, with 103 people (39.9%). The prevalence of knee OA severity was as follows: Grade 1 - 67 people (26%), Grade 2 - 73 people (28.3%), Grade 3 - 82 people (31.8%), and Grade 4 - 36 people (14%). According to a study by Sananta et al., in Batu City, Indonesia, among 37 OA patients, seven (18.9%) had Grade 1 knee OA, 13 (35.1%) had Grade 2, 16 (43.2%) had Grade 3, and one (2.7%) had Grade 4. Among 10 male patients, three (30%) under 65 years had Grade 1 knee OA, and four (40%) over 65 years had Grade 3. There were no male patients with Grade 4 knee OA46. Globally, more than one in 10 adults now live with diabetes. Furthermore, there are increasing numbers of countries where one in five or more of the adult population has diabetes. Since 2000, the estimated prevalence of diabetes in adults aged 20-79 has more than tripled from 151 million (4.6% of the global population at the time) to 537 million (10.5%). The Western Pacific region, which includes Indonesia, accounts for over one-third (38%) of the total number of adults living with diabetes. The Western Pacific region has the third-highest prevalence of diabetes in the world (11.9%).

Indonesia is the 5th country with the highest number of diabetes patients in 2021, with 19.5 million patients. Indonesia is also the 3rd country with the highest number of undiagnosed diabetes patients, with 14.3 million people. However, the proportion of people with diabetes in Indonesia is not very high, at 10.8%. In this study, there were 73 patients with DM (28.3%) and 185 non-DM patients (71.7%). The prevalence of diabetes mellitus increases with age, peaking at 55-64 years and decreasing after that age range. According to the 2013 and 2018 Riskesdas data, there was an increase in the prevalence of DM from 2013 to 2018 in the 45-54, 55-64, 65-74, and ≥75 age groups. In this study, the DM patient population increased with older age groups: 18-30 years: 2 patients (2.7%). 31-40 years: 1 patient (1.4%). 41-50 years: 6 patients (8.2%). 51-60 years: 29 patients (39.7%). >60 years: 35 patients (47.9%)48. According to the 2018 Riskesdas, the prevalence of diabetes mellitus in women was higher than in men, with a ratio of 1.78% to 1.21%. In the 2013 Riskesdas, the prevalence was 1.7% in women compared to 1.4% in men. In this study, the number of female DM patients was higher than male patients, with 21 male patients (28.8%) and 52 female patients (71.2%)48.

OA and DM often occur together in older adults. Diabetes mellitus (DM) and osteoarthritis (OA) are common diseases that are projected to increase in prevalence. Both conditions often co-occur coincidentally due to their high prevalence and shared risk factors. For instance, the relationship between OA and obesity is well-supported, and obesity is prevalent among most individuals with DM. Aging is a well-known risk factor for both DM and OA. The estimated prevalence of DM in the US is 4.6 million among individuals aged 18-44 years, increasing to 14.3 million in those aged 45-64 years and 12.0 million in those aged ≥65 years. Similarly, radiographically determined knee OA increases dramatically with age, affecting 14% of adults over the age of 25 and 37% of those over 60 years. There is an increased susceptibility to developing arthritis in individuals with DM, supported by the higher prevalence of arthritis observed in DM patients (52%) compared to those without DM (27%).

The traditional association between OA and DM has been linked to underlying comorbid risk factors, namely age and obesity. Emerging evidence suggests that changes in lipid metabolism and hyperglycemia may directly impact cartilage and subchondral bone health, contributing to the development and/or progression of OA. Adequate management of elderly patients with OA and DM is beneficial for a comprehensive understanding of the risk factors associated with these diseases6,43. In this study, the results showed that the proportion of respondents with DM was lower (28.29%) compared to non-DM patients (71.71%), with the highest severity of OA being grade 3 (31.78%) and the lowest being grade 4 (13.95%). Additionally, there was a significant relationship between DM and the severity of knee OA. Previous studies have proposed that alterations in glucose metabolism may serve as a direct link between OA and DM. Cartilage health depends on numerous metabolic processes that regulate cartilage growth and nutrition, which, if altered, can lead to its degradation. In a study by Rosa et al., the impact of glucose concentration on chondrocyte function was investigated, revealing that chondrocytes from individuals with OA were

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unable to regulate glucose transport into chondrocytes in a hyperglycemic environment compared to a normoglycemic environment. Higher levels of reactive oxygen species (ROS) were also detected in OA cartilage treated in hyperglycemic conditions, unlike ROS levels in normal chondrocytes treated with high glucose media. ROS are harmful to chondrocytes as they promote the production of cytokines such as IL-1β and transcription factors like NF-κB, which induce catabolic processes involved in cell degradation and apoptosis[49,6]. In summary, hyperglycemia in DM can interact to affect OA. Underlying mechanisms such as low-grade inflammation, oxidative stress, and dysregulation of cellular functions all lead to cellular toxicity and cartilage and bone abnormalities associated with OA. Hyperglycemia also appears to have a direct effect on cartilage health.[6] The prevalence of comorbidities among patients with osteoarthritis (OA) is quite high. Previous studies have shown that the prevalence of any comorbidity is 67 percent (95% CI 57-74) in individuals with OA, as concluded in a meta-analysis of 42 studies[51]. Common comorbidities in patients with OA include hypertension (50%), cardiovascular disease (35%), peptic ulcer disease (16%), and diabetes (14%). Other studies have indicated that metabolic syndrome is more frequent in patients with OA compared to controls[52].

In this study, there was no significant relationship between comorbid diabetes mellitus (DM) and the severity of knee osteoarthritis (OA). This could be due to the study population with comorbid DM not necessarily being accompanied by risk factors that could exacerbate OA in conjunction with DM, such as obesity, leading to a lack of significant association between comorbid DM and the severity of OA. Therefore, further analysis might be needed to assess the body mass index (BMI) profile, as previous studies have identified BMI as a confounding factor in the relationship between DM and OA[54]. The relationship between DM and OA is controversial in the reported studies. Various research studies on the relationship between DM and OA have not reached consistent conclusions[55]. A meta-analysis concluded that type 2 DM might be significantly associated with the development of OA[56]. According to the latest meta-analysis, two possibilities are suggested: first, that DM is not truly a risk factor for OA, and second, that when BMI is a strong risk factor for OA, weaker risk factors for OA may be masked by the confounding effect of BMI. Therefore, the independent risk estimate of DM for OA could be revealed in populations where BMI is more comparable among comparison groups. The study concluded that DM is not an independent risk factor for OA and that BMI might be the most important confounding factor[54].

In the study conducted by Murata et al. in 2019, 171 patients diagnosed with radiographic knee OA were grouped based on their HbA1c concentrations (HbA1c ≥6.5 and HbA1c <6.5). RT-PCR was used to compare the expression of TLR (TLR2, TLR4) and MMP (MMP2, MMP3, MMP9, and MMP13) in the synovial tissue of patients between the two groups. Regulation of MMP13 by the TLR4 ligand, lipopolysaccharide (LPS), in synovial tissue cells was examined in culture by stimulating synovial tissue cells with LPS or culture media for 24 hours. The results showed a significant increase in the expression of TLR4 and MMP13 in the HbA1c ≥6.5 group compared to the HbA1c <6.5 group. Conversely, the expression levels of TLR2, MMP2, MMP3, and MMP9 did not differ between the groups. The mRNA and protein levels of MMP13 in synovial tissue cells were significantly higher after stimulation with LPS compared to the media[57]. In this study, the results indicated no significant relationship between the severity of OA and HbA1c. This may be due to patients with comorbid DM and high HbA1c not necessarily having a high BMI. Based on previous meta-analyses, DM is not an independent risk factor for OA, but BMI plays an important role as a risk factor for the development of OA.

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CLOSING

Conclusion

There is a significant relationship between DM and the severity of genu OA ($p < 0.001$). Subjects in this study were predominantly female (59.7%), with the majority being over 60 years old (45%). The most common location for genu OA was in both knees (39.9%), with the most common severity being grade 3 (31.8%). Additionally, it was found that there were more non-DM patients (71.7%), and the majority of patients had comorbidities (60.9%). Among subjects with DM, females dominated (71.2%), with the majority being over 60 years old (47.9%). The most common location for genu OA was in both knees (42.5%), with the most common severity being grade 3 (34.3%). The majority of patients also had other comorbidities (87.7%). There was no significant relationship between DM comorbidity and the severity of genu OA ($p > 0.05$). In this study, it was found that age data in DM patients were normally distributed ($p > 0.05$), while HbA1c data were not normally distributed ($p < 0.05$), with an average age of 61.54 years and an HbA1c average of 8.46%. There was no significant relationship between the severity of OA and HbA1c ($p < 0.05$).

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

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