RISK FACTORS FOR KNEE PAIN IN FEMALE DIABETES MELLITUS PATIENTS AGED ≤ 45 YEARS

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Abstract

Diabetes Mellitus (DM) and Osteoarthritis (OA) coexist in the same population. Women with DM and OA have a higher prevalence of knee pain. Objective: to analyze knee pain in female DM patients aged ≤ 45 years. The research method uses a cross-sectional research design. The sample is the entire population, namely women diagnosed with DM aged ≤ 45 years in Cilacap Regency. Measurement of Knee Pain Degree using the Womac Index. The results of the study were that the average pain score of the respondents was 7.87, the stiffness score was 3.84 and the physical disorder score was 19.23. The average total score of pain, stiffness and functional impairment was 39.22. There was an association between Obesity PR = 8.77 (95% CI 3.23-23.79) and blood pressure PR 3.89 (95% CI 1.67-9.07) with the degree of knee pain in female DM patients ≤ 45 years of age. The conclusion was that 41.51% of respondents experienced pain, stiffness and mild functional disorders and 58.49% moderate/severe.
Keywords: Diabetes; Hypertension; Obesity; Woman ≤ 45; Womac.

INTRODUCTION

Diabetes Mellitus (DM) is a complex metabolic disorder characterized by hyperglycemia that occurs due to impaired insulin secretion by the pancreas or due to insulin resistance in peripheral tissues or impaired hepatic glucose production (1). Diagnostic criteria for DM are defined as two consecutive fasting blood glucose (FBS) tests >126 mg/dl; glucose levels two hours after the test >200 mg/dl (oral glucose tolerance test); random blood glucose levels >200 mg/dl. The global prevalence of diabetes in the 20–79 year age group in 2021

was 10.5% (536.6 million people), estimated to increase to 12.2% (783.2 million) in 2045. A relatively large increase in diabetes prevalence between 2021 and 2045 is expected to occur in middle-income countries (21.1%) compared to high-income countries (12.2%) and low-income countries (11.9%). Global diabetes-related health expenditure is estimated to reach 966 billion USD in 2021, and is projected to reach 1,054 billion USD in 2045 (2)(3).

The prevalence of diabetes increases with age, 12.37% of DM cases occur at the age of 45 to 55 years, 15.98% at the age of

55 to 65 and 16.52% among people aged ≥65 years). Based on educational background 14.52% of DM cases occur among illiterate people, 15.52% among people with primary education and 15.58% among people with secondary education or higher. Based on Body Mass Index, the prevalence of DM is more common at 8.18% in BMI 18.5 to 24.9, as much as 17.05% in BMI 25.0 to 29.9 and 22.54% among people with and ≥30.0. The prevalence of diabetes is higher among urban residents (19.04) than among rural residents (12.85%). Age between 55 and 65 years, obesity, history of hypertension and coronary heart disease, and lack of activity are significant risk factors for diabetes risk (4).

Diabetes is characterized by insulin disorders that cause increased blood sugar levels called hyperglycemia, which can cause chronic systemic inflammation that leads to changes in the body's organ systems and joints, and often causes complications (5)(6). Hyperglycemia can produce advanced glycation end products (AGEs) that can accumulate in the joints, thereby increasing cartilage stiffness and fragility.

DM is associated with increased pain severity and decreased walking speed in patients with knee osteoarthritis. Osteoarthritis (OA) is one of the most common degenerative joint diseases, resulting in inevitable joint damage that causes pain and joint immobility (7).

The presence of DM significantly alters biomarker expression in individuals with Osteoarthritis (OA) that can be distinguished from the baseline OA phenotype, these differences may help reveal the underlying mechanisms of accelerated OA progression associated with DM. Higher SF COMP levels in OA with DM indicate greater articular cartilage degradation. HbA1c was higher in the group with OA and DM compared to the OA without DM group. The population with DM and OA had significantly higher HbA1c than the DM without OA population (8).

Approximately 40% of individuals with OA complain of arthritis-related limitations in daily activities, and 30% face problems with work-related tasks, making OA a major source of disability and financial burden. There were 341,561 cases of OA among individuals with DM, with a

prevalence of 32.65%. Furthermore, there were 38.05% more females than males overall, and this difference was statistically significant. The incidence of OA was present across all age groups in the group of patients with DM; the 65-69 age group showed the highest prevalence (36.76%), and the 44-year age group was found to have the lowest prevalence (14.3%). Patients with Diabetes Mellitus also showed early symptoms of OA, which is potentially related to blood sugar control. Furthermore, the risk of OA increases with age in people with DM, and those with both conditions face significant limitations in activities that hamper their daily lives(9).

Women had a higher prevalence of OA, clinical pain and inflammation, decreased cartilage volume, physical difficulties, and smaller joint parameters and dimensions, compared to men. Compared to men, women showed higher levels of macrophage stimulators, pro-inflammatory mediators, including inflammatory interleukins, and estrogen receptor expression. Gender differences in OA patients were observed in terms of hip, hand, spine, femur, and tibia morphometry, as well as microarchitectural changes and bone remodeling. Women reported clinical pain, with higher VAS, higher knee pain scores, higher serum CRP concentrations, and more impaired function compared to men. Inflammatory cytokines (IL-6, IL-10, IL-1β, TNF-α) were higher in women, confirming that they experience more pain than men (10).

A Canadian study on the impact of diabetes status on pain and physical function after total joint arthroplasty for hip and knee osteoarthritis varied by gender and body mass index, finding that 54.9% of the sample suffered from hip pain and knee pain, and 13.0% reported diabetes (11).

The prevalence of diabetes in Indonesia is estimated to increase from 9.19% in 2020 (18.69 million cases) to 16.09% in 2045 (40.7 million cases). The prevalence will be lower to 15.68% (39.6 million) if program interventions are carried out, and to 9.22% (23.2 million) if the program is combined with risk factor prevention. The projected number of deaths due to diabetes will increase from 433,752 in 2020 to 944,468 in 2045. This prevalence has increased by 75.1% over 25 years, with an average

increase in prevalence of 3% per year. The province with the highest prevalence in 2045 is DKI Jakarta (23.11%) and the lowest is East Nusa Tenggara Province (8.91%). Based on seven regions, the Java-Bali region has the highest average prevalence of Diabetes (18.27%) (12).

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METHOD

This study used a Cross Sectional design. The sample of this study was all women diagnosed with DM from the results of the examination of the Kedungrejo Health Center and Cipari Health Center in Cilacap Regency, aged ≤45 years as many as 106 patients. Data collection was carried out for 3 months from June to August 2024. This study was conducted on female DM patients because cases of DM and OA were higher in women. The selection of DM women aged ≤ 45 years was intended to be able to detect pain, stiffness and impaired function in the knee joint earlier.

Diabetes was defined as a previous diagnosis reported by a health care professional based on fasting plasma glucose (FPG) >126 mg/dl and/or HbA1c >6.5%. Body mass index (BMI), which is the ratio of body weight in kilograms to height in meters squared. Obesity (BMI ≥ 30). Blood pressure (BP; mmHg) was measured with a pressure monitor in a sitting position. Data collection was carried out through interviews using the Womac Osteoarthritis Index questionnaire instrument.. The WOMAC index was used

to assess pain, stiffness, and physical function. The WOMAC index is a highly reliable questionnaire about activities of daily living used for patients with OA. This scale contains three subscales of pain, stiffness, and physical function. The 5-point Likert scale measures responses ranging from 0 (no disability) to 4 (very severe disability). Each question has five response options ranging from 0 (no, no difficulty or no symptoms), Mild (1), Moderate (2), Severe (3), and up to 4 (unable to perform activities or extreme symptoms). Subtotal scores for pain, stiffness, and function range from 0 to 20, 0 to 8, and 0 to 68. Higher scores indicate greater disability. The Western Ontario and McMaster Osteoarthritis Index (WOMAC) is a disease-specific questionnaire that is widely used in patients with knee and hip arthritis. The WOMAC has been translated and used in over 65 languages worldwide with excellent reliability, construct, content, and criterion validity(13). Bivariate analysis to explain the factors of Obesity and Hypertension) related to the occurrence of Osteoarthritis and Diabetes Mellitus. The analysis used in this study is the Chi square statistical test with α equal to 0.05.

This research has obtained ethical approval from the Health Research Ethics Commission of Mataram Health Polytechnic No. DP.04.03/F.XLVIII.14/335/2024 after discussions and assessments were carried out based on the Nuremberg Code and the Declaration of Helsinki.

RESULTS AND DISCUSSION

Results

1. Respondent Characteristics

Table 1. Data Centralization Measure of Female DM Patients Aged $\leq$ 45 Years at the Kedungrejo and Cipari Health Centers, Cilacap Regency in 2024

Variables	Mean	Median	SD	Minimum	Maksimum
Age	39.11	41.00	5.61	18	45
Systolic	128.54	125.00	18.92	90	200
Diastolic	83.77	80.00	9.70	70	110
BMI	24.28	22.55	5.51	15.42	35.38
Pain score	7.87	8.00	3.82	1	15
Stiff score	3.84	4.00	2.60	0	8

| Variables	Mean	Median	SD	Minimum	Maksimum
Physical Disorder Score	19.23	17.00	10.36	4	39
Skor Womac	32.22	29.69	16.83	6.25	62.50

Source: Data were obtained from the Womac Osteoarthritis Index questionnaire and doctor's diagnosis at Kedungrejo Health Center and Cipari Health Center in 2024.

The respondents' ages ranged from 18 to 45 years with an average age of 39 years. The average systolic blood pressure of the respondents was 128.54 mmHg (normotension) with the lowest systolic blood pressure being 90 and the highest systolic blood pressure being 200 mmHg. While the average diastolic blood pressure of the respondents was 83.77 mmHg (normotension) with the lowest diastolic blood pressure being 70 mmHg and the highest diastolic blood pressure being 110 mmHg. The average Body Mass Index of the respondents was 24.28 with the lowest BMI being 15.42 and the highest being 35.38. The average pain score of the respondents was 7.87, the stiffness score was 3.84 and the average physical impairment score was 19.23. The total score for pain, stiffness and functional impairment was 39.22. Based on the Womac Index Subtotal scores for pain, stiffness, and function range from 0 to 20, 0 to 8, and 0 to 68.

2. Pain

Pain measurement was carried out using the Womac Index, which is a self-reported lower extremity specific questionnaire containing 5 items of pain, namely pain when lying down, when resting, at night, when climbing stairs and when walking.
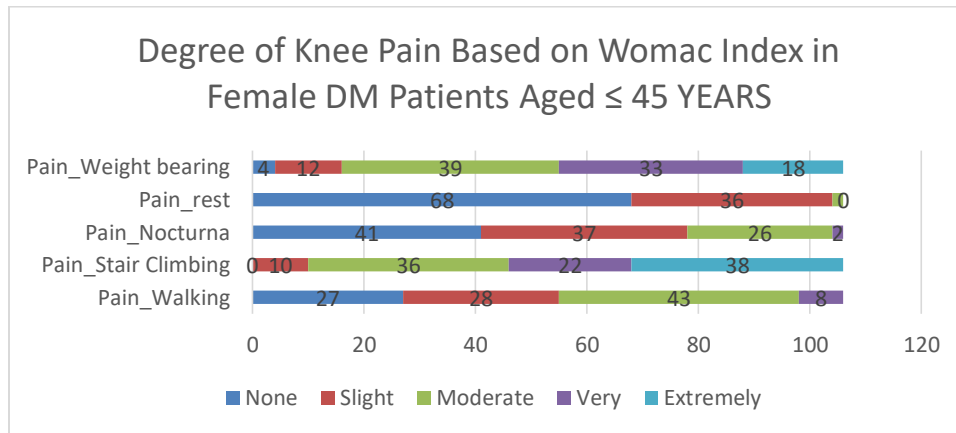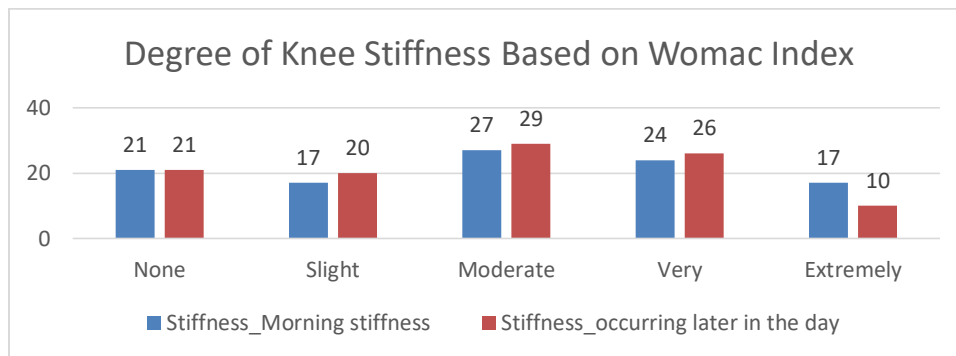
Graph 1. Degree of Pain in Women with DM Aged ≤ 45 Years in Cilacap Regency

The results of this study show that most respondents did not feel pain while resting and at night, but felt moderate pain when walking and getting out of bed. Most respondents also experienced very severe pain when climbing stairs. This can be seen in Graph 1.
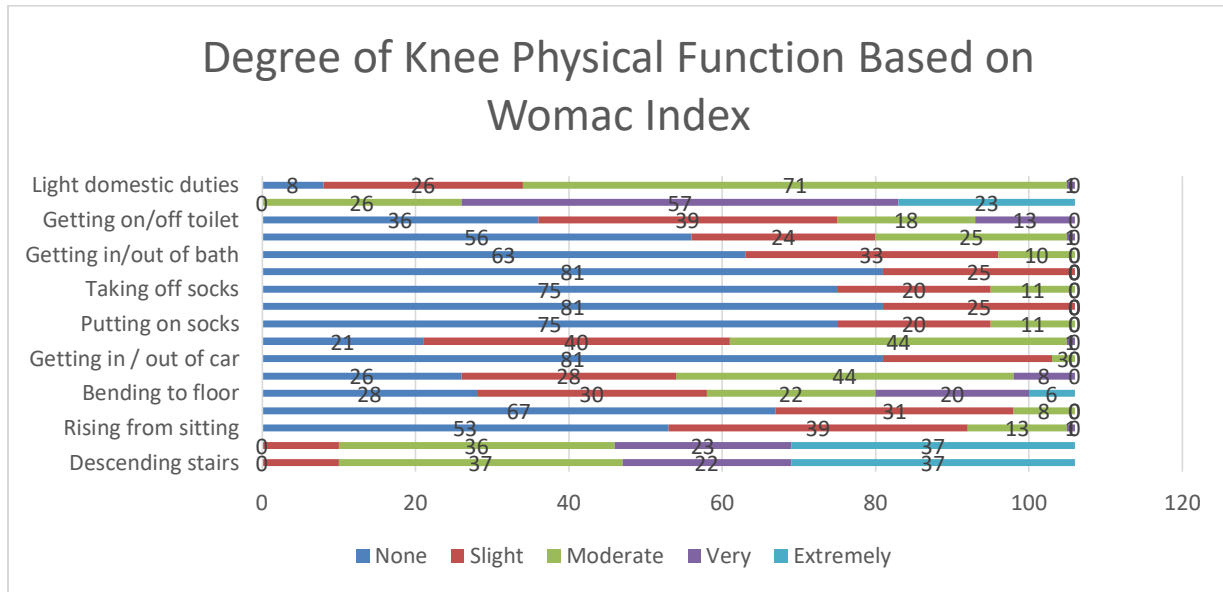
3. Stiffness

Graph 2. Degree of Stiffness in Female DM Patients Aged ≤ 45 Years in Cilacap Regency

The Womac Index used to measure the degree of stiffness in this study consists of 2 questions, namely stiffness in the morning and stiffness until the next day. Most respondents felt moderate stiffness in the morning and the next day.

4. Physical Disorders

Graph 3. Degree of Functional Disorders in Female DM Patients Aged ≤ 45 Years in Cilacap Regency

Physical dysfunction was measured using the Womac Index which includes 17 questions regarding physical dysfunction. Most respondents felt very severe functional impairment when going up and down stairs. Most respondents felt mild functional impairment when walking on the floor, and when getting up from the toilet. Most respondents felt moderate functional impairment when shopping, walking on a flat surface, and doing light housework. Most respondents experienced mild physical impairment when getting up from sitting, standing, getting in/out of a car, taking off socks, lying in bed, getting out of bed and sitting. Respondents were classified as having lower extremity functional limitations if they had difficulty performing any of the following tasks on a regular basis: getting up from a chair after sitting for a long time, climbing several flights of stairs without a break, or bending, kneeling, or squatting.

Table 2. Risk Factors of Obesity and Blood Pressure Associated with the Degree of Knee Pain in DM Patients in Cilacap Regency

Variabel	Moderate/Very		Slight		P-value	PR (95%CI)
	n	**%**	**n**	**%**		
Obesity						
Yes	36	85.7	6	14.3	0.000	8.77 (3.23-23.79)
No	26	40.6	38	59.4		
Total	62	58.50	44	41.50		
Blood pressure						
≥ 140/90 mmHg	35	76.1	11	23.9	0.003	3.89 (1.67-9.07)
< 140/90 mmHg	27	45.0	33	55		
Total	62	58.50	44	41.50		

Sumber: Primary Data, 2024

As many as 41.51% of respondents experienced pain, stiffness and mild functional impairment and 58.49% experienced moderate/severe pain, stiffness and functional impairment. Respondents with moderate/severe Osteoarthritis were more common in respondents who were Obese and had blood pressure ≥ 140/90 mmHg. There is a relationship between Obesity and the degree of knee pain in female DM patients aged ≤ 45 years (p-value 0.05). Female DM patients aged ≤ 45 years who are Obese are at 8 times greater risk of suffering from knee pain compared to those who are not Obese. There is a relationship between blood pressure ≥ 140/90 mmHg and knee pain in female DM patients aged ≤ 45 years. DM patients aged ≤ 45 years with blood pressure ≥ 140/90 mmHg are at 3 times greater risk of suffering from knee pain compared to those with blood pressure < 140/90 mmHg.

Discussion

The results of this study indicate that most respondents also experienced very severe pain when climbing stairs. This is in line with research in America on 202 OA respondents with DM and 2,279 without DM from Osteoarthritis sufferers. OA participants with DM reported more severe knee pain and more severe physical and mental problems compared to participants without DM. People with DM had worse KOOS pain regardless of BMI, OA severity, age, and gender. The negative effect of DM was also seen in the SF-12, and CES-D.

People with knee OA experienced higher pain intensity and worse physical condition on average. Individuals with diabetes mellitus (DM) have higher rates of occurrence and progressive osteoarthritis (OA) compared to the control group without DM (14).

Osteoarthritis (OA) is characterized by degeneration of hyaline articular cartilage, hypertrophic changes in the joint capsule, and destruction of the underlying bone with subchondral remodeling and osteophyte formation. The underlying pathogenesis of OA is likely multifactorial, with associations between obesity-related insulin resistance, diabetes mellitus, and OA (15).

DM adversely affects local factors around the knee or peripheral or central pain processing factors, such as central sensitization. Individuals with OA and DM have been shown to exhibit greater synovial tissue inflammation and higher cytokine concentrations in the synovial fluid compared to those without DM. DM is known to cause changes in nerve endings, including altered voltage-dependent sodium channel expression and phosphorylation, which may lead to abnormal activity of nociceptive fibers. In addition, increased levels of methylglyoxal have been reported in DM patients with neuropathic pain, compared to healthy controls or individuals with DM without pain (14).

The results of this study provide results that most respondents feel very severe functional impairment when going up and down stairs. Most respondents feel mild functional impairment when walking on the floor, and when getting up from the toilet. Most respondents feel moderate functional impairment when shopping, when walking on a flat surface, when doing light housework. Most respondents experience mild physical impairment when getting up from sitting, standing, getting in/out of the car, taking off socks, lying in bed, getting out of bed and sitting. This can be explained as follows: Hyperglycemia can cause chronic systemic inflammation that affects the entire body, including the joints. This condition can also cause the production of advanced glycation end products that can accumulate in the joints, increasing cartilage stiffness and bone fragility.

DM manifests as a state of chronic hyperglycemia that causes further cartilage

degeneration and joint inflammation, which causes an increase in advanced glycation end products (AGEs) and matrix hardening that prevents optimal joint cushioning. This process then contributes to a cycle of worsening OA symptoms with subsequent limitations in physical activity and weight gain. As a result, metabolic dysregulation and joint symptoms persist or worsen (8).

Women with uncontrolled diabetes (DM) are at increased risk of developing osteoarthritis (OA), which can be exacerbated by poor glycemic control. In addition, several risk factors, including obesity, metabolic syndrome, hypertension, estrogen-based hormone therapy, and hyperuricemia, in postmenopausal women may contribute to the development and exacerbation of OA. Management of OA and DM in women requires a multifaceted management plan that includes glycemic control, weight control, exercise, and pain management methods that meet the specific needs of the patient. Regular monitoring of joint health and early management, encouraging interdisciplinary collaboration, implementing preventive measures, and creating individualized care programs are

essential. A thorough understanding of the relationship between DM and OA will ultimately lead to better health outcomes and a brighter future for DM in women (9).

Obesity and Degree of Knee Pain

The results of this study indicate a relationship between Obesity and the degree of knee pain in women with DM aged $\leq$ 45 years (p-value 0.05). Women with DM aged $\leq$ 45 years who are Obese are 8 times more likely to suffer from knee pain compared to those who are not Obese.

Obesity is associated with OA, due to the effects of body weight and misalignment on the joints, especially weight-bearing joints that affect joint cartilage. Obesity is also associated with systemic metabolic dysfunction (7). Obesity and DM can cause low-grade systemic inflammation characterized by increased **C**-reactive protein, circulating IL-6 and TNF levels, endothelial dysfunction, and vascular inflammation. Adipose tissue is known to produce several proinflammatory mediators, including IL-1β, TNF, prostaglandin E2, and IL-6 (42), which are known to sensitize neurons. In addition, intra-articular mediators released by the infrapatellar fat

pad may adversely affect cartilage and synovium, or activate intra-articular macrophages and leukocytes. BMI and OA severity, various parameters seem to have an influence on OA and OA pain Women have a higher risk of OA in the general population and especially among DM patients(14).

Metabolic syndrome exacerbates these risks by promoting chronic inflammation and altering macrophage activity within the joint. The multifaceted effects of obesity and metabolic syndrome extend beyond joint burden. These conditions disrupt normal joint function by altering tissue composition, promoting inflammatory macrophage polarization, and disrupting chondrocyte metabolism. The prevalence of obesity has been found to affect 2.3 to 12% of the young adult population in developing countries, with 28.8% being overweight, predominantly female (16).

Metabolic syndrome (MetS), which is often associated with central obesity and is characterized by increased waist circumference, elevated fasting plasma glucose concentrations, elevated triglycerides, decreased high-density lipoproteins, and/or hypertension, has been implicated in the pathogenesis of OA. The mechanisms involved in the influence of MetS on OA, with a focus on the effects on macrophages and chondrocytes, are thought to play a role in the pathogenesis of OA (11).

Weight loss interventions improve pain, enhance joint function, and result in decreased inflammation in patients with knee OA. One pound of weight loss can result in a fourfold reduction in knee joint loading during monopodial gait in previously sedentary obese elderly subjects with clinical relevance in OA management. Weight loss management is one of the most important modifiable risks for the prevention and treatment of knee and hip OA (17).

Adipokine imbalance during obesity is known to be one of the most important contributors to the occurrence and worsening of degenerative diseases associated with MetS (insulin resistance, dyslipidemia, hypertension, prothrombotic status) as well as systemic inflammatory diseases such as rheumatoid arthritis, chronic inflammatory bowel disease

(Cron's), Lupus erythematosus, and OA (16).

The underlying pathogenesis of OA is likely multifactorial, with obesity-related insulin resistance, diabetes mellitus, and OA being linked. Overall, insulin increases the production of type II collagen and proteoglycans, and inhibits cartilage breakdown. And while mechanical forces play a significant role in OA (to varying degrees depending on the joint involved), inflammatory mediators are also major drivers of joint tissue damage. However, classic cellular inflammation (as seen in other forms of inflammatory arthritis) is typically absent in OA (15).

Studies in the United States also show that approximately 1 in 10 adults in the United States have diabetes, with the vast majority (90% to 95%) classified as having obesity-related DM, and more than two-thirds are overweight or obese. The incidence of OA is up to 5-fold higher in those who are obese, and its onset and severity are closely related to weight status and duration of obesity (18).

Hypertension and Degree of Knee Pain

The results of this study indicate that there is a relationship between blood pressure ≥ 140/90 mmHg and knee pain in women with DM aged ≤ 45 years. DM patients aged ≤ 45 years with blood pressure ≥ 140/90 mmHg are at risk of suffering from knee pain 3 times greater than those with blood pressure < 140/9- mmHg.

The study conducted by Shukla found that an important factor in the relationship between hypertension and OA, especially knee OA, is interleukin 6, one of the most significant pro-inflammatory cytokines. Respondents were aged 30-86 years, and the prevalence of hypertension in the OA group was higher in men and women, but the relationship with MetS was only found in women. These results indicate that the relationship between OA and hypertension also increases in premenopausal women. Additionally, mutations in the vitamin D receptor have been shown to contribute to the pathway linking OA to hypertension (9).

Hypertension is a common form of cardiovascular disease associated with OA and DM. The relationship between hypertension, OA, and DM has been studied as a risk factor for the development and

progression of OA. Vascular disorders due to hypertension may play a role in the development and progression of OA. Decreased blood flow in patients with hypertension causes subchondral ischemia, which is associated with cellular dysfunction in the joint, including osteocytes and articular cartilage. Another study conducted in Sweden on people registered with OA found that when obesity, hypertension, and diabetes occurred together, patients treated for knee OA reported more pain in the first month compared to those without any conditions. Similar results were observed for patients treated for hip OA when obesity, hypertension, and diabetes co-occurred When diabetes, hypertension, and obesity co-occurred with OA, patients not only experienced increased baseline pain compared to metabolically healthy individuals (7).

CONCLUSION

Risk Factors Associated with Knee Pain in Female Diabetes Mellitus Patients Aged ≤ 45 Years in the working area of Kedungrejo Health Center and Cipari Health Center, Cilacap Regency are Obesity and High Blood Pressure.

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