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Bone mineral density and osteoporosis related risk factors in type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus negatively affects bone tissue and unfavourably impacts bone mineral density (BMD), therfore increasing the probability of fractures through pathological mechanisms. This study aimed to explore the factors associated with BMD and osteoporosis risk in individuals with a diagnosis of type 2 diabetes mellitus (T2DM). An investigation was undertaken involving 49 patients diagnosed with T2DM who fulfilled the specified criteria. These individuals underwent BMD assessment as part of a cross-sectional study. The analysis encompassed both univariate and bivariate approaches, utilizing the Chi-square test (X^2) and binary logistic regression methods. A total of 30 participants (61%) have decreased BMD. Among the participants aged 60 years and above, 83.4% exhibited a decreased BMD status (osteopenia and osteoporosis), in contrast to the under 60 years age group, in which 40% displayed decreased BMD status. Older age (>60 years) is a risk factor for decreasing bone density onset of diabetes mellitus (DM) diagnosis, duration of DM, glycemic control, body mass index (BMI), use of thiazolidinediones (TZD) drugs, kidney function, were not associated with lower BMD in T2DM patients.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) exerts deleterious effects on bone tissue, thereby predisposing individuals to an increased risk of skeletal fractures, both vertebral and non-vertebral [1], [2]. The underlying mechanisms responsible for the impact of T2DM on bone health are intricate due to the frequent coexistence of obesity, which itself can have detrimental consequences on bone physiology. In addition, bone mineral density (BMD) increased variably in T2DM, an effect expected to increase bone strength [3], [4].

Osteoporosis is defined as the decrease in bone mass and damage to the microarchitecture of bone tissue that results in reduced bone density and strength and an increased risk of fracture [5], [6]. Large population-based studies of osteoporosis patients show that T2DM patients constitute 18% of the osteoporosis population [7]. Diabetes can contribute to skeletal disorders through various factors. These mechanisms involve changes in insulin and insulin-like growth factor (IGF) levels, hypercalciuria due to glycosuria, impaired kidney function, obesity, elevated levels of advanced glycation end products (AGEs) in collagen, vascular issues, nerve damage, and inflammation [8], [9].

Patients with both osteoporosis and diabetes mellitus (DM) exhibit a 16% higher prevalence of fractures compared to those with osteoporosis alone, even after adjusting for age and gender [7]. Among

women with type 2 DM, there is an elevated risk of hip and non-vertebral fractures [10]-[13]. Prolonged diabetes duration and inadequate glycemic control are associated with increased risk of fracture and decreased BMD [3], [14]. While a higher body mass index (BMI) is generally linked to greater bone density, the protective effect diminishes once BMI exceeds 25 kg/m2, leading to a higher likelihood of fractures in specific areas [15].

Elevated blood glucose levels in DM disrupt fat metabolism, reduce insulin sensitivity, and promote inflammation, thereby exacerbating osteoporosis [16]. The use of thiazolidinediones (TZDs) has been linked with an augmented osteoporosis and fractures [17]. Diabetic nephropathy, affecting up to 50% of DM patients, impairs bone metabolism due to insufficient vitamin D synthesis and reduced calcium absorption. Knowing the relationship between T2DM and osteoporosis, we aim to evaluate the profile of BMD and osteoporosis related risk factors that is present in individuals with T2DM. By examining these factors, the research aims to enhance understanding of osteoporosis in the T2DM population [14].

2. METHOD

A study with cross-sectional design was conducted in a Central General Hospital in Semarang, Central Java. The participants of this study were T1DM or T2DM patients who underwent BMD examination. Sampling was carried out using purposive sampling technique, obtaining a minimum sample size of 49 patients, referring to the results of the initial study obtained from the medical record installation and information system of the hospital reported that 49 patients with the main diagnosis of T2DM who had a BMD examination in the 2016-2021 period.

Inclusion criteria are patients previously diagnosed T2DM with complete clinical data who signed the informed consent. Exclusion criteria are patients with other types of DM, patients suffering from other diseases affecting bone metabolism, such as Cushing's syndrome, anorexia nervosa, premature menopause (age <40 years), hyperprolactinemia, panhypopituitarism, thyroid disease, parathyroid disease, gastrointestinal disease with impaired absorption of food, malignancy, hemophilia, thalassemia, epilepsy, multiple sclerosis, parkinsonism, rheumatoid arthritis, systemic lupus erythematosus, HIV/AIDS, amyloidosis, chronic obstructive pulmonary disease, tuberculosis, depression, and transplant recipients. Patients who perennially take drugs affecting bone metabolism, such as aluminum (in antacids), anticoagulants (heparin), anticonvulsants, aromatase inhibitors, barbiturates, cancer chemotherapy drugs, glucocorticoids (≥5 mg/day prednisone or equivalent for three months), gonadotropin-releasing hormone (GnRH) agonists, lithium, cyclosporine, tacrolimus, methotrexate, selective serotonin reuptake inhibitors, Tamoxifen® (premenopausal use), thyroid hormone, and warfarin.

Minimum sample size was calculated with 5% type I error and 10% type II error and data from previous literature. A minimum sample size of 14 was obtained for each group [18], [19]. The research procedure has been approved on 14th October 2021 by the Health Research Ethics Commission (No.927/EC/KEPK-RSDK/2021). Patients and/or their guardians provided signed informed consent documents.

The measurement of body mass index was conducted using either the Body Composition Analyzer or manual methods. The classification of obesity was adjusted based on the WHO guidelines for the Asia-Pacific region, with categories including obese (≥25), overweight (23-24.9), normal (18.5-22.9), and underweight (<18.5). For bone density assessment, a dual X-ray absorptiometry (DXA) device was utilized. If the individual was aged 50 years or older, the T-Score was categorized as normal (≥ -1.0), osteopenia (<-1.0, >-2.5), osteoporosis (≤-2.5), and severe osteoporosis (≤-2.5 with fracture). If the individual was younger than 50 years, the Z-Score was categorized as normal (≥-2.0) or below the normal limits based on gender and age (<-2.0).

The data underwent processing using Statistical Product and Service Solutions (SPSS) software version 19.0. Univariate analysis of categorical (nominal) data is presented in a frequency distribution, while numerical data is presented as minimum, maximum, mean ± standard deviation (SD). Bivariate analysis was carried out in 2 stages, descriptive bivariate using cross table/row and column analysis and analytical bivariate using Chi-square test (X^2). The significance of statistical test results using p-value <α (0.05) was considered statistically significant. Further binary logistics regression will be performed fro all known risk factors.

3. RESULTS AND DISCUSSION

This study was conducted during the period of January-February 2022, employing a sample of patients diagnosed with T2DM who underwent bone BMD examination. A total of 49 samples were selected and included in the final analysis. A total of 30 participants (61%) have decreased BMD. The average age of the subjects was determined to be 59.4 years, and 34.7% of the participants were male. A noteworthy observation from the data is that more than half of the participants (55.1%) were classified as obese. Detailed information regarding the participants' characteristics can be found in Table 1.

Table 1. Characteristics of study participants

Characteristics	n (%)	Mean ± SD
Age (years)		59.43 ± 8.77
Gender (Male)	17 (34.7%)	
History of smoking	9 (18.4%)	
History of fracture	8 (16.3%)	
Menopause	26 (53.1%)	
Use of pioglitazone	3 (6.1%)	
BMI		
Underweight	0 (0%)	
Normal	14 (28.6%)	
Overweight	8 (16.3%)	
Obese	27 (55.1%)	
Onset of DM Dx (years old)		49.80 ± 9.02
Duration of DM (years)		9.63 ± 7.75
HbA1c (%)		9.078 ± 1.99
eGFR (ml/min/1.73m^2)		61.83 ± 26.79

eGFR: estimated Glomerular Filtration Rate

The age distribution displayed a relatively even distribution of ≥60 years. Among the 24 participants aged of ≥60 years (16.7%) are exhibited a normal BMD status. In contrast, 25 participants the <60 years (60%) displayed normal BMD status. A comprehensive overview of the BMD status categorized by age can be found in Table 2.

Table 2. BMD status of patients according the age

BMD status	Age	
	≥60 Years	<60 Years
Normal	4 (16.7%)	15 (60 %)
Osteopenia	16 (66.7%)	5 (20%)
Osteoporosis	3 (12.5%)	4 (16%)
Severe osteoporosis	1 (4.2%)	1 (4%)

After analyzing between characteristics of study participants and decreased BMD, we found that age ≥60 years old is associated with decreased BMD. Other variables have no significant association with decreased BMD as shown in Table 3. Multiple binary logistic regression was performed with the result of only age is significant as a risk factor for decreasing bone density as shown in Table 4.

Table 3. Association between known risk factors and decreased bone density

Characteristic		Normal BMD (n=19)		Decreased bone density (n=30)		p-value
		n	%	n	%	
Age (years)	≥60	4	21.1	20	66.7	0.002
	<60	15	78.9	10	33.3	
Gender	Male	7	58	10	33	0.801
	Female	12	42	20	67	
Duration of DM (years)	<10	7	37	17	57	0.176
	≥10	12	63	13	43	
BMI	Normal	7	58.3	5	41.7	0.110
	Obese & Overweight	12	32.4	25	67.6	
History of smoking	Yes	4	21	5	17	0.699
	No	15	79	25	83	
History of fracture	Yes	2	0.11	6	20	0.382
	No	17	0.89	24	80	
Use of pioglitazone	Yes	0	0	3	10	0.155
	No	19	100	27	90	
HbA1c (%)	<7	3	33.3	6	66.7	0.711
	≥7	16	40.0	24	60.0	
eGFR (ml/min/1.73m^2)	≥ 60	13	68	14	47	0.136
	< 60	6	32	16	53	

Table 4. Multiple binary logistics regression between known risk factors and decreased bone density

Characteristics		n	Odds ratio	95% Confidence interval	p-value
Age (years)	≥60	4	14.64	2.12-100.7	0.006
	<60	15	reference		
Gender	Male	7	0.21	0.26-1.68	0.142
	Female	12	reference		
Duration of DM (years)	<10	7	0.53	0.09-2.98	0.473
	≥10	12	reference		
BMI	Normal	7	0.37	0.06-2.23	0.281
	Obese and overweight	12	reference		
History of smoking	No	15	1.13	0.13-9.57	0.908
	Yes	5	reference		
History of fracture	No	17	0.14	0.01-1.58	0.112
	Yes	2	reference		
Use of pioglitazone	No	19	0	0	0.999
	Yes	0	reference		
HbA1c (%)	<7	3	3.51	0.42-29.2	0.245
	≥7	16	reference		
eGFR (ml/min/1.73m^2)	≥60	13	6.61	0.95-38.75	0.057
	<60	6	reference		

Among individuals with osteoporosis, those who also have DM exhibited a higher incidence of comorbidities, resulting in a 16% increased prevalence of fractures when compared to osteoporosis patients without DM. This adjustment considered differences in age and gender distribution [7]. Several studies have shown that women with T2DM are at higher risk of fractures in the hip and non-vertebral bones to nondiabetic women [10]–[12]. An increased risk of hip fracture has been demonstrated by the odds ratio (OR) ranging from 1.2 to 1.7. While findings may differ, there seems to be a connection between extended duration of diabetes and inadequate glycemic control, leading to an elevated likelihood of fractures. Additionally, these factors are linked to a reduction in BMD [3], [14].

Our study observed a higher prevalence of decreased bone density in females compared to males, aligning with existing literature suggesting that postmenopausal estrogen deficiency in women makes them more susceptible to decreased bone density (type I involutional osteoporosis) [20]. This is supported by the Study of Women's Health Across the Nation (SWAN) study which examined changes in BMD of the total lumbar and femoral neck in a community-based cohort with 292 premenopausal women and 141 in early postmenopausal women [21]. BMD remains stable in pre and early perimenopause [22], [23]. However, during late perimenopause and early postmenopausal period, there is a significant acceleration of bone loss with annual rates ranging from 1.0-2.3%. Regardless of race/ethnicity, women with lower body weight experience 35-55% higher bone loss rates compared to those with higher body weight [24].

Studies have shown that there was a direct correlation observed between an increasing BMI and the incidence of T2DM, while also exhibiting an association with increased bone mineral density at weight-bearing sites [15]. However, this association was not seen in our study. Heavier body weight provides some protection against bone loss, but this correlation is not linear. Once BMI exceeds 25 kg/m2, weight gain does not provide additional bone protection, and obese individuals have a higher likelihood of fractures in specific locations [25]. Given the association between T2DM and obesity, separating their contributions can be challenging [3].

We did not discover any association between decreasing BMD and onset of diabetes or duration of diabetes. This contrasted with a study by Zhao *et al.* in a population of diabetic nephropathy, which concluded that the duration of DM in the osteoporosis group was significantly higher ($p<0.05$) [14]. The different result may be attributed to small sample size, population differences and underestimation of DM duration particularly if the patient is diagnosed only after developing complications.

Inadequate glycemic control and longer diabetes duration can result in an increased risk of fracture [15]. Owever, we did not discover any correlation between glycemic control in type 2 diabetes mellitus (T2DM) and bone mineral density (BMD). This outcome aligns with a study conducted in the UK, which revealed that although inadequate glycemic control is linked to a heightened risk of low-trauma fractures in individuals with type 1 diabetes mellitus, this impact is not evident in those with type 2 diabetes mellitus [26]. Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that intensive glycemic control was not significantly associated with fracture or risk of falls compared with standard therapy [27]. Participants with an HbA1c of 8% had a 63% higher risk of hospitalization for fracture compared to those with an HbA1c of below 8%. Patients with unknown diabetes and pre-diabetes before starting the study had no increased risk of hospitalization compared with those with an HbA1C below 5.7% [27]. A meta-analysis of observational studies reported the HbA1C levels of >8% and hypoglycemia increases the risk of fracture in diabetic patients [28]. The risk of falls is influenced by various factors related to vision and balance. Factors

associated with vision encompass diabetic retinopathy, cataracts, retinopathy laser therapy, and episodes of hypoglycemia. Risks related to balance encompass peripheral neuropathy, foot ulcers, excessive urination, nighttime urination, and diminished reflexes. The heightened risk of hip fracture is linked to an increased likelihood of falls rather than a decrease in BMD [29].

In a cohort study comprising over 9,000 T2DM patients, the utilization of TZDs was linked to a higher likelihood of experiencing hip fractures [17]. Furthermore, TZDs not only raised the risk of fractures but also led to a decrease in bone formation and an increase in bone resorption, ultimately resulting in a reduction in bone mass [28], [30], [31]. Double-blind, placebo-controlled randomized trials have shown that treatment with pioglitazone slightly increased risk of fracture compared to placebo. Population-based studies and meta-analyses have also reported an increased risk with women being more susceptible to the detrimental effects on bone than men [32]. The lack of a statistically significant association between the use of pioglitazone and osteoporosis incidence in this study may be attributed to the small number of samples (three patients).

Diabetic nephropathy affects up to 50% of diabetes patients and is a major cause of end stage kidney disease (ESKD). Insufficient vitamin D synthesis in diabetic nephropathy leads to insulin resistance, increased microalbumin secretion, and decreased renal hydroxylase activity. A reduction in 1.25-(OH)2D3 content reduces calcium absorption and bone formation, therefore the severity of diabetic nephropathy affects bone metabolism [14]. This is demonstrated in a Chinese study in a population of diabetic nephropathy patients, which concluded that the eGFR value in the osteoporosis group was significantly higher than the group without osteoporosis ($p<0.05$) [14]. However, we did not demonstrate any association between decreasing kidney function and decreasing BMD.

Caution is advised when interpreting the results of this study owing to several constraints. The primary limitation is the relatively small sample size, and a significant concern arises from the incomplete matching between subjects within each group. To enhance comprehension of the risk factors and the connection between type 2 diabetes and osteoporosis, it is advisable to undertake a more extensive case-control study with a balanced distribution of BMD outcomes. Such an investigation is anticipated to yield a more elucidating perspective on this subject.

4. CONCLUSION

Our study found that 61% of the T2DM sample population have decreased BMD. Older (>60 years) T2DM individuals have a higher proportion of decreasing BMD (83.4%) compare to the younger (<60 years) counterpart (40%). Older age (>60 years) is a risk factor for decreasing bone density. Onset of DM diagnosis, duration of DM, glycemic control, BMI, use of TZD drugs, kidney function was not associated with lower BMD in T2DM patients.

This study emphasizes the significance of acknowledging the heightened susceptibility of people with T2DM to bone health concerns related to osteoporosis, particularly in older individuals. The results underscore the necessity for targeted interventions and preventive strategies, especially among the elderly, to mitigate the increased likelihood of bone fractures in this demographic. Although the research offers valuable insights, its constraints underscore the requirement for broader and more extensive inquiries to gain a deeper understanding of the complex association between T2DM and bone health.

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