Factors Influencing Low Bone Mineral Density in Patients with Type 2 Diabetes Mellitus: Bangladesh Perspective

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ABSTRACT

Background: The association between type 2 diabetes mellitus (T2DM) and bone mineral density (BMD) remains unclear. Screening, identification and prevention of potential risk factors for osteoporosis in T2DM patients are important and necessary for preserving a good quality of life and decreasing the risk of fracture. This study is expected to help us find the trend of BMD in T2DM patients in Bangladesh and identify any risk factors that may predispose to low BMD.

Objective: To evaluate the bone mineral density in patients with long term history of type-2 diabetes mellitus.

Procedure: This cross sectional observational study was conducted in NINMAS for a period of 18 months among 200 patients with history of T2DM for more than five years who were referred for BMD test. The study subjects were divided according to duration of DM, glycemic status, BMI, menstrual status etc. DEXA scan was done and BMD was measured at lumbar (L1 to L4) vertebrae, right and left femoral necks. After getting the BMD report (normal, osteoporosis, osteopenia), the effects of independent variables (age, gender, duration of diabetes, status of diabetes and BMI) on dependent variable (BMD) were analyzed.

Result: Most patients were older (>50-60 and >60-70 years age group), female (85%), overweight and pre-obese. Mean age was 57.86 ±9.69 years. Most of them (158) were post-menopausal. Only 25.5% patients had good controlled diabetes. According to duration, most patients (61%) belonged to >5-10 years group. No statistically significant difference was found between the T-scores of the 'pre-menopausal' and 'post-menopausal' female. Among the patients, 67.5% had low spine BMD and 38% and 41% had low right and left femoral neck BMD respectively. Duration of DM had statistically significant association on BMD only in left femoral neck (p= 0.046). No statistically significant correlation was found between HbA1c and T-score. Women have more than five times chance of having low BMD than men (odds ratio= 5.185, p = <0.001) in spine. Independent risk factors for low BMD were female gender, increasing age and low BMI.

Conclusion: Significant portion of T2DM patients had low BMD. Low BMD in left femoral neck has statistically significant association with duration of T2DM. Low BMD is also related to increasing age, female gender and low BMI.

Keywords: Type 2 Diabetes mellitus, Bone mineral density, Dual Energy X-ray Absorptiometry (DEXA), Osteopenia, Osteoporosis

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INTRODUCTION

Throughout the world, diabetes is among the most prevalent non-communicable diseases. It has a significant negative impact on health and the economy since it is linked to morbidity and death (1). Type 2 diabetes mellitus (T2DM) constitutes nearly 90% of all diabetes and the trend of T2DM is increasing due to rapidly changing lifestyles. According to the International Diabetic Foundation (IDF), in 2021, 537 million adults (20 to 79 years old) had diabetes and the prevalence is increasing. It is predicted to rise to 643 million by 2030 and 783 million by 2045 (2). The magnitude of diabetes is also increasing in Bangladesh. According to the IDF, approximately 6.9 million Bangladeshi people have diabetes with a prevalence rate of 8.5% (3). In spite of continuous improvement in treatment, many people die because of their diabetes (4). In addition to that, fracture risk is higher in those with diabetes mellitus (DM) (5).

Bone mineral density (BMD) is the amount or mass of mineral content (mostly calcium and phosphorous) in bone per unit area. It is generally expressed as gm/cm2. It is an indirect indicator of osteoporosis and future fracture risk. BMD depends on various factors, such as age, sex, heredity, dietary factors, endocrine factors (estrogen, PTH hormone etc.), physical exercise and exposure to risk factors like certain drugs such as glucocorticoids. The association between T2DM and BMD is still unclear, and different studies show lower, higher or similar BMD values in comparison with healthy control subjects (5). It is assumed that, DM can influence bone through many mechanisms and some of the mechanisms have contradictory effects (6). Low levels of insulin, hyperglycemia, an alteration of vitamin-D metabolism and decreases in BMD may result from long-term T2DM.

Low level of insulin in diabetic patients causes decreased osteoblastic activity and lower BMD. Hyperglycemia causes low BMD by increasing the concentration of 'advanced glycation end products' and calciuria. Also, derangement of calcium homeostasis occurs in DM. Elevated cytokines in T2DM, such as TNF-α, RANKL, etc., cause accelerated bone resorption and lower BMD. Ethnicity plays a role as different trends of BMI are found in different regions of the world. As relatively low BMI is found in the Asian population, the risk of osteoporosis is also higher. The duration of DM also plays an important role on BMD. The patients with longer durations of DM had lower total hip and femoral neck BMDs than those with shorter durations (6-9).

On the other hand, obesity, which is common in T2DM, is substantially correlated with higher BMD, most likely as a result of hormonal factors such insulin, estrogen, and leptin as well as mechanical loading. Increased plasma leptin as well as hyperinsulinemia in the early stage of DM stimulate osteoblasts and promote bone formation; thus increasing BMD. Drugs used in DM such as insulin also cause weight gain and hence increase BMD. An increased cholesterol level may also increase BMD (1, 10)

A number of techniques have been proposed for measuring BMD, but Dual Energy X-ray Absorbtiometry (DEXA) is used across the world and considered the 'Gold Standard' for the diagnosis of osteoporosis (11). The DEXA machine uses two low-energy x-rays to produce an image with good contrast. Standard measurements are most commonly made over the lumbar spine (L1 to L4 vertebrae), except where a particular problem occurs at any vertebra, in which case it is excluded and over the upper part of the hip or femoral neck (11, 12). Results are expressed as T or Z scores. The T score is defined as the number of standard deviations (SDs) from the mean values in a young adult. The Z score is defined as the number of standard deviations (SDs) from the age- and sex-matched control mean values. The T score is generally used to define osteoporosis (11).

In this study, the BMD of patients with T2DM was evaluated and any risk factors that predispose to low BMD were identified, which will help us to improve the management protocol of T2DM to reduce the risk of fracture and maintain a high quality of life in those with diabetes.

PATIENTS AND METHOD

This cross sectional observational study was conducted in National Institute of Nuclear Medicine & Allied Sciences (NINMAS) from September 2022 to February 2024 and the study population was 200 patients with history of the T2DM referred to NINMAS for BMD test. Inclusion criteria were- patient with history of Type-2 diabetes mellitus for > 5 years and age more than 30 years. Patient with type1 Diabetes mellitus, patient with H/O thyroid disorders, hyperparathyroidism, chronic liver disease (CLD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), Patient taking drugs, like hormonal replacement therapy (HRT), corticosteroids, anticonvulsant medications, thyroxine and malignancy were excluded. Independent variables were- age, gender, duration of diabetes, menstrual status, BMI, status of Diabetes (identified by HbA1c) and dependent variable was BMD. Based on the selection criteria, patients were chosen. With proper approval from Medical Research Ethics Committee (MREC) of NINMAS, proper history was taken and the patient's medical records were collected, checked and documented on the formatted questionnaire.

The study subjects were divided according to duration of DM, glycemic status, BMI, menstrual status etc. The study subjects were divided according to duration of diabetes into three groups of five-year segments; Group-1: >5–10 years, Group-2: >10–15 years, and Group-3: >15 years. Study subjects were further divided into controlled diabetes (HbA1c <7%), fairly controlled diabetes (7-8%) and poorly controlled diabetes(>8%). The study subjects were also divided into five groups according to BMI, i.e., 1. low BMI group or underweight (<18.5 kg/m^2), 2. normal BMI group or normal weight (18.5-22.9 kg/m^2), 3. overweight (23-24.9 kg/m^2), 4. pre-obese (25-29.9 kg/m^2) and 5. obese (≥30 kg/m^2). DEXA scan was done by the 'Medix DR' bone dosimeter and BMD was measured at L1 to L4 vertebrae, right and left femoral necks. After getting the BMD report, the enrolled subjects were divided into three groups-1. Normal BMD, 2. Osteopenia and 3. Osteoporosis. The effects of independent variables (age, gender, duration of diabetes, status of diabetes and BMI etc.) on dependent variable were analyzed.

Data Processing and Statistical Analysis: Statistical analysis was done by using SPSS (The Statistical Package

for Social Sciences, version 26.0 for Windows) software. Chi-square test was used to measure the association or relationship between two qualitative variables. Unpaired t-test was used for quantitative variables to compare mean. Binary logistic regression was done to predict a qualitative binary dependent variable from one or more independent variables. Other tests were done in appropriate settings. P values < 0.05 was considered statistically significant for all the analyses that were performed.

RESULTS

Among 200 patients, most of them were older (>50-60 and >60-70 years age group), female (85%) and overweight and pre-obese. Mean age was 57.86 ±9.69 years. Most of them (158) were post-menopausal. Only 25.5% patients had good controlled diabetes. According to duration, most patients (61%) belonged to >5-10 years group (Table 1). No statistically significant difference was found between the T-scores of the 'pre-menopausal' and 'post-menopausal' female. Among the patients, 67.5% had low spine BMD and 38% and 41% had low right and left femoral neck BMD respectively. Duration of DM had statistically significant association on BMD only in left femoral neck (p= 0.046) (Table 2). No statistically significant correlation was found between HbA1c and T-score. Binary logistic regression was performed to assess the impact of several factors on right femoral neck BMD. The model contains five independent variables (gender, duration of diabetes, HbA1c, age and BMI). Duration of diabetes and HbA1c had no statistically significant contribution to the model. Only age and BMI made a statistically significant contribution. For every 1-year increase in age, the odds of having low BMD increases by a factor of 1.049 (odds ratio = 1.049, p= 0.006). On the other hand, for every 1-unit (kg/m2) increase in BMI, the odds of having low BMD decreased by a factor of 0.919 (odds ratio = 0.919, p= 0.025) (Table 3). In case of left femoral neck BMD, Duration of diabetes and HbA1c had no statistically significant contribution to the model. Only age and BMI made a statistically significant contribution. For every 1-year increase in age, the odds of having low BMD increases by a factor of 1.048 (odds ratio = 1.048, p= 0.006). On the other hand, for every 1-unit (kg/m2) increase in BMI, the odds of having low BMD decreased by a factor of 0.914 (odds ratio = 0.914, p= 0.016) (Table 4). In case of spine BMD, again duration of diabetes and HbA1c had no statistically significant contribution to the model but gender and BMI made a statistically significant contribution. Women have more than 5 times chance of having low BMD than men (odds ratio = 5.185, p= 0.000). On the other hand, for every 1-unit (kg/m2) increase in BMI, the odds of having low BMD decreased by a factor of 0.878 (odds ratio = 0.878, p= 0.001) (Table 5).

Table 1: Demographic characteristics of the study population (n=200)

Traits	Groups	Frequency	Percent %
Age (in years)	>30-40	5	2.5
Mean age± SD= 57.86±9.69	>40-50	34	17.0
Age(Min, Max)= 35,88	>50-60	83	41.5
	>60-70	59	29.5
	>70	19	9.5
Gender	Male (mean age=62.30 years)	30	15
	Female (mean age=57.07 years)	170	85
Menstrual status	Pre-menopausal	12	6.0
	Post-menopausal	158	79.0
Diabetes/Glycemic status (HbA1c)	Good control (<7 %)	51	25.5
	Fairly controlled (7-8 %)	92	46.0
	Poorly controlled (>8 %)	57	28.5
Duration (in years)	>5-10	122	61.0
	>10-15	37	18.5
	>15	41	20.5
BMI group (kg/m^2)	Underweight (<18.5)	9	4.5
	Normal (18.5-22.9)	47	23.5
	Overweight (23-24.9)	41	20.5
	Pre-obese (25-29.9)	71	35.5
	Obese (≥30)	32	16

Table 2: Association between BMD at left femoral neck and duration of diabetes (n=200)

Duration group (years)	Normal	Low BMD	*P*
>5-10	70	52	
>10-15	28	9	.046[s]
>15	20	21	

P value reached from Chi-Square test. s- Significant
Low BMD = Osteoporosis and osteopenia

Table 3: Effect of Independent variables on low BMD in right femoral neck (n=199)

Variables	*p*	*OR*	95% CI for OR	
			Lower	Upper
Gender (female)	.258	1.673	.686	4.081
Duration of Diabetes(year)	.542	1.016	.966	1.068
HbA1c (mmol/mol)	.826	1.030	.791	1.341
Age (year)	.006[s]	1.049	1.014	1.085
BMI(kg/m^2)	.025[s]	.919	.853	.989

Note. *OR*= Odds Ratio, s- Significant
Low BMD = Osteoporosis and osteopenia

Table 4: Effect of Independent variables on low BMD in left femoral neck (n=200)

Variables	*p*	*OR*	95% CI for OR	
			Lower	Upper
Gender (female)	.169	1.862	.768	4.515
Duration of Diabetes (year)	.929	.998	.949	1.049
HbA1c (mmol/mol)	.702	1.052	.811	1.364
Age (year)	.006[s]	1.048	1.013	1.084
BMI(kg/m^2)	.016[s]	.914	.849	.984

Note. *OR*= Odds Ratio, s- Significant
Low BMD = Osteoporosis and osteopenia

Table 5: Effect of Independent variables on low BMD in spine (n=200)

Variables	*p*	*OR*	95% CI for OR	
			Lower	Upper
Gender (female)	.000[s]	5.185	2.115	12.711
Duration of Diabetes (year)	.801	.993	.941	1.048
HbA1c (mmol/mol)	.613	1.078	.805	1.445
Age (year)	.107	1.029	.994	1.067
BMI(kg/m^2)	.001[s]	.878	.812	.949

Note. *OR*= Odds Ratio, s- Significant
Low BMD = Osteoporosis and osteopenia

DISCUSSION

Nearly 90% of cases of T2DM and as people's lifestyles change more quickly; there are an increasing number of T2DM patients (2). The study revealed that, a significant portion of T2DM patients had low BMD. Osteoporosis is more common in lumbar spine than in both femoral necks and female diabetic patients are more prone to osteoporosis in lumber spine than male patients. Low BMD in left femoral neck has statistically significant association with duration of T2DM. No statistically significant correlation was found between glycemic status (HbA1c) and T-score. Binary logistic regression analysis revealed that, increasing age, female gender and low BMI in type 2 DM patients are independent risk factors for low BMD.

It was observed that, 41.5% patients belonged to the age group >50–60 years, which is the highest among the five groups. The mean age was 57.86 years, with patients ranging in age from 35 to 88 years. In a study conducted by Asokan et al. the mean age for diabetics was 56 years (6). A similar study was conducted by Mathen et al., where 150 patients with T2DM (diagnosed at age > 30 years) and an equal number (n = 150) of age and sex matched healthy controls were involved and the mean age of the diabetic group was 51.29 (SD ±8.05) years (13).

In this current study, majority (85%) of patients were female. The mean age for males was 62.30 years and for females, it was 57.07 years. It was observed that, 158 patients (79%) were post-menopausal. Mean T-scores were slightly lower in post-menopausal women than in premenopausal women in both femoral neck and spine. In case of right femoral neck, mean T-score in premenopausal women was -0.0667 and in post-menopausal women was -0.5993. In case of left femoral neck, in premenopausal women was -0.433 and in post-menopausal women was -0.713; and in case of spine -1.667 and -1.828 respectively. But there was no statistically significant difference found between the T-scores of the 'post-menopausal' and 'premenaupausal' group (p= 0.190, 0.470 and 0.470 respectively for right femoral neck, left femoral neck and spine). It may be due to the effect of long-term diabetes on bones. In a study in comparison to post-menopausal controls, the authors found that post-menopausal women with T2DM had significantly reduced BMD at the femoral neck and lumbar spine (13).

In the present study, the majority (61%) patients were involved in >5–10 year duration group. Chi-square test shows the duration of DM had no statistically significant association on BMD in right femoral neck (p = 0.083) and

spine (p =0.381); but has statistically significant association on BMD in left femoral neck (p = 0.046). A study conducted by Jang et al. on 3383 Asian males (aged ≥50 years) also stated that a significant correlation existed between DM duration and a lower BMD in the femoral neck (14). But in another study, no correlation between BMD and disease duration was found (8).

In this study, only 25.5% patients had good glycemic control (HbA1c <7 %) and 28.5% had poor glycemic control (HbA1c >8 %). 35.5% patients were preobese, 20.5% patients were overweight and 16% were obese. On the other hand, 23.5% had a normal BMI and only 4.5% were underweight. In case of right femoral neck BMD, 63 patients (31.5%) had osteopenia and only 13 patients (6.5%) had osteoporosis and in case of left femoral neck, 69 patients (34.5%) had osteopenia and 13 patients (6.5%) had osteoporosis. On the other hand, in case of spine, 75 patients (37.5%) had osteopenia and 60 patients (30%) had osteoporosis. So, it can be said that, 67.5% of diabetic patients had low spine BMD and 38% and 41% of diabetic patients had low right and left femoral neck BMD respectively. So, osteoporosis is much more prominent in lumbar spine and majority of the DM patients in this study had low BMD at least in one site. Another study also found a similar overall result (13). As per their hypothesis, the following could be the causes of the observed decreased BMD in diabetic patients : 1) diabetic patients in our country are thinner (in this current study, mean BMI 25.66 kg/m2) compared to western diabetic patients (mean BMI 27.8 kg/m2) (15,16). 2) race also plays an important role, as several studies show that BMD tends to be lower in South Asians people (17). Other studies found that patients with type 2 diabetes had higher rates of osteoporosis and considerably lower T score values (7, 18). Prakash et al. reported that, among 96 T2DM patients, the prevalence of osteoporosis at the spine 39.6% and at the hip it was 20.9%. The overall incidence seen was 43.8 % (19). Another study showed that, in diabetic patients who had low BMD, the mean BMI was 24.1 kg/m2 and in those with normal BMD, the mean BMI was 25.3 kg/m2. That study suggested that, BMI as an important predictor of BMD and that low BMI is associated with low BMD, increased risk of osteoporosis as well as fracture (6).

Binary logistic regression was performed to assess the impact of several factors on BMD. It showed that, duration of diabetes and HbA1c had no statistically significant contribution to the models for both femoral necks and lumbar spine. A study conducted by Bridges et al. showed no correlation between BMD and HbA1c (8). Multiple studies also reported no significant correlation between BMD and HbA1c (1, 7, 8). On the other hand, current study showed that, women have more than five times chance of having low BMD than men (odds ratio= 5.185, p = <0.001) in spine. Independent risk factors for low BMD were female gender, increasing age and low BMI. A study conducted by Bridges et al. reported, BMD in the type 2 diabetic group was significantly correlated with age (r=-0.350, p=0.001) and BMI (r = 0.314, p = 0.003) (8). De Liefde et al. suggested DM patients has higher BMI and BMD but have an increased fracture risk due to increased glycation end products and insulin levels(20). But Mathen et al. mentioned decreased BMD in T2DM patients (13).

CONCLUSION

The current study revealed that, in Bangladesh, a significant portion of type 2 diabetes mellitus patients had low bone mineral density. Osteoporosis is more common in lumbar spine than in both femoral necks. Low bone mineral density in left femoral neck has statistically significant association with duration of type 2 diabetes mellitus . No impact of glycemic status on bone mineral density was found. Low bone mineral density is also related to increasing age, female gender and low BMI in type 2 diabetes mellitus patients which is also common in non-diabetic patients.

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