Association between bone mineral density and vertebral fractures among patients with diabetes attending Teaching Hospital Karapitiya

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ABSTRACT

Introduction: Diabetes mellitus (DM) impairs bone strength resulting in an increased risk of fractures. This study was designed to determine the association between bone mineral density (BMD) and vertebral fractures among a selected group of patients with Type 2 diabetes mellitus.

Methods: This cross-sectional study included patients with diabetes, selected from clinic attendees at Teaching Hospital Karapitiya. Serum creatinine, urine microalbumin to creatinine ratio and a lateral radiograph of the thoraco-lumbar spine were done in all patients. Those who were detected to have vertebral fracture/s underwent bone densitometry. BMD was also measured in a group of patients selected from the rest of the group who did not have vertebral fractures and another group of healthy individuals selected from the same community. They were matched for the age and gender.

Results: In patients with diabetes (n=160, females 110), the mean (SD) age and the duration of the disease were 62 (10) years and 10 (3) years, respectively. Of patients with diabetes screened, 20 had vertebral fractures (12.5% prevalence). Compared to healthy controls, patients with diabetes without vertebral fractures had significantly low BMDs in the proximal femur but comparatively higher BMD in the total spine. BMDs measured in the total spine and proximal femur were not different between patients with DM vertebral fractures and without vertebral fractures.

Conclusions: Our data indicate a 12.5% prevalence of vertebral fracture among patients with DM. Although patients with diabetes in general had lower BMDs in most of the regions examined, there was no significant difference in regional BMDs between those with fractures and without fractures.

Keywords: Bone mineral density, cross-sectional study, diabetes, vertebral fracture

Introduction

Diabetes mellitus (DM) and fragility fractures are associated with increased morbidity, mortality and health-care cost, hence they have become major public health issues, globally. According to predictions, diabetes and fragility fractures will be more prevalent in the future but an exponential rise is expected in certain regions such as Asia.

Although diabetes is not counted in fracture risk assessment tools such as FRAX algorithm, many studies have demonstrated that patients with type 2 DM are at increased risk of fractures at hip, proximal humerus and foot (1). Studies related to vertebral fractures among patients with DM, however, are limited and inconsistent. While Vestergaard, *et al.*, and Yammamoto, *et al.*, found an

increased prevalence of vertebral fracture (VF) among adult patients with DM, Gerdhem, *et al.*, and Schwartz, *et al.*, found no such association (1).

DM could influence bone strength in many ways. Factors such as hyperglycaemia, hypercalciuria, elevated levels of cytokines and impaired renal function seen in DM could reduce bone strength (2). Hyperglycemia could affect bone strength by increasing formation of advanced glycosylated end products in collagen which is a determinant of load bearing of bone tissue. Furthermore, microvascular complications of DM could reduce the bone strength resulting in fractures.

Although Bone Mineral Density (BMD) is a strong predictor of fractures among postmenopausal women (3) and in patients on long-term glucocorticoids (4), previous studies have not shown BMD to be a significant predictor of fractures among patient with DM. Normal or even higher BMD values have been seen in patients with type 2 DM with vertebral and non-vertebral fractures suggesting that BMD is not a major determinant of microarchitectural deterioration in them (5, 6). Hence, the aetiology and mechanism of the mechanical failure of bone tissue among patients with DM remain poorly understood.

Owing to the scarcity of studies, there is no uniform opinion whether patients with DM should be routinely screened for fracture risk. Further, if a patient with DM is found to have a fracture, the value of BMD assessment is not certain. Similarly, the contribution of other risk factors; skeletal and extra-skeletal, to the occurrence of fractures in diabetics is not known.

Osteoporosis and DM are prevalent diseases in Sri Lanka and the co-existence of DM and either vertebral or non-vertebral fracture is not an uncommon clinical observation (7). Furthermore, the number of patients with this disease combination can be expected to increase in the future. Physical activity, socio-economic and nutritional factors that are related to both DM and bone health are different among Asians compared to other populations and this disparity may play an important role in determining fractures among patients with DM in Asia. This research was designed to study the association between BMD and fractures among a selected group of diabetics.

Methods

Patients with Type 2 DM attending adult medical clinics at Teaching Hospital Karapitiya were invited to participate in a cross-sectional study of vertebral fractures. Written informed consent was obtained from all participants and the study protocol was approved by the Ethics Review Committee of Faculty of Medicine, University of Ruhuna.

Demographic and disease-related data were collected using a pre-tested interviewer-based questionnaire and by perusing medical records. Serum creatinine and urine microalbumin to creatinine ratio were measured adhering to standard protocols. Body weight was measured to the nearest 0.1kg without footwear and height was recorded using a portable stadiometer (Weight Master International, Model BW-110H) to the nearest 0.5cm while on barefeet. Estimated Glomerular Filtration Rate (eGFR) was calculated with the Cockcroft-Gault formula (8).

Lateral radiographs of the thoraco-lumbar spine were taken in all patients recruited for the study. Radiographs were taken under standard conditions by one technician using the same x-ray machine. X-ray beam was focused on to T10 vertebra with the tube-patient distance of 6 cms. Radiographs were assessed by two investigators, in blinded manner, using a semi-quantitative method described by Genant, *et al.*, in 1993 (9). VFs were classified as follows: mild, a reduction in height of 20 - 25%; moderate, 25 - 40%; severe, more than 40%. An agreement of both assessors was required to define a VF and when in disagreement, they came to consensus after a discussion.

All patients who were detected to have VFs underwent bone densitometry and BMD values of the lumbar spine (L1-L4; total spine) and proximal femur were measured by dual-energy X-ray absorptiometry (Hologic Discovery, Bedford, USA). Using a random number generating table, an equal number of age and sex matched patients were selected from the rest of the group who had diabetes but not VFs and they too underwent DXA evaluation similar to patients with VFs. Lateral radiographs of the thoraco-lumbar spine and BMD measurement were done in a group of age and sex matched healthy individuals who had no DM, selected from the community. These healthy

controls were selected in a random manner using the latest voters' registers from the community catchment area of the same hospital. All BMD measurements were done by the same technician adhering to the manufacture's guidelines. In-vitro precision of the DXA machine was checked on each scanning day by calibrating the phantoms provided by the manufacturer and in-vivo precision of the BMD estimations of the same machine has been published earlier (10).

Statistical analysis

Data are given as mean (SD) unless stated otherwise. ANOVA with Bonferroni correlation for multiple comparisons was used to compare continuous numerical data of the three groups. Comparisons of categorical variables were done using chi-squared test and $p < 0.05$ was used to define statistical significance.

Results

There were 160 (110 females) patients included in the study and the mean (SD) age and the duration of the disease were 62 (10) years and 10 (3) years, respectively. Of 160 clinic attendees screened, 20 had vertebral fractures (12.5% prevalence) and 19 of them were females. Among the patients who had

fractures 13 (65%) had mild fractures, 5 (25%) had moderate and 2 (10%) of them had severe fractures. Two patients had multiple fractures and each one of the rest had a fracture of a single vertebra. The distribution of fracture sites was as follows: 8 in T12, 4 in T11, 2 in T8, T10, T4, T7 each, 00 in L1 and 00 in L2. When demographic and biochemical data were compared, there was no significant difference in BMI, duration of DM, smoking habits, alcohol consumption, post-menopausal status (among women) and glomerular filtration rate between patients with DM with and without VFs (Table 1).

There were no VFs among the age and sex matched non-diabetic controls. Analysis of variance showed a significant difference between three groups of patients with regards to their BMDs at the neck of the femur, hip, and trochanteric region (Table 2). Post-hoc comparisons showed significantly lower BMD values in all regions of proximal femur among diabetics, regardless of the presence of VFs, compared to healthy controls. Total spine BMD among all patients with diabetes was significantly higher compared to healthy controls but the total body BMD was not different. There was no significant difference in BMDs at any skeletal site examined between patients with DM with VFs and without vertebral fractures (Table 2).

Table 1: Demographic and disease related data about the patients

Variable	Diabetics with vertebral fractures (n=19)	Diabetics without vertebral fractures (n=16)	Non diabetic controls (n=18)	p-value
Age (years)	64.5 (11)	59 (7.5)	62 (11)	0.13
BMI (kg/m ²)	25 (3.8)	23.2 (2.9)	24.2 (3.1)	0.17
Duration of DM (years)	9.5 (3.1)	8.9 (3.3)	-	0.25
eGFR (Estimated Glomerular Filtration Rate)	61.8 (26)	66.7 (15.7)	-	0.16
% currently on atorvastatin	73.7	87.5	-	0.31
% currently on metformin	68.4	62.5	-	0.71
% currently on insulin	5.3	2.5	-	0.10
% currently smoking	10.5	12.5	13	0.66
% current alcohol users	10.5	12.5	14	0.56
% menopausal women	88	79	81	0.17

None were on pioglitazone

Table 2: Comparison of bone mineral densities (BMDs) between patients with DM with and without VFs and healthy controls

Site	Patients with diabetes, with vertebral fractures (n=19)	Patients with diabetes, without vertebral fractures (n=16)	Healthy controls (n=18)	p-value
Total Body BMD	0.984 (0.160)	0.955 (0.120)	1.096 (0.120)	0.15
Femoral Neck BMD	0.706 (0.12)*	0.693 (0.09)*	0.780 (0.06)	0.02
Trochanter BMD	0.586 (0.10)*	0.593 (0.07)*	0.680 (0.05)	<0.01
Total hip BMD	0.832 (0.15)*	0.819 (0.09)*	0.940 (0.076)	<0.01
Total spine BMD	0.780 (0.17)*	0.751 (0.13)*	0.680 (0.05)	0.57

* indicate significant differences ($p < 0.05$) when compared with corresponding values of the healthy controls

Discussion

Our data indicates the differences in BMD among patients with diabetes with VFs compared to those with DM without fractures and healthy controls. There was 12.5% prevalence of VFs among patients with diabetes and they were mostly seen in women. Patients with diabetes have lower BMDs in all sites in the proximal femur regardless of the presence of VFs. Total spine BMD was higher among patients with diabetes and this probably a result of aortic calcification and degenerative changes commonly seen among patients with diabetes. Soft tissue such as major vessel and ligament calcification is common in diabetes and this may have erroneously increased spinal and total body BMDs (11, 12). BMDs in the proximal femur are relatively less affected due to above changes and more likely to reflect real BMD changes in diabetes.

In a previous study by Yamamoto, *et al.*, where 90% of study subjects were postmenopausal women with type 2 DM with a mean age of 63 years, 17.3 % were detected to have VFs (5). In another study which comprised of 76 postmenopausal diabetic women, 26.3% were detected to have VFs (13). A cross-sectional study with 137 postmenopausal women and 161 men reported prevalence figures 31.4% among women and 37.9% among men (14). Compared to all other studies this reported a very high prevalence of vertebral fractures among the diabetics. This could partly be due to the sample

they recruited. Compared to patients in other studies, these patients had advanced diabetes with worse HbA1C profiles (14). A study conducted in Brazil, reported a fracture prevalence of 23% (2). Volha, *et al.*, reported a prevalence vertebral fracture among patients with type 1 diabetes as 25% (Volha, Christina, *et al.*, 2013). Among the 82 patients they studied 20 patients had vertebral fractures. We found 12.5% prevalence of vertebral fractures among patients with Type 2 DM in our sample and this is relatively a low prevalence compared to other studies.

We found no difference in the duration of diabetes, diabetes complications, alcohol consumption, smoking status and postmenopausal status between those with and without vertebral fractures. Our findings are in keeping with observations made by Touminun, *et al.*, in 1999. (15). Furthermore, regional BMD values were not different between patients with VFs and without VFs among patients with DM. Hence we could assume that mechanism of VFs among patients with DM must be a result of reduced material quality independent of BMD. Accumulation of Advanced Glycation end-products (AGE) which lead to diabetic complications such as nephropathy and neuropathy have been found in bone tissue as well. These products may affect the mechanical properties of the bone and deteriorate the strength of the bones. Researchers have found

that pentosidine which is an AGE, present in the trabecular and cortical bones is associated with VFs, (16). They also proved that these changes in the bone quality occur independent of BMD values.

Previous studies examining BMD differences between Type 2 diabetics and non-diabetic controls have reported conflicting results. They reported higher (17), similar (15) and lower BMD values (18, 19) among diabetic patients compared to healthy controls. Our analysis showed lower BMD values among patients with DM with or without VFs compared to healthy controls at all sites except the spine. This difference could be explained by the methodological differences among the studies. For example Rotterdam study, which showed a higher BMD values for patients with type 2 DM than controls contained many patients who had mild disease and previously undiagnosed diabetes (17). In contrast, our study included patients with long standing disease. Different BMD values between the patients with DM and healthy controls could be explained by changing insulin levels over time in patients with type 2 DM. Insulin levels are usually high at the onset of disease and become low in long standing diabetes mellitus. Insulin by a direct act on bone probably via IGF 1 receptor and by an inverse effect on sex hormone binding globulin (SHBG) increases BMD. BMD can be expected to be higher among early diabetics with relatively higher insulin level compared to long standing diabetics who have depleted insulin level.

This was a cross-sectional study and we only considered vertebral fractures in this analysis. Longitudinal studies are needed to prove the importance of BMD in assessing vertebral fractures among diabetics.

The present study shows reduced BMDs in the proximal femur among diabetics regardless of the presence of VF. BMDs, however, were not different among patients with diabetes with and without fracture indicating that BMD is not a reliable measure of VF and BMD cannot be included in the fracture risk assessment in diabetes. Further studies should be done to assess bone quality such as microarchitecture to detect the determinants of mechanical failure of bone tissue among diabetics. Until such studies are done, clinicians will have to consider routine radiography as the reliable and easy way to detect those with VFs.

Conflict of interest

All authors have no conflict of interest.

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