Original Article

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Decreased Bone Mineral Density at the Femoral Neck and Lumbar Spine in South Indian Patients with Type 2 Diabetes

Internal Medicine Section

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ABSTRACT

Background: With prevalence of diabetes in India reaching epidemic proportions and increase in the population of geriatric age group and risks of falls, it is important to understand the effect that diabetes has on bone health.

Aim: The objective was to assess bone mineral density (BMD) of patients with type 2 diabetes mellitus (T2DM) and to study factors contributing to BMD in patients with T2DM.

Materials and Methods: This was a prospective cross-sectional study on 150 patients with T2DM (diagnosed at age > 30 years) and an equal number (n=150) of age and sex matched healthy controls from September 2012 to July 2014 at a tertiary care center located in Southern India. BMD was measured at the femoral neck and lumbar spine (L2–L4) by dual energy absorptiometry (DXA) in cases and controls. Serum total calcium, phosphorus and alkaline phosphatase (ALP) and 25-OH- vitamin D3 was measured in patient group.

Results: Mean age (SD) was 51.29 (±8.05) and 51 (±8.3) years in cases and controls, respectively. The femoral neck and lumbar spine BMD was significantly lower in T2DM cases compared to controls. Also the femoral neck and lumbar spine T-score was significantly lower in T2DM cases compared to controls. Femoral neck BMD among male patients with T2DM was significantly lower compared to controls (men). Among women, BMD at femoral neck as well as lumbar spine was significantly lower in cases when compared to controls. Ninety six out of 150 (64%) T2DM cases had Vitamin D values <20 ng/mL. There was weak negative correlation between age of patient, duration of diabetes and HbA1C with femoral neck BMD. There was weak negative correlation between HbA1C and lumbar spine BMD.

Conclusion: Indian subjects with type 2 diabetes have significantly lower BMD at both femoral neck and lumbar spine compared to age and sex matched healthy controls. We conclude that osteopenia and osteoporosis are overlooked complications of diabetes. Longitudinal studies are needed to see for actual incidence of fractures among this high risk group.

Keywords: BMD, Fractures, Osteoporosis, Vitamin D deficiency

INTRODUCTION

Several factors contribute to increased incidence of hip fracture in diabetics- such as hypoglycaemic episodes, orthostatic hypotension, which causes falls. Additionally poor bone microarchitecture and poor bone quality even in the presence of a high bone mineral density (BMD) contributes to high fracture risk in diabetics [1]. A recent meta-analysis comprising15 observational studies pooled data from 3437 subjects with type 2 diabetes mellitus (T2DM) and over 19000 controls showed that BMD was significantly higher in diabetics [2].

However, it was recently shown that Indian subjects with diabetes have low BMD [3]. Hence, we set out to study the BMD status of patients with T2DM attending the Diabetes Clinic of a tertiary care center located in Southern India. Based on currently available evidence we expected the BMD among our subjects with T2DM to be higher or comparable to healthy controls.

AIM

To assess BMD using dual energy X-ray absorptiometry (DXA) in patients with T2DM and to study factors contributing to BMD in patients with T2DM.

MATERIALS AND METHODS

A prospective cross-sectional study was conducted on 150 patients with T2DM (diagnosed at age >30 years and above) and an equal number (n=150) of age and sex matched healthy controls from September 2012 to July 2014, at a tertiary care center located in South India. The sample size was calculated to be 150 cases and 150 controls in order to detect a change in BMD by at least 0.2 g/cm2 with 80% power and alpha error of 5%. The diagnosis of T2DM was based on the criteria of the American Diabetes Association 2012 [4].

Patients with type 1 diabetes, those with chronic kidney disease (with calculated eGFR of <60mL/min/m^2), thyroid disease (either hypo or hyperthyroidism), patients on corticosteroids and non-ambulatory patients were excluded from the study.

Consecutive patients with T2DM attending the Diabetes Clinic were invited to participate in the study. Those who gave consent and were willing to undergo DXA scan and fulfilled the inclusion and exclusion criteria were included. Detail medical history was taken. This included duration of diabetes, treatment taken, smoking, history of fracture, and menopausal status in women. Patients were assessed for the presence or absence of microvascular complications such as retinopathy, nephropathy and neuropathy. The presence or absence of coronary artery disease (CAD) defined by finding of wall motion abnormality on echocardiogram or if CAD was detected by coronary angiogram was also noted. Plasma HbA1C was done in all patients.

Biochemical investigations

Serum total calcium, phosphorus and serum alkaline phosphatase (ALP) was measured in all patients. For estimation of 25 hydroxy vitamin D3 (Vitamin D), 5 ml of venous blood was drawn, blood was centrifuged, sera separated and stored at -20^0 degrees until assayed. Serum Vitamin D was estimated by commercial ELISA kit (ADVIA Centaur® ReadyPack™, Germany). It was also planned to use the separated sera for measuring intact PTH levels. However, on attempted measurement of iPTH levels in the sera, it was found that most samples showed values close to zero. This is most likely a problem with storage and handling of samples and hence analysis of iPTH values could not be done successfully and its analysis was abandoned.

Controls- After completion of recruitment of patients with T2DM, an equal number of aged and sex matched healthy controls were

recruited from community camps. The controls did not have diabetes or any other medical or surgical illness or any fractures. Biochemical tests were also done which included serum total calcium, phosphorus and ALP. However, we did not measure serum Vitamin D in the control group.

Informed written consent was obtained from all patients and controls before enrolling them into study. The study protocol was approved by the institute ethics committee.

Measurement of BMD

BMD was measured at the lumbar spine (L2–L4) and femoral neck by DXA (Hologic Discover Wi™ densitometer, Mass USA). The primary outcome measure was comparison of BMD (g/cm^2) in cases and controls.

STATISTICAL ANALYSIS

Data was analysed using both descriptive and differential statistics. Categorical data such as gender, menopausal status, clinical findings was presented as frequencies and percentages and was compared by Fisher's exact test. The normality of continuous variables such as HbA1c, serum calcium, phosphorus, alkaline phosphatase, Vitamin D levels and BMD was tested and accordingly expressed as mean with SD or median with range and was compared by using independent student t-test or Mann Whitney U-test. The relation between the continuous parameters was analysed by correlation analysis. Regression analysis was planned to be carried out to identify relationship between continuous variables. All statistical tests were carried out at 5% level of significance and p value <0.05 was considered significant. Data was analysed using SPSS software version 20 (IBM Corp, USA).

Characteristic	T2DM (n=150)	Controls (n=150)	p
Age in years	51.29 (±8.05)	51 (±8.3)	
†Men, n (%)	67 (44.6%)	63 (42%)	
BMI (kg/m^2)	25.63 (±4.83)	23.87 (±3.86)	<0.001
Waist circumference (cm)	87.92 cm (±7.49)	84.29 (±6.79)	<0.001
Calcium (mg/dL)	9.35 (±.68)	8.63 (±.72)	<0.001
Phosphorus (mg/dL)	3.67 (±.61)	3.77 (±.48)	0.0982
ALP (IU/dL)	105 (±44.42)	103.66 (±37.62)	0.7005
Femoral Neck BMD (g/cm^2)	0.7700 (±0.12)	0.8260 (±0.13)	<0.0001
Hip T score	-1.55 (±1.5)	-0.9946 (±1.08)	0.0003
Hip Z score	-0.48 (±1.08)	-0.48 (±1.02)	0.9967
Lumbar Spine BMD (g/cm^2)	0.8517 (±0.16)	0.8991(±.15)	0.01
Lumbar spine T score	-1.415(±1.27)	-0.9679(±1.31)	0.0029
Lumbar spine Z score	-0.8704(±1.32)	-0.5539(±1.18)	0.0298

[Table/Fig-1]: Baseline Characteristics and BMD of patients with type 2 diabetes mellitus and healthy controls
Abbreviations- BMD; bone mineral density; T2DM, type 2 diabetes mellitus; BMI, body mass index; ALP, serum alkaline phosphatase

RESULTS

Three hundred patients were studied (150 T2DM and 150 controls). There were 67 men and 83 women in the T2DM cases. In the control group there were 63 men and 87 women. The baseline characteristics are summarized in [Table/Fig-1]. Among patients with T2DM, 18 (12%) had evidence of CAD, 18 (12%) had nephropathy, 30 (20%) had peripheral neuropathy and 41 (27.3%) had retinopathy. Out of the 150 patients with T2DM, 8 (5.3%) patients were on dietary therapy alone; 51 (34%) were on insulin ± metformin; 87 (58%) were ononsulphonylureas ±metformin; and 4 (2.6%) were on pioglitazone + metformin.

Seven patients out of 150 (4.6%) T2DM patients gave history of fractures in the past. However, among this only one female patient had hip fracture secondary to trivial injury, rest of the fractures was related to trauma in road traffic accident.

BMD in Cases and Controls

[Table/Fig-1] shows the BMD (g/cm^2), T Score, Z score at femoral neck and lumbar spine between cases and controls. The BMD at femoral neck and lumbar spine was significantly lower in T2DM cases compared to controls. Also, the femoral neck and lumbar T-score was significantly lower in T2DM cases compared to controls.

BMD in men and women-The BMD at femoral neck among men was significantly lower in cases compared to controls (men). However the lumbar spine BMD and T-score was similar in diabetic men when compared with controls (men). Among women BMD at femoral neck as well as lumbar spine was significantly lower in cases compared to controls [Table/Fig-2].

BMD according to menopausal status in women

There were a total of 83 women among T2DM cases (83/150) and 87 female healthy controls (87/150). Among these women 61/83 T2DM cases and 60/87 controls were postmenopausal. We sought to see whether any difference in BMD was seen in this subgroup. As expected we found that post-menopausal women with T2DM had significantly lower BMD at both femoral neck and lumbar spine as compared to post-menopausal controls [Table/Fig-3].

Vitamin D Status in T2DM Cases

The mean serum Vitamin D in diabetes group was 20.31±12.37ng/mL. Ninety six out of 150 (64%) T2DM cases had Vitamin D values <20 ng/mL. So 64% of T2DM patients were Vitamin D deficient. While 43/150 (28.6%) had vitamin D levels between 20-20.99 ng/mL (insufficient levels); Just 11 patients (7.3%) had normal Vitamin D levels (>30 ng/mL).

Variable	Cases (n=61/83)	Controls (n=60/87)	p-value
Femoral Neck BMD (g/cm^2)	0.7301(±0.11)	0.7933(±0.13)	0.005
Lumbar spine (g/cm^2)	0.7801(±0.15)	0.8969(±0.12)	0.0005

[Table/Fig-3]: Bone mineral density of post-menopausal women with T2DM (cases) compared to post-menopausal controls (women)

Abbreviations- T2DM, type 2 diabetes mellitus; BMD, bone mineral density; Values are in mean ±SD

	Men			Women		
Variable	T2DM (n=67)	Controls (n=63)	p	T2DM (n=83)	Controls(n=87)	p
Femoral Neck BMD (g/cm^2)	**0.7854 (±0.12)**	**0.8372 (±0.11)**	**0.0002**	**0.7574(±0.12)**	**0.8179(±0.13)**	**0.003**
Hip T score	-1.818 (±1.33)	-1.2626 (±1.12)	0.01	-1.34(±1.61)	-0.8005(±1.02)	0.01
Hip Z score	-0.68 (±1.03)	-0.82 (±.98)	0.4	-0.32(±1.1)	-0.24(±0.97)	0.6
Lumbar spine BMD (g/cm^2)	0.8839 (±0.15)	0.8800 (±0.14)	0.8	0.8258(±0.17)	0.9129(±.15)	0.0007
Lumbar spine T Score	-1.48 (±1.15)	-1.12 (±1.30)	0.09	-1.35(±1.36)	-0.85(±1.32)	0.01
Lumbar spine Z Score	-1.02 (±1.21)	-0.8744 (±1.02)	0.4	-0.74(±1.39)	-0.32(±1.24)	0.03

[Table/Fig-2]: Comparison of BMD in men and women between T2DM and controls

Abbreviations- BMD, bone mineral density; T2DM, type 2 diabetes mellitus; Values are in mean ±SD

We classified the T2DM cases based on the T score (at femoral neck and lumbar spine) in to 3 groups- Those patients with osteoporosis (T Score <2.5), osteopenia (T score between -1 to -2.49) and those with normal T score (T score >-1) and determine the mean Vitamin D in each group. We found that mean Vitamin D in the three groups were similar [Table/Fig-4].

Hip T score	Vitamin D (ng/mL) mean ± SD	Lumbar spine T score	Vitamin D (ng/mL) mean ± SD
T score <2.5 (Osteoporosis)	22.53 (±11.4)	T score <2.5 (Osteoporosis)	20.19 (±12)
T score -1 to-2.49 (Osteopenia)	20.90 (±12.18)	T score -1 to-2.49 (Osteopenia)	22.1 (±14.4)
T score >-1 (Normal)	19.02 (±9.94)	T score >-1 (Normal)	17.87 (±6.22)

[Table/Fig-4]: Mean serum vitamin D levels in patients with type 2 diabetes mellitus (T2DM) cases classified as having osteoporosis, osteopenia and normal bone mineral density on hip T score and lumbar spine T score

Variable	Hip BMD (r)	Spine BMD (r)
Age of patient	-0.29	-0.16
Duration of diabetes	-0.29	-0.08
BMI	0.21	0.30
HbA1c	-0.26	-0.32
Calcium	-0.01	0.05
Phosphorus	0.00	0.03
ALP	-0.05	-0.07
Vitamin D	-0.01	-0.22

[Table/Fig-5]: Linear correlation analysis between clinical, laboratory parameters with bone mineral density (BMD)

Abbreviations-BMD, bone mineral density; BMI, body mass index; HbA1c, glycated haemoglobin; ALP, serum alkaline phosphatase; r, mean correlation coefficients

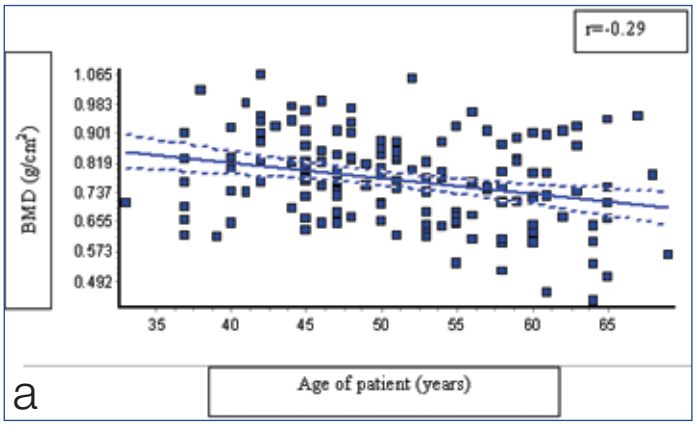
Correlation between clinical and laboratory parameters among cases and BMD- In order to address the second objective we performed linear correlation analysis between clinical and laboratory parameters of the T2DM cases. The parameters selected were age of patient, duration of diabetes, BMI, HbA1C, serum calcium, phosphorus, ALP and Vitamin D [Table/Fig-5]. There was weak negative correlation between age of patient and femoral neck BMD- [Table/Fig-6a]. Similarly longer duration of diabetes had a weak negative correlation with femoral neck BMD- [Table/Fig-6b]. The longer the diabetes duration, the lower is the BMD at the hip. Also, BMI positively correlated with BMD at femoral neck [Table/Fig-6c] and lumbar spine. The HbA1c levels had an overall weak negative correlation with BMD at femoral neck- [Table/Fig-6d] and lumbar spine BMD.

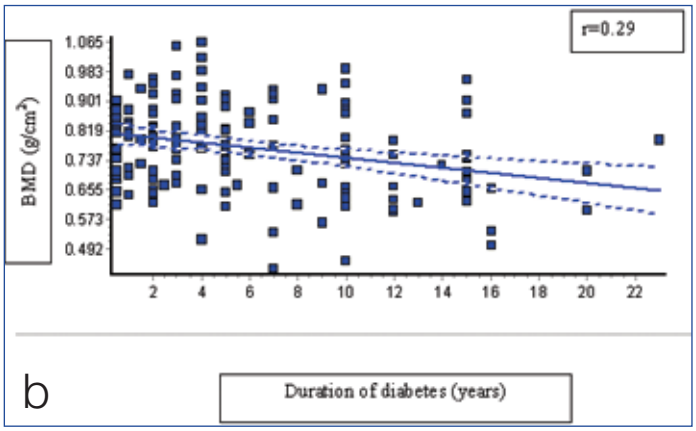
DISCUSSION

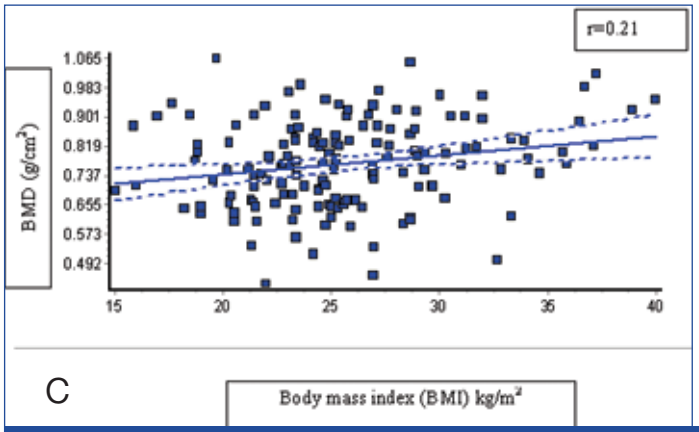
Contrary to studies done in developed countries [2], we found that our diabetic patients had significantly reduced BMD at both femoral neck and lumbar spine as compared to healthy non- diabetic controls.

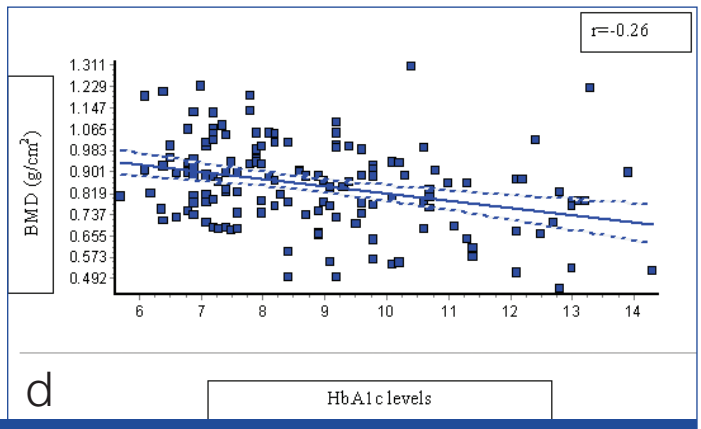
These findings are in line with a study done in the 1970s. Levin et al., studied 35 type 1 diabetes and 101 adult onset diabetes and found that BMD measured by DXA was significantly lower in diabetics as compared to gender and age matched controls [5]. This is also consistent with the more recent work by Suzuki et al., who studied 104 Japanese T2DM subjects and 108 healthy controls [6]. The authors found that BMD measured at second metacarpal bone by computed X-ray densitometry (CXD) was significantly lower in diabetics as compared to controls.

Reduced BMD in diabetes was also described from New Delhi [3] although there are differences in terms of the population from where the diabetic cases were drawn from and study design. The study was done in a tertiary care army hospital where majority of the cases









[Table/Fig-6]: (a) Correlation between age of patient and BMD at femoral neck. (b) Correlation between duration of diabetes and BMD at femoral neck. (c) Correlation between BMI and BMD at femoral neck. (d) Correlation between HbA1c and BMD at femoral neck.
Correlation between the age of patient and BMD at hip (femoral neck) (panel A); duration of diabetes and BMD at the hip (femoral neck) (panel B); BMI and BMD at hip (femoral neck) (panel C); mean HbA1c and BMD at hip (femoral neck). In the figure the BMD measurements at hip (femoral neck) were plotted against the age of patient (A), duration of diabetes (B), mean BMI (C) and mean HbA1c levels (D). The straight line reflects the regression and r mean correlation coefficients and dotted lines reflect the confidence intervals for each correlation

were army men, who tend to be active, healthier and taller than their civilian counterparts. Additionally, patients in their study had low BMI probably indicative of the active lifestyle of army men. Despite being from an army background, the BMD in these T2DM patients was lower compared to healthy controls. Likewise an earlier study from North India on 400 T2DM patients and 400 controls showed that T2DM patients have low BMD when compared to controls [7]. However, the BMD was measured by ultrasound technique, and therefore may not be directly comparable with our study.

The reasons for our observation of low BMD in diabetics could be several-

a) Indian diabetic subjects (mean BMI 22.2) are thinner compared to western diabetics (mean BMI 27.8) [8,9]. Probably this has a strong influence on the lower BMD findings in our study subjects. Our patients with diabetes had a mean BMI of 25.63 which is also lower than western averages.

b) Racial disparities in BMD have also been documented in several studies showing that BMD tends to be lower in south Asians. In a study in Leicester, BMD was compared between healthy ethnic Indians and whites; BMD at both hip and spine was significantly reduced in the Indian group [10].

c) Vitamin D insufficiency may be a contributing factor for lower BMD. Vitamin D deficiency is more prevalent among diabetics compared to non-diabetics. It has been shown recently by Subramanian et al., who studied 92 diabetics and an equal number of matched controls [11]. The mean vitamin D (ng/mL) was significantly lower in diabetics as compared to controls (11.0 ± 7.5 vs 15.5 ± 9.8, p = 0.001). In our study also, 64% of our T2DM cases have vitamin D deficiency and the mean Vitamin D concentration in the 150 cases was 20.07ng/mL, which falls in the deficient range.

Contrasting to our results, a recently published study from India reported that BMD in diabetes is comparable to controls [12]. The authors had studied 194 patients with T2DM and compared their BMD to 571 non-diabetics. They found higher BMD in cases compared to controls, but this significance disappeared on analysis of a BMI matched control subgroup. This study has some major differences from ours- in that they recruited relatively younger diabetic patients with age range of 30-50 years, without micro or macrovascular complications. It was interesting to note that the BMD was normal (Z score >-2) in 156 (80.5%) and low (Z score ≤ -2) in 38 (19.5%) patients in the diabetes studygroup. It is probable that low BMD in our study patients was contributed by the presence of microvascular and macrovascular complications and older age. However, we have not powered the study enough to detect the effect of complications of diabetes on BMD.

BMD in diabetic women- As expected post-menopausal diabetic women in our study cohort had lower BMD when compared to post-menopausal controls, as had been previously shown [3,7,13,14]. We presumed an increased and additive effect of T2DM on BMD in post-menopausal women. Hence post-menopausal women with diabetes should be a target for aggressive screening. DXA measurements may be undertaken in this high risk group though it is not conventionally indicated as per the WHO. Therapeutic intervention such as bisphosphonates may be beneficial [15].

BMD in diabetic men- We observed that diabetic men had a lower femoral neck BMD as compared to healthy controls, while the lumbar spine BMD is similar in cases and controls. Another observation that appears is that osteoporosis or osteopenia was present in 57% male controls as against 40% female controls and the trend is similar among cases as well; with 77.4% males and 55.3% females having osteoporosis or osteopenia. In a recent study of 200 otherwise normal Indian males above 50 years, it was observed that osteopenia and osteoporosis was prevalent up to 50% otherwise healthy men [16]. Hence we believe that osteoporosis an under recognized ailment of elderly males.

Linear correlation analysis showed that the older the patient is the lower is the BMD at the femoral neck. This is expected as age is the single most important risk factor for development of osteoporosis. Patients who had diabetes for a longer duration also had lower BMD at femoral neck. This is also expected as the pathogenic mechanisms which underlie poor BMD has to act for a critical duration before bone fragility actually occurs. We observed that 3 patients had osteoporosis within 6 months of being diagnosed with T2DM.

We found BMI to be correlating positively with BMD i.e. obese patients have better BMD. It is known that higher BMI is one of the important factors which determine BMD by increasing mechanical loading and remodeling forces on the bone. Recent studies [17] and a recent meta-analysis [18] showed that higher BMI is a strong independent factor leading to higher BMD in diabetic population. However, despite high BMD the overall bone quality is poor and overall fracture risk is higher compared to normal population as exemplified by the Rotterdam study [19].

We found that the degree of glycaemic control (using HbA1c as a surrogate marker) had a weak negative correlation with BMD. However, this correlation has not been consistently found in other studies [14,17,20]. Both the Indian studies failed to demonstrate any correlation between glycaemic control and BMD. However, the Rotterdam study demonstrated that inadequately controlled diabetes (HbA1C of ≥7.5%) is associated with increased fracture risk [19,21]. A more recently published large epidemiological study of 20,025 older patients with type 2 diabetes from Taiwan showed that patients with HbA1c levels exceeded 9.0% exhibited an increased risk of hip fracture [22]. Since the critical component of T2DM and the most important therapeutic target in diabetes is hyperglycemia, it was only expected from a clinical perspective to assume that worse glycaemic control leads to a poor bone quality and subsequent fractures in patients.

We found that serum calcium level was significantly higher in diabetics as compared to controls. However, this is unlikely to have any clinical relevance as none of the values are in hyocalcaemic range and there was no significant difference in ALP levels. However in the study by Dutta et al., it was found that diabetics had significantly lower ALP levels [3]. This probably is a reflection of poor bone health. ALP is produced by active osteoblasts when active bone synthesis is occurring. Diabetics tend to have dysfunctional osteoblastic activity leading to poor bone remodeling and overall poor bone health [23,24]. Although majority of our patients had vitamin D deficiency we found no association between vitamin D levels and BMD.

LIMITATIONS

The limitations of the study are cross-sectional study design and we have not assesses the effect of medications, the study was not designed to detect differences in BMD owing to treatment. This is a potential confounder as patients on insulin have been shown to have higher fracture risk [25], metformin appears to have protective effect on bone [25,26] and thiazolidinedione causes reduction of BMD [26]. More importantly we have not match the BMI for cases and controls. This has an important bearing on the results since BMI is an important determinant of the BMD. Also, we could not exclude the effects of smoking and alcohol on BMD.

CONCLUSION

Type 2 diabetes patients from Southern India have reduced BMD at both femoral neck and spine compared to age and sex matched healthy controls. This finding of low BMD was seen across subgroups viz; diabetic men, diabetic women and post-menopausal diabetic women. Osteoporosis and osteopenia is one of the overlooked complications of T2DM. Treating physicians are encouraged to take necessary steps for early detection and prompt treatment of this

condition. Longitudinal studies in India need to be done to look for actual incidence of fractures among this high risk group.

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