



Do proximal hip geometry, trabecular microarchitecture, and prevalent vertebral fractures differ in postmenopausal women with type 2 diabetes mellitus? A cross-sectional study from a teaching hospital in southern India

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Abstract

Summary This study from southern India showed that the trabecular microarchitecture and proximal hip geometry were significantly impaired in postmenopausal women with diabetes as compared to age and BMI matched non-diabetic controls. This is despite there being no significant difference in bone mineral density at the femoral neck and hip not between both groups. One-third of the study subjects with type 2 diabetes had prevalent vertebral fractures. Bone mineral density assessment as a standalone tool may not adequately reflect bone health in subjects with diabetes.

Introduction There is limited information with regard to bone health in Indian postmenopausal women with type 2 diabetes. We studied the bone mineral density (BMD), trabecular bone score (TBS), prevalent vertebral fractures (VF), proximal hip geometry, and bone mineral biochemistry in ambulatory postmenopausal women with and without type 2 diabetes mellitus (T2DM).

Methods This was a cross-sectional study conducted at a tertiary care center. BMD, TBS, prevalent vertebral fractures, and hip structural analysis (HSA) were assessed using a dual-energy X-ray absorptiometry (DXA) scanner. Bone mineral biochemical profiles were also studied.

Results A total of 202 ambulatory postmenopausal women known to have type 2 diabetes mellitus with mean (SD) age of 65.6 (5.2) years and 200 age and BMI matched non-diabetic controls with mean (SD) age of 64.9 (4.7) years were recruited from the local community. Although the prevalence of lumbar spine osteoporosis was significantly lower among cases (30.7%) as compared to controls (42.9%), the prevalence of degraded bone microarchitecture (TBS < 1.200) was significantly higher among cases (51%) than in controls (23.5%); $P < 0.001$. Prevalent vertebral fractures were not significantly different in cases and controls. The various geometric indices of the proximal hip were significantly impaired in subjects with diabetes as compared to controls.

Conclusion This study may highlight the utility of the trabecular bone score and hip structural analysis in subjects with diabetes, where the bone mineral density tends to be paradoxically high, and may not adequately predict fracture risk.

Keywords Hip structural analysis · India · Postmenopausal osteoporosis · Trabecular bone score · Type 2 diabetes mellitus · Vertebral fractures

Introduction

The prevalence of diabetes mellitus (DM) in India is increasing at a rapid pace, and with improved longevity, a significant

proportion of people living with diabetes are in their seventh decade of life [1]. The number of patients with diabetes mellitus in India has progressively increased from 26 million in 1990 to 64 million in 2016 and is projected to reach a figure of 134 million by 2045. In India, recent epidemiological studies have shown evidence of the emerging epidemic of DM across all classes, affecting both the affluent and poor alike. In 2016, the prevalence of diabetes was highest in Tamil Nadu, Kerala, and Delhi [2]. Poorly controlled diabetes mellitus is associated with neuropathy, retinopathy, and

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nephropathy leading to end-stage renal disease. Besides these micro-vascular complications, the non-communicable diseases that occur more commonly with diabetes include cardiovascular disease, cancer, osteoporosis, and fractures resulting from trivial trauma and increased skeletal fragility [3].

In India, about 30–50% of the ambulatory postmenopausal women are affected with osteoporosis [4]. The mortality after a hip fracture is estimated to be about 20% in the first year following the fracture. Several epidemiological studies have shown an increased fracture risk in individuals with diabetes. In the recently published INDIAB study, which is a community-based survey to estimate the prevalence of diabetes across India, it was found that the prevalence of self-reported fractures was significantly higher in subjects with diabetes (4%) as compared to those without (2.5%). Moreover, after gender stratification, diabetes emerged as an important risk factor for fractures only in women [5].

The presence of peripheral neuropathy, poor vision, and hypoglycemia further predispose subjects with diabetes to an increased risk of falls. Oral glucose-lowering medications such as thiazolidinediones may have an adverse effect on skeletal integrity. However, bone mineral density (BMD) which is a surrogate measure of bone strength is found to be elevated in patients with type 2 diabetes mellitus and is not necessarily reflective of the increased bone fragility inherent to diabetes. Some of the mechanisms postulated to cause an increase in BMD in individuals with diabetes include reduced bone turnover due to osteocyte dysfunction, accumulation of advanced glycation end products, impaired incretin response, and elevated sclerostin levels. Hyperinsulinemia and presence of obesity are also factors that contribute to an increase in BMD. Thus, measurement of BMD as a standalone test may not be a true indicator of bone strength in subjects with diabetes [6].

Despite a higher BMD, the increased fracture risk in subjects with diabetes has been attributed to deteriorated proximal hip geometry, increased cortical porosity, and degraded trabecular microarchitecture resulting in poor bone quality. Poor hip geometry in subjects with diabetes has previously been shown in the Baltimore Longitudinal Study, the Canadian Multicentre osteoporosis Study, and the Women's Health Initiative observational study [7]. In healthy individuals, both physical activity and mechanical properties of the proximal hip are significant players determining bone strength. Although few studies have shown better BMD and hip geometric parameters in insulin-treated subjects, when corrected for lean mass, geometric indices of bone resistance to axial (cross-sectional area) and bending (section modulus) forces were significantly lower than in non-diabetic women. The exact mechanism underlying the poor hip geometry in subjects with diabetes is unclear although it appears that the presence of hyperglycemia tends to diminish the response of bone to mechanical stimuli [8].

The inherent limitations with regard to mere assessment of BMD in subjects with diabetes mellitus may result in poor capture of microarchitectural alterations and geometric changes, both of which contribute significantly to fracture risk. Trabecular bone score (TBS) is a novel densitometric tool that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect measure of bone microarchitecture [9].

TBS improves fracture-risk prediction beyond that provided by BMD and clinical risk factors, and can be incorporated to the Fracture Risk Assessment tool (FRAX) to enhance fracture prediction [10]. In patients with diabetes mellitus with paradoxically higher BMD, trabecular bone score may be a better predictor of fracture risk. Hip structural analysis (HSA) is also performed by the DXA and evaluates different variables pertaining to proximal hip geometry such as the cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (Z), and buckling ratio (BR) [11, 12]. These geometric indices are measured at each of three sites namely the narrow neck (NN), the inter-trochanteric area (IT), and the femoral shaft (FS). There is limited literature on the utility of HSA and TBS in assessing skeletal integrity in postmenopausal women with diabetes mellitus.

In this study, we aimed to assess DXA-derived parameters including TBS, BMD, HSA, and vertebral fractures as well as bone biochemistry in ambulatory South Indian postmenopausal women with type 2 diabetes mellitus and compare them with age- and BMI-matched non-diabetic controls recruited from the community.

Material and methods

This was a cross-sectional study conducted over 1 year in which ambulatory postmenopausal women with type 2 diabetes mellitus, aged 60 years and more, were recruited from the Endocrinology out-patient clinic. Age- and BMI-matched healthy control subjects without diabetes ($\text{HbA1C} < 5.7\%$) were recruited from the community.

A simple random sampling method was utilized to recruit these subjects. This study was approved by the Institutional Review Board (IRB Min no. 12525). All subjects provided a written informed consent at the time of recruitment in the study. Postmenopausal women who were on treatment for osteoporosis, those with chronic kidney disease stages 4 and 5, those with secondary osteoporosis, and those taking medications known to affect bone health were excluded from the study. Among subjects with type 2 diabetes mellitus, those with Charcot's osteoarthropathy were excluded. Diabetic nephropathy was diagnosed based on an elevated urinary albumin:creatinine ratio on a first-morning urine sample at two separate time points. Peripheral neuropathy was assessed using a 10-g monofilament testing on the dorsal aspect of the great toe bilaterally. Vibration perception threshold (VPT)

was also examined by a single observer on the great toe of both feet using a biothesiometer. Neuropathy was diagnosed if the mean VPT as measured by the biothesiometer was ≥ 25 V or if the pressure sensation from a 10-g monofilament was not perceived [13]. A subject was considered having retinopathy if any grade of retinopathy, including maculopathy, was detected by direct and/or indirect ophthalmoscopy in one or both eyes and/or on a more detailed assessment by an ophthalmologist.

The sample size was calculated from a previous study by Ho-Pham et al., which compared the mean TBS between postmenopausal diabetic women and age-matched controls. Based on this study, to obtain an estimated mean difference in TBS of 0.019 between both groups, with a 95% CI, and an alpha error of 5%, the sample size was calculated to be 172 in each of the cases and control groups [14].

Clinical assessment

All study participants were subjected to a detailed clinical evaluation that included duration and treatment of diabetes, assessment of anthropometric parameters such as height and weight by standard measures, and evaluation of complications of diabetes.

Biochemical parameters

Glycemic control was assessed by glycated hemoglobin (HbA1c), and the presence of diabetic nephropathy was diagnosed with serum creatinine and urine microalbumin. Fasting (overnight for 8 h) venous blood samples were collected for the measurement of serum calcium (N 8.3–10.4 mg/dL), phosphate (N 2.5–4.5 mg/dL), alkaline phosphatase (N 40–125 U/L), albumin (N 3.5–5.0 g/dL), creatinine (N 0.6–1.4 mg/dL), 25-hydroxy vitamin D (N 30–75 ng/mL), and intact parathormone (N 8–50 pg/mL). Serum calcium, phosphate, albumin, creatinine, and alkaline phosphatase were measured using colorimetric method with Beckman Coulter (Beckman Coulter AU 5800). An iced sample for intact parathormone (iPTH) was collected and estimated by chemiluminescence assay (Advia Centaur XPT immunoassay system), and 25-hydroxyvitamin D (vitamin D) was measured using electrochemiluminescence assay (Roche Cobas 6000 - Immunoassay system). Bone turnover markers - Plasma CTX (N: 226–1088 pg/mL in postmenopausal women) and PINP (N: 16–73.9 ng/mL in postmenopausal women) were measured using electrochemiluminescence immunoassay (ECLIA) on a Roche Elecsys Modular E170 analyzer. Urine microalbumin was estimated by immuno-turbidimetry (N: < 30 mg/g of creatinine), and HbA1C was estimated by high-performance liquid chromatography (HPLC).

Dual-energy X-ray absorptiometry scan parameters

Bone mineral density

Areal BMD (g/cm^2) at the femoral neck, total hip, and lumbar spine (L1–L4) were assessed using DXA scanner Hologic machine Discovery A series. The categorization of BMD into osteoporosis, osteopenia, and normal was done based on T-scores, as defined by the ISCD (International Society for Clinical Densitometry) guidelines [15].

Vertebral fracture assessment

Lateral spine images by fan-beam DXA for the assessment of vertebral fractures were used to evaluate for the presence of vertebral fractures. Images were obtained at the same time as that of BMD measurement. Prevalent vertebral fractures were classified as mild, moderate, and severe as follows [16].

- Grade 0—normal
- Grade 1—mildly deformed, approximately 20–25% reduction in anterior, middle, and/or posterior height
- Grade 2—moderately deformed, approximately 25–40% reduction in anterior, middle, and/or posterior height
- Grade 3—severely deformed, approximately 40% or greater reduction in anterior, middle, and/or posterior height

As there is less consistency in the diagnosis of mild (grade 1) fractures as compared to moderate (grade 2) and severe (grade 3) fractures [17], in this study, a subject was classified as having prevalent vertebral fractures if she was diagnosed to have either moderate or severe vertebral fractures or both.

Trabecular bone score (TBS)

TBS is a novel non-invasive method that evaluates pixel gray-level variations in the spine DXA image and helps in assessing the microarchitecture of the bone [18]. A TBS value of more than 1.350 indicates normal microarchitecture, 1.200–1.350 indicates partially degraded microarchitecture, and a TBS < 1.200 indicates degraded bone microarchitecture [19].

Hip structural analysis

Hip structural analysis (HSA) is a simple tool to determine bone strength at the proximal femur by geometric assessment [20]. The HSA program performs its analysis at 3 femoral sites using averages from 5 parallel lines 1 pixel apart across the cross-section of three sites [8, 20].

- (1) Narrow neck (NN), which is the narrowest point of the femoral neck

- (2) Inter-trochanteric region (IT), along the bisector of the angle of the axes of the neck and femoral shaft
- (3) Femoral shaft (FS), a site across the shaft at a distance of 2 cm distal to the midpoint of the lesser trochanter

The following four parameters of HSA were assessed in all the three sites:

- a. Cross-sectional area (CSA) excluding soft spaces in the marrow and pores—an index of resistance to axial forces (cm^2).
- b. Cross-sectional moment of inertia (CSMI)—estimate of resistance to bending forces in a cross-section (cm^4).
- c. Section modulus(Z)—an index of strength calculated as the CSMI $\div$ the distance from the bone edge to the centroid (assumed here to be half the subperiosteal width) (cm^3).
- d. Buckling ratio (BR)—index of susceptibility to local cortical buckling under compressive loads [21].

Statistical methods

Data were analyzed using SPSS v 24.0 (SPSS IBM Corp, USA). Continuous variables were expressed as mean and SD, and categorical variables were expressed as frequencies and percentages. The differences in means of continuous variables in the two groups were compared using Student's *t* test for normally distributed parameters, and the Mann-Whitney test was used to compare the parameters that were not normally distributed. The differences in proportions were compared using the Pearson's chi-square test or the Fisher exact test as appropriate. The relationship between two quantitative variables was assessed using the Pearson's correlation coefficient. For all comparisons, a two-tailed *P* value of < 0.05 was considered statistically significant.

Results

Our study sample comprised a total of 202 ambulatory postmenopausal women with type 2 diabetes mellitus and 200 age- and BMI-matched non-diabetic controls recruited from the local community. The mean (SD) ages of cases and controls were 65.6 (5.2) years and 64.9 (4.7) years respectively. Among cases, the mean duration of diabetes was 11.0 (5.8) years. At baseline, the mean (SD) HbA1C of the cases was 7.5 (1.6) % and 60/202 (29.7%) of the subjects were on insulin therapy. The proportions of subjects with diabetic peripheral neuropathy, nephropathy, and retinopathy were 15%, 11%, and 10%, respectively.

The prevalence of vitamin D deficiency ($< 20 \text{ ng/mL}$) was not significantly different in cases and controls (34.2% vs

35%; $P = \text{NS}$). The prevalence of osteoporosis at the hip (10.4% vs 14.3%) and the femoral neck (23.8% vs 32.7%) trended lower in cases as compared to controls. Although the prevalence of lumbar spine osteoporosis was significantly lower among cases (30.7%) as compared to controls (42.9%), the prevalence of degraded bone microarchitecture (TBS < 1.200) was significantly higher ($P < 0.001$) among cases (51%) as compared to controls (23.5%). Prevalent vertebral fractures (moderate and severe) were seen in 67/202 (33.2%) of the subjects and were not significantly different when compared to controls 52/200 (26%); $P = 0.15$. The markers of bone resorption (CTX—432.5 (197.9) vs 621.4 (284.5) pg/mL; $P < 0.001$) and bone formation (P1NP—30.1 (9.9) vs 68.3 (36.9) ng/mL; $P < 0.001$) were significantly lower among postmenopausal women with diabetes as compared to age- and BMI-matched non-diabetic controls. Other clinical and biochemical parameters, bone mineral density, trabecular bone score, and prevalent vertebral fractures were compared between cases and controls and are shown in Tables 1 and 2.

The various geometric indices of the proximal hip were measured using the hip structural analysis program and are shown in Table 3. It was found that most parameters of proximal hip geometry were significantly impaired in subjects with diabetes as compared to controls.

Further, bone biochemical parameters and the densitometric variables were compared between diabetic subjects with vertebral fractures and controls with vertebral fractures. It was found that markers of bone turnover were significantly lower in diabetic subjects with vertebral fracture as compared to non-diabetic subjects with vertebral fracture (CTX—414.6 (156.4) vs 626.0 (324.5) pg/mL; $P < 0.001$ and P1NP—30.3 (9.2) vs 69.4 (40.7); $P < 0.001$) (Table 4). Among the DXA-derived parameters, it was observed that the BMD at the femoral neck, hip, and lumbar spine were not significantly different between these groups of subjects ($P = \text{NS}$). However, the trabecular bone score and most parameters of proximal hip geometry were significantly impaired among diabetic subjects with vertebral fractures as compared to controls with vertebral fractures ($P < 0.05$) (Table 5).

In a sub-group analysis among cases, it was noted that the buckling ratio trended higher in subjects with an HbA1C $\geq 7.5\%$ as compared to subjects with an HbA1C $< 7.5\%$ (11.6 (3.4) vs 10.7 (2.4) $P = 0.05$).

Discussion

This is the first study from India assessing comprehensive bone health including trabecular bone score (TBS), hip structural analysis (HSA), and prevalent vertebral fractures in ambulatory postmenopausal women with type 2 diabetes mellitus compared with age- and BMI-matched non-diabetic controls. In this study, it was found that the prevalence of osteoporosis

Table 1 Demography and bone biochemistry in cases (T2DM) vs controls (without T2DM)

Variable	Cases (<i>N</i> = 202) Mean (SD)*	Controls (<i>N</i> = 200) Mean (SD)*	<i>P</i> value
Age (in years)	65.2 (5.1)	64.9 (4.7)	NS
Time since menopause (years)	17.9 (6.0)	17.6 (7.5)	NS
BMI (kg/m ²)	27.2 (4.8)	26.4 (5.0)	NS
Calcium (mg/dL) N: 8.3–10.4 mg/dL	9.3 (0.4)	9.58 (0.4)	NS
Phosphate (mg/dL) N: 2.5–4.5 mg/dL	3.6 (0.6)	4.10 (0.5)	NS
Creatinine (mg/dL) N: 0.6–1.1 mg/dL	0.8 (0.3)	0.8 (0.2)	NS
Alk. Phos (U/L) N: 40–125 U/L	93.1 (19.1)	91.67 (21.9)	NS
25(OH) vitamin D (ng/mL) N: 30–75 ng/mL	25.3 (7.5)	25.61 (10.9)	NS
PTH (pg/mL)	60.4 (18.6)	66.91 (26.3)	NS
P1NP (ng/mL)	29 (23–34)	63.7 (42–84)	< 0.001
CTX (pg/mL)	345.5 (312–488)	595 (411–801)	< 0.001

*Except for P1NP and CTX for which median and IQR has been presented

at the femoral neck and hip trended lower among cases. The prevalence of degraded bone microarchitecture was significantly higher among cases as compared to controls, as opposed to the prevalence of lumbar spine osteoporosis which was significantly higher among non-diabetic controls. Moreover, the indices of proximal hip geometry were significantly impaired among subjects with diabetes as compared to controls. The prevalence of vitamin D deficiency and vertebral fractures were not significantly different between cases and controls. Among the bone biochemical parameters, it was found that both the CTX and the P1NP were significantly lower among postmenopausal women with diabetes than in non-diabetic controls. Moreover, in a sub-group analysis among subjects with vertebral fractures, it was found that most indices of hip geometry and the trabecular microarchitecture were significantly worse among postmenopausal women with diabetes as compared to non-diabetic controls.

In this study, the prevalence of osteoporosis at the femoral neck and hip was lower among subjects with diabetes as

compared to those without diabetes. In a previous study done from the authors' center, the prevalence of osteoporosis in postmenopausal women without diabetes was as high as 50% at any site [22]. Although the prevalence of osteoporosis at the lumbar spine was significantly lower among subjects with diabetes, the presence of degraded bone microarchitecture (TBS < 1.200) was more frequently encountered among subjects with diabetes as compared to non-diabetic controls. Schwartz et al. assessed BMD among postmenopausal women and showed that after adjustment for age and body mass index (BMI), there was a 2.9% higher BMD at femoral neck in subjects with diabetes mellitus as compared to those without diabetes mellitus [23]. In the abovementioned study, despite having a higher BMD, over 30% of subjects with diabetes mellitus sustained fragility fractures during a mean follow-up of 9.4 years. In a study done in a Korean population by Kim et al., similar findings were noted [24]. This implies that BMD may be a sub-optimal indicator for predicting fractures in subjects with diabetes mellitus.

Table 2 Bone mineral density and trabecular bone score in cases and controls

Variable	Cases (<i>N</i> = 202) Mean (SD)	Controls (<i>N</i> = 200) Mean (SD)	<i>P</i> value
Lumbar spine BMD (g/cm ²)	0.853 (0.170)	0.826 (0.141)	0.09
Femoral neck BMD (g/cm ²)	0.667 (0.121)	0.638 (0.106)	0.01
Hip BMD (g/cm ²)	0.808 (0.143)	0.777 (0.125)	0.023
TBS score	1.195 (0.097)	1.251 (0.068)	< 0.001
Prevalence of osteoporosis, low TBS, and vertebral fractures			
Variable	Cases <i>N</i> (%)	Controls <i>N</i> (%)	<i>P</i> value
Osteoporosis at lumbar spine	62 (30.7)	86 (42.9)	0.01
Osteoporosis at femoral neck	48 (23.8)	64 (32.7)	0.05
Osteoporosis at hip	21 (10.4)	28 (14.3)	0.286
TBS < 1.200	103 (51)	47 (23.5)	< 0.001
Vertebral fracture (%)	67 (33.2)	52 (26.0)	0.15

Table 3 Parameters of hip structural analysis compared between cases and controls

HSA variable	Cases (<i>N</i> = 202) Mean (SD)	Controls (<i>N</i> = 200) Mean (SD)	<i>P</i> value
NN (CSA) cm ²	2.43 (0.45)	2.51 (0.42)	0.09
NN (CSMI) cm ⁴	1.78 (0.51)	1.91 (0.52)	0.01
NN (Z) cm ³	1.02 (0.22)	1.34 (0.78)	0.01
NN (BR)	11.0 (2.8)	9.9 (2.6)	< 0.001
IT (CSA) cm ²	4.27 (0.93)	4.44 (1.40)	0.16
IT (CSMI) cm ⁴	10.18 (2.97)	10.89 (3.44)	0.03
IT (Z) cm ³	3.42 (1.05)	3.65 (1.38)	0.07
IT (BR)	8.9 (2.5)	8.4 (2.2)	0.02
FS (CSA) cm ²	3.61 (0.59)	3.66 (0.59)	0.41
FS (CSMI) cm ⁴	2.80 (0.64)	2.89 (0.74)	0.17
FS (Z) cm ³	1.90 (0.35)	2.02 (0.51)	0.005
FS (BR)	3.1 (0.8)	2.9 (0.7)	0.05
Hip axis length (HAL) (mm)	94.0(6.2)	95.2(5.9)	0.187

CSA, cross-sectional area; CSMI, cross-sectional moment inertia; Z, section modulus; BR, buckling ratio; NN, narrow neck; IT, intertrochanteric; FS, femoral shaft

Hyperinsulinemia, obesity, and reduced bone turnover are the postulated mechanisms for a higher BMD observed in patients with type 2 diabetes mellitus. A meta-analysis confirmed the presence of discrepancy in BMD in subjects with type 1 and type 2 diabetes mellitus with the former showing a lower BMD than the latter [25].

A study assessing the correlation of bone quantity (BMD) and quality (TBS) with various insulin resistance-related parameters such as visceral adipose tissue, intrahepatic lipids, and homeostatic model assessment of insulin resistance (HOMA-IR) showed negative correlation between TBS and all these parameters, which was not observed with BMD [26]. Thus, in patients with type 2 diabetes mellitus where insulin resistance is a major player, TBS may be a better predictor of bone health [17, 27]. Previous studies by Leslie et al. and Ebrahimpur et al. have also shown a significantly low mean TBS in patients with diabetes mellitus [28, 29].

Prevalent vertebral fractures (moderate and severe) were seen in about one-third of the study subjects and were not significantly different when compared to non-diabetic controls, despite a significantly higher BMD among the postmenopausal women with diabetes. The prevalence of vertebral fractures in this cohort was high as compared to European and Brazilian studies which documented a prevalence of 23 to 25% vertebral fractures in postmenopausal women with diabetes mellitus [30, 31]. In a population-based study from southern India, among postmenopausal women after excluding those with self-reported diabetes mellitus, 36.7% had prevalent vertebral fractures (moderate and severe) [32]. The possible explanations for the high prevalence of vertebral fractures in south Indian postmenopausal women include a large proportion of individuals with undiagnosed osteoporosis and the lack of awareness among physicians and patients in identifying and treating osteoporosis [33]

Table 4 Comparison of bone biochemistry between subjects with diabetes mellitus and vertebral fractures versus controls with vertebral fractures

Variable	Cases (<i>N</i> = 67) Mean (SD)	Controls (<i>N</i> = 52) Mean (SD)	<i>P</i> value
Calcium (mg/dL) N: 8.3–10.4 mg/dL	9.4 (0.4)	9.6 (0.4)	0.006
Phosphate (mg/dL) N: 2.5–4.5 mg/dL	3.6 (0.7)	4.1 (0.6)	< 0.001
Creatinine (mg/dL) N: 0.6–1.1 mg/dL	0.9 (0.3)	0.8 (0.2)	0.02
Alk. Phos (U/L) N: 40–125 U/L	92.6 (21.5)	90.8 (25.2)	0.67
25(OH) vitamin D (ng/mL) N: 30–75 ng/mL	25.6 (7.5)	26.4 (10.8)	0.64
PTH (pg/mL)	62.9 (19.0)	70.0 (28.0)	0.09
PINP (ng/mL)	30.3 (9.2)	69.4 (40.7)	< 0.001
CTX (pg/mL)	414.6 (156.4)	626.0 (324.5)	< 0.001

Table 5 Comparison of densitometric variables between subjects with diabetes mellitus and vertebral fractures versus controls with vertebral fractures

Variable	Cases (<i>N</i> = 67) Mean (SD)	Controls (<i>N</i> = 52) Mean (SD)	<i>P</i> value
Lumbar spine BMD (g/cm ²)	0.792 (0.173)	0.837 (0.139)	0.121
Femoral neck BMD (g/cm ²)	0.641 (0.113)	0.636 (0.094)	0.814
Hip BMD (g/cm ²)	0.774 (0.143)	0.765 (0.118)	0.713
TBS score	1.142 (0.095)	1.259 (0.076)	< 0.001
NN (CSA) cm ²	2.34 (0.41)	2.52 (0.44)	0.029
NN (CSMI) cm ⁴	1.69 (0.46)	1.95 (0.51)	0.006
NN (Z) cm ³	0.98 (0.19)	1.35 (1.74)	0.129
NN (BR)	11.7 (2.6)	10.1 (2.8)	0.002
IT (CSA) cm ²	4.00 (0.84)	4.44 (1.57)	0.072
IT (CSMI) cm ⁴	9.59 (2.86)	11.34 (4.27)	0.013
IT (Z) cm ³	3.22 (0.82)	3.69 (1.55)	0.050
IT (BR)	9.8 (2.6)	8.6 (2.3)	0.016
FS (CSA) cm ²	3.48 (0.64)	3.64 (0.67)	0.199
FS (CSMI) cm ⁴	2.77 (0.69)	2.95 (0.82)	0.205
FS (Z) cm ³	1.87 (0.37)	2.06 (0.56)	0.043
FS (BR)	3.4 (0.9)	3.1 (0.8)	0.062
Hip axis length (HAL) (mm)	96.1 (5.5)	94.7 (6.1)	0.348

Hip structural analysis (HSA) refers to the methodology used to assess bone strength based on the measurement of geometric characteristics in the proximal femur [34]. Low values of CSA, CSMI, and Z and a high BR denote poor hip strength and a higher tendency to fracture [35]. In the present study, it was observed that most indices of proximal hip geometry were significantly worse in subjects with diabetes as compared to non-diabetic controls. In a study by Lee et al., a buckling ratio of more than 10 was considered to have an adverse outcome [21]. Furthermore, in a sub-group analyses among subjects with vertebral fracture, it was found that the trabecular bone score and hip geometric parameters showed greater impairment despite similar BMD in subjects with diabetes as compared to controls.

In the current study, the bone turnover markers were significantly lower among cases as compared to controls. This is also in keeping with previous studies which have demonstrated that the bone turnover is suppressed in subjects with diabetes [36]. Pentosidine is an advanced glycosylation end product (AGE) that has been shown to have a negative association with the mechanical properties of femoral cortex and vertebra [37]. A study done by Yamamoto et al. showed that plasma pentosidine levels were significantly higher in postmenopausal women who had sustained vertebral fractures [38]. In our study however, assessment of pentosidine levels was not undertaken.

The key strength of this research work is that it is the first study from the Indian subcontinent comparing bone mineral parameters, bone mineral density, trabecular bone score, prevalent vertebral fractures, and hip structural analysis in

postmenopausal women with and without diabetes. This study highlights the utility of the trabecular bone score and hip structural analysis in subjects with diabetes, where the bone mineral density tends to be paradoxically high, thus not adequately predicting fracture risk. This study, however, is limited by its inherent cross-sectional design and prospective studies may be undertaken to further validate these findings.

Declarations

Conflicts of interest None.

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