

# Association between Bone Mineral Density and Type 2 Diabetes Mellitus- An Original Article

Sumesh Raj\*<sup>1</sup>, Baiju S J<sup>2</sup>, Rajesh Vijayan<sup>3</sup> and G.V. Rajan<sup>4</sup>

<sup>1</sup>Associate Professor of Internal Medicine, Sree Gokulam Medical College, Trivandrum, India

<sup>2</sup>Associate Professor of Internal Medicine, Travancore Medical College, Kollam, India

<sup>3</sup>Senior Lecturer in Orthopaedics, Sree Gokulam Medical College, Trivandrum, India

<sup>4</sup>Professor and Senior Consultant in Internal Medicine, Cosmopolitan Hospital, Trivandrum, India

\*Corresponding author e-mail: [drsumeshraj@yahoo.com](mailto:drsumeshraj@yahoo.com)

## ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) influences bone metabolism, but the relation of T2DM with bone mineral density (BMD) remains inconsistent across studies. The objective of this study was to estimate the difference in BMD ( $\text{g}/\text{cm}^2$ ) between diabetic and non-diabetic populations, and to investigate potential underlying mechanisms.

**Materials and methods:** The association between T2DM and BMD measured by dual energy X-ray absorptiometry was evaluated, including both healthy controls and subjects with T2DM.

**Results:** Analysis showed that BMD in diabetics was significantly higher than non-diabetic at various sites. The differences in forearm BMD were not significantly different between diabetics and non-diabetics. Analysis showed similar results in both sexes. Also, it was seen that younger age, male sex, higher body mass index and higher HbA<sub>1C</sub> were positively associated with higher BMD levels in diabetic patients.

**Conclusion:** Patients with T2DM have higher BMD levels when compared to non diabetics.

**Keywords:** Bone mineral density, Diabetes mellitus, Association.

## INTRODUCTION

Osteoporosis and diabetes are common diseases in India. Their coexistence was reported in 1948<sup>1</sup> but hitherto the

association between them remains unclear. Due to the different pathogenesis of type 1 and type 2 diabetes mellitus (T2DM), it is

not surprising that there is no uniform entity of diabetic bone disease as such. While decreased bone mineral density (BMD) has consistently been observed in type 1 diabetes patients<sup>2,3</sup> studies on BMD investigated in T2DM showed contradictory results with higher, lower or similar values in comparison with healthy control subjects<sup>4</sup>. It is well known that advanced age is a risk factor for bone loss and osteoporosis<sup>8</sup>. Some of the attributed mechanisms include increased production of inflammatory cytokines and cellular components, the incremental osteoclast precursor generation and decreased bone preservation due to gonadal failure resulting in lower tissue production of sex steroids<sup>10</sup>. Advanced age is also associated with increased fall, lack of exercise, use of drugs that negatively influence bone metabolism and renal function such as drugs prescribed for diabetes.

Gender also appears to have an important effect on the relation between BMD and T2DM. Barrett-Connor<sup>11</sup> found that older women with T2DM had higher BMD levels at all sites compared to those with normal glucose tolerance. It has also been suggested that obesity and hyperinsulinemia can lead to lower bone turnover in diabetic women<sup>12</sup>, so that the adverse effects of estrogen deficiency on bone mass are attenuated after menopause.

Diabetic patients have a higher body mass index (BMI), increased insulin levels, less physical exercise. These might influence bone metabolism independently of diabetes. aim of our study was to study the association difference between type 2 diabetics and healthy individuals in BMD levels measured at four anatomical sites. In addition, we evaluated factors influencing BMD variation like sex, age, BMI and glycemic control (HbA<sub>1c</sub> levels) evaluates possible mechanisms by which T2DM influences BMD.

## MATERIALS AND METHODS

One hundred and Sixty one case of Type2 Diabetes Mellitus diagnosed according to ADA criteria who attended Outpatient departments of Internal Medicine and Diabetology in three hospitals of South Kerala were studied. Same number of control population was also studied. All patients were subjected to physical examination, BMD was measured by dual energy X-ray absorptiometry (DXA) and expressed as an absolute value in g/cm<sup>2</sup>. The mean and its standard deviation (SD) of BMD measure at the calcaneus, femoral neck, total hip, spine and forearm were extracted to explore the pooled mean difference estimation. HbA<sub>1c</sub> was done in all patients. The weighted mean difference estimates of BMD in g/cm<sup>2</sup> comparing diabetes with controls were calculated as DerSimonian and Laird estimators using random effects models. All analyses were conducted with the use of Review Manager, version. To estimate the effects of gender, age, BMI and HbA<sub>1c</sub> on the BMD measured at the different sites analysis was performed using STATA 11.0.

## RESULTS

Participants in all study populations were aged 30 years and over and approximately 75 % were middle-aged or older. Mean age of males in the study was 52.6 and females was 52.4 respectively. Mean BMI of males was 25.4 and females was 27.2. Mean HbA<sub>1c</sub> was 7.2 and 7.4 in male and female diabetic patients. In addition, the most common covariates considered by the study was BMI or weight, cigarette smoking, alcohol use, physical activity, diuretic use, calcium intake estrogen use, menopause status, age at menarche and HbA<sub>1c</sub>.

BMD levels in diabetics and non-diabetics at four skeletal sites in the study

showed at the femoral neck, found a higher BMD in subjects with diabetes. At the total hip, significantly higher BMD was noted in diabetics. At the lumbar spine, almost all of the studies reported a higher BMD in diabetics. These differences were statistically significant at the forearm there were no significant differences between diabetics and non-diabetics. No major differences between genders were found. (See table 1.)

It was found that BMI was positively correlated with BMD. There was some evidence suggesting that other factors such as insulin levels also had a positive correlation with BMD. HbA<sub>1c</sub> levels had positive correlation with BMD.

Age was negatively associated with BMD at the hip, but positively at the lumbar spine. Higher BMI was a strong determinant of higher BMD at the femoral neck and lumbar spine, with no apparent effect on forearm BMD. Higher HbA<sub>1c</sub> levels (reflecting lesser glucose control) resulted in higher BMD at the femoral neck and total hip.

Age-adjusted, gender-specific BMD in patients with diabetes and controls per skeletal site. (See table 2 & 3 and figure 1.)

## DISCUSSION

The study provides insights into the relationship between T2DM and BMD. Our study concluded that overall individuals with T2DM have about 25–50 % SD higher BMD compared to non-diabetic control subjects.

Subjects with T2DM had elevated BMD at the femoral neck, hip, and spine. No major differences in BMD at the forearm were seen, but there are no obvious biological reasons we can attribute to them. This lack of association with forearm BMD may be the consequence of limited sample size. We also found no strong evidence suggesting there is a sex-specificity in the observed BMD differences between diabetics and non-diabetics.

The differences in glucose control and prevalence of diabetic complications may affect the outcome. Nevertheless, it is seen that in addition to BMI, HbA<sub>1c</sub> levels also have a significant positive effect on BMD measured at any site.

The mechanisms that might account for an association between T2DM and increasing BMD are plentiful and largely unclear. From a clinical perspective the most important factors which can influence the relationship between T2DM and BMD are.

### Obesity

Historically, overweight and hyperinsulinemia have been postulated as two important features of T2DM which are positively correlated with BMD. There are several complex pathways by which obesity may influence the relation between diabetes and BMD. Body fatness may have an impact on the accuracy of the DXA-based BMD measures as demonstrated in obese diabetic patients. On the other hand, adipose tissue releases a wide variety of adipokines that have been implicated either directly or indirectly in the regulation of bone remodeling. Plasma leptin concentrations have been shown to be higher in diabetic men than in healthy controls<sup>12</sup>. Leptin induces bone growth by stimulating osteoblast proliferation and differentiation<sup>13</sup>.

### Hyperinsulinemia

Insulin levels could mediate in part a positive association between T2DM and elevated BMD. Individuals with T2DM usually have an excess of insulin. Physiologically, insulin has an anabolic effect on bone due to its structural homology to IGF-1 by interacting with the IGF-1 receptor which is present on osteoblasts. The IGF-1 signaling pathway is crucial for bone acquisition<sup>11</sup>.

### Medication use

Thiazide use, which is expected to be higher in diabetic individuals has also been associated with higher BMD at different skeletal sites<sup>14</sup>. Also statin use (also more prevalent in diabetics) is associated with higher BMD<sup>10</sup>. Nevertheless, it is unlikely that this alone can explain the observed associations.

### CONCLUSION

Our study showed that diabetic individuals have higher BMD levels than non-diabetics independent of the skeletal site of measurement, gender, age, BMI or medication use. In addition, we could find that younger age, male gender, higher BMI and higher HbA<sub>1c</sub> are positively associated with higher BMD levels in diabetic individuals. The potential mechanisms underlying these associations remain complex, suggesting that several influential factors need to be considered while interpreting the association between T2DM and BMD.

Large prospective studies are needed to establish the mechanisms underlying this association, and most importantly the relationship with fracture risk, the most adverse consequence of osteoporosis.

### REFERENCES

1. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int.* 2007; 18(4):427–444.
2. Saller A, Maggi S, Romanato G, Tonin P, Crepaldi G. Diabetes and osteoporosis. *Aging Clin Exp Res.* 2008; 20(18852539):280–289.
3. Daele PL, Stolk RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study.

*Ann Intern Med.* 1995; 122 (7856988): 409–414.

4. Kahn A, Gibbons R, Perkins S, Gazit D. Age-related bone loss. A hypothesis and initial assessment in mice. *Clin Orthop Relat Res.* 1995; 7641500:69–75.
5. Tung S, Iqbal J. Evolution, aging, and osteoporosis. *Ann N Y Acad Sci.* 2007; 1116 (18083942): 499–506.
6. Barrett-Connor E, Holbrook TL. Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. *JAMA.* 1992; 268 (1453525): 3333–3337.
7. Isaksson A, Akesson K, Obrant KJ. Increased bone density and decreased bone turnover, but no evident alteration of fracture susceptibility in elderly women with diabetes mellitus. *Osteoporos Int.* 2005; 16(12):1506–1512.
8. Reid IR. Relationships between fat and bone. *Osteoporos Int.* 2008; 19(5):595–606.
9. Kanabrocki EL, Hermida RC, Wright M, et al. Circadian variation of serum leptin in healthy and diabetic men. *Chronobiol Int.* 2001; 18(2):273–283.
10. Hamrick MW, Della-Fera MA, Choi YH, Pennington C, Hartzell D, Baile CA. Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficient mice. *J Bone Miner Res.* 2005; 20(6):994–1001.
11. Pun KK, Lau P, Ho PW. The characterization, regulation, and function of insulin receptors on osteoblast-like clonal osteosarcoma cell line. *J Bone Miner Res.* 1989; 4 (2692404): 853–862.
12. Kawai M, Rosen CJ. Insulin-like growth factor-I and bone: lessons from mice and men. *Pediatr Nephrol.* 2009; 24 (7): 1277–1285.
13. Wasnich RD, Benfante RJ, Yano K, Heilbrun L, Vogel JM. Thiazide effect

on the mineral content of bone. *N Engl J Med.* 1983; 309 (6): 344–347.

14. Pasco JA, Kotowicz MA, Henry MJ, Sanders KM, Nicholson GC. Statin use,

bone mineral density, and fracture risk: Geelong Osteoporosis Study. *Arch Intern Med.* 2002; 162 (5): 537–540.

**Table 1.** Characteristics of the patients by gender

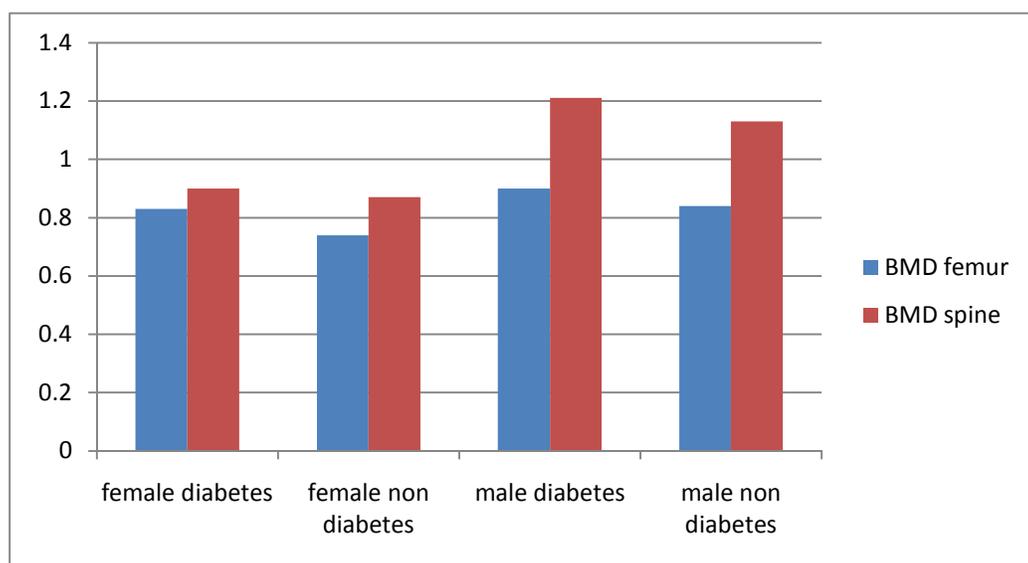
Male				Female			
Age (years)	BMI (kg/m <sup>2</sup> )	HbA <sub>1c</sub> (%)	Disease duration (years)	Age (years)	BMI (kg/m <sup>2</sup> )	HbA <sub>1c</sub> (%)	Disease duration (years)
52.6	25.4	7.2	9.4	52.4	27.2	7.4	8.2

**Table 2.** Skeletal site of BMD measurement: femoral neck

Female			Male		
Diabetes	Non-diabetes	P value	Diabetes	Non-diabetes	P value
0.830 ± 0.120	0.740 ± 0.110	<0.0001	0.900 ± 0.130	0.840 ± 0.110	0.03

**Table 3.** Skeletal site of BMD measurement: spine

Female			Male		
Diabetes	Non-diabetes	P value	Diabetes	Non-diabetes	P value
0.900 ± 0.160	0.870 ± 0.150	0.264	1.21±0.2	1.13±0.14	<0.001



**Figure 1.** BMD femur and BMD spine

y axis-BMD  
x axis- diabetic and non diabetic patients