International Journal of Advances in Medicine
Reema N et al. Int J Adv Med. 2020 Sep;7(9):1380-1387
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20203603

Original Research Article

A study of magnitude and correlates of altered bone mineral density in type 2 diabetes mellitus patients of central rural India

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Received: 28 June 2020
Accepted: 30 July 2020

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ABSTRACT

Background: Diabetes mellitus is fast becoming the epidemic of the 21st century. It is a metabolic disease that affects multiple organ system in the body including bone metabolism and bone mass. There is high prevalence of decreased bone mineral density (BMD) in type 2 diabetes mellitus (T2DM) patients leading to osteoporosis, osteopenia and fracture. The aim of the present study was to find the magnitude and correlates of altered BMD in T2DM patients of central rural India.
Methods: This cross-sectional study was carried out at a tertiary care teaching hospital in central rural India from 2014 to 2016. It comprises of 200 T2DM patients with aged ≥35 years. Bone mineral density measurements were done by using peripheral dual energy x-ray absorptiometry (DEXA).
Results: Mean age of study subjects was 56.13±11.12 years with 43.5% males and 56.5% females. Our study results showed the magnitude of decreased BMD was 82%. 53% of the study subjects were osteoporotic and 29% were osteopenic. Significant associations were detected between decreased BMD and old age, female gender, high body mass index, high fasting blood sugar, high HbA1c and low serum calcium on multivariate analysis.
Conclusions: The prevalence of decreased BMD in patients with T2DM of central rural India is high, especially in females' patients, obese patients, and uncontrolled diabetic patients. Awareness amongst the health care provider of this changes will directly affect the treatment decisions for patients, thereby preventing osteoporosis, osteopenia and mitigating potential fracture risk.

Keywords: Bone mineral density, DEXA, Osteoporosis, Type II diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is fast becoming the epidemic of the 21st century. India has earned the dubious distinction of "diabetes capital of World" with highest prevalence in World (62 million).[1,2] The metabolic dysregulation associated with DM causes patho-physiologic changes in almost all organ system in the body including bone metabolism and bone mass.[1-3] Causes of such changes are multifactorial and complex. Hyperglycemia increases osteoclast function but decreases osteoblast function, thereby leading to accelerated bone loss, osteopenia and osteoporosis. Bone loss may further be aggrevated by a decrease in neovascularization and other is advanced glycated end products (AGEs), which may eventually result in low-impact or fragility fractures.[4] Subsequently BMD is reduced in T2DM.[5] Bone mineral density (BMD) identifies osteopenia, osteoporosis and can predict

fracture risk. A 10% decrease in BMD at any site confers a 1.6-2.6 increased relative risk of hip fracture and 1.7-2.3 increased relative risk of vertebral fracture.[6] Multitude of variables of DM are also well associated with BMD alteration. Knowledge of the change in bone mass especially BMD status and its correlates can help clinician predict bone fragility, understand the correlates and its effect, give comprehensive treatment including prevention of bone fracture (over and above the diabetic management).

Unfortunately, there is no uniformity in reported prevalence of altered BMD in T2DM patients. Multiple international studies showed contradictory results with higher BMD, lower BMD or similar values in comparison with healthy control subjects.[2,3,7-9] Limited literatures are available from India, more so from population of Central India, hence the present study was conducted to assess the effect of T2DM on BMD , report its prevalence and study its associations with risk factors.

Aim and objectives of this study was to assess the prevalence of altered bone mineral density in T2DM patients and to study its association with age, gender, BMI of the patients, alcohol, smoking, HbA1c, serum calcium and the duration of the disease.

METHODS

There were 200 case subjects diagnosed with T2DM and aged ≥35 years who attended diabetes clinic in department of Medicine in 2014 - 2016 were recruited. DM was diagnosed on a clinical basis (symptoms and signs) along with biochemical test (fasting plasma glucose ≥126 mg/dl or 2 hours plasma glucose ≥200 mg/dl and /or HbA1c >6.5%).

Exclusion criteria being history of bone disorders such as multiple myeloma, lymphoma, mastocytosis, hypo/hyperparathyroidism, hypo/hyperthyroidism, chronic kidney disease, severe hepatic diseases, malignancy, rheumatoid arthritis, chronic drugs intake (more than 3 months), pregnancy and lactation or not consenting.

BMD measurement was done using "Osteosys EXA 3000" (South Korea) machine at 2 sites lower limb (calcaneum) and forearm (radius). World Health Organization (WHO) score for BMD in adults are given as T score. The T score compares to a healthy person of the same sex. According to the T score, the patients were allocated into 3 groups (0 to -1 as normal, -1 to -2.5 as osteopenic and ≤2.5 as osteoporotic). The study was approved by the ethical committee of our hospital.

Correlates studied were - age, sex, BMI, duration of diabetes, menopause, fracture history, personal habits (smoking, alcohol), biochemical parameters and drug history.

Sample size

Considering the prevalence of altered BMD levels in type 2 DM of 200 patients. At 95% Confidence Interval (C.I.) and 5% allowable error, the desired sample to estimate the raised prevalence of BMD between 25% to 35% -

$$n = \frac{Z^2 \times p \times q}{d^2}$$

[In this formula: n = number of study subjects, Z = standard normal deviation at a desired confidence level, p = reasonable estimation of population/prevalence, q = (1 - p)].

Statistical analysis

Continuous variables were summarized by descriptive statistics, using means and standard deviation (SD) and categorical variables were expressed as numbers and percentages. Crude odds ratio and adjusted odds ratio were used to assess the correlation between variables. All statistical analyses were two-sided, using a pre-specified 5% significance level, i.e. significance was defined as p value <0.05. Analysis was performed using SPSS software version 17.0 for windows (SPSS Inc, Chicago, Illinois, USA) and EPI-INFO 6.0 version.

RESULTS

A total of 260 patients with 35 years of age or older attended to the diabetic clinic during study period and 200 of them were recruited in the study (Figure 1). The baseline characteristic of the study subjects is shown in Table 1. The mean age of the study subjects was 56.1±11.1 years. Most 113 (56.6%) of the study subjects were female, out of which 61% were in post- menopausal age group. Mean BMI of study subjects was 24±2.7 kg/m^2. The mean duration of DM was 5.0±6.0 years (95% CI: 3.3-18.2). In majority 109 (54.5%) of the study subjects' duration of the disease since the time of diagnosis was 1 to 5 years.

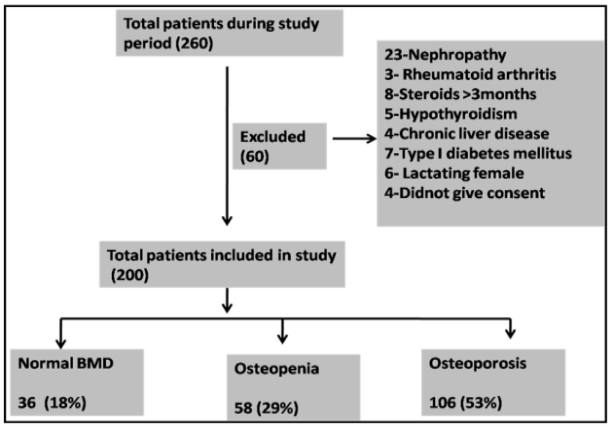

Figure 1: Flowchart of the study subjects.

Table 1: Summary of baseline characteristics of study subjects.

Characteristics	Study subjects No. (%) (n=200)	Study subjects with decreased BMD No. (%) (n=164)
Age (in years)		
35-50	64 (32)	43 (63.1)
51-65	94 (47)	81 (86)
66-80	42 (21)	40 (95.1)
Mean±SD	56.1 ± 11.1	
Gender		
Female	113 (56.5)	96 (88.8)
Male	87 (43.5)	68 (78)
BMI (kg/m^2)		
Normal (18.6-24.5)	86 (43)	68 (80.1)
Overweight & obese (>25)	114 (57)	95 (83.2)
Median ±IQR		
Duration of DM (years)		
<1	3 (1.5)	2 (66.6)
1-5	109 (54.5)	79 (72.4)
5-10	52 (26)	48 (92.3)
>10	36 (18)	35 (97.1)
Mean ±SD		
Menopausal status		
Menopausal	44 (43)	32 (72.7)
Post menopausal	69 (61)	64 (92.7)
Alcohol consumption		
Alcoholic	55 (27.5)	48 (87.2)
Non alcoholic	145(72.5)	116 (79.9)
History of smoking		
Smoker	58 (29)	53 (91.3)
Non smoker	142 (71)	111 (78)
HbA1C (%)		
5.5-6.5	41 (20.5)	23 (56)
6.5-7.5	74 (37)	58 (78.2)
7.5-8.5	55 (27.5)	55 (100)
>8.5	30 (15)	28 (93.3)
Mean ±SD		
Serum Calcium (mg/dl)		
Hypocalcemia (<9)	69 (34.5)	64 (92.7)
Normal calcium (9-11)	131 (65.5)	100 (76.3)

The prevalence of decreased BMD in the present study was 164 (82%), out of which 106 T2DM subjects (53%) were osteoporotic and 58 (29%) osteopenic (Table 2). BMD sheet of a patient with T score and Z score is shown in Figure 2. Majority of subjects (93) had Fasting blood sugar level of 200-300 mg/dl and this FBS levels corresponds to have the greatest number of lower BMD (65 osteoporosis and 14 osteopenia). This association was significant statistically (p value = 0.0001).81.8 % of the subjects (45) with uncontrolled T2DM with HbA1C levels of 7.5-8.5 had osteoporosis while 23 subjects had osteopenia. Duration of DM of 1-5 yrs had maximum number of subjects (109) and also had maximum number of reduced BMD (33 were osteoporotic (30.2%) and 46 osteopenic (42.2%)). Various T2DM treatment options of OHA, Insulin or combination were found to have no significant association. Bone fracture were detected in 28 subjects with most being due to osteoporosis (21 out of 28 subject). This association of decreased BMD with fracture history was statistically significant (p value <0.019).

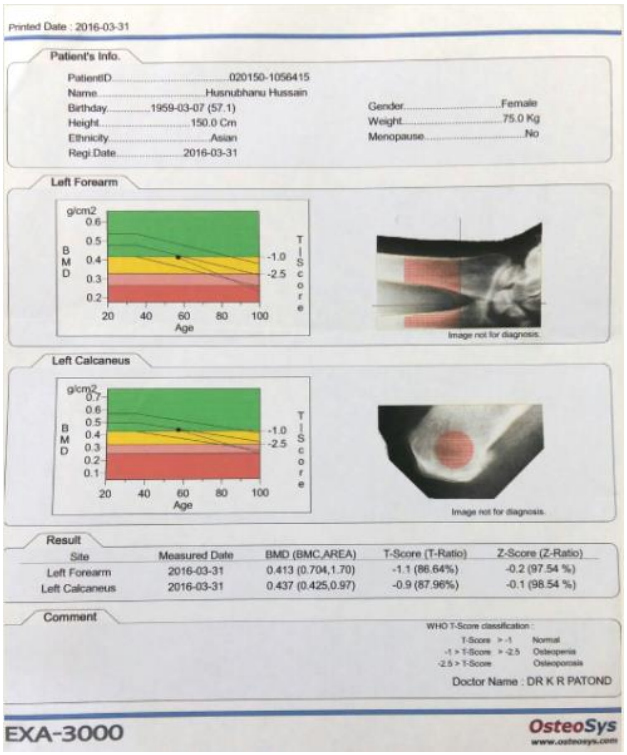

Figure 2: BMD sheet of a patient with T score and Z score.

Table 2: Categories based on BMD of study subjects (n=200).

Categories	Number	Percentage
Normal	36	18
Osteopenia	58	29
Osteoporosis	106	53
Total	200	100

Correlates of decreased BMD on multivariate regression analysis found to be statistically significant were old age, female gender, high BMI, alcohol consumption, smoking, positive fracture history, high HbA1c and hypocalcemia (Table 3). The age group of 66-80 years had the highest number of osteoporosis i.e. 32 (76.1%) whereas age group of 35-50 years had maximum percentage of osteopenia (39%). Mention may be made here that majority of subjects (61.1%) had attained menopause (among females) and also have osteoporosis (52subjects,

75.3%) and osteopenia (12,17.4%). Decreased BMD was reported more in subjects with high BMI (57%) than in normal BMI (43%). Amongst obese and overweight subjects, 62 (54.3%) had osteoporosis whereas 33 (28.9%) had osteopenia. Subjects with personal habits such as smoking and alcohol consumers had lower BMD [smokers (91.3%) and alcohol consumers (87.2%)]. Among the subjects (69 in no) with hypocalcemia 54 had osteoporosis while 10 had osteopenia. Magnitude of altered BMD in DM reported in different studies is shown in Table 4.

Table 3: Correlates of bone mineral density on Univariate analysis and Multivariate analysis.

Characteristics	Univariate analysis		Multivariate analysis	
	Crude OR	(95% CI)	Adjusted OR	95% CI
Age (in years)	1.077	1.041-1.118	1.089	1.021-1.169
Gender				
Female	1.578	0.7647-3.256	11.51	2.761-50.391
Male	1			-
BMI (kg/m^2)	0.891	0.814-0.973	0.830	0.723-0.936
Duration of DM (years)	1.313	1.151-1.544	1.025	0.865-1.266
Menopausal status				
Menopausal	1		1	-
Post menopausal	0.32	0.12-0.81	1.085	0.248-4.872
Alcohol consumption				
Alcoholic	1.71	0.70-4.18	3.898	0.923-18.273
Non alcoholic	1		1	-
History of smoking				
Smoker	2.96	1.08-8.04	5.766	1.317-30.295
Non smoker	1		1	-
HbA1C (%)	4.901	2.572-10.461	2.659	1.459-5.858
Serum Calcium (mg/dl) Hypocalcemia (<9) Normal calcium (9-11)	0.579	0.398-0.817	0.601	0.362-0.929

DISCUSSION

Most Indian studies reported the magnitude of decreased BMD to be around 16-39% in type 2 DM patients which corroborates with our study.[10] Studies carried out in Western World reported it to be in range of 13% to 46%.[11,12] (Shown in Table no.4). We found magnitude of osteopenia among type 2 DM patients to be 29% and osteoporotic to be 53%. Guven et al and Wang et al had reported a decreased BMD in subjects with type 2 DM patients.[13,14] A recent study from northern India also reported lower BMD in type 2 DM patients after adjusting for age, BMI, and waist hip ratio.[15] Dutta et al showed lower BMD in Type 2DM suggesting loss of trabecular bone with preservation of cancellous bone. Diabetic females had significantly lower BMD.[16] Marked differences in magnitude of decreased BMD with that of the Western study subjects could be because of different study settings, population studied and inter-population variations such as physical attributes, BMI, BMD, nutrition etc. Comparison with the Caucasian database could result in overestimation of low BMD and underestimation of normal BMD in our study. Generally, our population have high BMI (obese or overweight) which alters BMD independently as well as synergistically. Nutritionally, Indian rural population are poorly nourished and important nutrients of bone metabolism may be deficient (e.g. Vitamin D) which may exacerbate the BMD on lower side. Effect of the various known environmental factors especially sedentary lifestyle on lower BMD could not be underestimated. The magnitude of decreased BMD also depends on the different sites and techniques/methods of DEXA. Our studies were based on peripheral BMD measurement at radius and calcaneum due to non-availability of central DEXA in this rural hospital. Peripheral DEXA were more preferred out of cheaper costs, affordability of poor rural patients and comfortability to patients. Inadvertently ,our majority of the study subjects 136(68%) were above 50 years and such age group were prone for degenerative spine (osteophtyes), discs, spinal fractures, and osteoarthritic diseases which could maligned BMD interpretation if central DEXA were used.[17] Scientifically also, there is preferential reduction of BMD in radial and calcaneal site as compared to lumbar/iliac which may be a ramification of the already established fact that osteoporosis in DM patients preferentially develops first within the appendicular skeleton with predominantly cortical bone followed by affliction of axial skeleton. One of the authors found the Z score at the distal radius was lower than that at their own lumbar spine and femoral neck in T2DM patients.[11]

Table 4: Magnitude of altered bone mineral density in diabetes mellitus reported in different studies.

First author	Year	Country	Study type	Sample size	Age (years) and sex	Magnitute (%) or T score
Present study	2016	India	Cross sectional	200	>=35, Both	Osteopenia-29 Osteoporosis- 53
Camli et al[18]	2015	Turkey	Randomized control	126	40-65, Both	T Score −0.2±1.0
Bruckner et al[11]	2014	Germany	Cross sectional	243	28-87, Both	Decreased BMD 13 - 21.9
Kamalanathan et al[10]	2014	India	Cross sectional	194	30-50, Both	Decreased BMD 19.5
Dutta et al[16]	2008-2010	India	Prospective	67	>40, Both	T score= −1.18 • ± 1.65
Maghbooli et al[12]	2007	Iran	Cross sectional	518	40-80, Female	Osteopenia-40, osteoporosis– 41.6
Al-Maatouqet al[19]	2004	Saudi Arabia	Case control	104	>45, Females	Osteopenia- 43.6 Osteporosis- 46.8

In poorly controlled diabetes, hyperglycaemia acts on bone tissue cells through advanced glycation end-products (AGEs), with help of specific surface receptors leading to increased production of interleukin-6 (IL-6). The IL-6 stimulates osteoclasts to commence bone resorption. The accumulation of AGEs in collagen leads to inferior bone quality and strength. Furthermore, glycated collagen inhibits expression in osteoblasts.[20] Hyperglycaemia impairs gastrointestinal calcium absorption by increasing gastroparesis.[21] The development of osteoporosis is also promoted by the co-existence of chronic microvascular complications, which also affect the bone marrow blood vessels.[21] The presence of peripheral and autonomic neuropathies is associated with bone changes of Charcot's neuroarthropathy type, lead to increased bone resorption. The increased bone damage in patients with diabetic neuropathy may be related to overexpression of nuclear factor kappa B (NF-kB), leading to increased release tumor necrosis factor (TNF-alpha) and interleukin-1 b, which stimulates osteoclast synthesis.[22] In type 2 DM ,a negative calcium balance is also observed (due to intestinal absorption abnormalities and hypercalciuria secondary to hyperglycaemia) with low serum magnesium.[12] Gregorio et al suggested that in poorly controlled patients glycosuria (glucosuric induced osmotic dieresis) causes hypercalcuria (renal calcium leak) and is maintained by parathyroid hyperactivity.[41]

Leptin is an adipokine secreted from adipocytes which exerts anti-osteogenic effects by binding to its receptors in hypothalamus, stimulating the release of noradrenaline from sympathetic nerve fibre projecting into bone. Nor-adrenaline is then thought to inhibit bone formation by binding to B2 adrenergic receptors on osteoblasts. Higher concentration of leptin actually induces apoptosis of bone marrow stromal cells, decrease bone formation, increase bone resorption with subsequent decreased BMD.[24,25]

In our study most of the cases had altered BMD in form of decreased BMD. High BMD were not detected in our study. However there are studies that reported increased BMD.[26,27] In a study by Cooper et al, there was a higher BMD at total hip (p=0.006), femoral neck (p=0.026) and forearm (p<0.001) in type 2 women.[28] Due to the anabolic effect of insulin on bone, results in a higher BMD in type 2 DM.

Correlates of altered bone mineral density

Age, gender, HbA1c, fasting blood sugar, duration, fracture history and serum calcium were found to be significantly associated with decreased BMD on Multivariate Regression Analysis. It demonstrated statistically significant association of decreased BMD in patients with higher age groups as compared to the younger age group. Similar observation were reported by Baheiraei et al, Dutta et al, Nguyen et al, Kahn et al.[29,16,30,31] Tung et al attributed mechanisms such as increased production of inflammatory cytokines and cellular components, incremental osteoclast precursors generation and decreased bone preservation due to gonadal failure resulting in lower tissue production of sex steroids.[32] Advanced age is also associated with increased fall frequency, lack of exercise, use of drugs that negatively influence bone metabolism and renal function such as drugs prescribed for diabetes and hypertension.[32]

Osteoporosis and osteopenia were more commonly found in female study subjects (total female -113). The p-value for this association of BMD with gender was significant. Few authors suggested that women with obesity can lead to lower bone turnover in diabetic women and decreased BMD.[33] Similar gender predilections were shared by other previous authors such as by Dutta et al and Kamalanathan et al.[16,10] Out of 113 females, 69 (61.1%) study subjects had attained menopause. These T2DM post-menopausal subjects had less BMD in consistent with findings of Al-Maatouq et al who reported osteopenia (mean T-score= -1.8 SD) in 43.68% patients and osteoporosis (mean T-score= -3.3 SD) in 46.8% (45) patients.[42,19] This may be due to the

combined effects of estrogen deprivation(in menopause) and raising FSH production(declining ovarian function &estrogen) cause a marked stimulation of osteoclast with bone resorption and a period of rapid bone loss (bone porosity, enlarging resorption areas in trabecular areas) which is central for the onset of postmenopausal osteoporosis.[34]

Significant association (p = 0.016, Odd ratio= 0.81)) were found for decreased BMD and BMI in our study. Majority of the overweight study subjects (76 no) had decreased BMD The Chi square value was 12.82. Our results were in agreement to those observed by Fawzy et al (35) who showed that 35.6% were osteopenic and 25.7% osteoporosis and among patients with osteopenia and osteoporosis, about 77.4% were overweight or obese. BMD was low in 78.1% of overweight and 44.2% among obese. The association between BMI and BMD was found to be statistically significant (p<0.001) However studies by Nguyen et al and Baheiraei et al reported contradictory association of lower BMI with lower BMD.[30,29] Maghbooli et al explained that obesity enhances bone metabolism by increasing the load on the bone and a subsequently stronger bone and low bone turnover and/or hormone factors, or was due to measurement bias causing falsely high measured BMD in obese study subjects.[12]

In our study, alcohol (p=0.71) and smoking (P=0.07) had no statistically significant association with decreased BMD. However, it can cause decreased BMD due to (a) Free radical formation following smoking and contributing to bone resorption. (b) Lower Fat mass and Leptin in smokers influences BMD. (c) Impaired calcium absorption in smokers (>20 cigarettes/ day) lead hypocalcemia and decreased BMD. (d) Parathyroid hormone levels have been reported to correlate negatively with smoking. i.e. more parathyroid hormones lead bone resorption.[36]

We found significant association between BMD with fracture history (p value= 0.019) Similar finding of fracture in type 2 DM patients were reported by Gulay Sain , Guven and suggested an increased risk of hip and proximal humerus fractures (relative risk for femoral fractures in type 2 DM was 1.5-2.66.[13,37] A trend toward increased risk of vertebral, forearm, ankle and foot fractures were also reported. Alicja et al also suggested increased risk of bone fractures (which is about twice the risk in the general population) was due to inferior quality of bone., impaired micro- and macroarchitecture, coexisting sensory motor neuropathy, diabetic foot, and advanced diabetic nephropathy (develops secondary hyperparathyroidism leading to increased calcium resorption from bone).[23]

Duration of diabetes was found to associated significantly with decreased BMD (p value =0.0001). Likewise, association was observed by Alicja et al who found that study subjects with a longer duration of diabetes were at a higher risk of low BMD and fracture compared to women with a shorter duration of diabetes.[23] Increased duration leads to prolonged hyperglycemia state which acts on bone causing osteoclast activation through various stimulatory mechanism.

In our current study, most common oral hypoglycemia used was metformin i.e. 58.5 %. No significant association were found between antidiabetic drugs and decreased BMD. Metformin was known to cause osteoporosis by activating peroxisome proliferator activated receptor –γ(PPAR) leading to preferential inhibition of osteoblastogenesis thereby favours resorption and bone loss Kahn et al.[38,31] ADOP Trial noted increased incidence of limb fractures in women on rosiglitazone.[39] The other medication studied was HRT. HRT was not associated significantly with decreased BMD (p=0.56) since only 3.5% had taken HRT.

Among biochemical parameters, significant association were found for fasting blood sugar (p=0.0001), HbA1C (p value 0.0001) and serum calcium (p value 0.001) with decreased BMD. Majority of our study subjects 85 (42.5%) had poor glycaemia control (HbA1C >7.6) due uneducated, illiterate nature of the rural mass who were not aware for its importance. This negative correlation i.e. decreasing BMD with higher HbA1C were reported by Komatsu et al.[40] Gregario et al found more bone loss in poorly controlled diabetes (higher HbA1C) by measuring severe high osteocalcin (bone resorption marker) levels.[41] Further, the Fremantle study of 194 type 2 DM patients showed that HbA1c was independently associated with BMD at the hip and femoral neck.[42] Regarding the serum calcium ,in our study 69 study subject had low serum calcium level (34.5%). There were 64 had lower BMD. The Chi square value was 27.06. Significant association of BMD with BMI was found (p value =0.001. Odd ratio was 0.25). However, phosphate had no significant association with BMD as reported by Wakasugi et al.[42] However, Takeda E et al found that phosphate plays a critical role in skeletal development, mineral metabolism.[43] It is a vital component of bone mineralization with its deficiency leading to weaken bone and decreased bone density.

This study has several limitations. Our study includes all T2DM patients ≥35 years eliminating selection bias, the standardize protocol was used and sample size was adequate for total outcome events. However, our study had few limitations also since it was a single centre study. Being a cross-sectional study based on hospitalized patients, temporal associations could not be studied. We could not investigate vitamin D levels, because of the limitations of resources and central DEXA was not available. We did not exclude patients with co-morbidities and complications associated with diabetes such as neuropathy, microangiopathy, nephropathy, insulin resistant which could alter the outcome. Further studies at multiple centres involving patients at

community level should be conducted to assess the factors causing decreased BMD in these patients.

CONCLUSION

The decreased BMD (osteoporosis and osteopenia) were prevalent in patients with T2DM in Central India, with a higher frequency in females than in males. Decreased BMD was significantly associated with age, gender, fracture history, alcohol, smoking, body mass index, fasting blood sugar, glycosylated hemoglobin and serum calcium. We recommend improving the low-quality diabetes care to standards of diabetes health care at all health care levels in order to reduce the burden attributable to the DM along with reduction in modifiable factors which affects the BMD.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Reema N, Jain J, Singh TG, Banait S. A study of magnitude and correlates of altered bone mineral density in type 2 diabetes mellitus patients of central rural India. Int J Adv Med 2020;7:1380-7.