Original Article

Prevalence of Osteoporosis in Postmenopausal Type 2 Diabetic Women with Diabetic Peripheral Neuropathy

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Abstract

Introduction: There is evidence that diabetic peripheral neuropathy (DPN) is associated with increased risk for fractures in type 2 diabetes mellitus (T2DM). We planned a study to assess the prevalence of osteoporosis and vertebral fractures (VFs) in postmenopausal type 2 diabetic women aged 40–60 years with DPN and to find out their relationship with severity of DPN. **Methods:** This cross-sectional observational study included sixty-two postmenopausal type 2 diabetic women of age 40–60 years, out of them thirty-two were with DPN and thirty were without DPN. The presence of DPN was established based on history and clinical examination. Plain X-ray spine and bone mineral density (BMD) measured by dual-energy X-ray absorptiometry were used to assess vertebral fracture and osteoporosis, respectively. **Results:** The prevalence of osteoporosis in women with DPN was 68.75% at lumbar spine (LS) and 18.75% at femoral neck (FN), and osteoporosis at LS was statistically significant compared to those without DPN ($P = 0.002$). On subgroup analysis in women with DPN, the osteoporosis at LS showed significant association with lower body mass index (BMI) ($P = 0.015$), but not with severity of DPN. The prevalence of VFs in women with DPN was 6.25% with no statistical significance in comparison with other group. **Conclusion:** Our study revealed high prevalence of osteoporosis at LS in postmenopausal type 2 diabetics with DPN. VFs are most common consequence of osteoporosis, although we could not find significant prevalence of VFs in women with DPN that may be due to small sample size and cross-sectional study design.

Keywords: Diabetic peripheral neuropathy, osteoporosis, postmenopausal, type 2 diabetes mellitus, vertebral fractures

Introduction

Osteoporosis and type 2 diabetes mellitus (T2DM) are major public health concerns, as the age-adjusted (20–79 years) prevalence of T2DM in India is 9.6%.[1] Despite the significant impact of this disease, fragility fractures related to diabetes and diabetic bone disease are overlooked. Individuals with T2DM may have decreased, increased, or normal bone mineral density (BMD),[2-5] and these diabetic patients are at higher risk for fractures irrespective of their BMD status.[6] The commonest fracture due to osteoporosis is vertebral fracture (VF) and may occur in 20% of postmenopausal women.[7] The presence of even asymptomatic VF is associated with future risk for new vertebral and nonvertebral fractures, independent of BMD.[8] Diabetic peripheral neuropathy (DPN) is an important clinical risk factor for fractures as it is associated with an increased risk for falls and decreased physical activity.[9,10] DPN may have a direct effect on bone health by affecting local neurotransmitters on bone cells, potentially reducing neuropeptides such as calcitonin gene-related peptide (CGRP). CGRP is a neuropeptide with osteoanabolic potential, as it promotes osteogenesis, inhibits osteolysis, induces angiogenesis, and regulates the immune microenvironment.[11,12] Most of the earlier studies on the prevalence of osteoporosis and vertebral fractures (VFs) in postmenopausal type 2 diabetics included patients over 60 years of age. T2DM in Asian Indians differs from Caucasians with a younger age at onset, and Indian women experience menopause earlier than their western counterparts.[13,14] In addition, there is limited information on osteoporosis and VFs in younger Indian postmenopausal diabetic patients. Thus, our study aimed to assess the

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prevalence of osteoporosis and VFs in Indian postmenopausal type 2 diabetic women with DPN who were younger than 60 years of age.

Materials and Methods

Subjects

Sixty-two postmenopausal women with T2DM of age in between 40 and 60 years were included in this study from a tertiary care hospital. The lower age limit of 40 was set to exclude subjects with premature menopause. This age group of 40–60 years was chosen because there are limited data on osteoporosis and VFs in Indian patients in this age group. Menopause was defined as a complete cessation of menstruation for a period of 1 year. We excluded patients with type 1 diabetes mellitus, surgical menopause or menopause before 40 years of age, bedridden, active smoking, consumption of alcohol three or more units per day, thiazolidinedione or SGLT2 inhibitor therapy (as these medications are associated with a negative effect on BMD and may increase the risk of fractures), prior treatment of osteoporosis, history of vertebral or nonvertebral fracture, family history of fragility fracture, uncontrolled hyper and hypothyroidism, hyper and hypoparathyroidism, rheumatoid arthritis, current exposure to or had exposure to glucocorticoids for more than 3 months, gastrointestinal disorder causing malabsorption or Crohn's disease, scoliosis, or evidence of malignancy in recent 5 years.

Clinical assessment

Anthropometric parameters like height and weight were noted, and body mass index (BMI) was calculated by using the formula weight/height^2 (kg/m2). Study subjects were categorized into underweight (BMI <17.5 kg/m2), normal (BMI 17.5-22.99), overweight (BMI 23-27.49), obesity class I (BMI 27.5-32.49), class II (BMI 32.5-37.49), and class III (BMI ≥ 37.5).[15]

DPN was diagnosed on the basis of clinical history and examination. Diabetic Neuropathy Symptom (DNS) score[16] was used to assess symptoms related to neuropathy. Pressure perception was assessed by using 10 g Semmes–Weinstein monofilament. It was applied on each foot on the plantar surface of the great toe, planter surface of the 1st, 3rd, and 5th metatarsal heads. Failure to feel monofilament at any of the four sites is considered abnormal.[17]

Vibration sensation was assessed using a hand-held biothesiometer (Sensitometer, Dhansai Lab). It is an instrument that measures the threshold of appreciation of vibration sense. The amplitude of the stimulus is gradually increased until the threshold of vibratory sensation is reached, and the stimulus is appreciated by the subject. The vibration perception threshold (VPT) value was defined as the voltage level at which the subject first reported feeling the sensation of vibration. VPT was measured at six areas on the plantar aspect of the feet: hallux, 1st metatarsal head, 3rd metatarsal head, 5th metatarsal head, instep, and heel. The mean of all the areas tested was taken as the VPT of the subject. The VPT was measured in volts. In the present study, a voltage of more than 15 V was taken as the presence of neuropathy. The severity of neuropathy was further divided based on the mean VPT value into two grades.[18,19]

Grade 1 or mild: mean VPT 15–24 V and

Grade 2 or moderate to severe: mean VPT ≥ 25 V

Patients were also assessed for the presence or absence of pinprick, temperature sensation, and ankle reflex.

After clinical history and examination, participants were divided into cases and controls. Cases were patients with DPN, and controls were those without DPN.

Bone densitometry and X-ray spine

In all study subjects, areal BMD (g/cm^2) was measured at the lumbar spine (L1–L4; LS-BMD) and femur neck (FN-BMD) using dual-energy X-ray absorptiometry (DXA) (GE Healthcare Lunar DPX-NT enCORE software). The DXA machine was operated by a professional technician. The coefficient of variation of the lumbar spine (LS) and of the femur neck (FN) measurements was less than 3%. Normal BMD, osteopenia, and osteoporosis were defined by the T-score at the LS and FN as per the WHO criteria.[20]

Plain X-rays of the dorsolumbar spine with anteroposterior and lateral views were obtained and visually inspected or assessed for presence of VFs. Severity of VFs was defined according to the Genant visual semiquantitative assessment method[21] and graded as normal (grade 0), mildly deformed (grade 1: reduction of 20-25% of height and 10-20% of projected vertebral area), moderately deformed (grade 2: reduction of 26-40% of height and 21-40% of projected vertebral area), and severely deformed (grade 3: reduction of >40% of height and projected vertebral area). All X-ray assessments were performed by a radiologist, and he was blinded to the clinical information of the study subjects.

Biochemical parameters

Blood samples were taken for assessment of hematological and biochemical parameters. Fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), HbA1c, serum creatinine, serum calcium, serum phosphorus, and serum total alkaline phosphatase (ALP) were measured. HbA1c was measured by high-performance liquid chromatography (HPLC), ion exchange principle. Plasma glucose was measured enzymatically using the GOD-POD method. The investigations were done on a fully automated Mindray SAL 6000.

Statistical analysis

Categorical variables were presented in the form of numbers and percentages (%), and the quantitative data were presented as the means ± SD. The comparison of quantitative variables was analyzed through an independent *t*-test, while qualitative variables were analyzed using a chi-square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was

done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, a *P* value of less than 0.05 was considered statistically significant.

Ethical aspects

After the Institutional Ethics Committee (ECR/526/Inst/UP/2014/RR-20) Institute of Medical Sciences approval (No. Dean/2021/EC/2735, dated 23/06/2021), the study was conducted with the standards as per the Helsinki Declaration of 1964, as revised in 2013. The study participants were recruited after obtaining written informed consent.

Results

Table 1 shows a comparison of cases (postmenopausal women with DPN) and controls (postmenopausal women without DPN). Mean age, menopausal duration, and BMI were comparable between groups. The mean diabetes duration (years) of cases was longer compared to controls (9.47 ± 5.07 vs. 3.7 ± 3.7), and a higher proportion of cases had diabetes duration >5 years. Most cases (71.88%) had grade 2 or moderate to severe DPN. Diabetic foot ulcer (DFU) was present in 5 cases, and all these cases had grade 2 DPN.

VF was noted in two cases, one with D12 vertebrae fracture of grade 3 severity. This case had LS-BMD of 0.788 g/cm², with a T-score of -3.4 and Z-score of -1.6, and FN-BMD of 0.856 g/cm², with a T-score of -1.2 and Z-score of 0.1. Another case with D9 vertebrae fracture of grade 2 severity had LS-BMD of 0.729 g/cm2, with a T-score of -3.8 and Z-score of -2.9, and FN-BMD of 0.740 g/cm2, with a T-score of -2.0 and Z-score of -0.8. We could not find any control with VF. The prevalence of VFs in cases was 6.25%, which was comparable to controls with no statistical significance (*P* value = 0.492).

Table 2 shows the results of BMD and T-score. We found 68.75% cases with osteoporosis at LS, which was significantly higher compared to controls (68.75% vs. 30%, respectively). Osteoporosis at FN was comparable between cases and controls (18.75% vs. 10%, respectively). Proportion of cases with osteopenia at FN was significantly higher as compared to controls (62.50% vs. 33.33%).

Table 3 shows biochemical parameters. No significant difference was seen in HbA1c, FPG, PPG, serum calcium, serum phosphorus, and serum total ALP level in between cases and controls. The mean estimated glomerular filtration rate (eGFR, mL/min/1.73 m²) in cases was 81.64 ± 26.17, significantly lower compared to controls (93.73 ± 17.64), with a *P* value of 0.036. Out of thirty-two patients with DPN, four of them had diabetic kidney disease (DKD), while only one patient without DPN had DKD.

Table 4 shows the association of osteoporosis at LS in cases

A significant association of BMI was noted with LS osteoporosis. Mean ± SD BMI (kg/m²) in cases without osteoporosis was 27.87 ± 6.2, which was significantly higher as compared to cases with osteoporosis 23.29 ± 3.81 (*P* value = 0.015). Otherwise, we did not find a significant association of osteoporosis at LS with duration of diabetes or menopause, severity of neuropathy, and HbA1c in cases.

Discussion

T2DM patients have a higher risk for vertebral and nonvertebral fractures irrespective of their BMD status. A decrease in bone quality, rather than bone mass, is responsible for such fractures.[22] DPN can potentially affect bone health and could be related to an increased risk of fractures in these patients.[23] DPN is associated with an increased risk for falls due to balance and gait disturbance, loss of proprioception, orthostatic hypotension, and loss of reflexes. These patients also have lack of activity or low physical activity, particularly those with painful neuropathy.[9,10] DPN can influence bone metabolism via modulation of neurotransmitter on bone cells.[11,12] All these factors consequently affect bone health and can increase risk for osteoporosis and fractures. The present study found 6.25% prevalence of VFs in postmenopausal T2DM women with DPN, which did not have any statistical significance with a *P* value of 0.492.

Kirkizlar TA *et al*.[24] observed a significant association between DPN and VFs in postmenopausal women. Similarly, Lee RH *et al*.[25] showed that DPN was the most important mediator of fracture risk in a cohort of older male Veterans. Contrary to this, Yamamoto *et al*.[6] revealed that VFs were not associated with diabetic complications like retinopathy or

Table 1: Characteristics of study subjects

Characteristics	Cases (subjects with DPN) *n*=32	Controls (subjects without DPN) *n*=30	*P*
Age (years, mean±SD)	53.12±4.43	51.8±3.91	0.218
Menopausal duration (years, mean±SD)	7.08±3.8	6.28±3.72	0.409
BMI (kg/m², mean±SD)	24.72±5.06	26.16±5.03	0.267
Diabetes duration (years, mean±SD)	9.47±5.07	3.7±3.7	<0.0001*
<5 years (*n*, %)	7, (21.88%)	22, (73.33%)	0.0003*
>5 years (*n*, %)	25, (78.12%)	8, (26.67%)	
Grade 1/mild DPN (*n*, %)	9, (28.12%)		
Grade 2/moderate to severe DPN (*n*, %)	23, (71.88%)		

*Statistically significant

neuropathy and duration of diabetes in patients with T2DM in both genders.

Viégas M *et al*. showed an increase in the prevalence of VFs in postmenopausal T2DM women from 7.9% in those aged between 41 and 59 years to 34.1% in those older than 60 years, with no significant association to DPN although it was present in 60.1% of their cohort. The prevalence of VFs in women younger than 60 years in Viégas M *et al*.[26] study was comparable to our study.

In our study, women with DPN showed significant osteoporosis at LS compared to those without DPN (68.75% vs. 30%, respectively), and significant osteopenia was observed at FN (62.50% vs. 33.33%, respectively). Similarly, Rasul S *et al*.[27] observed lower LS-BMD in postmenopausal women with DPN compared to those without DPN and also demonstrated increased bone turnover markers in patients with established DPN. Li T *et al*.[28] revealed that the presence of DPN was one of the influencing factors of osteopenia as well as osteoporosis in T2DM women between 45 and 60 years of age. Viégas M *et al*. and Hyassat D *et al*. also showed higher % of osteoporosis at LS and higher % of osteopenia at FN in postmenopausal T2DM; however, they did not categorize the patients according to the presence or absence of DPN.[26,29]

On subgroup analysis of cases, we observed a significant association of osteoporosis at LS in DPN women with lower BMI. This finding is consistent with various previous studies from India. Dutta *et al*., Mathen PG *et al*., and Sharma B *et al*. observed a significant positive correlation of BMI with spine and hip BMD.[30-32] Bone turnover may be affected by mechanical factors associated with BMI. Larger body mass forces a greater mechanical loading on bone; thus, the bone mass increases to accommodate this load. It was observed that women in the top weight tertile had 35%–55% slower rate of bone loss from spine and hip than in lowest tertile.[33] We could not find any statistically significant association of osteoporosis at LS with severity of DPN, diabetes duration, menopausal duration, and HbA1c.

Diabetes or menopausal duration has a dose-dependent effect on osteoporosis, which means longer duration with higher prevalence. Majumdar SR *et al*. and Koh W-P *et al*. showed high risk for osteoporotic fracture when diabetes duration is >10 years and >15 years, respectively.[34,35] Menopausal or

Table 2: BMD and T-score

	Cases (subjects with DPN) *n*=32	Controls (subjects without DPN) *n*=30	*P*
LS-BMD (g/cm^2, mean±SD)	0.84±0.14	0.94±0.15	0.007*
T-score (mean±SD)	-2.67±1.05	-1.8±1.14	0.003*
Z-score (mean±SD)	-1.74±0.98	-1.12±1.09	0.023*
Osteoporosis at LS (*n*, %)	22, (68.75%)	9, (30%)	0.002*
Osteopenia at LS (*n*, %)	7, (21.88%)	12, (40%)	0.122
FN-BMD (g/cm^2, mean±SD)	0.78±0.11	0.84±0.15	0.076
T-score (mean±SD)	-1.66±0.86	-1±0.97	0.006*
Z-score (mean±SD)	-0.74±0.83	-0.28±0.92	0.042*
Osteoporosis at FN (*n*, %)	6, (18.75%)	3, (10%)	0.475
Osteopenia at FN (*n*, %)	20, (62.50%)	10, (33.33%)	0.022*

*Statistically significant

Table 3: Biochemical parameters

	Cases (subjects with DPN) *n*=32	Controls (subjects without DPN) *n*=30	*P*
FPG (mg/dl, mean±SD)	212.47±58.75	203.97±90.37	0.665
PPG (mg/dl, mean±SD)	287.91±70.35	289.5±110.8	0.947
HbA1c (%, mean±SD)	10.44±2.15	9.41±2.09	0.062
Calcium (mg/dl, mean±SD) [Normal range 8.5-10.5 mg/dl]	9.53±0.5	9.66±0.6	0.377
Phosphorus (mg/dl, mean±SD) [Normal range 2.5-4.5 mg/dl]	3.82±0.59	3.71±0.54	0.455
Total alkaline phosphatase (U/L, mean±SD) [Normal range 110-310 U/L]	233.56±101.78	229.67±66.41	0.86
Serum creatinine (mg/dl, mean±SD)	0.95±0.43	0.76±0.18	0.029*
eGFR (ml/min/1.73m2, mean±SD)	81.64±26.17	93.73±17.64	0.036*

Table 4: Association of LS osteoporosis in cases (subjects with DPN, *n*=32)

Characteristics	Cases with LS osteoporosis *n*=22	Cases without LS osteoporosis *n*=10	*P*
BMI (kg/m2, mean±SD)	23.29±3.81	27.87±6.2	0.015*
Severity of DPN			
Grade 1 (*n*, %)	4, (18.18%)	5, (50%)	0.096
Grade 2 (*n*, %)	18, (81.82%)	5, (50%)	
Duration of diabetes (years, mean±SD)	9.11±5.07	10.25±5.25	0.565
Menopausal duration (years, mean±SD)	7.82±4.05	5.45±2.69	0.103
HbA1c (%, mean±SD)	10.16±2.36	11.06±1.52	0.277

*Statistically significant

diabetes duration in our DPN patients was ≤ 10 years; this may be the possible reason for no association of osteoporosis with these parameters in our study. In the available literature, there are scarce studies regarding association of osteoporosis with severity of DPN and conflicting results regarding association of HbA1c to osteoporosis.[36,37] HbA1c, in fact, reflects blood glucose concentration during the past 8–10 weeks, whereas the process of bone turnover requires more time.

There is a recommendation to screen for osteoporosis at an earlier age (younger than 60 years) in Indian postmenopausal diabetic women based on their clinical risk factor profile.[38] The presence of DPN in this cohort of patients can be an important clinical risk factor that is associated with increased risk of fracture and osteoporosis. Thus, this early screening of postmenopausal women with DPN, taking into account DPN as a risk factor, can be beneficial, and even DPN can be considered as a clinical risk factor input in the fracture risk assessment tool (FRAX) to predict future fracture risk

Strength of the present study is that it included postmenopausal women younger than 60 years of age. This study has several limitations. First, a small sample size. Second, nonmeasurement of serum vitamin D levels. Adequate levels of vitamin D have an important effect on bone mass in the young and old. Hypovitaminosis D causes defective bone mineralization and leads to decreased BMD.[39] Thus, patients with low BMD may be misdiagnosed to have osteoporosis in the presence of vitamin D deficiency. Third, a sole focus on clinical diagnosis of DPN. Adding nerve conduction study (NCS) for diagnosing subclinical DPN, especially in the control group, may have added more value in the diagnosis of DPN. In addition, analyzing study subjects using a cutoff of T-score ≤ -2.0, as recommended by the recent American Diabetes Association consensus[40] for therapeutic intervention in diabetics at this T-score, compared to our use of a conventional cutoff of T-score ≤ -2.5, could make a difference in study outcome.

Conclusion

Postmenopausal women with DPN showed a high prevalence of osteoporosis at LS and osteopenia at FN. These findings could have important clinical implications for the early screening of osteoporosis in postmenopausal women, taking into account DPN as a risk factor. We found 6.25% prevalence of VFs in postmenopausal women with DPN. Even though it is not statistically significant, it could be beneficial to investigate for the presence of subclinical VFs in these women. A positive association of osteoporosis at LS with lower BMI was noted. However, we did not find an association with the severity of DPN, diabetes, or menopausal duration and HbA1c. A larger sample size and long follow-up would establish the association of low BMD with DPN and its relevance to VFs.

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Author's contribution

SKS conceived the study idea, guided the study and revised the manuscript critically. SK selected the study subjects, performed clinical assessment, data analysis and drafted the initial manuscript. SS revised the manuscript and put forward critical inputs. All authors approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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