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**Original Research Article**

# The incidence of osteoporosis and vertebral fracture in women with postmenopausal type 2 diabetes mellitus and predisposing factors of vertebral fractures

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## ABSTRACT

**Background:** Type 2 diabetes mellitus (DM) has an increased fracture risk due to loss of bone quality and tendency to falling. The aim of the study was to analyze the incidence of osteoporosis and vertebral fractures (VF) in postmenopausal women with type 2 DM and to define the risk factors of VF in terms of clinical, metabolic characteristics and diabetes related microvascular complications.
**Methods:** The 42 postmenopausal patients with type 2 DM were included to the study in Haseki Training and Research Hospital outpatient clinics.
**Results:** Osteoporosis with regard to lumbar spine (LS) and femur neck (FN) was 8.4%, 19.4%, respectively. Vertebral fracture ratio was 31%. There was no statistical significance between vertebral fracture and osteoporosis. In logistic regression analysis, longer postmenopausal period, higher postprandial blood glucose (PBG), presence of peripheral neuropathy was found associated with vertebral fracture (p=0.04, 0.04, and 0.05, respectively).
**Conclusions:** In this study we suggest to consider the length of postmenopausal period, PBG and peripheral neuropathy for assessing the risk of VF.

**Keywords:** Menopause, Type 2 DM, Fracture, Vertebrae

## INTRODUCTION

Type 2 diabetes mellitus (DM) and osteoporosis are significant public health problems especially in elderly population. Type 2 DM was found associated with increased fracture risk in the studies despite normal or high bone mineral density (BMD).[1-3] Hyperglycemia, hypoglycemia, advanced glycation end products (AGEs), vitamin D insufficiency, diabetes related complications, obesity, hyperinsulinism, oral antidiabetics, sclerostin were accused in terms of the tendency to fractures by directly with unfavorable effects on bone quality and indirectly with increasing the risk of falling. Recent studies have disclosed that type 2 DM damages bone quality via impairing osteoblast activity and increasing bone resorption even in high or normal BMD. It is believed that low resolution measurement techniques, complex physiopathology of type 2 DM, measurement of BMD in different zones and difference of study designs do not reflect the bone microstructure and quality which is impaired in this patient group and consequently cause deceptive evaluation.[4,5] Osteoporosis precipitates painful fractures via bone loss even though asymptomatic in the beginning. Vertebral fracture (VF) is the most common problem due to osteoporosis and can occur 20% of postmenopausal women.[6] Presence of vertebral fracture is a risk factor for vertebral and non-vertebral fractures independent of BMD and associated with mortality, morbidity and quality of life.[7]

At the present time, the lifetime of patients with type 2 DM is getting longer consequently increasing elderly

population with type 2 DM and the patients with chronic diabetes related complications such as fractures. Due to incompatible assessment of fracture risk with BMD, the markers which are related with bone turnover were investigated for predicting fracture risk and were found sufficient. However, the markers of bone turnover are difficult to reach and costly for daily practice using.[8] Because of that, we thought to estimate the vertebral fracture risk via clinical and metabolic markers and disease status which are available and attainable easily. The aim of our study was to analyze the incidence of osteoporosis and morphometric vertebral fractures and to define the correlations between vertebral fractures and clinical, metabolic characteristics and chronic diabetes related complications in postmenopausal women with type 2 DM.

## METHODS

Forty-two postmenopausal women with type 2 DM were analyzed retrospectively in Haseki training and research hospital outpatient clinic between May 2011-August 2011. Data were collected from the files. Ethical committee approval was not requested due to being a retrospective study in our country.

Postmenopausal patient was described as having no menstrual period at least as long as 12 months or having >20 U/l follicle stimulating hormone (FSH) level in patients with hysterectomy. Exclusion criterions were designated as having type 1 DM, newly diagnosed type 2 DM, usage of chronic glucocorticoids, uncontrolled hyper or hypothyroidism, existence of hyper or hypoparathyroidism, rheumatoid arthritis, Paget's disease, existence of malignancy recent five years, malabsorption syndromes, advanced scoliosis, having any bone disease that prevent to interpret direct X-rays accurately, exposure to hormone replacement therapy or glitazones, history of vertebral or non-vertebral fracture.

Weight, height, length of type 2 DM, date of last menstrual period, duration of exercises, amount of intaking calcium daily, usage of cigarette and alcohol and medications especially statins, bisphosphonates, oral antidiabetics and insulin, blood pressure measurements, fasting blood glucose (FBG) (8-12 hour fasting), glycolyzed hemoglobin A1c (HbA1c), serum total cholesterol- HDL cholesterol (HDL-K)- LDL cholesterol (LDL-K)- triglycerides (TG), creatinine, and FSH and postprandial blood glucose (PBG) (second hour after meal) and proteinuria in 24 hour urine, BMD measurements, X-ray graphics of vertebrae were collected from the files and e-files. Body mass index (BMI) was calculated by the formula kg/m$^2$ and defined by World Health Organization (WHO) criterions as underweight (BMI <18.5 kg/m$^2$), normal weight (BMI 18.5-24.9 kg/m$^2$), overweight (BMI 25-40 kg/m$^2$), obese and morbid obese (BMI ≥40 kg/m$^2$). High blood pressure was approved as above 140 mmHg for systolic or above 90 mmHg for diastolic measurement according to National Institutes of Health (NIH) 2004.[9] Abdominal obesity was defined as above 88 cm in compliance with National Cholesterol Education Program (NCEP) 2001 report.[10] Siemens Advia 2400 biochemistry analyzer was used for FBG, PBG, serum total cholesterol, LDL-K, HDL-K, TG, creatinine and proteinuria, Siemens Advia Centaur XP hormone analyzer was used for serum FSH by immunoassay method, Bio-Rad variant device was used for HbA1c by high performance liquid chromatography (HPLC) method. Creatinine clearance was calculated by Cockcroft-Gault formula while glomerular filtration rate (GFR) according to Modification of Diet in Renal Disease (MDRD) study. Staging of chronic kidney failure was made by GFR in compliance with 2003 chronic kidney failure guideline of National Kidney Foundation.[11]

Bone mineral density (BMD) of LS and femur neck (FN) were measured with dual energy X-ray absorptiometry (DEXA) system by use of Norland device. BMD results were interpreted by T score and defined as osteoporosis which was ≤ (-2.5) and osteopenia which was between (-1) and (-2.5) according to WHO.[12]

The presence of vertebral fracture was evaluated by Genant semiquantitative method as measuring anterior, middle and posterior height of vertebras between thoracal 4 (T4)-lumbar 5 (L5) thoracolumbar anterior-posterior and lateral X-ray graphics which were performed by general proteus device. Fractures were defined as grade I or mild: loss of the height of anterior vertebrae between 20%-25%, grade II or moderate: loss of the height of anterior vertebrae between 25%-40%, or deformation of anterior or middle vertebrae (loss of the height level 20-25%), grade III or severe: severe deformation or ≥40% volume loss compared to neighbor vertebrae.[13]

We used SPSS (statistical package for social sciences) 16.0 programme for statistical analysis. For continuous variables, we obtained the mean and standard variation. We used Mann-Whitney U test for continuous variables and Chi square or Fisher's exact test for categorical variables. We performed logistic regression analysis for predicting vertebral fracture. P≤0,05 was regarded as statistically significant.

## RESULTS

Median age of the patients was 60 years, the median length of type 2 DM was 8.28 years, the median BMI was 25.38, median length of postmenopausal period was 11.5 years.

No active smoking and usage of alcohol was encountered in the patient group. All patients had abdominal obesity (median 114 cm). Median BMD of LS was -0.9 and FN was -1.55. Characteristics of the study group were shown in Table 1 and 2.

Osteoporosis and osteopenia with regard to LS and FN was 8.4%, 41.6%, 19.4%, 58.3%, respectively. We determined the ratio of vertebral fracture as 31% and most of them (76.9%) was grade I status.

**Table 1: Characteristics of the study group (n=42).**

| Variables | Median±SD[a] |
|---|---|
| **Age (years)** | 60.07±6.99 |
| **BMI[b] (kg/m$^2$)** | 25.38±4.40 |
| **The length of postmenopausal period (years)** | 11.5±7.85 |
| **The length of type 2 DM[c] (years)** | 8.28±6.96 |
| **FBG[d] (mg/dl)** | 194.26±99.11 |
| **PBG[e] (mg/dl)** | 235.29±108.60 |
| **HbA1c (%)** | 8.69±2.28 |
| **Total cholesterol (mg/dl)** | 212.69±40.18 |
| **HDL cholesterol (mg/dl)** | 44.21±11.90 |
| **LDL cholesterol (mg/dl)** | 126.98±30.06 |
| **Triglycerides (mg/dl)** | 196.79±76.51 |
| **Proteinuria (mg/ 24 hours)** | 127.25±109.00 |
| **Creatinine clearance (ml/min)** | 94.31±31.24 |
| **GFR[f] (mg/dl)** | 78.17±23.45 |
| **Abdominal circumference (cm)** | 114.05±9.63 |
| **BMD[g] (LS)[h]** | -0.5±1.19 |
| **BMD (FN)[ı]** | -1.55±1.23 |

a: standard deviation, b: body mass index, c: diabetes mellitus, d: fasting blood glucose, e: postprandial blood glucose, f: glomerular filtration rate, g: Bone mineral density, h: lumbar spine, ı: femur neck.

**Table 2: Characteristics of the study group.**

| Variables | N (%) |
|---|---|
| **Hysterectomy** | 6 (14.3) |
| **Exercise (10 min/week)** | 13 (31) |
| **Daily $Ca^{++}$ intake (<600 mg/ 600-1000 mg/ >1000 mg)** | 9 (21.4)/ 26 (61.9)/ 7(16.7) |
| **Active smoking** | 0 (0) |
| **Active usage of alcohol** | 0 (0) |
| **Lack of sunbathing** | 36 (85.7) |
| **Usage of statins** | 16 (38.1) |
| **Usage of bisphosphonates** | 1 (2.4) |
| **Usage of insulin** | 16 (38.1) |
| **Usage of oral antidiabetics** | 39 (92.9) |
| **Compliance of diabetic diet** | 29 (69) |
| **Hypertension** | 21 (50) |
| **Peripheral neuropathy** | 16 (38.1) |
| **Retinopathy** | 12 (28.6) |
| **GFR[a] (mg/dl) >90/ 90-60/ 60-30/ 30-15/ <15** | 15 (35.7)/ 21 (50)/ 5 (11.9)/ 1 (2.4)/ 0 (0) |
| **Genant score I/ II/ III** | 10 (76.9)/ 3 (23.1)/ 0 (0%) |
| **Vertebral fracture** | 13 (31) |

a: glomerular filtration rate.

There was no statistical significance between vertebral fracture and osteoporosis of LS or FN (p=0.12 and 0.32, respectively).

HDL cholesterol level was higher in non-osteoporotic patients rather than osteoporotic patients and this was statistically significant between groups (p=0.04 and 0.01 in terms of FN and LS osteoporosis, respectively). The length of postmenopausal period was longer and statistical different in patients who had vertebral fracture when compared to patients who did not have (p=0.03). Any other clinical and laboratory evidence was found significant in terms of osteoporosis and vertebral fracture between groups.

In logistic regression analysis, the length of postmenopausal period, PBG, peripheral neuropathy was found associated with vertebral fracture (p=0.04, 0.04 and 0.05, respectively).

## DISCUSSION

Diabetes Mellitus and osteoporosis are frequent costly diseases in society. Al-Maatouq et al, Anafaroğlu et al and Viegas et al found the ratio of osteoporosis 46.8%, 20.4%, 30.4% due to LS and 19.8%, 3.6%, 9.5% due to FN in postmenopausal women with type 2 DM, respectively.[6,14,15] Raska et al announced the prevalence of osteoporosis as 25%, in 2017.[16] In our study, we determined osteoporosis 8.4% in LS and 19.4% in FN and it was lower in terms of LS BMD according to literature.

Type 2 DM is thought to be protective for osteoporosis due to obesity, hyperinsulinism, increasing of estradiol and testosterone. However, lower quality of bone structure and higher risk of falling in this patient group increase the fracture risk.[17,18] The risk of falling approximately 50% in type 2 DM patients and it is believed that diabetic neuropathy or retinopathy or hypoglycemic episodes or older age are predisposing factors for falling consequently for fracture.[1,19] Low calcium intake, vitamin D insufficiency, low exercise period and smoking are accused for osteoporosis.[16] In the study which was conducted in >65 age diabetic patients was presented the association fracture risk with vision problems, history of stroke and peripheral neuropathy.[20] Glycemic control and lipid profile were thought to be related to bone loss in type 2 DM patients. In the studies, glycemic control results were diverse while HDL cholesterol was protective on BMD.[21-23] Besides this, longer postmenopausal period, normal or overweight BMI, lower exercise, inadequate sun exposure, older age, history of fracture, lower calcium intake and higher caffeine intake were associated with osteoporosis while immobilization, smoking and HbA1c level were not in a study which was conducted in 1079 Jordanian postmenopausal women.[24] In our study, we also demonstrated the protective effect of HDL cholesterol on BMD when compared osteoporotic and non-osteoporotic patients. We did not find any association between other characteristics and osteoporosis.

There is a lack of to determine the fracture risk because of deceptive BMD despite a useful measurement method such as DEXA and tendency to falling in this patient group. Some bone turnover biomarkers were used for predicting fracture risk and were found efficient. However, these biomarkers are not generally used in health centers

except clinical researches due to problems of cost, standardization and attainability.[8] Fracture risk scores were defined as FRAX which has not validated for type 2 DM and Q fracture score which can be an alternative for type 2 DM patients.[25] In type 2 DM patients, fracture histories and presence of VF via spinal X-ray assessment are recommended for predicting fracture risk in clinical practice according to some clinicians.[8,26]

Vertebral fractures are the most common fracture type in postmenopausal women although small part of them is diagnosed and treated. The diagnose of vertebral fracture is difficult in asymptomatic patients without imaging techniques. Choi et al found the incidence of VF 46% in 873 postmenopausal women with type 2 and only 2% of them were diagnosed previously and 33% of them had symptoms.[19,27] Yamamoto et al. and Yamaguchi obtained any association with BMD and VF while Kanazawa et al. obtained association between VF and low BMD.[26,28,29] Also Viegas et al revealed lower BMD in patients with VF.[6] In our study, VF ratio was 31% as similar to literature and VF was not associated with osteoporosis according to FN or LS. This could result from ethnical differences and patient' characteristics such as none of patients was using alcohol/cigarette and all of patients had abdominal obesity that may have positive impact on bone metabolism.

With regard to VF risk factors, in the studies the length of type 2 DM and menopause, diabetic retinopathy, advanced glycation end products and sclerostin increased the incidence of VF.[2,3,6,29-32] Viegas et al showed lower creatinine clearance and higher PBG and HbA1c in patients with VF than non-VF.[6] In a Japanese study, there was no difference in diabetes status and BMD between type 2 DM patients with and without VF.[26] Yamamoto et al revealed that diabetic complications such as retinopathy or neuropathy and the length of diabetes were not associated with VF in multivariable logistic regression analysis in patients with type 2 DM in both gender.[28] In our study, the length of postmenopausal period, PBG, peripheral neuropathy were found associated with VF. However, there was no association with nephropathy or retinopathy and VF. We think neuropathy induce of falling via orthostatic hypotension, loss of reflex and balance deficits and consequently causing VF. In terms of association with VF and longer postmenopausal period, the lack of estrogen which has protective effects on bone metabolism may accelerate fracture risk.

The limitations of the study were lack of the number of patients, being retrospective, using a semiquantitative method for VF assessment and lack of previous spinal X-ray imaging for comparing. Hypoglycemia attacks that may induce falling and history of trauma of the patients were not known.

## CONCLUSION

In clinical practice history of fracture and presence of VF via spinal X-ray technique seem more important than BMD for assessing VF risk in postmenopausal patients with type 2 DM. We also suggest to be aware that having of longer postmenopausal period, higher PBG and peripheral neuropathy regarding VF in this patient group.

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