



Effect of type 2 diabetes mellitus on treatment outcomes of patients with postmenopausal osteoporosis: a retrospective study

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Abstract

Objectives The aim of this study is to investigate the effect of type 2 diabetes mellitus (T2DM) on the treatment outcomes of patients with postmenopausal osteoporosis (PMOP).

Material and method Thirty-five patients who had been diagnosed as PMOP by lumbar and/or femoral neck bone mineral density screening (BMD) and who had comorbid T2DM were included in the study. Thirty-five patients who had been diagnosed as PMOP but who had no comorbidity including DM constituted the control group. Demographic features, biochemical parameters, femoral and lumbar T scores were all recorded. All patients were treated with bisphosphonate, calcium and vitamin D and the same parameters were evaluated at the end of the first and fifth year.

Results Lumbar T scores and serum osteocalcin levels before treatment were significantly lower in the DM + PMOP group ($p < 0,05$). At the end of 5 years, despite the lumbar T score having increased, the femoral T score was found to be significantly lower in the DM + PMOP group. In the PMOP group, there was significant improvement in the T scores and serum osteocalcin levels following a 5-year treatment period ($p < 0,05$).

Conclusions T2DM has unfavorable effects on treatment prognosis in patients with PMOP. Different risk factors of PMOP which differ in the general population maybe more important when evaluating fracture risk in patients with T2DM.

Keywords Postmenopausal · Osteoporosis · Type 2 diabetes mellitus · Treatment

Introduction

Diabetes mellitus (DM) is a major problem for healthcare providers as it is associated with multi-system complications resulting in increased risk of morbidity and mortality. Bones may also be involved in such complications over time. Decreased bone mineral density (BMD) and increased risk of fracture are well known complications of type 1 DM (T1DM) [1]. There is a large consensus on the increased risk of fracture although an apparent paradox of T scores can be observed in patients with type 2 DM (T2DM). This contradiction between fracture risk and T scores can be attributed to several reasons. Obesity is prevalent in T2DM patients and excessive mechanical load or hormonal imbalance

including insulin, leptin and estrogen may be a reason for normal BMD in patients with T2DM [2, 3]. Moreover, T1DM is characterised by hypoinsulinemia and low levels of insulin like growth factor 1 (IGF-1) in contrast with T2DM which is characterised by hyperinsulinemia and high levels of IGF-1. These mediators are known to be stimulating factors for bone formation. Therefore, increased bone turnover may attenuate age related bone loss in patients with T2DM [4, 5]. Increased fracture risk against high levels of anabolising hormones in T2DM patients suggests the involvement of other pathogenic mechanisms such as diabetic complications including hyperglycemia and lifestyle factors [6]. Experimental animal studies report hyperinsulinemia induced reduced transvers bone accrual and increased osteoclastogenesis during growth [7] resulting in high levels of bone in quantity but low in quality.

Different comorbidities and risk factors including lifestyle and dietary factors may contribute to osteoporosis. Bone metabolism is affected as well as other metabolic pathways in patients with T2DM. Both bone formation and resorption are accelerated in these patients resulting in the failure of bone

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architecture and bone quality. The risk factors of osteoporosis such as accompanying T2DM may affect bone metabolism in different ways.

The aim of this study is to investigate the effect of additional T2DM on the treatment outcomes of patients with postmenopausal osteoporosis (PMOP).

Material and method

Study design

Seventy (70) patients who were followed up by our clinic between 2010 and 2015 and that met WHO osteoporosis criteria were evaluated. Patient data was evaluated retrospectively for biochemical and BMD screening tests. The study was constituted as a retrospective cohort including patients with PMOP. Cases (exposure positive group) were defined as patients with postmenopausal osteoporosis (PMOP) and comorbid T2DM. Control group (exposure negative group) was defined as patients with PMOP without any comorbidities.

Thirty-five (35) patients who had been diagnosed as PMOP with lumbar and/or femoral neck BMD screening but who had no history of PMOP treatment including calcium and vitamin D, had comorbid T2DM and had been treated with oral anti-diabetic drugs (OAD) for at least 1 year were included in the study. The control group was constituted with 35 patients who had been diagnosed as PMOP but had no comorbidity including DM and who had not received any PMOP treatment including calcium and vitamin D. Patients who had additional comorbidity other than T2DM or who were diagnosed with any comorbid disease during follow up, had taken PMOP treatment irregularly, were under 50 years of age, had secondary osteoporosis or premature menopause, or had used any medication apart from OAD including antihypertensive drugs, statins and so on, were excluded.

Patients were informed about the study and their written consent was obtained at the beginning of the study. The study was approved by the local Ethical Board and was performed in accordance with the principles of the Declaration of Helsinki.

Three (3) individuals from the DM + PMOP group and 6 individuals from the PMOP group were excluded because of the diagnosis of additional comorbidity, irregular usage of medication or missed follow up and the study was completed with 32 patients in the DM + PMOP and 29 in the PMOP group.

Demographics and disease characteristics

Demographic features of patients including age, height, weight, body mass index ($BMI = \text{weight}/\text{height}^2$, g/cm^2), educational level, number of pregnancies, age of menarche and menopause, daily calcium, coffee and tea consumption, smoking, daily exercise level, clothing style, maternal history of fracture and

duration of T2DM disease were all recorded. Educational level was determined as “not reader and/or writer”, “only reader and/or writer”, “primary school degree” (5 years of formal education), “junior high school degree” (8 years of formal education), “high school degree” (11 years of formal education) or “university degree” (over 11 years of formal education). Clothing style was determined as “closed clothing” which refers to clothes that cover the body completely, “traditional clothing” which refers to clothes that cover the arms and legs and “modern clothing” which refers to clothes that do not cover the arms and legs. Daily calcium intake was evaluated by the frequency of consumption of 250 ml of milk, 30 g of cheese or 200 g of yoghurt which consists of 150 mg of calcium. Responses were recorded as ‘daily’, ‘at least twice a week’ or ‘never’. Tea, coffee and alcohol consumption was considered to be “overuse” if over 150 mg/day and “normal” if below that figure. Individuals who walked at least 30 min a day were accepted as “normally physically active” and if not were considered to be “physically inactive”.

Measurements of BMD were performed by using a DXA (Norland XR-46 system, Coopersurgical, Fort Atchinson, WI, USA). The BMDs of the lumbar spine (L1 to L4) and the hip region (total hip and femoral neck) were measured according to standard protocols and T scores of the measurements were assessed. Biochemical parameters for all subjects including serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), calcidiol (25(OH)D3), osteocalcine (oc) and urine Ca and P levels were recorded. Serum glucose and haemoglobin A1c (HbA1c) levels were also included for the DM + PMOP group.

Treatment

All individuals were instructed for daily PMOP exercises (range of motion, stretching and isokinetic exercises) and daily activities. 70 mg of alendronate weekly, 2500 mg of calcium carbonate (equivalent to 1000 mg of calcium ion) and 880 international units (IU) of vitamin D3 daily were prescribed for all subjects. All subjects were followed up over a 5 year period with the same BMD and biochemical measurements.

Comparisons

BMD values and biochemical parameters were compared in and between the DM + PMOP and PMOP groups before treatment, 1 year and 5 years after treatment.

Statistical analysis

Data analyses were made using the Statistical Package for the Social Sciences (SPSS) 22.0 for Windows. The continuous variables were evaluated with the Kolmorow-Smirnow test as to whether or not they were different from normal

distribution. Descriptive statistics were shown as mean ± standard deviation for continuous variables and frequencies and percentages (%) for nominal variables using chi-square tests. Statistically significant differences in repeated measurements within the group were evaluated with the repeated measurement ANOVA test. For all in-group analysis, Bonferroni correction was used to avoid type 1 mistake and $p < 0.017$ values were accepted as significant. Parameters were compared in and between groups before treatment, 1 year and 5 years after treatment with Mann Whitney U test (The BMDs of the lumbar spine and femoral neck scores and all biochemical parameters) and $p < 0.05$ scores were accepted as significant.

Results

The median age of all subjects was 58 years. Most of the patients had a primary school degree ($n = 25, 41\%$). The median BMI of patients was $28,72 \text{ g/cm}^2$. The median duration of disease for T2DM patients was 6,52 years. There was no significant difference between the groups ($p > 0,05$). The distribution of the demographic features of the individuals are given in Table 1.

The T scores and biochemical parameters of the DM + PMOP and PMOP groups before treatment are given in Table 2.

The mean total T score for lumbar BMD analysis (L1-L4) of the subjects was $-2,60$ while the T score for femoral neck was $-2,57$. Serum 25(OH)D3 levels of the subjects were low (median $13,64 \text{ ng/mL}$) while PTH levels nearly reached the upper limits (median $60,21 \text{ IU}$).

The T scores and biochemical parameters of the DM + PMOP and PMOP groups after treatment at first and fifth years are given in Tables 3 and 4.

After the first year of treatment there were no significant differences between the groups concerning their T scores and biochemical parameters ($p > 0.05$). After the fifth year, the lumbar and femoral neck total T scores were seen to be significantly higher in the PMOP group ($p < 0.05$).

The variation and distribution of the T scores and biochemical parameters before treatment and after one and 5 years of treatment are presented in Table 5.

In the group with DM + PMOP, only improvement in the femoral neck T scores was significant while in the PMOP group both lumbar and femoral neck T score changes were significant (Fig. 1).

In group analysis, a significant decrease in femoral neck T scores between the first and fifth year of treatment ($p = 0.007$)

Table 1 Demographic features of the patients

Parameters	DM + PMOP ($n = 32$) ave ± SD n (%)	PMOP ($n = 29$) ave ± SD n (%)	p
Age (year)	62.53 ± 9.48	58.21 ± 9.72	0.084
BMI (kg/m^2)	29.99 ± 4.38	28.88 ± 5.46	0.785
Education level			0.132
not reader and/or writer	3 (9.4)	1 (3.4)	
only reader and/or writer	12 (37.5)	10 (34.5)	
primary school degree	16 (50.0)	9 (31.0)	
junior high school degree	0	4 (13.8)	
high school degree	0	3 (10.3)	
university degree	1 (3.1)	2 (6.9)	
Number of pregnancies	4.71 ± 3.10	3.37 ± 2.42	0.067
Menarche age (year)	14.06 ± 1.58	14.58 ± 1.93	0.251
Menopause age (year)	54.37 ± 6.30	54.82 ± 6.19	0.779
History of fragility fracture	7 (16.3)	6 (20.7)	0.656
before menopause			
Daily Ca intake			0.518
everday	3 (9.4)	3 (10.3)	
at least twice a week	16 (50.0)	17 (58.7)	
never	13 (40.6)	9 (31.0)	
Tea, coffee and alcohol consumption			0.228
Overuse	3 (9.4)	6 (20.7)	
Normal	29 (90.6)	23 (79.3)	
Clothing style			0.326
closed clothing	1 (3.1)	2 (6.9)	
traditional clothing	29 (90.6)	21 (72.4)	
modern clothing	2 (6.3)	6 (20.7)	
Physical activation			0.786
physically inactive	11 (34.4)	9 (31.0)	
normal physically active	21 (65.6)	20 (69.0)	
Maternal history of fracture	3 (9.4)	4 (13.8)	0.220

ave ± SS average ± standart deviation, BMI Body Mass Index

Table 2 T scores and biochemical parameters of the DM + PMOP and PMOP groups before treatment

Parameters	DM + PMOP (<i>n</i> = 32) ave ± SD n (%)	PMOP (<i>n</i> = 29) ave ± SD n (%)	p
Total L1–4 T score	−3.03 ± 0.96	−2.42 ± 0.67	0.033
Total femur neck T score	−2.95 ± 1.20	−2.61 ± 0.66	0.311
Serum Ca (9–11 mg/dl)*	10.90 ± 2.02	9.35 ± 1.57	0.252
Serum P (3–4.5 mg/dl) *	3.64 ± 0.73	3.50 ± 0.91	0.273
Serum ALP (30–120 U/l) *	167.03 ± 104.35	159.03 ± 113.39	0.599
Serum PTH (12–65 ng/L) *	60.88 ± 42.27	64.65 ± 41.62	0.149
Serum 25(OH)D3 (20–40 ng/mL) *	19.23 ± 11.53	18.56 ± 5.94	0.153
Serum osteocalcine (3–13 µg/L) *	6.80 ± 5.55	8.65 ± 6.10	0.037
Urinary Ca (5–15 mg/day)*	8.81 ± 12.91	8.52 ± 12.47	0.312
Urinary P (0.4–1.3 g/day) *	0.97 ± 0.73	0.87 ± 0.83	0.183

Bold statements are statistically significant parameters

*Normal values, ave. ± SS:average ± standart deviation

Table 3 T scores and biochemical parameters of the DM + PMOP and PMOP group 1. year after treatment

Parameters	DM + PMOP (<i>n</i> = 32) ave ± SD n (%)	PMOP (<i>n</i> = 29) ave ± SD n (%)	P
Total L1–4 T score	−2.87 ± 0.52	−2.32 ± 0.78	0.053
Total femur neck T score	−2.08 ± 0.84	−2.16 ± 1.34	1.000
Serum Ca (9–11 mg/dl)*	10.75 ± 2.41	10.25 ± 1.49	0.351
Serum P (3–4.5 mg/dl) *	3.66 ± 0.59	3.54 ± 0.58	0.211
Serum ALP (30–120 U/l) *	137.66 ± 62.24	138.25 ± 62.49	0.751
Serum PTH (12–65 ng/L) *	65.60 ± 35.06	67.08 ± 31.07	1.000
Serum 25(OH)D3 (20–40 ng/mL) *	21.65 ± 16.33	20.60 ± 7.49	0.181
Serum osteocalcine (3–13 µg/L) *	7.75 ± 4.84	8.90 ± 4.76	0.067
Urinary Ca (5–15 mg/day)*	9.15 ± 1.75	9.06 ± 7.35	0.138
Urinary P (0.4–1.3 g/day) *	0.86 ± 0.51	0.82 ± 0.73	0.981

*Normal values, ave. ± SS:average ± standart deviation

Table 4 T scores and biochemical parameters of the DM + PMOP and PMOP group 5. year after treatment

Parameters	DM + PMOP (<i>n</i> = 32) ave ± SD n (%)	PMOP (<i>n</i> = 29) ave ± SD n (%)	P
Total L1–4 T score	−2.83 ± 1.58	−1.75 ± 1.13	0.011
Total femur neck T score	−3.33 ± 1.46	−2.30 ± 0.97	0.006
Serum Ca (9–11 mg/dl)*	9.76 ± 3.06	9.27 ± 2.37	0.549
Serum P (3–4.5 mg/dl) *	3.69 ± 0.60	3.66 ± 0.45	0.453
Serum ALP (30–120 U/l) *	106.00 ± 79.30	129.75 ± 69.15	0.180
Serum PTH (12–65 ng/L) *	68.43 ± 48.08	69.93 ± 46.61	0.881
Serum 25(OH)D3 (20–40 ng/mL) *	23.70 ± 17.80	21.05 ± 16.43	0.827
Serum osteocalcine (3–13 µg/L) *	8.41 ± 1.95	9.15 ± 1.35	0.187
Urinary Ca (5–15 mg/day)*	8.66 ± 4.98	8.55 ± 6.81	0.881
Urinary P (0.4–1.3 g/day) *	1.33 ± 1.64	1.21 ± 1.55	0.724

Bold statements are statistically significant parameters

*Normal values, ave. ± SS:average ± standart deviation

Table 5 The variation and distribution of the T scores and biochemical parameters before treatment and after 1. and 5. years of treatment

Parameters	DM + PMOP (<i>n</i> = 32) ave ± SD	PMOP (<i>n</i> = 29) ave ± SD	P
Total lumbar (L1–4) T score			
Before-1.year treatment	0.23 ± 0.47	0.09 ± 0.59	0.057
Before-5.years treatment	0.40 ± 0.48	1.14 ± 0.94	0.014
1. year-5.years treatment	0.06 ± 0.26	0.56 ± 0.28	0.003
Total femur neck T score			
Before-1.year treatment	0.52 ± 0.53	0.44 ± 0.98	0.935
Before-5.years treatment	−0.50 ± 0.12	−0.28 ± 0.96	0.012
1. year-5.years treatment	−1.52 ± 1.50	−0.23 ± 0.54	0.001
Serum Ca (9–11 mg/dl)*			
Before-1.year treatment	−0.02 ± 1.65	−0.05 ± 0.24	0.229
Before-5.years treatment	−0.07 ± 0.10	−0.09 ± 1.89	0.665
1. year-5.years treatment	−0.03 ± 0.43	−0.06 ± 1.02	0.211
Serum P (3–4.5 mg/dl) *			
Before-1.year treatment	0.04 ± 0.60	0.02 ± 0.85	0.606
Before-5.years treatment	0.02 ± 0.40	0.06 ± 0.99	0.107
1. year-5.years treatment	0.08 ± 0.51	0.08 ± 0.77	0.972
Serum ALP (30–120 U/l) *			
Before-1.year treatment	−36.18 ± 33.17	−32.33 ± 106.80	0.261
Before-5.years treatment	−56.67 ± 66.22	−47.58 ± 56.87	0.368
1. year-5.years treatment	−33.01 ± 67.02	−29.94 ± 28.65	0.480
Serum PTH (12–65 ng/L) *			
Before-1.year treatment	4.59 ± 2.19	3.73 ± 1.88	0.513
Before-5.years treatment	6.41 ± 4.82	5.75 ± 7.70	0.745
1. year-5.years treatment	2.10 ± 2.68	2.28 ± 2.73	0.861
Serum 25(OH)D3 (20–40 ng/mL) *			
Before-1.year treatment	1.59 ± 1.94	1.41 ± 1.65	0.881
Before-5.years treatment	2.50 ± 1.49	1.78 ± 1.03	0.104
1. year-5.years treatment	1.14 ± 1.23	1.06 ± 0.92	0.762
Serum osteocalcine (3–13 µg/L) *			
Before-1.year treatment	0.75 ± 0.75	0.37 ± 0.11	0.051
Before-5.years treatment	1.12 ± 0.23	0.98 ± 0.55	0.430
1. year-5.years treatment	0.59 ± 0.73	0.65 ± 0.13	0.456
Urinary Ca (5–15 mg/day)*			
Before-1.year treatment	1.00 ± 0.82	1.17 ± 0.72	0.380
Before-5.years treatment	−0.37 ± 1.90	−0.64 ± 1.50	0.356
1. year-5.years treatment	−0.61 ± 0.26	−0.28 ± 0.68	0.124
Urinary P (0.4–1.3 g/gün) *			
Before-1.year treatment	−0.48 ± 0.68	−0.49 ± 0.27	0.991
Before-5.years treatment	0.67 ± 0.13	0.78 ± 1.02	0.724
1. year-5.years treatment	1.05 ± 1.37	0.98 ± 1.02	0.617

Bold statements are statistically significant parameters

*Normal values, ave. ± SS:average ± standart deviation

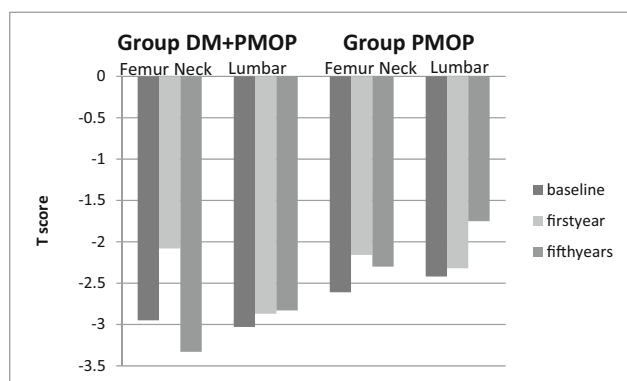
was found in the DM + PMOP group. In the PMOP group, a significant increase in femoral neck and total lumbar T scores between the baseline and fifth year of treatment ($p = 0.001$, $p = 0.003$ respectively) and between the first and fifth year of treatment were found ($p = 0.008$ and $p = 0.014$ respectively).

Discussion

There is a large consensus about the relationship between T2DM and PMOP indicating that T scores of lumbar and

femoral neck regions are significantly higher in patients with T2DM than in non-diabetic patients [8, 9]. However, some studies state that these values are inconsistent and may be lower or equivalent to those non-diabetics [10, 11]. In the present study, we found significantly lower T scores in the lumbar and femoral neck regions in patients with T2DM when compared with non-diabetic individuals.

Osteoporosis is defined as a skeletal disorder characterized by decreased bone strength including “BMD” and “bone quality” and increased risk of fracture [12]. Risk factors for osteoporosis include age, gender, diet regimen (poor calcium



BMD: Bone Mass Density, **DM:** Diabetes Mellitus, **PMOP:** Postmenopausal Osteoporosis

Fig. 1 The variation of T scores of femur neck and lumbar T scores between baseline, one and 5 years after treatment. *BMD* Bone Mass Density, *DM* Diabetes Mellitus, *PMOP*

intake), family history, body weight, fracture history, ethnicity, smoking, alcohol consumption, diseases such as rheumatoid arthritis or medications like steroids. The contrast of our results according to previous data may be related with the other risk factors of PMOP. In our study, we found low 25(OH)D3 levels and upper limit PTH levels before treatment in both groups. These may be attributed to the clothing style and low Ca intake in our population and therefore might interfere with our results. Osteocalcin and bone ALP are secreted proteins, the former stemming from mature osteoblasts and osteocytes, whereas the latter stem from pre-osteoblasts and are associated with bone formation [13]. Our study showed decreased levels of these proteins suggesting that bone formation is suppressed in patients with T2DM before treatment. On the other hand, the Ca, P, PTH and 25(OH)D3 levels that we found indicate reactive but inadequate bone formation correlated with lower T scores which suggest that bone formation is inadequate in terms of “quality” as well as “quantity” because of immature mineralization of the bone tissue.

The main content of the bone matrix is type I collagen and the cross-links between collagen units maintain the mechanical strength of the bone. Many complications of T2DM are associated with advanced glycation end products (AGEs). Pentosidine is one of these AGEs which consists of cross-linked arginine lysine by a pentose molecule. Both experimental animal studies [14] and pathological examinations of fractured bones [15] indicates high levels of pentosidine. Increased levels of pentosidine are shown to be in association with higher risk of fracture in clinical studies [16]. AGEs have specific receptors on cell surface (RAGEs) that are responsible for diabetic complications [17]. Cell culture studies indicate hyperglycemia and AGE-RAGE interaction suppresses osteoblastic differentiation and mineralization resulting in low BMD [18]. These findings may reflect the low T scores in our study in patients with T2DM.

There is a positive correlation between BMD and fat mass [19]. The interaction between bone and adipose tissue is

mediated by certain biologically active molecules such as leptin, adiponectin and resistin which are known to be adipokines [20]. Recent studies have indicated that this relationship is bidirectional and bone tissue may influence glucose metabolism and indirectly fat metabolism by OC [21]. OC is showed to increase insulin secretion and sensitivity, β cell proliferation and adiponectin expression in patients with T2DM and decreased fat mass [22]. Osteoblast cells express a functional insulin receptor and insulin seems to stimulate the proliferation and differentiation of these cells [23]. OC is produced by osteoblasts and accumulates in the bone matrix. However, osteoclasts are essential for the effects of OC on glucose metabolism [24]. On the other hand, insulin stimulates not only osteoblastic proliferation and bone formation but also activates osteoclasts and bone resorption by inhibiting osteoprotegerin (OPG) which acts as a decoy receptor for receptor activation of nuclear factor kappa-B ligand (RANKL). In our study, we found OC levels to be significantly lower in patients with T2DM compared to nondiabetic subjects before treatment. Lower T scores that we have found in our study may also be attributed to lower OC levels. At the end of 5 years of treatment there was no difference in terms of OC levels between the PMOP and DM + PMOP groups.

The incidence of T2DM and PMOP increase with aging. Although both diseases are viewed as different entities, recent studies have demonstrated common metabolic pathways suggesting that bone and glucose metabolism have bidirectional interactions. Some risk factors of PMOP like biomechanical stress, ethnicity and diet regimen maybe more important. There is a general consensus on increased fracture risk despite high T scores in patients with T2DM. The results of the present study are in contrast with recent data and this contradiction may be attributed to other risk factors of PMOP which may vary in the general population. Data about the relationship between T2DM and PMOP in the Turkish population is poor. Cakmak et al. reported significantly lower lumbar and femoral neck BMD values in hypertensive diabetic subjects when compared to the non-diabetics in the Turkish population, similar to our results [25]. These findings among the Turkish population, supports our hypothesis that the importance of the risk factors of PMOP differs from population to population. Moreover, the BMD measurement with DXA may not reflect the real bone quantity in patients with T2DM. Different techniques like quantitative computed tomography (pQCT) may show the real bone quantity. Petit et al. reported greater volumetric bone mineral density (vBMD) but a smaller bone area in both the distal tibia and radius in men with T2DM [26]. Further studies with this technique may offer different results.

The number of subjects, lack of evaluation with pQCT are the main limitations of our study. Further studies in large groups using pQCT in the Turkish population are necessary.

Conclusion

Osteoporosis and DM are common problems of elderly. Our results suggest that comorbidity of DM is associated with poorer outcomes in patients with PMOP. This comorbidity should not be undermined when evaluating treatment outcomes of PMOP.

Compliance with ethical standards

Conflict of interest There is no conflict of interest among the authors. There is no financial and/or nonfinancial disclosure for this study.

Informed consent Informed consent was taken from participants and available if requested.

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