Bone mineral density and fracture risk in prediabetes: a controlled cross-sectional study

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ABSTRACT

Objectives: There is comparatively scarce data on bone health in prediabetes (PD). This study aimed to evaluate osteoporosis, fracture risk, and to determine related factors in adults with PD comparing them with healthy participants.

Materials and Methods: A controlled, observational, cross-sectional study was conducted. All postmenopausal women and men aged over 65 years were recruited from a tertiary care hospital. A total of 120 participants (90 prediabetic, 30 control group) were enrolled in the study. All participants were screened for clinical status, Dual-Energy X-ray Absorptiometry(DEXA) was used to assess for osteoporotic fracture risk factors, and then the Fracture Risk Assessment Tool (FRAX) was calculated.

Results: Age, gender, body mass index (BMI), presence of obesity, and risk factors for osteoporotic fracture were similar between groups. Frequency of osteoporosis was higher in the PD group (p=0.045). Bone mineral density (BMD) and T scores of the lumbar and femoral neck regions were lower in the PD group (p=0.042, p=0.039, p=0.039, and p=0.042, respectively). Although there were statistically significant differences in BMD and T scores, 10-year probability of hip fracture and major osteoporotic fracture were similar in both groups. In the femoral neck region, BMD and T scores were weakly and negatively correlated with age. FRAX-major was correlated positively and weakly with age and FRAX-hip was positively and weakly correlated with age and negatively weakly correlated with BMI.

Conclusions: Almost one quarter of the postmenopausal prediabetic women had osteoporosis and osteoporosis was more common in the prediabetics than in the normoglycemic control group participants. While evaluating prediabetics, it is important to assess bone mineral density.

Keywords: Bone density; Osteoporosis; Prediabetic state.

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and microarchitecture degradation of the skeleton leading to increased bone fragility and tendency to fracture[1]. In 2009, there were about 24,000 hip fractures reported in Turkey and those are estimated to increase to nearly 64,000 in 2035[2]. In 2012, the prevalence of osteoporosis in the femoral neck was 7.5% in men and 33.3% in women, who were 50 years and over in Turkey[2]. In the USA, where approximately half of the population over 50-years-old has osteoporosis, the economic burden of osteoporosis and its complications on the health care system are estimated to be $25.3 billion annually by 2025[3]. Although osteoporosis inherently affects all bones, both hip and vertebral fractures are more specific for osteoporosis than others[1].

Bone mineral density (BMD), which is evaluated in the femoral and lumbar spine regions, is accepted as the optimal diagnostic method of osteoporosis. WHO announced diagnostic criteria of osteoporosis as using the BMD connected to peak bone mass in healthy people[4]. The measurement of BMD is recommended for elderly people, postmenopausal women, and those with secondary diseases with an

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increased frequency of osteoporosis to prevent complications leading to high cost and decreased quality of life[1,3,4]. The prevalence of secondary osteoporosis is reported in 17-30% females and 21-80% males according to the extensive study results in literature. Given the secondary causes of osteoporosis, endocrinological diseases occupy a wide range. One of them is diabetes mellitus (DM), with which the world struggles with its complications[5,6].

Prediabetes (PD), diagnosed based on plasma glucose criteria according to the American Diabetes Association, is an intermediate stage between DM and normoglycemia[7]. Recent studies conducted in adults stated that based on population, the prevalence of PD is 38% in the USA[8], 35.7% in China[9], and 30.8% in Turkey[10]. It was also emphasized that the incidence of PD has experienced a serious yearly increase in many studies[7,10,11].

The goal in the management of DM is to prevent the development of complications by providing normoglycemia[7]. Diabetes is a kind of cardiovascular disease and its common complications are known as microvasculary (retinopathy, nephropathy, and neuropathy) and macrovasculary (cardiovascular events, cerebrovascular disease, and peripheral artery disease)[12]. Although these complications are relatively rare in PD compared to DM, they can be seen even in the prediabetic stage of hyperglycemia[13,14]. In addition, PD has been shown to be associated with periodontal disorders, cognitive dysfunction, hypertension, obstructive sleep apnea syndrome, erectile dysfunction, metabolic syndrome, cancer, nonalcoholic fatty liver disease, and steatohepatitis, just like diabetes[15-18]. What about osteoporosis and bone health in prediabetics? Could osteoporosis, which is closely related to diabetes and shown as a complication of diabetes in some sources, have a relationship with PD? There is comparatively scarce data on this subject[19-21].

Therefore, the aims of this study were to evaluate osteoporosis, fracture risk, and to determine related factors in adults with PD by comparing them with healthy participants.

METHODS

PARTICIPANTS

A cross-sectional study was conducted from May 2019 to November 2019. Fasting plasma glucose (FPG) and HbA1c levels were measured for all participants, who were admitted to an internal medicine outpatient clinic for routine health checkups. Glucose values of oral glucose tolerance test (OGTT) were conducted for all participants without diagnosed diabetes. PD was defined as 0-hour plasma glucose value (OGTT-0) of 100-125 mg/dL (IFG) and/or 2-hour plasma glucose value (OGTT-2nd) of 140 mg/dL to 199 mg/dL (IGT). An HbA1c value of 5.7to 6.4% was also considered PD[7].

Then, patients with blood glucose levels in the prediabetic or normal range and those who had screening indication for osteoporosis were included in the study, consecutively[1,3,4]. Men aged over 65 years and all the postmenopausal women were screened for osteoporosis by Dual-Energy X-ray Absorptiometry (DEXA), assessed for osteoporotic fracture risk factors, and then the Fracture Risk Assessment Tool (FRAX) was calculated.

A total of 120 participants (90 prediabetic and 30 control group participants) were enrolled in the study. Exclusion criteria were as follows: a history of DM or a medication for DM, using any medication known to affect bone turnover and having causes of secondary osteoporosis, such as rheumatoid arthritis, corticosteroid use, hyperthyroidism, etc. When evaluating causes of secondary osteoporosis, both laboratory analyzes were performed and patients were asked by anamnesis.

HEALTH INDICATORS

Height and weight were measured and body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. BMI was categorized as obesity (BMI: 30 kg/m^2 and above) and non-obesity (BMI <30 kg/m^2)[22].

MEASUREMENT OF LABORATORY PARAMETERS

A fasting venous blood sample was collected after an overnight fast of at least 12-h for biochemical investigations and samples were processed in the hospital laboratory on the same day. Fasting plasma glucose, serum blood urea nitrogen (BUN), serum creatinine (sCre), and plasma and urine protein were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). Plasma glucose values at 0 and the 2nd hour were conducted by OGTT, and glycated hemoglobin (HbA1c) levels were measured for all participants. HbA1c levels were estimated using an Adams A1C HA-8180V au-

tomatic analyzer (Arkray Diagnostics, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers.

BONE MINERAL DENSITY

Bone mineral density was assessed by DEXA (DRA: Stratos 800) in the lumbar spine (L1-L4 vertebrae) and proximal femur (neck and total). Participants were sub grouped according to the criteria defined by the World Health Organization (WHO) as having osteoporosis with a T-score ≤ -2.5 standard deviation (SD) in either the lumbar spine or hip[23].

FRACTURE RISK (FR)

The 10-year probabilities of hip fracture and a major osteoporotic fracture were calculated using the Turkish FRAX model (version 4.1), which includes age, BMI, assessment of prior fragility fracture, parental history of hip fracture, current tobacco smoking, use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption. The BMD value of the femoral neck was also included in the calculation of the FRAX (http://www.shef.ac.uk/FRAX)[24,25].

STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Number of cases and percentages were used for categorical variables. Categorical data was analyzed by Chi-square or Fisher's exact test, where appropriate. The Shapiro-Wilks test and histograms were used to determine whether continuous variables were normally distributed. Normally distributed variables were presented as means and standard deviations (SD), non-normally distributed variables were presented as medians and interquartile ranges (IQR). Two independent groups of parametric variables were compared using the Student t test. For non-parametric variables, the Mann Whitney U test was administered. Relationships between non-parametric variables were analyzed by Spearman correlation tests and relationships between parametric variables were analyzed by Pearson correlation tests. A p value of <0.05 was considered to indicate statistically significant differences.

ETHICAL ISSUES

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The patient's written informed consent to publish the clinical information and materials was obtained. Local Ethical Committee approval was received (Date: 22.05.2019, Approval Number: 2019/380).

RESULTS

A total of 90 prediabetic patients and 30 control group participants were enrolled in the study. There were 81 females (90%) in the prediabetic and 27 (90%) in the control group participants. Risk factors for osteoporotic fracture, age, gender, BMI, presence of obesity, and smoking status were similar between the groups (Table I). Frequency of osteoporosis was higher in the PD group (n=21, 23.3%) than in the control group (n=2, 6.7%) (p=0.045). Although BMD and T scores of the lumbar and femoral neck region were lower in the PD group than in the control group (p=0.042, p=0.039, p=0.039, and p=0.042, respectively), Z scores were similar between groups. In the region of total femur, T scores were lower in the PD group than in the control group (p=0.043), but BMD and z scores were similar between groups (p>0.05). Although there were statistically significant differences in BMD and T scores, 10-year probability of hip fracture and major osteoporotic fracture were similar in both groups (Table I).

In correlation analyses, DEXA values did not have any relationship with age, BMI, OGTT 0 and 2nd, and HbA1c. In the femoral neck region, while BMD and T scores were weakly and negatively correlated with age (r=-0.254, p=0.016 and r=-0.325, p=0.002, respectively), Z scores were positively and weakly correlated with BMI (r=0.273, p=0.009). In the total femoral region, both BMD and T scores were positively and weakly correlated with BMI (r=0.258, p=0.015 and r=0.358, p=0.001, respectively), likewise Z scores were positively and weakly correlated with BMI (r=0.392, p<0.001). The FRAX-major was correlated positively and weakly with age (r=0.306, p=0.003), FRAX-hip was positively and weakly correlated with age and negatively weakly correlated with BMI (r=0.350, p=0.001 and r=-292, p=0.005, respectively). All correlation analyses in the PD group are in Table II.

Prediabetic patients with or without osteoporosis were also compared in terms of age, BMI, OGTT 0 and 2nd values, and HbA1c. All of them were similar between groups (Table III).

TABLE I. COMPARISON OF PREDIABETIC PATIENTS WITH CONTROL GROUP

	Prediabetes (n=90)	Control (n=30)	P value
Gender (F/M), n (%)	81 (90) / 9 (10)	27 (90) / 3 (10)	1.000
Age (year), mean (SD)	57.8 (7.2)	57.1 (7.2)	0.666
Smoking, n (%)			
Never	72 (80)	22 (73.3)	
Quit	9 (10)	1 (3.3)	
Smoker	9 (10)	7 (23.3)	0.209
BMI (kg/m2), mean (SD)	34.2 (6.5)	32.9 (5.9)	0.324
Obesity (+)ve, n (%)	66 (73.3)	19 (63.3)	0.297
OGTT-0th, mean (SD)	104.5 (8.9)	91.3 (5.8)	<0.001
OGTT-2nd, mean (SD)	133.5 (32.3)	101.2 (14.4)	<0.001
HbA1c, median (per 25-75)	6 (5.9-6.2)	5.5 (5.4-5.6)	<0.001
Osteoporosis (+)ve, n (%)	21 (23.3)	2 (6.7)	0.045
Osteoporosis risk factors, n (%)			
Aged ≥65 years old	15 (16.9)	3 (10)	0.557
Alcohol 3 or more units/day	6 (6.7)	1 (3.3)	0.679
Parent Fractured Hip	5 (5.6)	1 (3.3)	1.000
Previous Fracture	0 (0)	0 (0)	-
Secondary osteoporosis	0 (0)	0 (0)	-
Rheumatoid arthritis	0 (0)	0 (0)	-
Glucocorticoids	0 (0)	0 (0)	-
DEXA; L1-L4			
BMD, gr/cm2;median (per 25/75)	0.878 (0.811 / 1.022)	0.952 (0.849/1.160)	0.042
T score, median (per 25/75)	-1.7 (-2.3/-0.7)	-1.15 (-1.9/-0.3)	0.039
Z score, median (per 25/75)	-0.4 (-1.0/0.9)	0.1 (-0.5/1.0)	0.072
DEXA ; Femur Neck			
BMD, gr/cm2, mean (SD)	0.876 (0.144)	0.955 (0.184)	0.039
T score, mean (SD)	-0.3 (1.2)	0.4 (1.6)	0.042
Z score, mean (SD)	0.9 (1.2)	1.6 (1.5)	0.430
DEXA ; Femur Total			
BMD, gr/cm2, mean (SD)	1.0 (0.2)	1.0 (0.2)	0.667
T score, mean (SD)	-0.5 (1.0)	-0.3 (1.1)	0.043
Z score, mean (SD)	0.2 (1.0)	0.3 (1.0)	0.613
FRAX			
Major, median (per 25/75)	3.2 (2.8/4.3)	3.0 (2.5/3.6)	0.084
Hip, median (per 25/75)	0.1 (0.1/0.6)	0.1 (0.0/0.2)	0.135

X-ray Absorptiometry; BMD: Bone mineral density; FRAX: Fracture Risk Assessment Tool; DEXA: Dual-Energy X-ray Absorptiometry. (P<0.05 considered statistically significant)

DISCUSSION

To our best information, the present study is the first attempt to introduce the relationship between PD and osteoporosis by including both genders in a cross-sectional study. As well as the confounders including sociodemographic and lifestyle related risk factors (age, gender, race, education level, BMI) being similar, we found evidence of a lower BMD and a higher prevalence of osteoporosis in both lumbar spine and femoral neck in patients with PD compared with normoglycemic participants.

BMD values of patients with DM compared to those without DM have been repeatedly shown in literature. Type 1 diabetes has a lower BMD, while type 2 diabetes is characterized with average or high-

TABLE II. CORRELATION ANALYSES OF PATIENTS WITH PREDIABETES

	Age		BMI		OGTT-0th		OGTT-2nd		HbA1c	
	r	p	r	p	r	p	r	p	rho	p
DEXA; L1-L4										
BMD	-0.182	0.091	0.134	0.217	0.084	0.442	0.027	0.803	0.035	0.748
T score	-0.219	0.041	0.158	0.144	0.079	0.464	0.012	0.909	0.023	0.832
Z score	0.143	0.185	0.186	0.084	0.128	0.236	0.046	0.675	0.187	0.087
DEXA; F-Neck										
BMD	-0.254	0.016	0.181	0.088	0.134	0.207	0.003	0.981	-0.133	0.218
T score	-0.325	0.002	0.236	0.025	0.105	0.327	0.011	0.918	-0.119	0.269
Z score	-0.074	0.489	0.273	0.009	0.116	0.275	0.060	0.576	-0.064	0.553
DEXA; F-Total										
BMD	-0.078	0.467	0.258	0.015	0.211	0.047	0.009	0.930	0.072	0.509
T score	-0.184	0.084	0.358	0.001	0.198	0.062	0.026	0.811	0.057	0.599
Z score	0.070	0.514	0.392	<0.001	0.203	0.056	0.064	0.549	0.135	0.214
FRAX										
Major	0.306	0.003	-0.170	0.109	-0.141	0.186	0.015	0.891	0.080	0.459
Hip	0.350	0.001	-0.292	0.005	-0.040	0.706	-0.030	0.782	0.135	0.209

BMI: body mass index; OGTT: oral glucose tolerance test; HbA1c: glycated hemoglobin; DXA: Dual-Energy X-ray Absorptiometry; BMD: Bone mineral density; FRAX: Fracture Risk Assessment Tool.
(P<0.05 considered statistically significant)

TABLE III. COMPARISON OF PREDIABETIC PATIENTS WITH OR WITHOUT OSTEOPOROSIS

	Osteoporosis (+)ve, (n=21)	Osteoporosis (-)ve, (n=69)	P value
Age (year), mean (SD)	60.3 (8.2)	57.0 (6.7)	0.100
BMI (kg/m2), mean (SD)	32.42 (6.12)	34.74 (6.57)	0.148
OGTT-0th, mean (SD)	102.4 (8.7)	105.2 (9.0)	0.249
OGTT-2nd, mean (SD)	134.3 (33.7)	133.4 (32.1)	0.692
HbA1c, median (per25/75)	5.90 (5.82-6.20)	6.00 (5.90-6.10)	0.797

BMI: body mass index; OGTT: oral glucose tolerance test.
(P<0.05 considered statistically significant)

er BMD[26-30]. Considering the suffering of patients with fracture, both type 1 and type 2 diabetes are reported among the causes of secondary osteoporosis[25,31]. The effect of PD on the skeletal system is not clear, whereas there are many studies in literature on the relationship between diabetes and osteoporosis[27-31]. Yet, few studies have documented the relationship between PD and bone health. In studies comparing prediabetic patients with healthy controls, there are results showing that BMD values are low, high, and similar[21,32-34]. In a large cross-sectional study by Ebrahimpur, participants aged 60 years and over were compared based on glycemic index (diabetic, prediabetic, and normoglycemic individuals). They reported that spinal and femoral osteoporosis was observed more commonly in normoglycemics than in prediabetics, while it was more common in prediabetics than in diabetics[35]. There is a severe conflict with these results, which is incompatible with literature. Regardless of BMD values, diabetic patients have been proven many times in prospective, large population-based studies and meta-analysis that the risk of fractures is higher than in non-diabetics[26-31]. It is also a serious criticism that con-

founding factors such as age, gender, and BMI are statistically different between groups in their study. However, in the present study, where confounders were statistically similar, both femoral neck and spinal osteoporosis were found higher in prediabetics than the healthy controls.

It is also known that the higher the BMD and T scores, the lower the prevalence of osteoporosis, whereas those decrease with older age[3,25,26,32]. Although inadequate glucose control increases the risk of bone fracture in DM, the effects of glycemia in patients with PD are insufficient[19,27]. In this study, compatible with literature, BMD and T scores were weakly and negatively correlated with age in the femoral neck region. However, none of them could be correlated with the glycemic index.

Both type 1 and type 2 diabetics have repeatedly been shown to have a high risk of bone fractures. Fractures and DM are associated with large health costs, morbidity, and mortality[21,27-31]. In a large population study, the risk of fractures in patients with diabetes was demonstrated to be 28% higher after adjusting for other risk factors[36]. Even if incompatibility between BMD value and the presence of osteoporosis in patients with type 2 DM makes it difficult to evaluate the risk of fracture, it is observed that the risk of fractures increases even in people with diabetes with a high BMD value[21,26,27,30,36]. Moreover, limitations in the use of BMD due to the lack of age, race, and comorbidities have made it necessary to develop the scale for fracture risk prediction. FRAX is the most widely used of these algorithms worldwide[24,25]. It has been reported in studies that diabetic patients have a higher fracture risk than the general healthy population although contrary findings are obtained according to the FRAX[26,37,38].

Nevertheless, the impact of PD on fracture risk is completely unclear. To the best of our knowledge, the present study, in which the fracture risk in patients with PD is calculated, was performed by us for the first time in literature. In a study, the FRAX score calculated by adding BMD revealed that there is no statistical difference between patients impaired fasting glucose with normoglycemic ones[39]. Due to the nature of the work structured by de Abreu, the fact that age and BMI were different between groups, it is not suitable for an ideal comparison. Moreover, their study includes only patients with impaired fasting glucose, but PD is a more comprehensive disorder. In the present study, in which the confounders were similar, the 10-year probability of fracture tended to be higher in prediabetic patients compared to normoglycemics according to major fracture, which is calculated by adding BMD, even if not statistically significant (p=0.084). Furthermore, 10-year probability of hip fracture was similar between the groups. Regarding the correlation situations, while 10-year probability of major fracture was correlated positively and weakly with age, hip fracture was positively and weakly correlated with age and negatively weakly correlated with BMI in accordance with literature[3,25,26,32]. The fact that the glycemic state in PD has no correlation on FRAX has been shown for the first time in literature.

Although the pathophysiology of bone fractures in diabetic patients has not been elucidated clearly, it is interpreted as the accumulation of glycosylation end products in the bone matrix with the effect of hyperglycemia, turning to fragile form[27]. It is also suggested that there may be a defect in the trabecular skeletal microstructure due to the nature of a metabolic disease in DM[40]. Therefore, FRAX is untrustworthy in estimating the risk of fractures in diabetics. If our study is considered from this point of view, further studies are needed to measure bone microarchitecture in PD. All of the prediabetic patients recruited to the present study were newly diagnosed patients because of the study design. This outcome also suggests that the earlier PD is diagnosed, the more osteoporosis and economic burden can be prevented.

There were some limitations in this study. Firstly, the number of male patients were low. Secondly, it was not a multi-center study. For this reason, we cannot make generalizations.

CONCLUSION

Almost one quarter of post-menopausal prediabetic women have osteoporosis and osteoporosis is more common in prediabetics than in normoglycemic control group participants. While evaluating prediabetics it is important to assess bone mineral density. Further analysis on a large cohort of patients would be helpful to understand the potential of PD.

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