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Osteoporosis and Related Factors in Patient with Type 2 Diabetes and Prediabetes

Tip 2 Diabetes Mellituslu ve Prediyabetli Hastalarda Osteoporoz ve İlişkili Faktörler

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Abstract

Objective: Osteoporosis is a disease leading to increased morbidity and mortality. Untreated patients are prone to fracture. In consequence, early diagnosis of osteopenia and osteoporosis is important. Diabetes mellitus (DM) is among the leading causes and is associated with an increased risk of skeletal fractures. The high prevalence of osteoporosis and associated fractures is an important health problem. Although many studies have been conducted to evaluate the frequency of osteoporosis in DM, there are only limited data for prediabetes.
Materials and Methods: Prediabetes patients and type 2 patients with DM applying to our internal medicine and endocrinology and metabolic diseases outpatient clinics were included in this cross-sectional study. Twenty-nine women and 6 men with prediabetes, and 53 women and 8 men with DM were evaluated. Lumbar spine and femur bone mineral densities were investigated using dual-energy X-ray absorptiometry. The study was conducted in accordance with the Declaration of Helsinki.
Results: Lumbar spine T-scores were lower in patients with diabetes. Also, FRAX value for major fracture risk was higher. Prediabetes patients bone mineral density measurements revealed osteopenia. In our study, a major risk factor for osteoporosis was advanced age.
Conclusion: Prediabetic patients are at risk of osteopenia and osteoporosis. Therefore, the necessity of preventive measures starting from the prediabetic period is underlined.
Keywords: Osteopenia, osteoporosis, prediabetes, type 2 diabetes mellitus, bone mineral density, fracture risk

Öz

Amaç: Osteoporoz, morbidite ve mortalitenin artmasına neden olan bir hastalıktır. Tedavi edilmemiş hastalarda artmış kırık riski ile ilişkilidir. Osteopeni ve osteoporozun erken teşhisi bu nedenle önemlidir. Diabetes mellitus (DM) artmış iskelet kırıkları ile ilişkilidir. Osteoporoz ve ilişkili kırıklar önemli bir sağlık sorunudur. DM'de osteoporoz sıklığını değerlendirmek için birçok çalışma yapılmış olsa da prediyabet için yalnızca sınırlı veri vardır.
Gereç ve Yöntem: Kesitsel tipteki bu çalışmaya dahiliye ve endokrinoloji ve metabolizma hastalıkları polikliniğimize başvuran prediyabet hastaları ve tip 2 DM hastaları dahil edildi. Yirmi dokuz kadın ve 6 erkek prediyabet, 53 kadın ve 8 erkek diyabet hastası olarak değerlendirildi. Lomber omurga ve femur kemik mineral yoğunlukları dual-enerji X-ışını absorbsiyometri ile araştırıldı.
Bulgular: Diyabetik hastaların lomber omurga T-skorları daha düşüktü. Ayrıca majör kırık riski için FRAX değeri daha yüksekti. Prediyabet hastalarının kemik mineral yoğunluğu ölçümleri osteopeni olduğunu gösterdi. Çalışmamızda osteoporoz için majör risk faktörü ileri yaştı.
Sonuç: Prediyabetik hastalar osteopeni ve osteoporoz açısından risk altındadır.
Anahtar kelimeler: Osteopeni, osteoporoz, prediyabet, tip 2 diabetes mellitus, kemik mineral yoğunluğu, kırık riski

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Introduction

Diabetes and osteoporosis are increasing and important health issues worldwide (1,2). Poorly controlled diabetes may lead to nephropathy, retinopathy, neuropathy, and cardiovascular diseases. Although diabetes has been included as a secondary cause for osteoporosis, in clinical practice osteoporosis is not screened usually as the other complications (3,4). Osteoporosis may lead to impaired quality of life, and disability due to hip and vertebral fractures. As a natural course of longer life expectancy, the number of fractures increases throughout the world (3-6). Hip fracture especially was found to be related with increased mortality and morbidity (3,4). All types of fractures will also increase the economic expenditure (3,4). There are inconsistent reports for osteoporosis in type 2 diabetes mellitus (T2DM) (3-6). Janghorbani et al. (6) evaluated this risk and concluded in their meta-analysis that diabetes and hip fracture are correlated.

Evaluating a patient with T2DM for osteoporosis only with bone mineral density (BMD) is not adequate, and may lead to underestimation of fracture risk (7). Bone turnover was low in diabetes because markers of bone resorption and formation has been found to be lower than in controls (8). The Women's Health Initiative stated that women with T2DM at baseline had a 20% increased risk of fracture at any part of the body (9). Strotmeyer et al. (10) proposed that patients with impaired fasting glucose (IFG) may be releated with an intermediate risk of fractures. Poor glycaemic control was interreleated with increased likelihood of osteoporosis and osteopenia (11).

Another problem in diabetes may be accompanying obesity, because increased fat may lead to under or over estimation of BMD calculated using dual energy X-ray absorptiometry (DEXA). Quantitative computer-assisted tomography should be an alternative in these patients, by giving more accurate measurements in severe obese patients (12). Bone turnover is decreased in T2DM and the microstructure of bone is altered, especially in patients presenting microvascular complications. The pathophysiological mechanisms underlying bone fragility may be correlated with hyperglycaemia and oxidative stress. Also accumulation of advanced glycation end products (AGEs) may compromise collagen properties and the function of osteocytes (13). Patients with T2DM generally tend to develop sarcopenia with time and they are prone to falls. Alteration in cortical bone structure and bone pattern may also contribute to the risk of fragility. Another problem is that medications used to treat diabetes may interfere with bone health (14).

Bone turnover has been reported to be low both in diabetic and prediabetic patients. The pathophysiologic mechanism of bone changes in diabetes have not yet been explained in details (15,16).

There are many studies about BMD in diabetes, while studies about prediabetes are limited. The purpose of our study was to appraise osteoporosis and related factors such as total calcium intake, D vitamin status, and fracture risk in diabetes as well as in prediabetes patients.

Materials and Methods

A hospital-based cross-sectional study was conducted and all patient were chosen consecutively from our endocrinology and internal medicine department outpatient policlinics between January 2019 and January 2020. All selected participants were patients presenting T2DM or prediabetes and older than 18 years. T2DM was diagnosed based on the standards of medical care in diabetes by the American Diabetes Association as follows: (a) hemoglobin A1c (HbA1c) ≥6.5%; or (b) fasting blood glucose (FBG) ≥126 mg/dL (no caloric intake for 8 hours at least); or (c) 2-h blood glucose ≥200 mg/dL by oral glucose tolerance test (using glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water); or (d) random blood glucose ≥200 mg/dL in patients with typical hyperglycaemia symptoms or hyperglycaemia crisis, which occurs in the absence of unequivocal hyperglycaemia. The results were confirmed by repeating tests (17). Prediabetic patients were defined as patient with IFG, impaired glucose tolerance and/or HbA1c values between 5.7 and 6.4. The exclusion criteria inclusive (a) diagnosis of malignant tumour and severe organ failure; (b) diagnosis of endocrinologic diseases; (c) long-term bedridden patients.

Written informed consent was taken from each patient. The patients were asked for eventual smoking, alcohol consumption and exercising. Also previous histories of fractures and lactose intolerance were queried. Daily calcium intake from each patient was calculated using iofbonehealth-calcium-calculator.

BMD measurement: DEXA (Hologic-Discovery, USA) was used to detect the BMD of each patient at three sites: total lumbar, femur neck, and total hip.

FRAX score was calculated for each patient. Vitamin D levels were measured using a Beckman coulter DxI 800 immunoassay system. Laboratory analyses were performed with a Beckman Coulter AU5800.

This study was approved by the Kütahya Health Sciences University Non-Invasive Clinical Research Ethics Committee (decision no: 2019/2, date: 30.01.2019).

Statistical Analysis

Analyses in prediabetes and diabetes patients were performed separately. Results were expressed as mean value ± standard deviation to describe continuous variables and with n values or percentages to describe categorical variables. Chi-square tests were used for categorical variables, One-Way ANOVA for normally distributed continuous variables, and the Kruskal-Wallis test for skewed continuous variables. Also logistic regression analysis was used to assess the relationship between BMD measurements and affecting factors. A univariate model was used first. Then a multivariate analysis was performed. A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Table 1 shows a comparison between diabetic and prediabetic patients. Twenty-nine women (30%), and 6 men (0.06%)

with prediabetes and 53 women (0.55%) and 8 men (0.08%) with T2DM were included in the study. The mean body mass index was higher in diabetic patients. Other variables such as age, weight, height, and smoking and alcohol consumption were similar between the groups. Calcium intake and lactose intolerance were also similar. Forty-seven women in the diabetic group and 26 women in the prediabetic group did not have any complaint for lactose intolerance. Three women with prediabetes and 6 women with diabetes described lactose intolerance. This numbers were 2 in prediabetic group and 1 in diabetic group for men, respectively (Table 1). Properties and related complications of diabetic patients are given in Table 2. Biochemical values of the patients were similar, but creatinine levels were slightly higher and hemoglobin levels were slightly lower in the diabetic group (Table 3). BMD measurements for hip and lumbar spine, and T-score results for both groups were similar, but FRAX major osteoporosis risk was higher in the diabetic group (Table 4). Among the prediabetics, 8 patients did already know that they had osteoporosis and 1 of them had experienced a fracture, while they were 22 and 3 respectively among the diabetic patients (22 patients presented osteoporosis history; 3 had fractures) (Table 5). Although not all patients with insufficient daily calcium intake had lactose intolerance, all lactose intolerant patients were not ingesting enough calcium daily. Also, none of the patients with sufficient calcium intake had lactose intolerance (Table 6). The frequencies of osteopenia published by World Health Organization (WHO) are given in Table 7. Prediabetes group did not differ from the diabetes group at the hip and lumbar spine for frequency of osteopenia. The osteoporosis frequencies published by WHO are given in Table 8. The frequency of osteoporosis was not different in the prediabetes group at the femoral neck, but it was more frequent at lumbar spine in the diabetic patients.

In order to evaluate factors that may affect osteopenia and/or osteoporosis, a logistic regression analysis was performed. In multivariate analysis, the most important factor was age (Table 9).

In the prediabetes group, there were 2 patients using acarbose and 7 patients using metformin. In the T2DM group, 55 patients were using metformin, 10 patients were using acarbose, 6 patients were using glinides, 21 patients were using sulphonylurea, 10 patients were using pioglitazone. Thirty-seven patients were on DPP-4 inhibitor therapy. Eleven patients were using SGLT-2 inhibitors, 8 patients were using GLP-1 analog therapy and 30 patients were using insulin.

Table 1. Characteristics of the study sample

	DM	Prediabetes	p
Gender (female) (n; %)	53 (64.6%)	29 (82.9%)	NS
Age (year)	59.9±1.2	57.7±2.3	0.202
Height (cm)	1.57±0.01	1.59±0.01	0.239
Body weight (kg)	78.3±1.9	73.9±1.9	0.137
BMI (cm/kg^2)	31.6±0.8	29.1±0.8	0.028*
Menopause (n)	46	21	0.144
Smoker (n)	8	9	0.152
Alcohol consumption (n)	2	0	0.159
Daily Ca intake (mg)	780±41	752±27	0.586
Lactose intolerance	6 female,1 male	3 female, 2 male	0.692

*Although the p-value was <0.05, it was not considered clinically significant.
BMI: Body mass index, DM: Diabetes mellitus, Ca: Calcium

Table 2. Characteristics of and frequency of related complications among the diabetic patients (n=61)

Diabetes variable	
Diabetes duration	12.3±0.9/year
HbA1c level (%, mean ± SD)	7.6±0.1%
Peripheral neuropathy (%)	33.8%
Retinopathy (%)	9.6%
Micro albuminuria (%)	32.2%
Hypertension (%)	44.8%
CAD (%)	19%
Cerebrovascular event (%)	1.6%
Peripheral vascular disease (%)	3.2%

CAD: Cardiovascular disease, SD: Standard deviation

Table 3. Biochemical properties of the study group

	DM	Prediabetes	p
25-(OH)D (ng/mL)	35.7±2.0	32.8±1.2	0.319
Ca levels (mg/dL)	9.4±0.1	9.6±0.07	0.201
Phosphorus (mg/dL)	3.5±0.08	3.5±0.06	0.918
Magnesium (mg/dL)	1.8±0.04	1.9±0.01	0.077
Hemoglobin (g/dL)	13.1±0.1	13.7±0.1	0.013*
Creatinine	0.89±0.02	0.83±0.01	0.035*
ALT (U/L)	21.6±1.8	20.0±1.6	0.565
AST (U/L)	20.2±0.8	21.6±1.3	0.381
HDL (mg/dL)	49.4±1.5	51.3±2.6	0.595
LDL (mg/dL)	116.0±4.5	122.3±4.0	0.202
Triglyceride (mg/dL)	162.5±11.5	145.6±11.1	0.239

*Although the p-value was <0.05, it was not considered clinically significant.
DM: Diabetes mellitus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Ca: Calcium, 25(OH) D: 25-hydroxyvitamin D

Table 4. DEXA results and FRAX risk of the patients

	DM	Prediabetes	p
Femur neck T-score	-0.91±0.17	-0.76±0.19	>0.05
Femur neck BMD (gr/cm^2)	0.747±0.018	0.781±0.025	>0.05
L1-L4 T-score	-1.00±0.19	-0.73±0.19	>0.05
L1-L4 BMD (gr/cm^2)	0.944±0.021	0.972±0.024	>0.05
FRAX major osteoporosis risk (%)	6.7±0.5	5.3±0.7	<0.05*
FRAX femur fracture risk (%)	1.3±0.1	1.1±0.3	>0.05

*There was no significant difference in the risk of femoral fracture between the diabetes and prediabetes groups.
BMD: Bone mineral density, DM: Diabetes mellitus, DEXA: Dual energy X-ray absorptiometry

Table 5. Fracture and history for old osteoporosis diagnosis distribution

				Prediabetes	Diabetes
Old osteoporosis diagnosis	No	Fracture	No	25	34
			Yes	2	5
	Yes	Fracture	No	7	19
			Yes	1	3

Table 6. Distribution of lactose intolerance according to groups, gender and daily calcium intake

					Prediabetes	DM
Male	Lactose intolerance	No	Calcium consumption	Low	4	7
				Enough	0	0
		Yes	Calcium consumption	Low	2	1
				Enough	0	0
Female	Lactose intolerance	No	Calcium consumption	Low	25	36
				Enough	1	11
		Yes	Calcium consumption	Low	3	6
				Enough	0	0

DM: Diabetes mellitus

Table 7. Frequency of osteopenia according to T-scores			
	Prediabetes	**DM**	**p**
Femur neck	37	31	NS
Lumbar spine (L1-L4)	31	29	NS

Data are expressed as percentages. NS: Not significant osteopenia were similar among diabetics and prediabetics for femur neck and lumbar spine, DM: Diabetes mellitus

Table 8. Frequency of osteoporosis according to T-scores			
	Prediabetes	**DM**	**p**
Femur neck	8.6	8.2	NS
Lumbar spine (L1-L4)	8.6	21.3	0.001

Data are expressed as percentages. NS: Not significant osteopenia were similar among diabetics and prediabetics for femur neck and lumbar spine, DM: Diabetes mellitus

Table 9. Logistic regression analysis for osteoporosis and affecting factors								
	Univariate model				**Multivariate model**			
	OR	**95% CI**		**p**	**OR**	**95% CI**		**p**
Age	1.840	1.370	1.133	0.000	1.068	1.021	1.118	0.004
Height	0.000	0.000	0.016	0.001	1.084	1.037	1.133	0.000
Weight	0.957	0.925	0.913	0.546	-	-	-	-
BMI	0.980	0.913	1.051	0.562	-	-	-	-
Smoking	0.950	0.324	2.786	0.926	-	-	-	-
Exercise	0.478	0.147	1.553	0.220	-	-	-	-
DM year	0.995	0.947	1.045	0.838	-	-	-	-
FBG	1.006	0997	1.015	0.201	-	-	-	-
HbA1c	0.932	0.681	1.275	0.657	-	-	-	-
25-(OH)D	0.954	0.901	1.010	0.108	-	-	-	-
Corrected Ca	0.662	0.304	1.442	0.299	-	-	-	-
Phosphorus	0.787	0.384	1.614	0.514	-	-	-	-
Magnesium	0.111	0.010	1.258	0.076	-	-	-	-
Ca intake	1.001	0.999	1.002	0.403	-	-	-	-
Lactose intolerance	2.100	0.586	7.522	0.254	-	-	-	-
Retinopathy	1.467	0.234	9.206	0.683	-	-	-	-
Neuropathy	0.946	0.364	2.458	0.909	-	-	-	-
Micro albuminuria	1.583	0.580	4.321	0.370	-	-	-	-

DM: Diabetes mellitus, BMI: Body mass index, 25(OH)D: 25-hydroxyvitamin D, Ca: Calcium, OR: Odds ratio, CI: Confidence interval, FBG: Fasting blood glucose

Discussion

T2DM population is growing in Turkey and in the world (18). T2DM is correlated with increased risk of skeletal fractures, despite of increased BMD (9,19). Women's Health Initiative study confirmed that women with T2DM at baseline had a 20% increased risk of fracture at any site (9,20). Valderrábano and Linares (9) mentioned that high BMD in T2DM is not enough to be protective, and bone strength could indeed be lower than what is predicted for BMD. They also stated that the microvascular damages of diabetes may be releated with microarchitectural bone defects, which may lie behind bone fragility. Increased risk of fracture in patients with T2DM despite increased BMD may be explained with high propensity for falls, poor blood glucose control, and AGEs. AGEs like pentosidine and carboximethyl lysine may be produced in collagen fibers and may thus deteriorate bone strength. Hyperglycaemia can also inhibit osteoclastogenesis.

The study Health in Aging and Body Composition confirmed that older people with T2DM had increased risk of fractures, while patients with IFG did not have a significantly increased risk (9,10). The pathophysiology of increased risk of fracture in these patients has been described, but there are only few studies about fracture risk in prediabetes patients and studies about

the prevalence of osteopenia and osteoporosis in prediabetes are also very limited. Chen et al. (21) examined the trends of osteoporosis and osteopenia in prediabetes. U.S. adults over 40 years tended to have lower BMD and high number of case of bone patology at the femoral neck and lumbar spine between 2005 and 2014. They also reported that prediabetes patients were associated with a higher prevalence of fracture than healthy people. Natour et al. (22) investigated the forearm bone density in inuit women with IFG and diabetes. They found that the forearm bone density and T-score was lower in diabetics in comparison to patients with IFG levels.

Dietary calcium is a basic nutrient, which is important for bone health, and its insufficiency constitutes a risk factor for osteoporosis (23). Our study revealed that daily calcium consumption is unfortunately low in our region. Mean daily calcium consumption was 780±41 mg for diabetics and 752±27 mg for prediabetics. This is lower than the recommended level. Another restrictive factor for sufficient calcium consumption is lactose intolerance (24). Calcium intake was also insufficient in all lactose intolerant patients. Education may be proposed and other foods rich in calcium may be recommended to these persons presenting risk for osteopenia and osteoporosis.

In the present study, BMD and T-score measurements at the lumbar spine and femur were compared between T2 diabetic and prediabetic patients. Furthermore, the frequencies of osteopenia and osteoporosis in these two groups and possible confounding factors were investigated. BMD measurements were generally similar for prediabetes and diabetes, but the frequency of osteoporosis at the lumbar spine is higher in diabetics compared to prediabetics.

It has been suggested that hyperglycaemia may lead to osteoblast dysfunction (25). Decreased osteoblast function may induce accelerated bone loss, osteopenia and osteoporosis. Hyperglycaemia stimulates production of macrophage colony stimulating factor, tumour necrosis factor-α and receptor activator of nuclear factor-κB ligand. These are osteoblast-derived activators of osteoclast proliferation and differentiation (26). FBG and HbA1c levels were not correlated in our study population. The HbA1c value of our diabetic patients was not very high and this may have influenced the results.

Diabetic complications were not correlated with osteoporosis/osteopenia in our study. Patients with macroalbuminuria or renal failure were not included in our study. Including patients with more complicated renal failure may affect the results of the study. One study from our country revealed that among the chronic diabetic complications only microalbuminuria had a negative impact on femoral neck BMD (27).

There are contradictory studies for lipid levels and BMD measurements (28). In a study from Asia, a significantly negative correlation was proposed between serum cholesterol levels and BMD in both men and women with T2DM (29). In our study, lipid levels were not correlated with BMD measurements.

Another important factor for osteoporosis is aging. Fracture risk has been defined to be greater with advancing age (30). Afshinnia et al. (31) reported that in patients with diabetes, older age, low body weight, low serum calcium, and low-density lipoprotein cholesterol levels were independently associated with lumbar spine osteoporosis. In our study, the most important confounding factor was age.

Lactose intolerance history was only asked in patients, no lactose intolerance test was performed, which constitutes a limitation of our study. Another limitation is the number of male patients. Further evaluation with a larger study group may be more informative.

Conclusion

In conclusion, T2DM patients have more frequent lumbar osteoporosis than prediabetic patients. Candidates for diabetes (prediabetes) and diabetic patients should be evaluated for osteopenia/osteoporosis. Aging is an important risk factor and early screening may prevent any fractures is this population at risk.

Ethics

Ethics Committee Approval: This study was approved by the Kütahya Health Sciences University Non-Invasive Clinical Research Ethics Committee (decision no: 2019/2, date: 30.01.2019).

Informed Consent: Written informed consent was taken from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ü., K.O., T.P.K., Concept: D.Ü., K.O., T.P.K., Design: D.Ü., K.O., T.P.K., Data Collection or Processing: D.Ü., K.O., T.P.K., Analysis or Interpretation: D.Ü., K.O., T.P.K., Literature Search: D.Ü., T.P.K., Writing: D.Ü.

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References

1. World Health Organization (WHO). Diabetes [İnternet]. Available from: URL: https://www.who.int/news-room/factsheets/detail/diabetes. Accessed August 25, 2019.
2. World Health Organization (WHO). Prevelance of diabetes and related factors [İnternet]. Available from: URL: https://www.who.int/diabetes/country-profiles/tur_en.pdf?ua=1. Accessed August 25, 2019.
3. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol 2010;6:99-105.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22:465-75.
5. Randell A, Sambrook PN, Nguyen TV, Lapsley H, Jones G, Kelly PJ, et al. Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. Osteoporos Int 1995;5:427-32.
6. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495-505.

7. Shanbhogue VV, Mitchell DM, Rosen CJ, Bouxsein ML. Type 2 diabetes and the skeleton: new insights into sweet bones. Lancet Diabetes Endocrinol 2016;4:159-73.
8. Hygum K, Starup-Linde J, Harsløf T, Vestergaard P, Langdahl BL. MECHANISMS IN ENDOCRINOLOGY: Diabetes mellitus, a state of low bone turnover-a systematic review and meta-analysis. Eur J Endocrinol 2017;176:137-57.
9. Valderrábano RJ, Linares MI. Diabetes mellitus and bone health: epidemiology, etiology and implications for fracture risk stratification. Clin Diabetes Endocrinol 2018;4:9.
10. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Bauer DC, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. Arch Intern Med 2005;165:1612-7.
11. Xu H, Wang Z, Li X, Fan M, Bao C, Yang R, et al. Osteoporosis and Osteopenia Among Patients With Type 2 Diabetes Aged ≥50: Role of Sex and Clinical Characteristics. J Clin Densitom 2020;23:29-36.
12. Yu EW, Thomas BJ, Brown JK, Finkelstein JS. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res 2012;27:119-24.
13. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol 2017;13:208-9.
14. Cortet B, Lucas S, Legroux-Gerot I, Penel G, Chauveau C, Paccou J. Bone disorders associated with diabetes mellitus and its treatments. Joint Bone Spine 2019;86:315-20.
15. Holloway-Kew KL, De Abreu LLF, Kotowicz MA, Sajjad MA, Pasco JA. Bone Turnover Markers in Men and Women with Impaired Fasting Glucose and Diabetes. Calcif Tissue Int 2019;104:599-604.
16. Starup-Linde J, Vestergaard P. Biochemical bone turnover markers in diabetes mellitus-A systematic review. Bone 2016;82:69-78.
17. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2017;40:S11-24.
18. Chen L, Magliona DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. Nat Rev Endocrinology 2012;8;228-6.
19. Janghorbani M, Feskanich D, Willet WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. Diabetes Care 2006;29;1573-8.
20. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, et al. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. J Clin Endocrinol Metab 2006;91:3404-10.
21. Chen C, Chen Q, Nie B, Zhang H, Zhai H, Zhao L, et al. Trends in Bone Mineral Density, Osteoporosis, and Osteopenia Among U.S. Adults With Prediabetes, 2005-2014. Diabetes Care 2020; 43:1008-5.
22. Natour NA, Morin SN, Egeland GM, Weiler HA. Forearm bone density is not elevated in Inuit women with impaired fasting glucose or type 2 diabetes mellitus. Int J Circumpolar Health 2019;78:1-7.
23. Balk EM, Adam GP, Langberg VN, Earley A, Clark P, Ebeling PR, et al. Global dietary calcium intake among adults: a systematic review. Osteoporosis Int 2017;28:3315-4.
24. Nicklas TA, Qu H, Hughes SO, He M, Wagner SE, Foushee HR, et al. Self-perceived lactose intolerance results in lower intakes of calcium and dairy foods and is associated with hypertension and diabetes in adults. Am J Clin Nutr 2011;94:191-8.
25. Im JA, Yu BP, Jeon JY, Kim SH. Relationship between osteocalcin and glucose metabolism in postmenopausal women. Clin Chim Acta 2008;396:66-9.
26. Wongdee K, Charoenphandhu N. Osteoporosis in diabetes mellitus: Possible cellular and molecular mechanisms. World J Diabetes 2011;2:41-8.
27. Anaforoglu I, Nar-Demirer A, Bascil-Tutuncu N, Ertorer ME. Prevalence of osteoporosis and factors affecting bone mineral density among postmenopausal Turkish women with type 2 diabetes. J Diabetes Complications 2009;23:12-7.
28. Brownbill R, Ilich JZ. Lipid profile and bone paradox: higher serum lipids are associated with higher bone mineral density in postmenopausal women. J Womens Health (Larchmt) 2006;15:261-70.
29. Yang Y, Liu G, Zhang Y, Xu G, Yi X, Liang J, et al. Association Between Bone Mineral Density, Bone Turnover Markers, and Serum Cholesterol Levels in Type 2 Diabetes. Front Endocrinol (Lausanne) 2018;9:646.
30. Kotwal A, Drake MT. Our Evolving Understanding of the Relationship Between Diabetes and Bone. Am J Med Sci 2017;354:333-4.
31. Afshinnia F, Chacko S, Zahedi T. Association of lower serum cholesterol levels with higher risk of osteoporosis in type 2 diabetes. Endor Pract 2007;13:620-8.