CMJ Original Research December 2015, Volume: 37, Number: 4

Cumhuriyet Medical Journal 259-264

http://dx.doi.org/10.7197/cmj.v37i4.5000161253

Does Type II diabetes mellitus affect bone turn-over markers in premenopausal women? A single center experience

Tip II diyabetes mellitusun premenapozal kadınlarda kemik turnover belirteçleri üzerine etkisi, tek merkez deneyimi

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Received/Accepted: December 21, 2015/December 23, 2015

Conflict of interest: There is not a conflict of interest.

SUMMARY

Objective: Diabetes mellitus (DM) is known to cause osteoporosis in premenopausal women with type II DM. The aim of this study was to show changes in bone turnover markers in diabetic premenopausal women.

Methods: Ninety-two women treated for type 2 DM and a control group of 33 women without diabetes were evaluated in terms of bone mineral density, osteocalcin, c-terminal telopeptide of type I collagen and homocysteine levels. Demographic data including body mass index, age and smoking status were recorded in both the patient and control groups. DM regulation was classified according to the European Association for the Study of Diabetes database (EASD).

Results: Age, BMI, smoking and duration of disease did not affect BMD or bone turnover markers. When the treatment modalities were evaluated, laboratory analysis revealed abnormal osteocalcin levels in patients using oral antidiabetics (p= 0.006). Homocysteine levels were abnormal in the diabetic group compared to the control group (p=0.018).

Conclusion: Our results demonstrate that DM adversely affected femoral BMD and bone turnover markers such as homocysteine. Some DM pharmacotherapies have side-effects on markers such as osteocalcin. Although some reports in the literature have suggested that the regulation of DM may affect the risk of osteoporosis, our results do not support that idea.

Keywords: Osteoporosis, Type 2 Diabetes Mellitus, bone turnover markers, bone densitometry

ÖZET

Amaç: Tip 2 diyabeti olan premenapozal bayanlarda diyabetin osteoporoza zemin hazırlayan bir antite olduğu bilinmektedir. Bu çalışmada amaç kemik turnover belirteçlerindeki değişimin gösterilmesidir.

Yöntem: Çalışmamızda Tip 2 diyabet tanısı ile izlenen 92 kadın hasta ve 33 diyabeti olmayan kontrol grubu demografik veriler toplandıktan sonra kemik mineral dansitesi (KMD) belirlenip, osteokalsin (OC), c terminal tip I kollagen (CTX) ve homosistein (HCY) düzeyleri ölçüldü. Diyabetik hastalar DM regülasyon durumuna gore sınıflandırıldı (European Association for the Study of Diabetes (EASD) verilerine göre).

Sonuç: Yaş, vücut kitle indeksi (BMI) ve sigara içimi, hastalık süresi gibi paremetrelerin kemik turnover belirteçleri ve KMD üzerine etkisi saptanmadı. Diyabetik grupta homosistein düzeyi kontrol grubuna göre anormal olarak saptandı (p= 0,018). Tedavi modaliteleri incelendiğinde oral antidiyabetik alanların osteokalsin düzeyleri düşük saptandı (p= 0,006).

Tartışma: Sonuç olarak çalışmamızda DM hastalarında femur KMD değerlerinin ve homosistein gibi kemik turnover markırlarının olumsuz etkilendiği görülmüştür. Literatürde diyabet regülasyonunun osteoporoz riskini etkilediğine dair yayınlar olsa da çalışmamızda bu konuda anlamlı sonuç saptanmamıştır.

Anahtar sözcükler: Osteoporoz, Tip 2 Diyabetes Mellitus, kemik turnover belirteçleri, kemik dansitometrisi

INTRODUCTION

The relationship of diabetes mellitus (DM) and osteoporosis is complex, and the pathogenesis of diabetic osteopenia is still unknown. Type 2 DM and healthy populations have previously been compared in terms of bone mineral density, wıth higher[1], equal[2] or lower[3] levels being reported. In recent studies, despite high bone mineral density (BMD) measurements, type 2 DM has been reported to be a risk factor for fractures of the proximal humerus, hip and foot[4]. The risk of fracture is influenced by numerous factors, such as duration of disease, body mass index (BMI) and medical treatment[5]. The purpose of this study was to show changes in bone turnover markers in premenopausal diabetic women, even if osteoporosis is not determined.

Bone turnover markers generally reveal different stages of bone turnover in a fast, sensitive and dynamic way. These markers are divided into 3 categories, indicating the number of osteoblasts, bone formation or resorption[6]. Bone turnover markers are used to determine the response to osteoporosis treatment and risk of fracture independently of bone mineral density. After treatment of osteoporosis, bone turnover markers increase before bone mineral density. Osteocalcin (OC) is a specific and sensitive marker of bone formation. C - terminal type I collagen (CTX) is an independent risk factor for bone fractures and provides important information regarding quality. Homocysteine, a metabolite of L-methionine amino acids is another marker related to collagen cross-linking. A homocysteine value >15 mmol/L is associated with an approximately 2.5-fold increased risk of bone fracture.

MATERIALS AND METHODS

Ninety-two premenopausal Type 2 diabetic women under monitoring at the Ministry of Health Dışkapı Yıldırım Beyazıt Education and Research Hospital internal medicine clinic, Turkey, and 33 healthy female volunteers were enrolled in the study.

Demographic data (age, BMI, smoking status and diabetic complications) were recorded. Bone turnover markers [homocysteine, osteocalcin and C terminal type I collagen (CTX)] and bone mineral densitometry were measured and compared between the study and control groups.

Statistical analysis

All analyses were performed using two-sided P values. Differences between categoric variables were analyzed using Pearson's Chi-square test, and those between continuous variables using the independent t-test or one-way ANOVA where applicable. Statistical differences between groups were analyzed using the log-rank test. Analyses were performed on Statistical Package for the Social Sciences (SPSS, version 22) software. Differences were regarded as significant at $p<0.05$.

RESULTS

Demographic data

Demographic data are shown in Table 1. Duration of diabetes was 5 years in 45% of patients, 5-9 years in 23%, 10-14 years in 19% and >15 years in 8%.

Of the patients in the study, 4.3% were receiving a diabetic diet, 51.1% were being treated with oral antidiabetics (OAD), 12% were receiving insulin and 32.6% were receiving insulin and OAD. The microvascular complications retinopathy, neuropathy and nephropathy were documented in 26.3%, 29.3% and 3.3% (stage 1-3) of diabetic patients, respectively. Regulation status of DM was classified based on the European Association for the Study of Diabetes (EASD) database. Accordingly, 20.7% of patients had good regulation, 43.5% moderate and 35.9% insufficient.

Table 1: Demographic data.

Variables	Control group (n=33)	Patients (n=92)	p
Age			**0.034**
30-39 years	39.4%	16.3%	0.006
40-44 years	27.3%	26.1%	0.895
45-49 years	24.2%	39.1%	0.124
50-55 years	9.1%	18.5%	0.207
Body mass index			**0.066**
Normal	9.1%	7.6%	
Overweight	42.4%	23.9%	
Obese	48.5%	62.0%	
Morbidly obese	-	6.5%	
Smoking status			**0.244**
No	84.8%	75.0%	
Yes	15.2%	25.0%	

Table 2: Comparison of demographic status of high and normal CTX groups in DM patients.

Variables	Normal	High	p
Age			**0.808**
30-39 years	17.3%	12.5%	
40-44 years	21.2%	37.5%	
45-49 years	44.2%	37.5%	
50-55 years	17.3%	12.5%	
Body mass index			**0.325**
Normal	5.8%	-	
Overweight	23.1%	50.0%	
Obese	63.5%	37.5%	
Morbidly obese	7.7%	12.5%	
Smoker	28.8%	50.0%	**0.249**
Duration			**0.577**
<1 year	11.5%	-	
1-4 years	26.9%	37.5%	
5-9 years	25.0%	12.5%	
10-14 years	25.0%	37.5%	
>14 years	11.5%	12.5%	
Treatment			**0.912**
Diet	1.9%	-	
OAD	42.3%	37.5%	
Insulin	17.3%	25.0%	
Insulin + OAD	38.5%	37.5%	
Regulation status			**0.824**
Good	21.2%	12.5%	
Moderate	42.3%	50.0%	
Insufficient	36.5%	37.5%	

Table 3: Comparison of demographic status of high and normal osteocalcin groups in DM patients.

Variables	Normal	High	p
Age			**0.395**
30-39 years	16.0%	17.6%	
40-44 years	24.0%	35.3%	
45-49 years	38.7%	41.2%	
50-55 years	21.3%	5.9%	
Body mass index			**0.842**
Normal	6.7%	11.8%	
Overweight	25.3%	17.6%	
Obese	61.3%	64.7%	
Morbidly obese	6.7%	5.9%	
Smoker	28.0%	11.8%	**0.222**
Duration			**0.320**
<1 year	13.3%	23.5%	
1-4 years	28.0%	41.2%	
5-9 years	25.3%	23.5%	
10-14 years	24.0%	5.9%	
>14 years	9.3%	5.9%	
Treatment			**0.006**
Diet	2.7%	11.8%	0.154
OAD	45.3%	76.5%	0.020
Insulin	14.7%	-	0.207
Insulin + OAD	37.3%	11.8%	0.042
Regulation			**0.926**
Good	21.3%	17.6%	
Moderate	42.7%	47.1%	
Insufficient	36.0%	35.3%	

Lumbar spine and femoral BMD were measured. Lumbar BMD values were normal in 67.3% of patients, while 30.4% were osteopenic and 2.1% were osteoporotic. In terms of femoral BMD, 81.5% of patients were normal, 16.3% were osteopenic and 2.1% osteoporotic.

There was no statistical significance between demographic data (age, BMI, smoking status, duration of DM, retinopathy, nephropathy and neuropathy) or in BMD and bone turnover markers (CTX, homocysteine and osteocalcin) in the DM patients (Table 2, 3, 4).

Regulation status and BMD were compared in the DM patients, and the difference was not statistically significant (p=0.54 lomber BMD and p=0.82 femur BMD). Regulation status and CTX levels (p=0.82), homocysteine (p=0.94) and osteocalcin (p=0.92) were also compared.

A statistical significance was observed between treatment modalities and osteocalcin levels (p= 0.006). Osteocalcin levels were abnormal in 76.4% of diabetic patients treated with OAD.

Table 4: Comparison of demographic status of high and normal homocysteine groups in DM patients.

Variables	Normal	High	P
Age			0.178
30-39 years	15.7%	17.1%	
40-44 years	27.5%	24.4%	
45-49 years	31.4%	48.8%	
50-55 years	25.5%	9.8%	
Body mass index			0.357
Normal	9.8%	4.9%	
Overweight	19.6%	29.3%	
Obese	66.7%	56.1%	
Morbidly obese	3.9%	9.8%	
Smoker	19.6%	31.7%	0.183
Duration			0.565
<1 year	19.6%	9.8%	
1-4 years	31.4%	29.3%	
5-9 years	25.5%	24.4%	
10-14 years	15.7%	26.8%	
>14 years	7.8%	9.8%	
Treatment			0.580
Diet	5.9%	2.4%	
OAD	52.9%	48.8%	
Insulin	13.7%	9.8%	
Insulin + OAD	27.5%	39.0%	
Regulation			0.940
Good	19.6%	22.0%	
Moderate	43.1%	43.9%	
Insufficient	37.3%	34.1%	

Lumbar spine BMD values were normal in 68.5% of the diabetic group and 57.6% of

the control group. The difference was not statistically significant (p= 0.534). Femoral BMD values were normal in 81.5% of the diabetic group and 100% of the control group. There was a higher risk of osteopenia and osteoporosis in diabetic patients based on femoral BMD than in the control group (p= 0.036).

Osteocalcin was normal in 81.5% of the diabetic group and 60.6% of the control group (p= 0.016). Homocysteine values were higher in the control group than in the diabetics (p= 0.018). No significant difference was observed in CTX values (p=0.12).

DISCUSSION

The aim of this study was to investigate the prevalence of osteoporosis and changes in bone turnover markers in diabetic premenopausal women.

The relationship of diabetes mellitus (DM) and osteoporosis is complex, and the pathogenesis of diabetic osteopenia is still unknown. Hormonal, vascular or mechanical factors may be involved[7, 8]. Low turnover osteopenia associated with osteoblast dysfunction has been shown in patients with diabetes. Decreased bone formation is probably associated with a reduction in osteoblast activity. Insulin deficiency may cause abnormalities in bone and cartilage proteoglycan composition. Oxidative stress in diabetes may also play a role in the pathogenesis of osteoporosis[9]. Intensive treatment of diabetes can prevent osteoporosis. Elevated BMI and bone turnover markers and the presence of retinopathy are also important in the progression of diabetic osteopenia. No statistically significance was determined between demographic data (age, BMI, smoking status, duration of DM, retinopathy, nephropathy and neuropathy) and BMD and bone turnover markers (CTX, homocysteine and osteocalcin) in this study.

Some trials have reported duration of DM and insulin therapy[5] are associated with an increased risk of fracture[10], while others have determined no such association[11]. Recent studies have identified an increased risk of fracture in the proximal femur and foot in type 2 DM patients despite high or normal hip BMD values[4].

Regulation status of DM was classified based on the EASD database. Accordingly, 20.7% of patients had good regulation, 43.5% moderate and 35.9% insufficient. Regulation status and BMD were compared in the diabetic patients (p:0.54 lomber BMD and p:0.82 femur BMD). According to the Fremantle Diabetes Study, regulation status is an important predictor of low BMD in men with type 1 DM.[12]. Regulation status has been shown to affect bone tissue irrespective of insulin therapy in several animal and human studies[13-15]. According to one hypothesis, hyperglycemia reduces osteoblast functions by increasing osmolarity. Of the patients in the study, 4.3% were receiving a diabetic diet, 51.1% were being treated with oral antidiabetics (OAD), 12% were receiving insulin and 32.6% were receiving insulin and OAD. There was a statistically significant relation between treatment modalities and osteocalcin levels. Osteocalcin levels were abnormal in 76.4% of diabetic patients treated with OAD. Previous studies have compared the incidence of osteoporosis with oral antidiabetic therapies. Schwartz et al.[16] reported increased bone mineral loss in diabetic women treated with thiazolidinediones. The December 2006 ADOPT trial demonstrated a higher risk of osteoporosis in patients treated with rosiglitazone than in those treated with metformin or glyburide[17]. In Takeda et al.[18] trial, a higher risk of osteoporosis was determined in 24,000 patients treated with pioglitazone. In the light of these studies, thiazolidinediones, and especially pioglitazone, may be included among the risk factors for osteoporosis.

Osteopenia and osteoporosis levels based on femoral BMD were higher in diabetic patients in this study, while homocysteine values were higher in the control group than in the diabetics. One recent study reported that although elderly Type 2 diabetic women had higher femoral and lumbar BMD than the control group, their CTX and osteocalcin levels were significantly lower[19]. Studies of diabetic mice have reported a decrease in the numbers of osteoblasts and osteoclasts[20]. These trials showed a low bone turnover in diabetic

patients, such as those using glucocorticoids[21-22]. A decrease in bone resorption leads to a higher BMD values by age but increased bone fragility predisposing to injury.

In conclusion; our results demonstrate that DM adversely affects femoral BMD and bone turnover markers such as homocysteine. Some DM pharmacotherapies have side-effect on markers such as osteocalcin. Although some reports in literature have suggested that regulation of DM may affect the risk of osteoporosis, our results do not support that. Diabetes affects bone quality and fragility, so BMD values may not reflect the risk of fracture. BMD measurement might not be a gold standard for osteoporosis in diabetic patients.

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