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Bone turnover markers and bone mineral density in patients with type 2 diabetes

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ABSTRACT

Objectives: This study was designed in order to evaluate bone and mineral metabolism in type 2 diabetic patients and its relationship with bone mineral density and diabetic microvascular complications.

Methods: Forty-two type 2 diabetic patients and 23 healthy cases were included in the study. Serum osteocalcin, procollagen type I C-peptide (PICP), total and bone-specific alkaline phosphatase (bone ALP), urinary deoxypyridinoline (free DPD), parathormone (PTH), serum and urinary calcium and phosphorus levels were measured. Bone mineral densities of all subjects were studied in lumbar vertebra and femur region using dual X-ray absorptiometry (DXA).

Results: Serum osteocalcin and bone ALP levels of the diabetics were found to be significantly lower and total alkaline phosphatase and calcium levels were higher in diabetic patients compared to healthy controls, but PICP and free DPD levels were not different between these two groups. There was a positive correlation between PTH levels and urinary DPD excretion. Among diabetics, serum osteocalcin levels increased with the impairment of renal functions. Bone mineral densities were lower in diabetics with worse renal functions.

Conclusions: Bone turnover is slow in type 2 diabetes and there is no prominent bone loss related to this condition. PTH is an important factor determining the rate of bone resorption in diabetics. Renal functional impairment is the most important factor affecting bone mass in type 2 diabetic patients.

Keywords: Diabetes, bone mineral density, bone turnover, diabetic complications

Bone mineral density is an important marker of the pathophysiological condition of bone and is accepted to be a reliable index for the risk of future fractures. Alterations in the rate of both bone formation and resorption can lead to changes in bone mass. Biochemical markers of bone turnover enable to determine the alterations in the metabolic activity of bone. There are many reports suggesting the existence of altered bone and mineral metabolism in diabetes mellitus. Low bone mineral content has been described for type 1 diabetes, but the relationship between type 2 diabetes and bone mass is less clear. The bone mass has been reported to be normal, increased, or decreased in type 2 diabetes [1-6]. Also bone formation and turnover seem to be decreased in both types of diabetes [7-10]. But the chronic complications of diabetes and even the type of therapy may also affect bone turnover and bone mineral density [10-13]. There are

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also publications regarding the increased risk of fractures despite normal or high bone mineral density [14, 15].

In this study, we aimed to evaluate bone and mineral metabolism in type 2 diabetic patients with biochemical markers of bone turnover and its relationship with bone mineral density and diabetic microvascular complications.

METHODS

Twenty-seven females and 15 males total of 42 type 2 diabetic patients (mean age: 56.2 ± 1.65 years) were studied. Thirteen females and 10 males, total 23 healthy subjects (mean age: 53.9 ± 1.81 years) comprised the control group. The study was conducted in the Endocrinology outpatient Department of Eskisehir Osmangazi University Faculty of Medicine Hospital. None of the subjects in both groups had a condition that could affect bone and mineral metabolism and none of the subjects were taking medications known to interfere with bone metabolism. All of the women were in the postmenopausal stage. The mean duration of diabetes was 9.46 ± 1 years. Twenty-six of the diabetic patients were receiving oral hypoglycemic medications, and 16 were receiving insulin. None of the patients were on thiazolidinediones.

Blood was drawn after 12 hours of fasting from all subjects and serum calcium (Ca), albumin, phosphorus (P), creatinine (Cr), and total alkaline phosphatase (ALP) levels were studied. Parathormone (PTH) was studied with Immulite (DPC, Los Angeles USA) solid phase two-site chemiluminescence immunometric assay in fasting blood samples.
In all subjects serum osteocalcin (OC), procollagen type I C-terminal propeptide (PICP) and bone-specific alkaline phosphatase (Bone ALP) levels were measured in fasting blood samples by ELISA (Metra Biosystems, Mountain View, Ca). Osteocalcin and PICP levels were expressed as ng/ml and bone-specific alkaline phosphatase levels as U/L.

Creatinine and calcium levels were studied in 24-hour urine collections. Based on these results creatinine clearance (Ccr) and 24-hour calcium excretion (calciuria) were determined. Urinary free deoxypyridinoline crosslink excretion (free DPD) was measured by ELISA (Pyrilinks-D; Metra Biosystems) in morning urine specimens. Results were expressed as nanomol deoxypyridinium / milimol creatinine (nM DPD /mM cr). Also, urinary calcium and creatinine levels were studied in second void morning urine specimens and urinary calcium/creatinine ratios were calculated. HbA1c levels of the diabetics were measured by BM-Hitachi 911 autoanalyzer using Boehringer Mannheim kits and the results were expressed as %. Body mass indices (BMI) of all subjects were calculated.

Bone mineral densities of all subjects were measured with Hologic- Q DR 4500 W Fan beam X-ray densitometer using the Dual photon X-ray absorptiometry (DXA) method. Values regarding lumbar and femoral regions were determined as g/cm^2.

Diabetic patients were evaluated for the chronic complications of diabetes. Retinal examinations were performed using direct and indirect ophthalmoscopy and fluorescein angiography were performed if necessary. Patients were classified according to these findings as patients with normal retinal examinations and patients with retinopathy. In order to determine diabetic neuropathy, patients were questioned for the symptoms regarding peripheral diabetic neuropathy. The superficial and deep sensation was examined and electroneuromyography (ENMG) were performed to all diabetics. According to the findings patients with and without peripheral neuropathy were determined. Twenty-four hour proteinuria levels were determined with BM-Hitachi 911 biochemical autoanalyzer using Boehringer Mannheim kits. Patients were divided into 2 groups according to their creatinine clearance as Ccr < 70 mL/min and Ccr ≥ 70 mL/min.

Informed written consent was obtained from all of the subjects recruited to the study. The study was approved by the local ethical committee of Kutahya Dumlupinar University (Reference number: 2017-6/2). The work was carried out in accordance with Declaration of Helsinki.

Statistical Analysis

Statistical significance was checked by Student's "t" test for paired and when appropriate, Pearson correlation analysis and variance analysis were used. Data were presented as mean ± SEM. $P < 0.05$ were considered to be statistically significant.

RESULTS

Characteristics of the study population are given in Table 1. Serum levels of OC and bone ALP were lower and total alkaline phosphatase levels were higher in the diabetics than in the healthy controls. Serum PICP and urinary-freeDPD levels did not differ significantly between these two groups. Serum mean Ca levels were higher in diabetics compared to healthy controls, but were in the normal range. All the patients and the controls had albumin levels in the normal range. Mean BMI of the patients with diabetes was higher than the control group. Mean calculated creatinin clearence values of the diabetics were lower than the healthy subjects. There was no significant difference in the other parameters between these groups.

Bone mineral densities of the diabetics were found to be slightly lower than of the healthy controls at the intertrochanteric and total hip regions (Fig. 1). Among diabetics, there was a positive correlation between serum osteocalcin levels and proteinuria levels (r: 0.331, $p < 0.05$) and a negative correlation between serum osteocalcin levels and Ccr values (r: -0.382, $p < 0.05$). There was a strong positive correlation between urinary DPD levels and serum PTH levels in diabetic subjects (r: 0.625, $p < 0.001$). Further, a slight negative correlation was observed between DPD and calciuria levels (r: -0.408, $p < 0.05$). There was no significant correlation between turnover markers and other parameters.

Correlations found to be significant between bone turnover markers and bone mineral densities are shown in Table 2. Serum OC correlated with L1, L2, L3, and L1-4 vertebrae bone mineral densities negatively in diabetic subjects. In contrast, a negative correlation was found between urinary-free DPD levels and bone mineral densities of the femoral site.

Diabetics treated with oral hypoglycemic drugs were compared with diabetics treated with insulin. Serum OC of the patients treated with insulin were

Table 1. Characteristics of the study population

	Diabetics (n = 42)	Controls (n = 23)	*p* value
Gender (Female)	64.2% (27/42)	%56.5 (13/23)	> 0.05
Age (years)	56.2 ± 1.65	53.9 ± 1.81	> 0.05
Duration of diabetes (years)	9.46 ± 1 (n = 41)		
HbA1c (%)	8.84 ± 0.5 (n = 41)		
Serum Ca (mg/dL)	9.72 ± 0.08	9.25 ± 0.19	**< 0.01**
Serum P (mg/dL)	3.75 ± 0.09	3.66 ± 0.15	>0.05
ALP (U/L)	208.21 ± 17.1	140.73 ± 10.2	**< 0.01**
Bone ALP (U/L)	12.73 ± 1.25	22.52 ± 2.52	**< 0.001**
Osteocalcin (ng/mL)	7.407 ± 0.42	14.336 ± 1.13	**< 0.001**
PICP (ng/mL)	81.732 ± 4.11	94.550±7.9	> 0.05
DPD (nM/mMcr)	11.60 ± 1.27	10.79 ± 1.18	> 0.05
Proteinuria (mg/d)	384.7 ± 151.4 (n = 39)	134.34 ± 20.9	> 0.05
Ccr (ml/min)	85.8 ± 5.5 (n = 39)	106 ± 5.4	**< 0.05**
BMI (kg/m^2)	30.24 ± 0.91(n = 28)	28.44 ± 0.90	**< 0.05**
PTH (pg/ml)	60.2 ± 10.3 (n = 28)	37.89 ± 4.88	> 0.05
Calciuria (mg/d)	180.1 ± 24.6(n = 33)	212.26 ± 33	> 0.05

Data are given as mean ± standard deviation or n (%). HbA1c = glycated hemoglobin, Ca =calcium, ALP = alkaline phosphatase, PICP = procollagen type I C-peptide, DPD = deoxypyridinoline, CCr = creatinine clearance, BMI = body mass index, PTH = parathormone

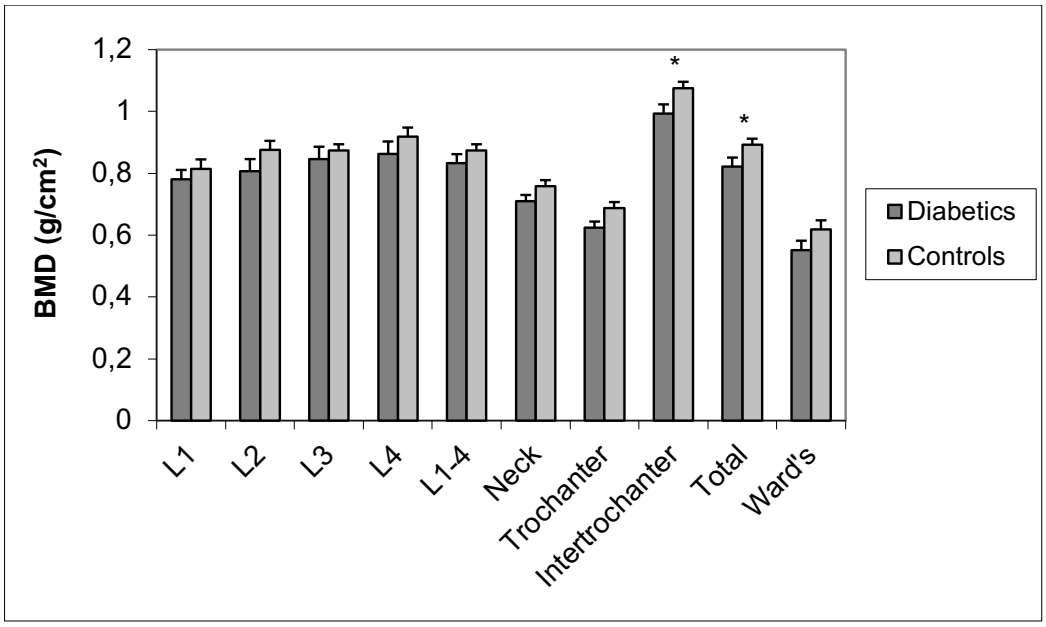

Fig. 1. Bone mineral densities (BMDs) of the diabetics and of the control group. * $p < 0.05$.

found to be higher than those treated with oral hypoglycemic drugs (9.10 ± 0.80 vs. 6.31 ± 0.36, $p < 0.01$). Mean BMI of the group treated with insulin was significantly higher than the group treated with oral drugs (34.21 ± 1.51 vs. 27.98 ± 0.85, $p < 0.001$). There was no other significant difference between patients treated with insulin and oral hypoglycemic drugs. Bone mineral densities did not differ between these groups.

Serum OC levels of the diabetics with retinopathy were higher than those without retinopathy (8.36 ± 0.69 vs. 6.58 ± 0.5, $p < 0.05$). But, the mean Ccr of the diabetics with retinopathy was also significantly lower than the diabetics with normal retinal examinations (66.83 ± 5.72 vs. 102.14 ± 7.41, $p < 0.01$). There was no other significant difference between patients with and without retinopathy. Likewise, bone mineral densities of these two groups, although slightly lower in patients with retinopathy, did not show any significant difference.

Biochemical markers of bone turnover and bone mineral densities did not differ between patients with and without peripheral neuropathy.

Bone mineral densities of the diabetics that have a Ccr < 70 mL/min were significantly lower than those that have a Ccr ≥ 70 mL/min (Table 3).

Table 2. Correlations found to be significant between bone mineral densities and biochemical markers of bone turnover in diabetic patients

	L_{1-4} (g/cm²) (n = 29)	L_1 (g/cm²) (n = 29)	L_2 (g/cm²) (n = 29)	L_3 (g/cm²) (n = 29)	L_4 (g/cm²)	Neck (g/cm²) (n = 29)	Trochanter (g/cm²) (n = 29)	Inter-trochanter (g/cm²) (n = 29)	Total hip (g/cm²) (n = 29)
OC (ng/ml)	r:-0.44	r:-0.37	r:-0.42	r:-0.40					
p-value	**< 0.05**	**< 0.05**	**< 0.05**	**< 0.05**					
Free DPD (nM/mMcr)						r:-0.49	r:-0.44	r:-0.42	r:-0.42
p-value						**< 0.01**	**< 0.05**	**< 0.05**	**< 0.05**

L = Lumbar spine, OC = Osteocalcin, DPD = deoxypyridinoline

Table 3. Bone mineral densities of the diabetic patients classified according to Ccr levels

	Ccr < 70 (n = 8)	Ccr ≥ 70 (n = 21)	*p* value
L_{1-4} (g/cm^2)	0.699 ± 0.07	0.883 ± 0.02	**< 0.01**
L_1 (g/cm^2)	0.697 ± 0.06	0.809 ± 0.03	> 0.05
L_2 (g/cm^2)	0.644 ± 0.10	0.867 ± 0.03	**< 0.01**
L_3 (g/cm^2)	0.705 ± 0.08	0.900 ± 0.03	**< 0.05**
L_4 (g/cm^2)	0.781 ± 0.04	0.894 ± 0.05	>0.05
Neck (g/cm^2)	0.642 ± 0.04	0.735 ± 0.0	**< 0.05**
Trochanter (g/cm^2)	0.536 ± 0.06	0.657 ± 0.01	**< 0.05**
Intertrochanter (g/cm^2)	0.887 ± 0.06	1.033±0.02	**< 0.05**
Total (g/cm^2)	0.719 ± 0.05	0.860±0.02	**< 0.05**

Data are given as mean ± standard deviation. L = Lumbar spine, CCr = creatinine clearance

DISCUSSION

In this study, bone formation markers serum osteocalcin and bone specific alkaline phosphatase levels were found to be lower in type 2 diabetic patients than the healthy controls. Serum PICP levels, another bone formation marker, were not significantly different in diabetic patients compared to nondiabetic subjects. PICP is an early osteoblastic marker and the finding of normal PICP levels while the other formation markers are depressed may suggest that bone formation rate is slow in type 2 diabetes and the disorder of osteoblastic functions is primarily a maturation defect [16].

In contrast, ALP levels of the diabetics were higher than of the healthy controls. As the levels of ALP are highly affected by the extraosseous contribution, higher than normal levels found in type 2 diabetics is probably not an indicator of bone formation rate. Total alkaline phosphatase levels were reported to be elevated in diabetics. The evaluation of plasma ALP isoenzymes revealed that liver isoenzyme was elevated profoundly in diabetics [15]. Furthermore, body mass indices of the diabetics evaluated in our study were higher than nondiabetic controls which suggests that obesity and liver steatosis might help total alkaline phosphatase levels to rise.

There was no significant difference between urinary-free DPD levels of the diabetics and of the healthy controls which might indicate that bone resorption was not markedly increased in type 2 diabetes [16, 17].

According to the study data, serum Ca levels tend to be slightly higher in type 2 diabetics compared to healthy controls. There are various reports showing disturbances in Ca homeostasis in diabetics [18, 19]. In long-term animal models of diabetes, Ca hyperabsorption and low bone turnover was demonstrated [20]. Pedrazzoni *et al*. [10] found increased levels of serum Ca levels in diabetics and concluded subsequent PTH suppression to be responsible from the reduction of bone turnover.

Bone mineral densities of the diabetic patients were slightly lower than the healthy controls only on intertrochanteric and total lumbar regions. However, if it is taken into account that the diabetics were more obese and the controls had better renal functions, lower bone mineral densities seen in diabetics can not be attributed solely to diabetes itself.

Serum osteocalcin levels increased with declining renal functions in our study. It seems likely that the increase in osteocalcin levels accompanying the glomerular and tubular damage does not show the increase in bone formation rate but its retention due to decrease in its clearence. Increased osteocalcin levels were reported in children with renal failure [20].

Serum osteocalcin levels of type 2 diabetics treated with insulin were higher than those treated with oral hypoglycemic drugs. This finding may suggest

the higher insulin levels to slow bone turnover rate. But at the same time, insulin treated diabetic patients were more obese than the patients receiving oral hypoglycemic drugs. As this condition can reflect the effect of insulin on bone, it can also be related with the contribution of obesity. No significant difference was observed regarding bone mineral densities between these two treatment groups. In accordance with our study, Gregorio *et al*. [5] found osteocalcin levels to be higher in insulin treated than oral hypoglycemic treated type 2 diabetics, but could not show any significant effect of the type of treatment on bone mineral density.

Serum osteocalcin levels of the diabetics with retinopathy were found to be higher than those without retinopathy. But, also renal functions of the diabetics with retinopathy were significantly lower than the patients without retinopathy. Kidneys are the main route of the degradation of osteocalcin and significant retention in serum can be observed in renal failure [21, 22]. The increase observed in osteocalcin levels of the patients with retinopathy may indicate the decline in its clearence due to accompanying nephropathy. Bone mineral densities were not affected by the presence of retinopathy.

No correlation could be shown between the presence or the degree of diabetic peripheral neuropathy with either bone mineral density or biochemical markers of bone turnover.

A significant correlation was found between urinary deoxypyridinium levels and serum PTH levels among diabetics. This finding may show PTH levels to be the primary factor determining the rate of bone resorption in type 2 diabetics. It can be concluded that there is an increase in bone resorption only in diabetics with elevated PTH levels [23].

There was a negative correlation between femoral region bone mineral densities and DPD excretion rate. It seems likely that the increase in bone resorption rate effects mainly femoral region bones that consist primarily cortical bone. Also, a negative correlation was found between serum osteocalcin levels and lumbar spine bone mineral density.

Bone mineral densities were lower in diabetics with impaired glomerular filtration rates. This condition was evident on both lumbar spine and hip bones. Although, mean Ccr levels of the diabetics with retinopathy were also lower than the patients without retinopathy, the difference in their bone densities was not significant. This may be because only some of the patients with retinopathy have also nephropathy. Among the diabetic microvascular complications, the one that effects the bone mass most negatively seems to be the diabetic nephropathy. It appears that there is no osteopenia attributable to type 2 diabetes per se. But the conditions accompanying diabetes such as nephropathy may lead to bone loss. In another study no association was found between parathormone levels and glucose homeostasis in type 2 diabetes [24]. In our study we observed that the increase in osteocalcin levels with the deterioration of renal functions were associated with bone mineral loss in lumbar spine consisting mostly trabecular bone. But, in diabetics with renal function impairment bone loss was detected on both lumbar vertebrae and on hip bones. It was determined that DPD levels increased with increasing PTH and bone loss reflected by DPD excretion rate affected the hip site bones negatively. This finding may suggest that, renal functional impairment seen in diabetics may be operative in bone loss in two ways; by secondary hyperparathyroidism that influences mostly the cortical bone mass and by another way, might be uremia, that is effective mostly on the trabecular bone mass. Renal function impairment is the most important factor affecting the bone mass negatively in type 2 diabetics.

Limitations

However, there are some limitations of our study. First of all, our study population is small and including larger number of patients would have increased the power of our results. Although we tried to compose an age and gender matched control group, BMI of the diabetics were higher than the control group. Since obesity can influence bone metabolism and bone mineral density it would be better to form a BMI matched control group. Although a small study our study shows the importance of renal impairment on bone loss among the other diabetic complications and gives a clue about the types of bone loss in diabetics.

CONCLUSION

Our findings suggest that bone turnover is suppressed especially on the side of formation in diabetic patients

and bone loss seen in diabetics seems to be related mostly with the renal functional impairment. Besides our results suggests that the formation defect seen in diabetics preferentially shows itself on trabecular compartment of the bone and the increased resorption probably mediated by the excess parathormon affects the femoral site which is composed largely of cortical bone.

Authors' Contribution

Study Conception: AA, FBE, İÖA; Study Design: AA, KO, GY; Supervision: GY; Funding: N/A; Materials: AA, FBE; Data Collection and/or Processing: GY, KO; Statistical Analysis and/or Data Interpretation: AA, İÖA; Literature Review: AA, KO; Manuscript Preparation: AA, GY and Critical Review: AA, FBE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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