Bone mineral density and bone metabolism in postmenopausal women with type 2 diabetes in a Chinese community: a cross-sectional study

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Research article

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Abstract

Background: There is growing evidence of a complex interaction between type 2 diabetes (T2DM) and osteoporosis. The purpose of this study was to further study the relationship between Bone turnover markers (BTMs) and fasting blood glucose (FBG) in postmenopausal patients with type 2 diabetes and to analyze the effect of hyperglycemia on bone metabolism.

Methods: Six hundred and twelve (612) postmenopausal women were included, including one hundred and seven (107) subjects with T2DM and five hundred and five (505) subjects without diabetes. Bone mineral density (BMD) was measured by DXA (dual-energy X-ray absorptiometry). Markers of bone formation Type 1 collagen N-terminal peptide (P1NP) and resorption C-telopeptide of type I collagen (CTX) were quantified.

Results: Compared to controls, postmenopausal women with diabetes had a higher prevalence of previous osteoporosis fracture (27.1% vs. 17.4% for diabetic and nondiabetic women, respectively) and a higher BMD. The P1NP level in women with T2DM was 49.451 ng/ml, while in N-DM individuals, it was 58.633 ng/ml, ($p = 0.017$). The CTX level in women with T2DM was 0.325 ng/ml, while in N-DM individuals, it was 0.412 ng/ml ($p=0.039$). In addition, P1NP was significantly negatively associated with age ($\beta=-0.590$; $p= 0.002$) and FBG ($\beta=-1.950$; $p = 0.035$). CTX was negatively associated with FBG ($\beta=-0.029$; $p = 0.015$).

Conclusions: T2DM was associated with higher BMD and paradoxically, with an increased risk of fracture. Postmenopausal women with T2DM had lower bone turnover than controls. With increased levels of FBG, bone formation and bone resorption were reduced, and the overall bone turnover level was reduced.

Background

As the population ages, the incidence of osteoporosis and diabetes is increasing. Observational studies in recent years have analyzed several aspects of the association between diabetes and osteoporosis with conflicting results.

Bone mineral density (BMD) is the most commonly used measurement in the assessment of osteoporosis status and risk for osteoporosis fracture in the elderly population. The diagnostic criteria for osteoporosis are based on BMD, and thus far, there is less information on the BMD of patients with type 2 diabetes. BMD significantly decreases in type 1 diabetes mellitus (T1DM)[1-4]; however, in type 2 diabetes mellitus (T2DM), the results are controversial. Early studies suggested that BMD in T2DM patients was lower than, equal to, or higher than that of the control groups[5-8]. Interestingly, studies in recent years have shown that these subjects have significantly higher BMD than nondiabetic people. It is well-known that individuals with T2DM have a higher risk of fracture of the hip, spine, and peripheral sites than nondiabetic individuals[9-12].

Patients with T2DM have multiple chronic complications, such as retinopathy, kidney disease, neuropathy, coronary heart disease, stroke and dementia. Bone is also one of the organs that is affected by T2DM. It is estimated that patients with T2DM have a 1.7-fold increased risk of fracture compared with nondiabetics[13]. Recent studies [14, 15] suggest a complicated relationship between bone metabolism and glucose metabolism. Osteoporosis fracture is considered to be one of the complications of DM, and is called diabetic osteopathy, or "diabetic osteoporosis(DOP)".The Fracture Risk Assessment Tool (FRAX) model and BMD underestimate major osteoporotic and hip fracture risks. Bone turnover markers (BTMs) may be a useful exploratory method[16]. BMD is mainly determined by the mineral composition in the bone, but cannot reflect the changes of organic components such as type I collagen in the bones and the changes in bone metabolism in the short term. The BTMs can not only sensitively reflect the dynamic changes of bone metabolism, but also can be used to monitor the efficacy of anti-OP drugs. BTMs are chemical compounds, a set of proteins and their derivatives, released during bone remodeling by osteoblasts or osteoclasts[17]. Type 1 collagen N-terminal peptide (P1NP) is a specific marker reflecting the activity of osteoblasts. BTMs can reflect the activity of osteoclast cells, such as C-telopeptide of type I collagen (CTX), N-telopeptide of type I collagen (NTX), tartrate-resistant acid phosphatase (TRAP), and deoxypyridinoline[18].PINP and CTX are recommended as bone markers by the International Osteoporosis Foundation (IOF) and are widely used in clinical practice.

The current study aimed to identify the relationship between bone turnover markers and fasting blood glucose (FBG) in postmenopausal patients with type 2 diabetes in a Chinese population. The effect of hyperglycemia on bone metabolism was also determined.

Methods

Subjects and Methods

We performed a cross-sectional study, enrolling 1000 postmenopausal women aged 45–74 years from January to December 2017 from Danyang Lianhu Community Service Center in Jiangsu. All T2DM individuals had been diagnosed according to the 2010 criteria of the American Diabetes Association (ADA) and the 1999 World Health Organization definition. We excluded individuals with diseases and those who were taking medicine known to affect BMD and bone metabolism, i.e., subjects who had hepatic, gastrointestinal, kidney, thyroid or malignant disorders causing low BMD and subjects who had been treated with hormone therapy, calcium supplements, vitamin D, bisphosphonates, antipsychotic drugs, diuretics or thiazolidinediones. Finally, a total of 612 participants (107 subjects with T2DM and 505 subjects without diabetes) were retained for further analysis.

Baseline data were recorded during a face-to-face interview by a trained professional using a structured questionnaire, which included questions about age, medical history, menopause age, physical activity, related treatment and family history. The participants were accurately measured for height, weight, and blood pressure.

BMD by DXA

DXA (dual-energy X-ray absorptiometry) was performed on all participants on the lumbar spine (L1–L4) and femoral regions (femoral neck and total hip) with Hologicequipment (Danyang Lianhu Community Service Center; variation coefficient<1%). According to the World Health Organization (WHO) 1994 osteoporosis diagnostic criteria, in postmenopausal women, normal BMD is indicated by a T score ≥-1.0; osteopenia is indicated by -2.5≤T score≤-1.0); and osteoporosis is indicated by a T score ≤ -2.5.

Biochemical parameters

In the morning, after approximately eight hours of fasting, blood samples from each participant were collected for total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, P1NP and CTX. Blood samples for fasting blood glucose were centrifuged at 1500 g for 10 minutes at room temperature and analyzed on the same day. Plasma glucose concentrations were measured by an Olympus AU2700 analyzer using the manufacturer's kits. The bone formation marker P1NP and the bone resorption marker CTX were determined by electrochemiluminescence immunoassay (Roche).

Osteoporosis fracture ascertainment

In this study, the diagnostic criteria for osteoporosis fractures were residents' self-reported history of fragility fractures or resident-reported imaging fractures. A fragility fracture is defined as a fracture that results from a fall to the ground or a similar degree of trauma from a standing position or lower than a standing position[19].

Ethical aspects

The study was approved by Danyang People's Government and Danyang Lianhu Community Service Center in Jiangsu. All participants provided written informed consent.

Statistical analyses

Baseline data were input into the computer with Epidata3.1. All statistical analyses were performed with IBM-SPSS version 24.0 for Windows (SPSS, Chicago, Illinois), based on the above two groups. Descriptive statistics, including means, frequencies, and percentages, were used to describe the study population and look at differences between groups. Continuous data were expressed as the mean and standard deviation (mean ± SD). The comparison of the means of the two groups was performed by independent sample t test. The categorical variables were analyzed by chi-squared test, and the regression analysis was peformed by multiple linear regression after adjustment for age, menopause age, weight and BMI. P-values≤0.05 were considered statistically significant.

Results

Basic characteristics of the participants

The clinical characteristics of the enrolled subjects are summarized in Table 1. All subjects included in this study were postmenopausal women. There were no statistically significant differences in age, menopause age, diastolic pressure, height□total cholesterol , LDL cholesterol and weekly moderate physical activity between the two groups (p□0.05). However, the patients with T2DM had significantly higher systolic pressure, weight, body mass index, fasting blood glucose and triglycerides, and lower HDL cholesterol levels than the controls (p<0.05). 75 of 107 patients received Oral anti-diabetic agents treatment ,18 patients used Insulin only, and 14 patients were using combination therapy. In the study, diabetic patients were more likely than nondiabetic patients to have complications with hypertension (57.9% vs. 40.6%, respectively, p=0.001) and cerebral apoplexy (5.9% vs. 1.0%, respectively, p=0.001). There was also no statistically significant difference in family history of fractures. However, postmenopausal women with diabetes had a higher prevalence of previous osteoporosis fracture than those without diabetes (27.1% vs. 17.4%, P=0. 021).

Table 1

Basic characteristics of the participants

Characteristics	T2DM	N-DM	p-Value
Number	107	505	...
Age (years)	66.81±9.05	66.78±7.36	0.970
Menopause age (years)	49.24±3.69	49.50±3.73	0.516
Systolic pressure (mmHg)	138.27±20.04	133.15±16.77	0.006
Diastolic pressure (mmHg)	85.00±9.97	83.83±9.06	0.234
Height (cm)	155.45±5.25	155.15±5.79	0.617
Weight (kg)	62.29±10.06	59.09±8.78	0.001
BMI (kg/m2)	25.74±3.72	24.55±3.41	0.001
FBG (mmol/L)	7.92±2.02	5.23±0.58	0.000
TC (mmol/L)	5.16±1.05	6.51±28.26	0.621
TG (mmol/L)	2.40±1.59	1.88±1.24	0.000
LDL (mmol/L)	2.74±0.90	3.45±13.88	0.594
HDL (mmol/L)	1.37±0.51	1.48±0.48	0.029
Moderate activity□1h per week	63□58.9%□	398□78.8%□	0.233
Oral anti-diabetic agents	75□70.1%□	None	NA
Insulin	18□16.8%□	None	NA
Insulin+Oral anti-diabetic agents	14□13.1%□	None	NA
Hypertension	62 (57.9%)	205 (40.6%)	0.001
Hyperlipidemia	12 (11.2%)	43 (8.5%)	0.375
Cerebral apoplexy	6 (5.9%)	5 (1.0%)	0.001
Coronary heart disease	9 (8.4%)	25 (4.9%)	0.156
Family history of fractures	6□5.6%□	14□2.8%□	0.134
Osteoporosis fracture	29(27.1%)	88(17.4%)	0.021
Wrist	9	21	
Hip	8	33	
Others bone	12	34	

Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as n (%)

BMI body mass index, *FBG* fasting blood glucose, *TC* total cholesterol, *TG* triglycerides, *LDL* LDL cholesterol, *HDL* HDL cholesterol

The postmenopausal women with T2DM had higher BMD (in the femoral regions) than the N-DM controls.

As shown in Table 2, the lumbar spine BMD was not significantly different between groups (T2DM 0.708 ± 0.47 g/cm2 vs. Nondiabetes 0.666± 0.43 g/cm2, P = 0.373). There were differences in the femoral neck

and total hip (Femoral neck: T2DM 0.830 ± 0.14 g/cm2 vs. Nondiabetes 0.764±0.12 g/cm2, P=0.000; Total hip: T2DM 0.882 ± 0.14 g/cm2 vs. Nondiabetes 0.817±0.13 g/cm2, P=0.000). The T-scores of all regions were significantly higher in the T2DM group than in the nondiabetic group (Lumbar spine: p=0.002; Femoral neck: P=0.000; Total hip: P=0.000).

Table 2 BMD and T-scores for T2DM and N-DM subjects

		T2DM	N-DM	p-Value
Lumbar spine	g/cm2	0.708±0.47	0.666±0.43	0.373
	T-score	-0.761±1.39	-1.18±1.26	0.002
Femoral neck	g/cm2	0.830±0.14	0.764±0.12	0.000
	T-score	-0.839±1.13	-1.389±1.02	0.000
total hip	g/cm2	0.882±0.14	0.817±0.13	0.000
	T-score	-0.713±1.07	-1.221±1.01	0.000

Data are expressed as the mean ± SD
BMD bone mineral density

Postmenopausal women with T2DM had lower BTMs than N-DM controls.

As shown in Table 3 and Figure 1, the BTMs were lower in subjects with T2DM compared with subjects without diabetes: P1NP levels were significantly lower in T2DM subjects compared to controls (T2DM, 49.451±35.73 ng/ml vs. controls, 58.633±36.21 ng/ml; p=0.017), and CTX levels were also significantly lower in T2DM subjects compared to controls (T2DM, 0.325±0.24 ng/ml vs. controls, 0.412±0.42 ng/ml; p=0.039).

Table 3 Bone turnover biomarkers, P1NP and CTX in T2DM and N-DM subjects

	T2DM	N-DM	t-Value	p-Value
P1NP (ng/mL)	49.451±35.73	58.633±36.21	-2.388	0.017
CTX (ng/mL)	0.325±0.24	0.412±0.42	-2.071	0.039

Data expressed as mean ± SD
P1NP procollagen 1 N-terminal peptide, *CTX* procollagen 1 C-terminal peptide

Multiple linear regression analysis was used to analyze the data for all subjects to search for possible associations between BTMs and the above biochemical parameters (Table 4). The data showed that P1NP was significantly negatively associated with age (β=-0.590; p= 0.002) and fasting blood glucose (β=-1.950; p = 0.035). CTX was negatively associated with fasting blood glucose (β=-0.029; p = 0.015) but not with age (β=-0.003; p = 0.142).

Table 4 Multiple linear regression analysis for association of P1NP and CTX as dependent variables with age, menopause age and above biochemical parameters

Independent variables	β	Std.Error	Standardized Beta	p-Value	95%Confidene Interval for B	
					Lower Bound	Upper Bound
P1NP						
Age	-0.590	0.190	-0.125	0.002	-0.976	-0.246
FBG	-1.950	1.028	-0.077	0.035	-3.845	0.075
CTX						
Age	-0.006	0.013	-0.118	0.062	-0.012	-0.002
FBG	-0.029	0.011	-0.104	0.015	-0.049	-0.005

Discussion

To the best of our knowledge, this is a relatively large-sample study in a Chinese community with complete markers of bone metabolism and a large Chinese cross-sectional study that investigates the associations of T2DM and BMD, BTMs, and osteoporosis fracture in postmenopausal women. In our study, we found a negative correlation between FPG and BTMs and speculated that lower levels of P1NP and CTX may be associated with an increased fracture risk in patients with type 2 diabetes. We hypothesized that the underlying mechanism might be that hyperglycemia leads to bone marrow alterations and damaged differentiation potential, which changes bone metabolism, resulting in reduced bone turnover, poor bone quality, and ultimately fractures.

The effect of T2DM on BMD remains controversial, although fracture risk significantly increases in patients with T2DM[20, 21]. Epidemiological surveys show that in patients with type 1 diabetes, BMD is reduced, bone mass decreases and the incidence of osteoporosis ranges from 48% to 72%[22]. BMD is increased, decreased or unchanged for patients with T2DM. These results have been reported in both domestic and foreign literature[23]. In our study, there was a significant increase in BMD in patients with type 2 diabetes, which was consistent with other studies[9, 24]. This further confirms that BMD may be an inappropriate tool for assessing the risk of bone loss and fracture in patients with type 2 diabetes. For patients with diabetes, T value greater than -2.5 may be required as a cut-off value for osteoporosis diagnosis.

Recent studies have shown that osteoporosis fracture is one of the complications of diabetes in the skeletal system, but the specific mechanism is not clear[20, 25]. The higher incidence of fractures in the diabetic population may be associated with specific complications of diabetes, including peripheral neuropathy, impaired visual, postural hypotension, hypoglycemic attacks, and vascular disease. The deficiency of this article is that there is no additional detailed information about the specific types of fracture observed. Therefore, it is difficult to further clarify the causal relationship between diabetes and osteoporosis fractures.

BTMs are considered independent diagnostic and prognostic indicators or as a supplementary index to BMD for osteoporosis fractures. Previous studies of bone turnover markers in diabetes have been limited and controversial, but most scholars have agreed that BTMs might be an important link between bone

metabolism and glucose metabolism. Hussein RM [26]{Hussein, 2017 #133} and showed that patients with T2DM exhibited a significantly lower serum osteocalcin and calcium and a higher alkaline phosphatase compared to the controls. Moreover, osteocalcin was negatively correlated with FBG and DM duration. Wang J analyzed three BTMs in the Chinese population. The levels of N-terminal osteocalcin (N-MID), type 1 collagen N-terminal peptide (PINP) and type 1 collagen carboxyl-terminal peptide (CTX) were significantly decreased in the T2DM groups compared to the controls ($P<0.01$), revealing that BTMs are highly associated with T2DM, insulin sensitivity and beta cell function,which are compatible with ours. Another study concluded that bone formation was inhibited in postmenopausal women with T2DM, but that inconsistent with our research is that there was no significant difference in bone resorption[27]. Reyes-García R[28] showed lower levels of bone resorption markers and PTH-i compared with the levels of controls. The lower the bone metabolism is, the higher the incidence of fracture.

In our study, women with T2DM showed lower bone turnover compared with N-DM controls. These results also supported the above findings. Multiple regression analysis showed that both PINP and CTX were affected by fasting blood glucose. The higher the levels of FBG were, the lower the levels of PINP and CTX. This finding suggests that postmenopausal T2DM patients with increased FBG have decreased bone formation, bone resorption, and overall bone turnover. In this study, there was a lack of data on the course of diabetes, diabetes treatment plans, blood glucose control, glycosylated hemoglobin and other more accurate data. There are too many factors affecting FBG, which alone may be insufficient.

Advanced glycosylation end products (AGEs), stable cross-linking products, are formed by a series of nonenzymatic reactions between glucose and protein and are significantly increased in individuals with T2DM[29]. AGEs affect attachment to the collagen matrix and interfere with the development of osteoblasts[30, 31]. AGEs may also decrease bone resorption by altering the structural integrity of matrix proteins and inhibiting osteoclastic differentiation[29]. In postmenopausal T2DM patients with increased fasting glucose, both formation and bone resorption were decreased, and the level of overall bone transformation was decreased. *RANKL* is an agonist that regulates important aspects of osteoclasts, such as differentiation, fusion, survival, activation, and apoptosis[32]. Hyperglycemia has been shown to inhibit the above pathway mediated by RANKL and could induce low bone turnover[33]. Although there is no significant reduction in BMD in patients with T2DM, another factor that may contribute to the increase in fractures is microstructural abnormalities. Increased cortical porosity is a key determinant of bone fragility[34]. In a recent community study, T2DM and elevated fasting glucose levels resulted in unfavorable cortical microarchitecture at the distal tibial cortex[35]. This may indicate that the weakening of bone biomechanics is beyond the range of BMD measurements and that there may be significant microscopic contributors to osteoporosis fracture. Thus, BTMs may be a more sensitive alternative to BMD in assessing fracture risk in patients with diabetes.

Our study has some limitations. First, in our cross-sectional study, we only observed an association between BTMs and glucose metabolism, not a causal relationship. Further forward-looking and biomechanical studies are needed to confirm other potential associations. Second, FBG is only a

temporary phenomenon, and there are too many factors influencing it. We need a more stable long-term indicator, such as glycosylated hemoglobin or glycosylated plasma protein, to further explore the relationship between blood glucose and bone metabolism. Third, a few subjects with diabetes may have T1DM as we could not distinguish between type 1 and type 2 diabetes. Fourth, we lack data on the relationship between BTMs and glucose metabolism in premenopausal women, which may be different from the population included in this study. According to previous data, the level of sex hormone can affect bone metabolism[15]. This means that we truly need to explore this issue further in different populations.

In conclusion, postmenopausal women with T2DM had higher BMD, but the risk of osteoporotic fracture was relatively high, and BMD underestimated the risk.. The study suggested that actively controlling blood glucose may help maintain bone turnover balance and improve bone mass, thereby reducing the risk of fracture. The detection of BTMs in patients with type 2 diabetes can predict the risk of diabetes complicated with osteoporosis earlier than BMD, which is convenient for early intervention and treatment.

Abbreviations

BMD Bone mineral density

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus

P1NP Type 1 collagen N-terminal peptide

CTX C-telopeptide of type l collagen

NTX N-telopeptide of type l collagen

TRAP Tartrate-resistant acid phosphatase

FBG Fasting blood glucose

ADA American Diabetes Association ADA

DXA Dual-energy X-ray absorptiometry

AGEs Advanced glycosylation end products

Declarations

All the authors of article, including Han Wu, Yufan Zhang, Wenbin Zhou, Guolong Zhang, Jindi Wang, Jingjing Xu, Tao Yang, Jing Dai,Wei He declare that they have no conflicts of interest.

Ethics approval and consent to participate

The study was approved by Danyang People's Government and Danyang Lianhu Community Service Center in Jiangsu. All participants provided written informed consent.

Consent for publication

Not applicable.

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Figures

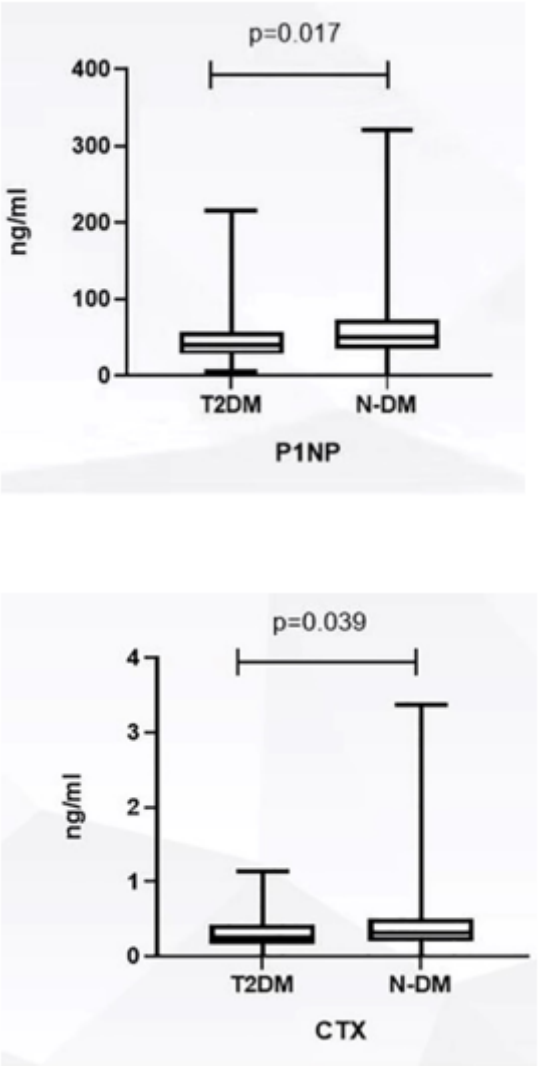
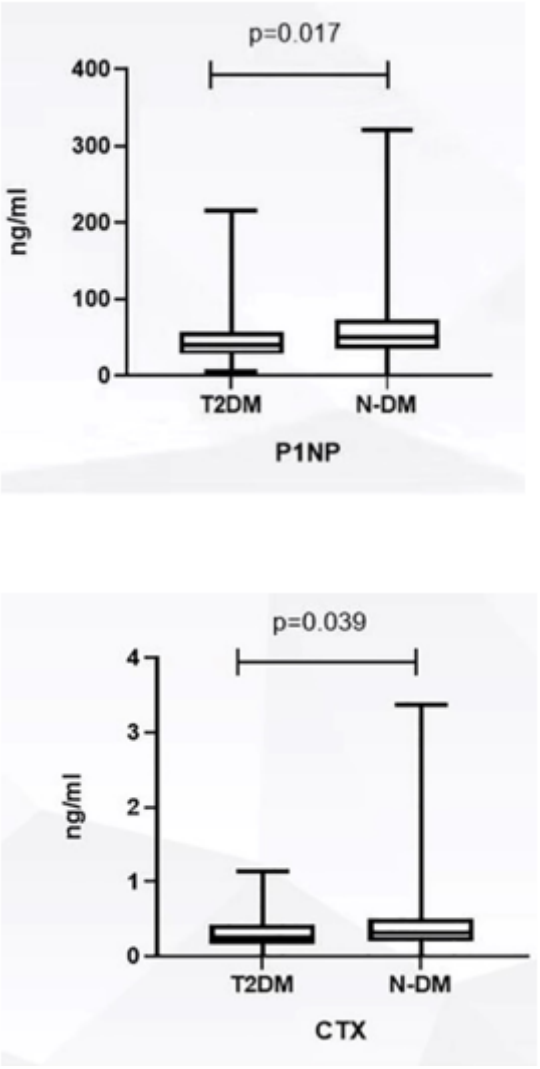


Figure 1

Lower bone turnover in postmenopausal women with T2DM compared to N-DM. Individuals with T2DM had lower levels of P1NP (left panel) and CTX (right panel) than N-DM controls.



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