BMC Musculoskeletal Disorders

RESEARCH

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Association between bone turnover markers and FRAX predicted fracture risk in Chinese adults: a cross-sectional study

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Abstract

Objective Our study investigated the associations between bone turnover markers (BTMs) and bone mineral density (BMD) and fracture risk over the next 10 years. The objective of the study was to evaluate the potential effects of BTMs in fracture risk.

Methods Our cross-sectional study enrolled 580 participants (380 postmenopausal women and 200 men over the age of 50). All participants completed a questionnaire and dual-energy X-ray absorptiometry examination. We obtained BMD values for the lumbar spine, femoral neck, and total hip joint and biochemical indicators such as creatinine, type 1 procollagen N-terminal propeptide (P1NP), and beta cross-linked C-telopeptide of type 1 collagen (β-CTX). Furthermore, we used an online fracture risk assessment tool (FRAX) to calculate the probability of major osteoporotic fractures (PMOF) and hip fractures (PHF) over the next 10 years. We divided the participants into three groups based on the BMD T-score criteria: normal bone mass group (T-score ≥ − 1.0 SD), osteopenic group (− 2.5 SD < T-score < − 1.0 SD), and osteoporotic group (T-score ≤ − 2.5 SD). We compared differences in BTMs, BMD, and fracture risks among the three groups. Additionally, we evaluated differences in indicators between males and females and explored risk factors associated with BMD and fracture risk.

Results Postmenopausal women showed higher bone turnover markers, osteoporosis prevalence, and fracture risks compared to men. In a multivariate stepwise regression analysis, we identified P1NP was positively correlated with fracture risk for both PMOF ($\beta = 0.087$, $p = 0.005$) and PHF ($\beta = 0.135$, $p < 0.001$) over the next 10 years. In the logistic regression analysis, after adjusting for sex, we found that for every standard deviation increase in P1NP, the future 10-year risk of fractures increased by approximately 5.2-fold in the high PMOF group and 5.6-fold in the high PHF group.

Conclusion Our study demonstrated that elevated serum P1NP levels were associated with increased fracture risk over a 10-year period. These findings suggested that serum P1NP measurement could be a valuable complementary tool alongside BMD measurements and FRAX assessments for identifying individuals at high risk of fracture.

Keywords Bone turnover markers, Bone mineral density, Fracture risk, FRAX

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Introduction

Osteoporosis is a systemic bone disease characterized by reduced bone mass and increased fracture risk with increasing age [1]. In China's aging population, the prevalence rate of osteoporosis and the number of fractures are increasing. Early diagnosis and treatment can effectively reduce the social and economic burden caused by bone fractures [2–4].

The risk of osteoporotic fractures is predicted based on bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) [5]. However, only less than 50% of the changes in bone strength are due to changes in BMD [6–8]. Bone turnover markers (BTMs), by-products of bone remodeling, which can be detected in urine or serum, play significant roles in the diagnosis and assessment of treatment efficacy [9]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) have reported that BTMs play important roles in fracture risk prediction [10]. Among them, P1NP is produced when osteoblasts secrete type I collagen, and β-CTX is a breakdown product generated when osteoclasts degrade mature type I collagen [11]. Studies had reported that elevated carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX-I) levels are inversely correlated with BMD in women [12, 13]. Several prospective studies have found that BTMs can predict future fractures. The EPIDOS [14] and OEFLY studies [15] have identified correlations between bone resorption markers and osteoporotic fracture risk. Compared with women with only low BMD or high bone resorption markers, women with both T-score ≤ – 2.5 SD and high CTX levels have higher risk of hip fracture. Conversely, a study found that both serum CTX and P1NP levels are not correlated with hip fracture risk (CTX, $p = 0.22$, P1NP, $p = 0.53$) [16]. Elevated β-CTX levels may increase the probability of a major osteoporotic fracture risk (PMOF) and probability of a hip fracture (PHF) by 33 and 19.5 times, respectively [17]. In addition, researchers have proposed that combining BMD with BTMs and fracture risk may increase the accuracy of fracture risk prediction. However, the use of BTMs in the prediction of fracture risk remains controversial.

In this study, we assessed the relationship between BTMs and BMD in the Chinese population. Few studies have evaluated whether serum BTMs are related to fracture risk [16–19]. In this study, we explored the relationship between BTMs and BMD and between BTMs and fracture risk (PMOF and PHF) in postmenopausal women and middle-aged and elderly men and evaluated the role of BTMs in fracture risk prediction.

Materials and methods

Study participants

The study participants were mainly from the Health Improvement Program of Bone study, an ongoing prospective study involving patients who have undergone physical examination at the Health Management Center of the 2nd Xiangya Hospital (Changsha, China). The purpose of the Health Improvement Program of Bone study was to establish a fracture risk prediction model for the Chinese population. Our study selected 580 people from the cohort, including 380 healthy postmenopausal women and 200 men over the age of 50. The inclusion criteria were (1) postmenopausal women and men aged 50 years or older who completed BMD measurements and serological testing for bone turnover markers (P1NP and β-CTX) at the Health Management Center of the Second Xiangya Hospital of Central South University; (2) participants capable of standing independently and completing height and weight measurements; and (3) participants with full civil capacity who agreed to participate and provided signed informed consent. The exclusion criteria were (1) premenopausal women and men less than 50 years old; (2) patients who had undergone hip arthroplasty and lumbar surgery and could not undergo DXA testing; and (3) patients who had received effective anti-osteoporosis drugs or had a history of malignant tumors.

Methods

Laboratory assessments

Following an eight-hour fast, we collected blood (5 mL) from the study participants at 08:00. The medical laboratory of the Second Xiangya Hospital measured the biochemical indexes and BTMs. The concentrations of serum creatinine, and P1NP and β-CTX were measured by electrochemical luminescence. We measured height and body weight using an ultrasonic body scale. Body mass index (BMI) was calculated by dividing weight by squared height.

BMD assessment

We assessed BMD at the lumbar spine (L1–L4), left femoral neck, and total hip using DXA (Discovery Wi S/N87556, Hologic, USA). According to the World Health Organization (WHO) [20] and BMD reference databases established by our group [21], subjects with BMD T-scores ≤ – 2.5 were considered osteoporotic. All participants were divided into three groups, according to the T-score criteria: normal bone mass group (T-score ≥ – 1.0 SD), osteopenic group (– 2.5 SD < T-score < – 1.0 SD), and osteoporotic group (T-score ≤ – 2.5 SD).

Fracture risk assessment

We used an online fracture risk assessment tool (FRAX) (http://www.shef.ac.uk/FRAX) to measure the 10-year PMOF and PHF, which included the results of femoral neck BMD. We designed a structured questionnaire to evaluate risk factors for osteoporosis, which included age, sex, height, weight, previous fractures, secondary osteoporosis, family history of hip fractures, smoking history, use of glucocorticoids, history of rheumatoid arthritis, and daily alcohol consumption [22].

Statistical analysis

We analyzed the data using IBM SPSS statistics 25.0. Continuous data were assessed for normality and analyzed using the independent sample T-test or the Mann–Whitney U test. We log-transformed continuous variables with a skewed distribution to attain a normal distribution. We used pearson correlation analysis and partial correlation analysis to assess the correlations between BTMs and BMD and between BTMs and fracture risk. To assess the relationship between BTMs and BMD, PMOF, and PHF we used multivariate stepwise regression analysis. We generated a logistic regression model to estimate the odds ratio (OR) for the 95% confidence interval (CI) of the high-fracture risk group. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

Table 1 shows the characteristics of the 580 participants consisting of 380 postmenopausal women and 200 middle-aged and elderly men over the age of 50. The participants were divided into three groups based on their BMD T-scores. There were 279 participants (48.1%) in the normal group, 109 (18.8%) in the osteopenic group, and 192 (33.1%) in the osteoporotic group. The BMD of different sites (e.g., femoral neck, hip, and lumbar spine) was lower in the osteoporotic than in the other two groups. Furthermore, the 10-year risk of fractures (PMOF and PHF) was higher in the osteoporotic group. Specifically,

Table 1 Basic characteristics of the 580 participants

Characteristics	Normal	Osteopenia	Osteoporosis	*p* value
N = 580	279(48.1%)	109(18.8%)	192(33.1%)	
Men	139 (49.82%)	33 (30.28%)	28 (14.58%)	< 0.001
Women	140 (50.18%)	76 (69.72%)	164 (85.42%)	< 0.001
Age (year)	64.21 ± 8.35	64.74 ± 7.89	66.96 ± 7.82	< 0.001
Height (cm)	159.86 ± 7.83	156.44 ± 6.58	154.39 ± 6.87	< 0.001
Weight (kg)	62.70 ± 9.10	56.34 ± 9.61	53.50 ± 8.49	< 0.001
BMI (kg/m^2)	24.49 ± 2.89	22.97 ± 3.21	22.41 ± 3.00	< 0.001
Cr (umol/L)	72.27 ± 20.85	70.29 ± 29.91	63.62 ± 17.41	< 0.001
FN BMD (g/cm^2)	0.75 ± 0.12	0.61 ± 0.09	0.55 ± 0.08	< 0.001
TH BMD (g/cm^2)	0.89 ± 0.10	0.74 ± 0.07	0.67 ± 0.10	< 0.001
LS BMD (g/cm^2)	0.96 ± 0.13	0.80 ± 0.07	0.66 ± 0.09	< 0.001
FN T-score	-1.24 ± 0.89	-2.21 ± 0.71	-2.58 ± 0.72	< 0.001
TH T-score	-0.51 ± 0.79	-1.67 ± 0.38	-2.06 ± 0.85	< 0.001
LS T-score	-0.40 ± 1.02	-1.80 ± 0.45	-2.92 ± 0.72	< 0.001
lgP1NP (lg ng/ml)	1.63 ± 0.18	1.70 ± 0.21	1.72 ± 0.20	< 0.001
lgβ-CTX (lg pg/ml)	2.60 ± 0.22	2.64 ± 0.26	2.67 ± 0.24	< 0.001
PMOF	3.34 ± 1.93	4.97 ± 2.61	7.50 ± 4.21	< 0.001
PHF	0.81 ± 0.88	1.80 ± 1.40	3.27 ± 2.65	< 0.001
Previous fracture n (%)				0.052
NO	238 (85.30%)	90 (82.57%)	147 (76.56%)	
Yes	41 (14.70%)	19 (17.43%)	45 (23.44%)	
Parent fractured hip n (%)				0.248
NO	252 (90.32%)	104 (95.41%)	174 (90.62%)	
Yes	27 (9.68%)	5 (4.59%)	18 (9.38%)	
Current smoking n (%)				< 0.001
NO	217 (77.78%)	93 (85.32%)	185 (96.35%)	
Yes	62 (22.22%)	16 (14.68%)	7 (3.65%)	
Current drinking n (%)				< 0.001
NO	250 (89.61%)	107 (98.17%)	192 (100%)	
Yes	29 (10.39%)	2 (1.83%)	0 (0%)	

BMI, body mass index; Cr, creatinine; P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen; FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density; PMOF, probability of major osteoporotic fractures; PHF, probability of hip osteoporotic fractures

Table 2 Basic characteristics of the 580 participants between men and women

Gender	Men	Women	*p* value
N = 580	200	380	
Age (year)	64.89 ± 7.73	65.39 ± 8.40	0.489
Height (cm)	164.29 ± 6.17	153.79 ± 5.68	< 0.001
Weight (kg)	65.65 ± 8.94	54.68 ± 8.17	< 0.001
BMI(kg/m^2)	24.29 ± 2.98	23.11 ± 3.14	< 0.001
FN BMD (g/cm^2)	0.75 ± 0.12	0.61 ± 0.11	< 0.001
TH BMD (g/cm^2)	0.89 ± 0.12	0.74 ± 0.12	< 0.001
LS BMD (g/cm^2)	0.95 ± 0.15	0.77 ± 0.15	< 0.001
FN T-score	-1.69 ± 1.05	-1.95 ± 0.98	0.004
TH T-score	-0.94 ± 1.07	-1.40 ± 0.98	< 0.001
LS T-score	-0.56 ± 1.26	-1.99 ± 1.21	< 0.001
Cr (umol/L)	75.99 ± 23.35	65.33 ± 20.48	< 0.001
lgβ-CTX (lg pg/ml)	2.57 ± 0.23	2.67 ± 0.24	< 0.001
lgP1NP (lg ng/ml)	1.62 ± 0.17	1.70 ± 0.20	< 0.001
Previous fracture n (%)			0.003
No	177 (88.50%)	298 (78.42%)	
Yes	23 (11.50%)	82 (21.58%)	
Parent fractured hip n (%)			0.94
No	183 (91.50%)	347 (91.32%)	
Yes	17 (8.50%)	33 (8.68%)	
Current smoking n (%)			< 0.001
No	119 (59.50%)	376 (98.95%)	
Yes	81 (40.50%)	4 (1.05%)	
Current drinking n (%)			< 0.001
No	172 (86.00%)	377 (99.21%)	
Yes	28 (14.00%)	3 (0.79%)	

BMI, body mass index; Cr, creatinine; P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen; FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density; PMOF, probability of major osteoporotic fractures; PHF, probability of hip osteoporotic fractures

PMOF and PHF were 7.50 ± 4.21% and 3.27 ± 2.65% in the osteoporotic group, 4.97 ± 2.61% and 1.80 ± 1.40% in the osteopenic group, and 3.34 ± 1.93% and 0.81 ± 0.88% in the normal group, respectively. Serum P1NP and β-CTX levels were relatively higher in the osteoporotic group compared to the other two groups. P1NP levels were 1.72 ± 0.20 lg ng/mL in the osteoporotic group, 1.70 ± 0.21 lg ng/mL in the osteopenic group, and 1.63 ± 0.18 lg ng/mL in the normal group, while β-CTX levels were 2.67 ± 0.24 lg pg/mL in the osteoporotic group, 2.64 ± 0.26 lg pg/mL in the osteopenic group, and 2.60 ± 0.22 lg pg/mL in the normal group. The differences were statistically significant ($p < 0.001$).

Compared to men, postmenopausal women had significantly lower height, weight, BMI, and BMD at different sites ($p < 0.001$). The number of postmenopausal women with osteoporosis was significantly higher than that of men (164 vs. 28). Additionally, women had significantly higher levels of serum P1NP and β-CTX than men. Specifically, P1NP levels were 1.70 ± 0.20 lg pg/mL in women and 1.62 ± 0.17 lg pg/mL in men, and β-CTX levels were 2.67 ± 0.24 lg pg/mL in women and 2.57 ± 0.23 lg pg/mL in men. Women had significantly higher fracture risks (PMOF and PHF) compared to men, with PMOF of 6.18 ± 3.70% in women and 2.83 ± 1.52% in men, and PHF of 2.26 ± 2.34% in women and 0.97 ± 0.92% in men. These differences were statistically significant ($p < 0.001$; Table 2).

Table 3 Partial correlation analyses between BTMs and BMD in participants

Parameters	lgP1NP		lgβ-CTX	
	r	*p* values	*r*	*p* values
FN BMD (g/cm^2)	-0.183	< 0.001	-0.160	< 0.001
TH BMD (g/cm^2)	-0.205	< 0.001	-0.149	< 0.001
LS BMD (g/cm^2)	-0.163	< 0.001	-0.128	0.003
PMOF	0.151	< 0.001	0.085	0.047
PHF	0.174	< 0.001	0.098	0.022

FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density; PMOF, the probability of major osteoporotic fractures; PHF, the probability of hip osteoporotic fractures. P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen. Adjusted for age, sex, BMI, previous fracture, current smoking, current drinking, parent fractured hip, Cr

Correlations between BTMs and BMD, PMOF, and PHF

Table 3 shows the correlations between BTMs and BMDs, PMOF, and PHF. The serum levels of P1NP (a bone formation marker) and β-CTX (a bone resorption marker) were inversely correlated with BMD of all

Table 4 Multivariate Stepwise regression analysis showing the factors determining the BTMs and BMD (g/cm^2)

Parameters	FN-BMD (g/cm^2) (Adjusted R^2 = 0.396)		TH-BMD (g/cm^2) (Adjusted R^2 = 0.429)		LS-BMD (g/cm^2) (Adjusted R^2 = 0.223)	
	β	*p* value	β	*p* value	β	*p* value
Gender	-0.382	< 0.001	-0.401	< 0.001	-0.409	< 0.001
Age	-0.244	< 0.001	0.286	< 0.001	-	-
BMI	0.241	< 0.001	-0.21	< 0.001	0.228	< 0.001
Previous fracture	-0.088	0.008	0.079	0.017	-0.075	0.028
Current drinking	0.086	0.011	-0.077	0.018	0.072	0.043
Current smoking	-	-	-	-	-	-
lgβ-CTX	-	-	-	-	-	-
lgP1NP	-0.14	< 0.001	-0.153	< 0.001	-0.129	< 0.001

FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density; BMI, body mass index; P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen; BMI, body mass index

Table 5 Multivariate Stepwise regression analysis showing the factors determining the PMOF, PHF probability of fracture in participants

Parameters	PHF (Adjusted R^2 = 0.349)		PMOF (Adjusted R^2 = 0.474)	
	β	*p* values	β	*p* values
Gender	0.199	< 0.001	0.253	< 0.001
Age	0.352	< 0.001	0.406	< 0.001
BMI	-0.133	< 0.001	-0.081	0.009
Previous fracture	0.284	< 0.001	0.364-	< 0.001
Current drinking	-	-	-	-
Current smoking		-		-
lgP1NP	0.135	< 0.001	0.087	0.005
lgβ-CTX	-	-	-	-

BMI, body mass index; P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen; PMOF, probability of major osteoporotic fractures, PHF, probability of hip osteoporotic fractures

sites, after adjusting for sex, age, BMI, previous fracture history, family history of hip fracture, smoking history, alcohol consumption, and creatinine levels. Serum P1NP levels were positively correlated with PMOF and PHF (PMOF, $r = 0.116$, $p < 0.005$; PHF, $r = 0.166$, $p < 0.001$) after adjusting for the confounding factors. The correlation between β-CTX and PMOF and between β-CTX and PHF was statistically significant (PMOF, $r = 0.085$, $p = 0.047$ vs. PHF, $r = 0.098$, $p = 0.022$).

Relationship between BTMs and BMD, PMOF, and PHF

We performed multiple linear regression analysis, which identified parameters as significant and independent determinant factors of BMDs (Table 4). BMD was the dependent variable, while sex, age, BMI, previous fracture history, smoking history, alcohol consumption, P1NP, and β-CTX were the independent variables. In the femoral neck BMD model, the significant independent variables were sex, age, BMI, previous fracture history, smoking history, alcohol consumption, and P1NP. These variables explained 39.6% of the BMD variance ($R^2 = 0.396$). In the total hip BMD model, the significant independent variables were sex, age, BMI, previous fracture history, smoking history, alcohol consumption, and P1NP. These variables explained 42.9% of the BMD variance ($R^2 = 0.429$). In the lumbar spine BMD model, the significant independent variables were sex, BMI, previous fracture history, smoking history, alcohol consumption, and P1NP. These variables explained 22.3% of the BMD variance ($R^2 = 0.223$). These results revealed that P1NP significantly affects BMD and shows positive correlation with both PMOF (β = 0.087, $p < 0.005$) and PHF (β = 0.130, $p < 0.001$), with no correlation between β-CTX and PMOF or between β-CTX and PHF (Table 5). These findings suggest that higher levels of P1NP may be associated with fracture risk over the next 10 years.

Effect of BTMs on fracture risks

We used logistic regression analysis to evaluate the effect of BTMs on PMOF and PHF. Prior to the regression analysis, we defined individuals in the study population with PMOF ≥ 5.55% and PHF ≥ 2.05% as high-risk for fractures [23]. The high PMOF group consisted of 185 participants (32%), while the low PMOF group consisted of 395 participants (68%). The high PHF group consisted of 168 participants (29%), while the low PHF group consisted of 412 participants (71%). The results revealed that with increasing P1NP levels, the 10-year risk of fractures in the high PMOF group increased almost 5.2 times (OR 5.181, 95% CI = 1.233–21.768) (Table 6). Similarly, in the high PHF group, after adjusting for sex, the 10-year risk of fractures increased almost 5.6 times (OR 5.595, 95% CI = 1.356–23.086). The effect of β-CTX on the high PMOF group (OR 0.367, 95% CI = 0.112–1.205) and high PHF group (OR 0.558, 95% CI = 0.173–1.791) was not significant (Table 6). The study results indicate that P1NP may play a significant role in the early diagnosis of high-fracture risk individuals.

Discussion

In our cross-sectional study, we found that participants with osteoporosis had lower BMD, higher serum PMOF and PHF levels, and higher serum P1NP and β-CTX

Table 6 Odds ratios for having increased PMOF, PHF by different BTMs after adjusting for sex

Variables	Increased PMOF		Increased PHF	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
lgP1NP	5.181(1.233–21.768)	0.025	5.595(1.356–23.086)	0.017
lgβ-CTX	0.367(0.112–1.205)	0.098	0.558(0.173–1.791)	0.328

P1NP, procollagen type 1 N-propeptide; β-CTX, beta cross-linked C-telopeptide of type 1 collagen; PMOF, probability of major osteoporotic fractures, PHF, probability of hip osteoporotic fractures; CI, Confidence interval; OR, odds ratio

levels, in agreement with past study findings [24–26]. These results suggest that serum β-CTX and P1NP levels may reflect changes in bone metabolism, which is beneficial in the early diagnosis and treatment of osteoporosis. Additionally, PMOF and PHF levels were significantly higher in postmenopausal women than in middle-aged and elderly men. Previous studies have found that before the age of 50, men are more prone to fractures compared to women [27–29], which may be attributed to the fact that men are more likely to experience high-intensity traumatic events at a younger age. However, after the age of 50, the overall incidence of fractures is higher in women than in men [30, 31], which may be attributed to the decline in estrogen in postmenopausal women. Estrogen is crucial in bone growth [32–34] because it plays a key role in the development and maintenance of bone mass. The main mechanism of androgen action on bones is believed to be linked to the aromatization of androgens to estrogens in the ovaries and extra glandular tissues. Moreover, all bone-forming cells have receptors for both androgens and estrogens with a predominance of androgen receptors on osteoblast cells [35]. Studies have shown that there is a positive correlation between estrogen levels and BMD [36–38].

We evaluated the associations between BTMs and BMD and fracture risk. Serum P1NP and β-CTX levels were negatively correlated with BMD in different sites (lumbar spine, femoral neck, and total hip), consistent with past studies [39, 40]. In postmenopausal women, Azizieh et al. [41] found that ratio between P1NP and β-CTX was significantly correlated with hip and spinal BMD. However, β-CTX was not correlated with BMD. Zhao et al. [42] concluded that serum β-CTX and P1NP levels were significantly negatively correlated with lumbar spine, femoral neck, and total hip BMD ($p < 0.01$). Qu et al. [43] reported that β-CTX was significantly higher in an elderly female fracture group than in the non-fracture group. The authors concluded that high serum β-CTX levels are more likely to predict fracture risk than P1NP, in contrast to our study findings. There are several reasons to explain these differences, such as fasting status, health status, and lifestyle factors, which affect BTM levels [44]. In addition, we found that serum P1NP and β-CTX levels were positively correlated with PMOF and PHF. These findings are consistent with our hypothesis that serum P1NP and β-CTX levels are associated with an increased risk of osteoporosis and hip fracture. We speculate that with increasing bone turnover, the synthesis of P1NP and β-CTX increases, contributing to an imbalance between bone formation and bone resorption, reducing BMD, and increasing fracture risk. Randomized controlled studies or prospective studies are required to reveal specific causality and mechanisms.

Using multiple stepwise regression analysis, we found that serum P1NP levels were negatively correlated with BMD. Serum P1NP, but not serum β-CTX, was an independent predictor of BMD. Additionally, serum P1NP was an independent predictor of PMOF and PHF. Currently, there is a lack of information regarding the role of P1NP and β-CTX in predicting fracture risk. The EPIDOS studies found an association between urinary CTX and increased risk of hip fracture, but no association was found with urinary N-terminal crosslinking telopeptide of type I collagen (NTX), even after adjusting for fracture history [14]. The reasons for the discrepancies between the results of the EPIDOS study and our study are unclear. It is possible that these differences stem from variations in participant selection and research design. For example, the EPIDOS study did not include the bone resorption marker P1NP. Notably, the average age of participants included in the EPIDOS study was 82 years, which was significantly higher than the average age of participants in our study. Furthermore, while we collected blood samples from participants after an eight-hour fasting period, the EPIDOS study collected urine samples, and their study population did not strictly adhere to the study fasting requirements. Bauer et al. [45] found that serum P1NP and β-CTX levels were similarly effective in predicting fracture risk. Their findings revealed that higher baseline serum P1NP and β-CTX levels were associated with an increased risk of subsequent hip and non-spinal fractures in elderly men. However, after considering baseline BMD, there was no statistically significant relationship between BTMs and fracture risk. Johansson et al. [46] concluded that measuring serum P1NP and β-CTX levels could improve the accuracy of fracture risk prediction; however, there was no significant difference in the relative predictive effects between the two markers. A Norwegian study found a negative correlation between serum P1NP and BMD ($r = -0.36$, $p = 0.001$) and incidence of hip fractures in both men and women with P1NP > 60 μg/L [47], which

suggested that P1NP was important in predicting the risk of fractures, consistent with our study results. Meier et al. [48] conducted a nested case-control study on 989 Australian men (mean age 71 ± 5.2 years) to investigate the relationships between three BTMs and fracture risk. The study found that serum I-type collagen C-terminal telopeptide, a marker of bone resorption, was associated with an increased risk of fracture. However, β-CTX and P1NP were not associated with fracture risk, even after adjusting for baseline hip BMD and other confounding factors. In contrast, serum I-type collagen C-terminal telopeptide remained associated with risk of fracture (RR = 1.4 per SD increased, 95% CI = 1.1–1.7) after adjusting for all confounding factors. Currently, there is not enough evidence that suggests that P1NP is superior to β-CTX in predicting fracture risk. Furthermore, a prospective longitudinal study confirmed that P1NP and CTX-I were the two best predictive factors for hip fractures in Asian populations [49]. This finding suggests that an increase in BTMs reflects inherent abnormalities in the bone matrix, leading to bone loss and increased fragility. Higher P1NP and β-CTX levels are associated with an increased risk of fractures. While the detailed mechanisms have not been elucidated, we speculate that when bone turnover is accelerated, there is excessive synthesis of P1NP and β-CTX in the bone matrix. Another prospective case-control study suggested that serum CTX and P1NP levels were not significantly associated with hip fracture risk [16]. The role of BTMs in predicting fracture risk remains controversial, with most studies suggesting that bone resorption markers play a larger role in fracture risk prediction, which seems to contradict our research findings. However, Veitch et al. [50], who measured serum P1NP levels after a fracture, found that P1NP levels doubled within the first 12 weeks post-fracture, which remained elevated compared to baseline levels during the subsequent one-year follow-up period. Ivaska et al. [51] reported that, similar to CTX, P1NP increased in the first two weeks following a fracture, gradually decreased in the following two to three months, and reached levels close to pre-fracture stage within six months. These findings suggest that P1NP may play a role in predicting fractures. Even some studies indicate that measuring both P1NP and β-CTX together may be better in predicting fracture risk than measuring only one biomarker. Therefore, it is important to measure BTMs after BMD measurements or FRAX assessments to screen individuals at high risk of fractures and implement early intervention or treatment to reduce fracture incidence.

According to the fracture risk intervention thresholds set by the National Osteoporosis Foundation, patients with 20% PMOF and 3% PHF are defined as high fracture risk. Few of our study subjects reached these thresholds, with only 0.05% reaching PMOF ≥ 20%. A study found significant variations in intervention thresholds for assessing fracture risk with FRAX among different Asian countries and regions, due to differences in population characteristics, fracture epidemiology, medical resources, and cultural background [52]. In our study population, only three individuals met the PMOF ≥ 20% threshold. Therefore, based on our previous research, we defined the high fracture risk groups as PHF ≥ 5.55% and PMOF ≥ 2.05% [23]. In our logistic analysis, after adjusting for sex, we found that for every standard deviation increase in P1NP, the 10-year risk of fractures increased by approximately 5.2-fold in the high PMOF group and 5.6-fold in the high PHF group. Our results suggest that P1NP, a bone formation marker, may be more closely related to fracture risk. Even though a strong correlation between P1NP and BMD is not clear, this phenomenon may indicate that the increase in serum P1NP reflects inherent abnormalities in the bone matrix, leading to overall bone loss and increased fragility.

Our study had a few limitations. First, while our cross-sectional findings suggested promising associations between P1NP and fracture risk, we acknowledge that prospective cohort studies incorporating comprehensive predictive analyses are needed to definitively establish the predictive value of BTMs. Second, the differences in various parameters may not be accurately assessed due to the limited sample size. Future studies with larger cohorts are needed to validate our findings. Finally, the participants were mainly from Changsha. Therefore, whether our findings can be applied to other geographical areas remains to be verified.

In conclusion, high serum P1NP levels may play a significant role in the early diagnosis of high-fracture risk individuals. Measuring serum P1NP levels should be encouraged in individuals who have undergone BMD measurements or FRAX assessments.

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
BTMs	Bone turnover markers
CI	Confidence interval
Cr	Creatinine
CTX-1	Carboxy-terminal cross-linked telopeptide of type 1 collagen
DXA	Dual energy X-ray absorptiometry
FN	Femoral neck
FRAX	Fracture risk assessment tool
IFCC	International Federation of Clinical Chemistry
IOF	International Osteoporosis Foundation
LS	Lumbar spine
NTX-1	N-terminal crosslinking telopeptide of type I collagen
OP	Osteoporosis
OR	Odds ratio
P1NP	Procollagen type 1 N-propeptide
PHF	Probability of hip osteoporotic fracture
PMOF	Probability of major osteoporotic fracture
TH	Total hip
WHO	The World Health Organization
β-CTX	Beta cross-linked C-telopeptide of type 1 collagen

Acknowledgements
We appreciate all of all the participants for their agreement to participate in our study.

Author contributions
XQ, YL performed the data analysis. XQ wrote the manuscript. ZS, LX and QW contributed to the manuscript revise. XQ, CL and LT contributed to literature search and data extraction. ZS, LX and XQ conceived and designed the study. All authors have read and approved the final version of the manuscript.

Funding
This work was supported by grants from the National Natural Science Foundation of China[grant number 81870622], the Hunan Provincial Natural Science Foundation of China[grant number 2022JJ30828 and 2023JJ30747], the Fundamental Research Funds for the Central Universities of Central South University[grant number 2022ZZTS0947 and 2023ZZTS0585], Degree& Postgraduate Education Reform Project of Central South University[grant number 512190112] and Scientific Research Project of Hunan Provincial Health Commission[grant number C202303067096 and 202112070631], Bethune Charitable Foundation, BCF [grant number GX2021B04], Central Subsidy for Prevention and Control of Major Infectious Diseases and HANS CARING Inc.The Hunan Province Smart Chronic Disease Management Clinical Medical Research Center [grant number 2023SK4042].

Declarations

Ethics approval and consent to participate
The Ethics Committee of The Second Xiangya Hospital at South China University, Changsha, China, approved this study (Approval Number: LYF20210015). We conducted all methods in compliance with pertinent guidelines and regulations, adhering to the principles of the Declaration of Helsinki. Participants were informed about the study's objectives, the significance of their involvement, and the assessment procedures. Upon agreement, each participant provided their signed informed consent.

Competing interests
The authors declare no competing interests.

Received: 11 October 2023 / Accepted: 21 March 2025
Published online: 13 May 2025

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