

Association of Serum Periostin Level with Classical Bone Turnover Markers and Bone Mineral Density in Shanghai Chinese Postmenopausal Women with Osteoporosis

Ran Li^{1,2,*}

Xiaoyi Zhu^{1,2,*}

Mengxi Zhang^{1,2,*}

Guannan Zong^{1,2}

Keqin Zhang^{1,2}

¹Department of Endocrinology and Metabolism, Tongji Hospital, School of Medicine, Tongji University, Shanghai, 200065, People's Republic of China;

²Institute of Osteoporosis and Metabolic Bone Diseases, School of Medicine, Tongji University, Shanghai, 200065, People's Republic of China

*These authors contributed equally to this work

Background: It has been reported that serum periostin levels are significantly higher in postmenopausal patients with osteoporotic fractures. Nonetheless, the levels of serum periostin in postmenopausal women with different bone mass remain unclear.

Purpose: The objective of the study was to identify the levels of serum periostin in Chinese postmenopausal women with different bone mass, and the correlations between the periostin levels and the classical bone turnover markers (BTMs), and bone mineral densities (BMDs) at different sites.

Patients and Methods: This study enrolled 331 Chinese postmenopausal women in Shanghai; their clinical features were collected; their levels of serum periostin and traditional BTMs were measured by ELISA or the fully automated immunoassay analyzer; their BMDs at different sites were measured by dual-energy X-ray absorptiometry (DXA).

Results: According to the *T*-value of bone mineral density (BMD), these postmenopausal women were divided into normal group (*n*=84), osteopenia group (*n*=126) and osteoporosis group (*n*=121). There was no significant difference in the serum periostin levels among the above three groups of subjects. In addition, Spearman correlation analysis also revealed that no correlation was observed between the value of serum periostin and those of traditional BTMs, and BMDs at different sites, respectively. The values of traditional BTMs were negatively correlated with those of BMDs at all measured sites. Furthermore, the receiver-operating characteristic (ROC) curves analysis indicated that among the periostin and traditional BTMs mentioned above, the best predictors for postmenopausal osteoporosis in Shanghai Chinese postmenopausal women were osteocalcin (OC) and procollagen type 1 N-terminal propeptide (PINP) [the areas under the ROC curve (AUC)=0.746 and 0.761, respectively].

Conclusion: Serum periostin may not be used as a marker of systemic bone metabolism in Shanghai Chinese postmenopausal women without prior fracture. In addition, serum PINP and OC levels may be the predictors of osteoporosis occurrence in Chinese postmenopausal women.

Keywords: postmenopausal women, periostin, bone turnover markers, bone mineral density

Introduction

Osteoporosis is a systemic metabolic disease mainly characterized by bone mass loss and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and prone to bone fractures.¹ The pathogenesis of osteoporosis is the imbalance of bone remodeling.² Estrogen deficiency play an important role in the occurrence of osteoporosis by increasing bone structure remodeling.³ Early

Correspondence: Keqin Zhang
Department of Endocrinology and Metabolism, Tongji Hospital, School of Medicine, Tongji University, No. 389, Xincun Road, Shanghai, 200065, People's Republic of China
Tel +86 21-66112032
Email keqzhang2018@163.com



epidemiological studies indicated that in many countries, the prevalence of osteoporosis in postmenopausal women is significantly higher than that of men.^{4–6} Osteoporosis and osteoporotic fractures decrease the quality of life, increase the risk of death and result in severe economic burden on families and the global economy.⁴ Overall, postmenopausal osteoporosis is becoming an urgent global health concern. Therefore, it is necessary to early detect and diagnose osteoporosis and to identify patients at high risk for fracture.

The World Health Organization (WHO) defines that bone mineral density (BMD), usually measured by dual-energy X-ray absorptiometry (DXA), is the diagnostic criteria for osteoporosis and the predictor of fracture risk. Osteoporosis is defined as a BMD value which is equal to or more than 2.5SD (*T*-score) below the mean value of peak BMD of young woman.⁷ However, several studies have shown that there were several limitations of using BMD to predict fracture risk. Siris et al⁸ found that 82% of postmenopausal women with fractures had *T*-scores which were above -2.5 . Similarly, Schuit et al⁹ demonstrated that only 44% of women with non-vertebral fractures had *T*-scores which were at or below -2.5 . In general, using only BMD to diagnose postmenopausal osteoporosis (PMOP) may not accurately predict fracture risk. Therefore, if using BMD as the indicator for treatment, there may be a large proportion of women with PMOP who cannot receive timely treatment.

Due to the defect of BMD in clinical practice, researchers have explored the role of bone turnover markers (BTMs) in blood and urine, which are divided into bone formation markers and bone resorption markers. Traditional bone formation markers, such as procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (BALP) and osteocalcin (OC), are related to the activity of osteoblasts. Conversely, traditional bone resorption markers, such as cross-linked C-telopeptide of type I collagen (CTX), cross-linked N telopeptide of type I collagen (NTX) and tartrate-resistant acid phosphatase 5b (TRACP 5b), reflect activity of osteoclasts.¹⁰ Vasikaran et al¹¹ performed prospective cohort studies and concluded that high levels of BTMs may predict fracture risk in postmenopausal women independently of BMD and reflect treatment-induced dynamic changes in bone metabolism. In addition, studies have shown that the combination of BTMs and BMD will improve the risk prediction of PMOP fractures.¹² However, the traditional BTMs currently in widespread use also have limitations, ie, they mainly reflect endosteal bone remodeling, but not the periosteal metabolism.¹³ A study has shown that periosteal

metabolism also plays an important role for the maintenance of skeletal integrity.¹⁴

Periostin is an extracellular matrix protein mainly secreted by osteocytes and osteoblasts in the periosteum.^{15,16} Periostin has shown to play a vital role in the maintenance of bone microarchitecture and bone strength by regulating collagen crosslinking and osteoblast cell adhesion.¹⁷ Furthermore, absence of periostin gene in mice exhibited lower bone mass, lower cortical bone volume, disordered arrangement of collagen fibril and decreased bone strength, which may be related to decreased proliferation and increased apoptosis of osteoblasts.^{15,18} Conversely, other researchers have reported that overexpression of periostin gene in rats and osteoblastic cells increased bone formation and bone mass due to the increased osteoblast proliferation and differentiation.¹⁵ Interestingly, in a 7-year prospective analysis of the study, higher serum periostin levels have been reported to be associated with increased fracture risk in postmenopausal women from the Os des Femmes de Lyon cohort study independently of age, bone turnover markers, and BMD.¹⁹ Other clinical studies have also demonstrated that circulating periostin levels were positively correlated with non-vertebral fractures after adjustment for BMD and potential confounders in Korean postmenopausal women.²⁰ Similarly, high periostin levels were negatively related with femoral neck BMD in Chinese older women with acute hip fractures.²¹ However, Anastasilakis and his colleagues¹⁸ found that there was no difference in circulating periostin levels between Caucasian postmenopausal women with normal bone mass (BMD *T*-score of >-1.0) and low bone mass (BMD *T*-score of ≤ -2.0).

Traditional bone formation markers, such as P1NP, OC and BALP, are secreted by osteoblasts.¹⁰ Periostin is also highly expressed by osteoblasts and osteocytes.^{15,16} Therefore, we hypothesized that serum periostin may also reflect the bone formation activity, such as P1NP, OC and BALP. To date, few studies have investigated the associations of serum periostin level with those of traditional BTMs and with bone mineral densities (BMDs) at different sites respectively in Chinese postmenopausal women. Therefore, our aim was to answer the above questions by epidemiological study in Shanghai local population.

Methods

Patients and Methods

Postmenopausal women were recruited in Community Health Service Center, Ganquan Street, Putuo District, Shanghai from January 2017 to September 2018.

According to the recommendation of the WHO, we classified BMD *T*-score [at the lumbar spine (L1-L4) and/or the left hip] ≥ -1 as the normal group, $-2.5 < T\text{-score} < -1$ as the osteopenia group, and $T\text{-score} \leq -2.5$ as the osteoporosis group. We selected the lowest BMD value among all measured sites as the value for diagnosis in every subject. The inclusion criteria of this study were as follows: 1) menopause for more than 1 year; 2) the person lived in China for more than 10 years; 3) the person signed informed consent. The exclusion criteria of this study were as follows: 1) patients with secondary osteoporosis; 2) patients with a history of fractures; 3) patients with diseases that could affect bone metabolism; 4) patients who discontinued bisphosphonates for less than 1 year and other medications that could affect bone metabolism for less than 6 months. All subjects provided informed consent to participate in this study. The study protocol and procedures conform to the ethical guidelines of the 1975 Declaration of Helsinki. The present study was approved by the Ethics Committee of Tongji Hospital, Tongji University.

Laboratory Measurements

All participants' blood samples were collected after an overnight fast and stored at -80°C until analysis. All blood samples were tested by the clinical laboratory of Tongji Hospital of Tongji University. The levels of serum periostin were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Wu HaoBio-Tech Co., LTD., Shanghai, China) according to the manufacturer's instructions. The intra-assay coefficient of variation (CV) was $<10\%$ and inter-assay CV was $<12\%$. Serum BALP and TRACP 5b were measured using ELISA kit (Gukang Bio-Tech Co., LTD., Guangdong, China). The intra- and inter-assay CV of BALP and TRACP 5b were both $\leq 10\%$. The levels of serum PINP, β -CTX and OC were measured using the fully automated immunoassay analyzer (Cobase 601, Roche Diagnostics Co., LTD., Germany). The intra- and inter-assay CV were $<4.5\%$ and $<5.5\%$ for PINP, $\leq 4.0\%$ and $\leq 6.0\%$ for β -CTX, and $<5.0\%$ and $<7.0\%$ for OC, respectively.

Bone Mineral Density Measurements

The BMD was measured by DXA (Hologic, Bedford, MA, USA) at the lumbar spine (L1-L4) and the left hip including femoral neck, trochanter and the total hip. The results were expressed in g/cm^2 and *T*-score. We calibrated the instrument daily, and the same technician completed the measurement. The daily CV of BMD measurements in the lumbar spine model were $<1\%$.

Statistical Analysis

All data were analyzed by the statistical package for social sciences (SPSS) version 22.0. Kolmogorov-Smirnov test assessed whether continuous variables followed a normal distribution. The data were presented as mean \pm standard deviation (SD) if it followed normal distribution. Otherwise, it was presented as the median (interquartile range). The three groups were analysed with one-way ANOVA followed by the least significant differences (LSD) or Dunnett's T3 post hoc multiple comparison test. Spearman correlation analysis was performed to explore the correlations between serum periostin and other BTMs, and between traditional BTMs and BMDs at different sites. Receiver operating characteristic (ROC) curve analysis was constructed to determine predictors for PMOP. *P*-value <0.05 was considered statistically significant.

Results

The Baseline Characteristics of the Postmenopausal Women

The baseline characteristics of the 311 postmenopausal participants are presented in Table 1, including demographics, clinical characteristics and BMD. The participants were divided into three groups based on the BMD *T*-score: the normal group ($n=84$), the osteopenia group ($n=126$), and the osteoporosis group ($n=121$). There were no differences among the three groups in age and menopausal age. Body weight and body mass index (BMI) were significantly lower in the osteopenia group than in the normal group. In addition, the osteoporosis group had a statistically significant lower levels of height, weight and BMI than the normal group or the osteopenia group. As expected, the BMD values at all measured sites in the osteopenia group or the osteoporosis group were significantly decreased compared with the normal group. Consistently, the BMDs of lumbar spine (L1-L4), femoral neck and total hip were lower in the osteoporosis group than those in the osteopenia group.

Differences in Serum Levels of Periostin and Traditional BTMs Among the Three Groups

For serum periostin, no significant difference was observed between the normal group, the osteopenia group and osteoporosis group (Figure 1A).

Table 1 The Clinical Characteristics of the Postmenopausal Women.

| Variables | | Normal Group (n=84) | Osteopenia Group (n=126) | Osteoporosis Group (n=121) |
|--------------------------|--------------|---------------------|--------------------------|----------------------------|
| Age (years) | | 60.5±5.2 | 60.5±4.5 | 61.3±4.2 |
| Menopausal age (years) | | 51.0±3.5 | 50.3±3.5 | 50.0±3.8 |
| Height (cm) | | 159.5±5.0 | 159.4±5.5 | 157.5±5.1*** |
| Body weight (kg) | | 63.7±8.5 | 61.3±8.4* | 56.6±7.7*** |
| BMI (kg/m ²) | | 25.0±2.9 | 24.2±3.1* | 22.8±2.9*** |
| BMD (g/cm ²) | LS (L1–L4) | 1.0722±0.105 | 0.902±0.054** | 0.749±0.079*** |
| | Femoral neck | 0.821±0.106 | 0.705±0.070** | 0.625±0.078*** |
| | Trochanter | 0.770±0.086 | 0.641±0.188** | 0.606±0.101** |
| | Total hip | 0.973±0.091 | 0.838±0.132** | 0.774±0.097*** |

Note: * $P<0.05$, ** $P<0.01$ vs normal group; *** $P<0.01$ vs osteopenia group.

Abbreviations: LS, lumbar spine; BMI, body mass index; BMD, bone mineral density.

For bone formation markers, serum OC and PINP levels in the osteopenia group was significantly higher than those in the normal group. Furthermore, serum BALP, OC and PINP levels in osteoporosis group were remarkably increased compared with those of both normal group and osteopenia group (Figure 1B–D). For bone resorption markers, serum β -CTX

level in the osteoporosis group was higher than those in the normal group and the osteopenia group. However, serum TRACP 5b levels were not significantly different among the three groups (Figure 1E and F). Our data indicated that low BMD is associated with high BTMs in postmenopausal women.

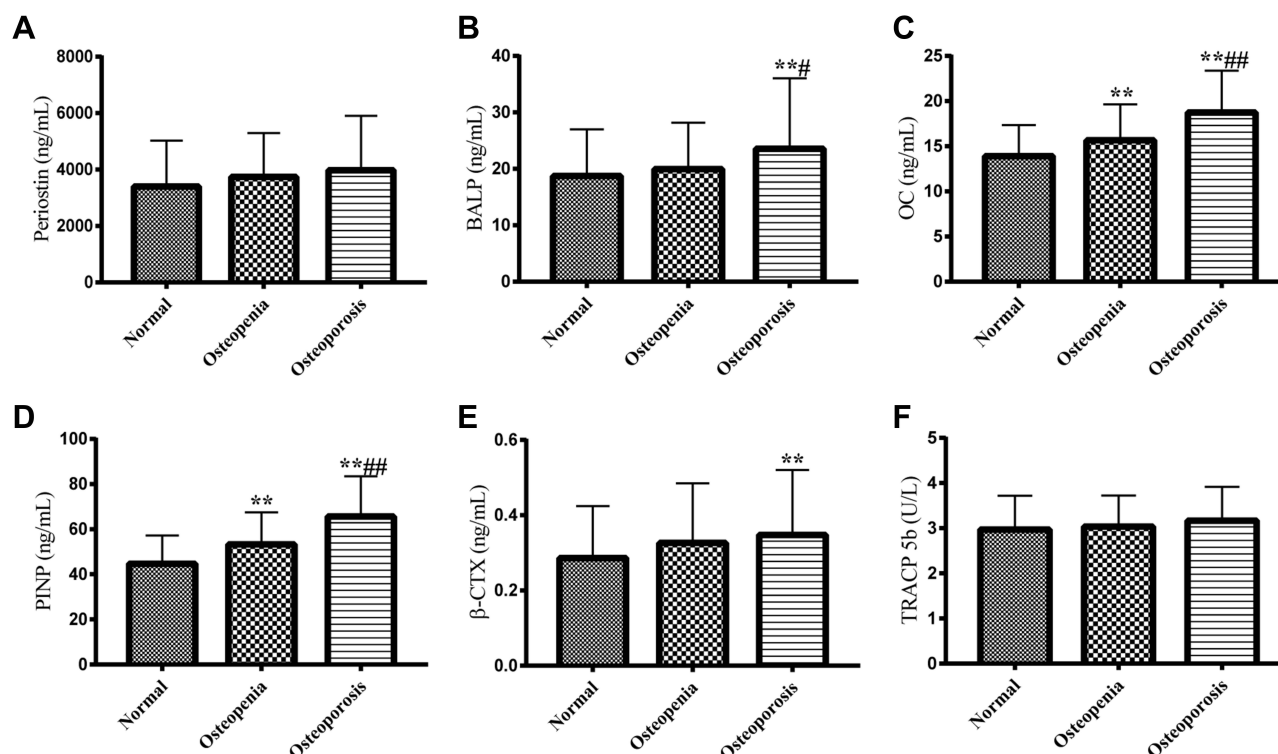


Figure 1 Differences in serum periostin and traditional BTMs levels among the normal group, the osteopenia group and the osteoporosis group. (A) Serum periostin levels among three groups. (B–D) Serum bone formation markers, such as BALP (B), OC (C) and PINP (D) among three groups. (E and F) Serum bone resorption markers, such as β -CTX (E) and TRACP 5b (F) among the three groups.

Notes: ** $P<0.01$ vs normal group; * $P<0.05$, *** $P<0.01$ vs osteopenia group.

Abbreviations: BTMs, bone turnover markers; BALP, bone-specific alkaline phosphatase; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; β -CTX, β cross-linked C-telopeptide of type I collagen; TRACP 5b, tartrate-resistant acid phosphatase 5b.

Table 2 Spearman Correlations Between Serum Periostin Levels and Traditional BTMs or BMDs at Various Sites Among Postmenopausal Women Studied.

| | BALP (ug/mL) | OC (ng/mL) | PINP (ng/mL) | β -CTX (ng/mL) | TRACP 5b (U/L) | Lumbar Spine (L1-L4)(g/cm ²) | Femoral Neck (g/cm ²) | Trochanter (g/cm ²) | Total Hip (g/cm ²) |
|----------|-----------------|---------------|-----------------|-------------------------|-------------------|---|--------------------------------------|------------------------------------|-----------------------------------|
| γ | 0.093 | -0.021 | 0.030 | -0.050 | -0.040 | -0.071 | 0.002 | 0.041 | 0.043 |
| <i>P</i> | 0.102 | 0.721 | 0.612 | 0.384 | 0.481 | 0.217 | 0.969 | 0.515 | 0.456 |

Note: Statistical significance at the $P < 0.05$ level.

Abbreviations: BTMs, bone turnover markers; BMDs, bone mineral densities; BALP, bone-specific alkaline phosphatase; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; β -CTX, β cross-linked C-telopeptide of type I collagen; TRACP 5b, tartrate-resistant acid phosphatase 5b.

The Associations Between Serum Periostin Levels and Classic BTMs or BMDs at All Measured Sites

As shown in Table 2, there was no significant association of serum periostin with traditional BTMs, including BALP, OC, PINP, β -CTX and TRACP 5b. In addition, circulating periostin concentration was not significantly associated with BMDs at all different sites, including lumbar spine (L1-L4), femoral neck, intertrochanter and total hip.

The Association Between Classic BTMs and BMDs at All Different Sites

The correlation between traditional BTMs and BMDs at all different sites in the postmenopausal women was shown in Table 3. Bone formation markers such as BALP, OC and PINP and bone resorption markers such as β -CTX and TRACP 5b were inversely correlated with the BMD values in all different sites.

ROC Curves

ROC curve was established, and the area under the ROC curves (AUCs) of serum periostin and traditional BTMs was observed (Figure 2). Serum OC and PINP could better distinguished the PMOP patients from the non-PMOP subjects [AUC=0.746 for OC, $P < 0.001$, 95% confidence interval (CI): 0.686–0.805; AUC=0.761 for PINP, $P < 0.001$, 95% CI: 0.702–0.821].

Discussion

Periostin is a 93.3 kD secreted extracellular matrix protein (in humans), named for its high levels of expression in the periosteum of long bones.¹⁵ In bone, periostin is mainly expressed by periosteal osteoblasts and osteocytes.¹⁶ Its expression level is controlled by growth factors such as transforming growth factor β (TGF- β) and bone morphogenetic protein 2 (BMP2), cytokines such as tumor necrosis factor α (TNF- α), interleukin (IL)-4 and IL-13, mechanical stimuli and parathyroid hormone (PTH). All of these factors play important roles in the regulation of

Table 3 Spearman Correlations Between Traditional BTMs and BMDs at Various Sites Among All Participants Studied.

| | | Lumbar Spine (L1-L4) (g/cm ²) | Femoral Neck (g/cm ²) | Trochanter (g/cm ²) | Total Hip (g/cm ²) |
|----------------------|----------|---|--------------------------------------|------------------------------------|-----------------------------------|
| BALP (μ g/mL) | γ | -0.141* | -0.276* | -0.261* | -0.203* |
| | <i>P</i> | 0.013 | <0.001 | <0.001 | <0.001 |
| OC (ng/mL) | γ | -0.405* | -0.464* | -0.493* | -0.441* |
| | <i>P</i> | <0.001 | <0.001 | <0.001 | <0.001 |
| PINP (ng/mL) | γ | -0.442* | -0.457* | -0.494* | -0.458* |
| | <i>P</i> | <0.001 | <0.001 | <0.001 | <0.001 |
| β -CTX (ng/mL) | γ | -0.153* | -0.316* | -0.375* | -0.286* |
| | <i>P</i> | 0.007 | <0.001 | <0.001 | <0.001 |
| TRACP 5b (U/L) | γ | -0.133* | -0.241* | -0.228* | -0.157* |
| | <i>P</i> | 0.019 | <0.001 | <0.001 | 0.005 |

Note: *Statistical significance at the $P < 0.05$ level.

Abbreviations: BTMs, bone turnover markers; BMDs, bone mineral densities; BALP, bone-specific alkaline phosphatase; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; β -CTX, β cross-linked C-telopeptide of type I collagen; TRACP 5b, tartrate-resistant acid phosphatase 5b.

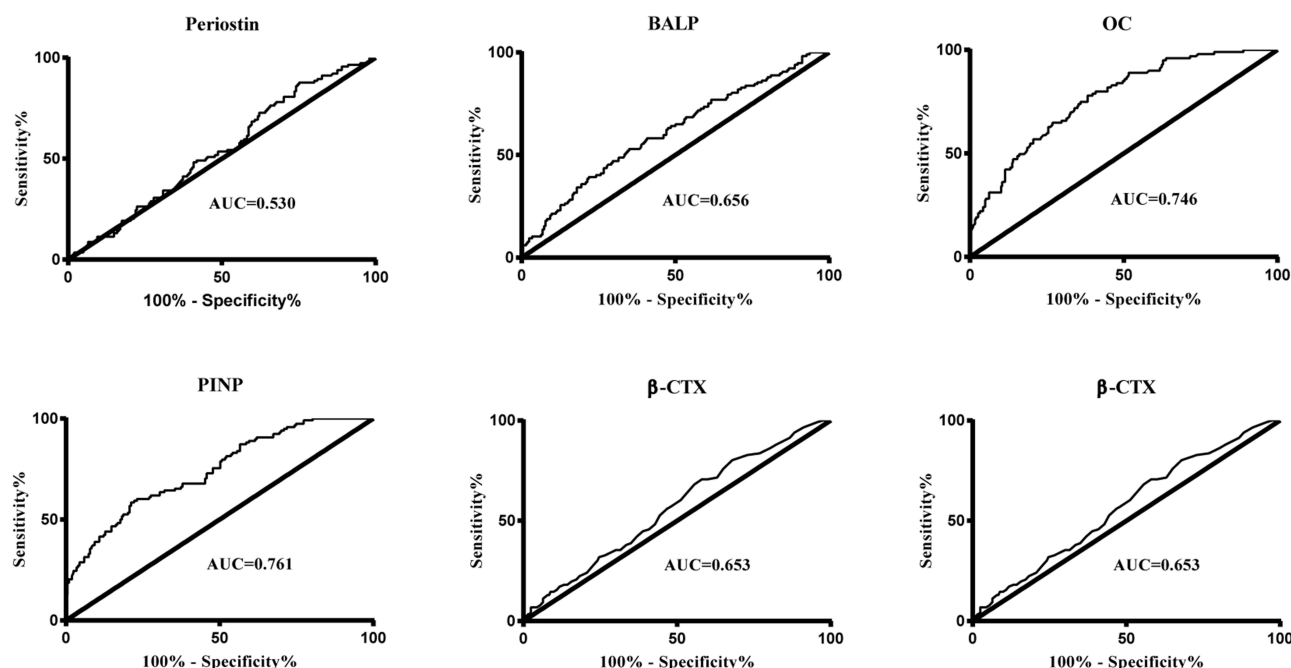


Figure 2 ROC for the ability of the serum periostin and BTMs to differentiate the postmenopausal women with osteoporosis. AUC=0.656 for BALP, $P<0.001$, 95% CI 0.588–0.724; AUC=0.746 for OC, $P<0.001$, 95% CI 0.686–0.805; AUC=0.761 for PINP, $P<0.001$, 95% CI 0.702–0.821; AUC=0.653 for β -CTX, $P<0.001$, 95% CI 0.587–0.719; AUC=0.647 for TRACP 5b, $P<0.001$, 95% CI 0.578–0.716; AUC=0.530 for periostin, $P=0.425$, 95% CI 0.458–0.601.

Abbreviations: ROC, receiver-operating characteristic curves; BTMs, bone turnover markers; AUC, area under the ROC curve; CI, confidence interval; BALP, bone-specific alkaline phosphatase; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; β -CTX, β -cross-linked C-telopeptide of type I collagen; TRACP 5b, tartrate-resistant acid phosphatase 5b.

bone homeostasis.¹⁵ Periostin has been reported to play a key role in bone formation and fracture healing.^{15,22,23} In rodent fracture models, periostin mRNA and protein expression levels are rapidly upregulated in fracture healing area.¹⁵ Therefore, periostin may be associated with bone turnover. In addition, overexpression of periostin in MC3T3-E11 osteoblastic cells increases cell adhesion and mobility.²⁴ What's more, Li et al²⁵ have demonstrated that 17 β -estrogen promotes periostin expression at the endosteal surface and bone formation in ovariectomized rats. In view of the above basic research results, we believed that it is necessary to conduct clinical studies to observe the serum periostin levels in Chinese postmenopausal women with different bone mass.

In order to demonstrate the consistency of this studied population with the population in other studies, all traditional BTMs were also measured in this study. It was shown that all measured BTMs were negatively correlated with BMDs at different sites. These results were generally consistent with previous studies demonstrating the effectiveness of our research data.^{26,27}

Our study found no significant difference in serum periostin levels among Chinese postmenopausal women with different bone mass, and no correlation between

serum periostin levels and traditional BTMs, especially bone formation markers such as OC, BALP and PINP. Anastasilakis et al¹⁸ have also revealed no significant increase in serum periostin level in Caucasian postmenopausal women with low bone mass (T -score ≤ -2.0) compared to the control group with normal bone mass (T -score ≥ -1.0 at the lumbar spine and the nondominant femoral neck). However, it has been observed that circulating levels of periostin were significantly increased during acute osteoporotic hip fractures in 261 Chinese older women.²¹ It has been clearly known that primary bone healing after fracture is intramembrane ossification, and the bone tissue in intramembrane ossification is directly synthesized by osteoblasts,²⁸ which may be one of the reasons for the significantly increased periostin expression in postmenopausal women after fracture. Besides this, mechanical strain may be elevated in the fracture site, which in turn stimulates the expression of periostin and promotes the bone formation.^{19,20} Therefore, our results that the serum periostin levels are not synchronized with traditional bone formation markers in Chinese postmenopausal women without fractures are a very interesting phenomenon. Further studies may be needed to explore the changes of periostin expression in the cortical bone

among postmenopausal women with different bone mass and the relationship between periostin levels in the cortical bone and traditional BTMs, especially traditional bone formation markers.

The relationships between serum periostin and traditional BTMs, and BMDs at different sites in postmenopausal women remain controversial. Anastasilakis et al¹⁸ found that serum periostin levels were not correlated to BMD at different site and serum CTX, but positively correlated with serum BALP in postmenopausal Caucasian women. Interestingly, Kim et al²⁰ showed that serum periostin levels in Korean postmenopausal women with non-vertebral fractures were inversely associated with all hip BMDs measured, whereas periostin levels in women with vertebral fractures were not correlated with lumbar BMD. Gossiel et al²⁹ proved that in PMOP with teriparatide treatment, changes in periostin were unrelated to the changes in PINP and CTX, but positively correlated with changes in the femur neck and the lumbar spine BMD.

In addition, the ROC curve analysis indicated serum PINP and OC may be the predictors of Chinese PMOP in our study. This result may provide a reference for the diagnosis of osteoporosis in countryside region of China without DEXA.

There are some limitations to the present study. Firstly, the overall number of the postmenopausal women was relatively small and unequal among the three groups. Secondly, this is a cross-sectional study, and there is no follow-up to observe the changes in serum periostin, traditional BTMs and BMD in postmenopausal women over time.

Conclusions

Although periostin is highly expressed by osteoblasts and osteocytes, there were no significant correlations between serum periostin and the classic BTMs or BMDs at different sites, suggesting that serum periostin may not reflect the overall bone metabolism in Chinese postmenopausal women without prior fracture.

Abbreviations

BTMs, bone turnover markers; BMDs, bone mineral densities; BALP, bone-specific alkaline phosphatase; OC, osteocalcin; PINP, procollagen type 1 N-terminal propeptide; β -CTX, β cross-linked C-telopeptide of type I collagen; TRACP 5b, tartrate-resistant acid phosphatase 5b; DEXA, dual-energy X-ray absorptiometry; ROC, the

receiver-operating characteristic; WHO, World Health Organization; CV, coefficient of variation; PMOP, postmenopausal osteoporosis.

Data Sharing Statement

All data and materials have been presented in the manuscript. No outliers were omitted from the main statistical analysis. Related information is available upon request to the corresponding author.

Ethics Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the declaration of Helsinki principles and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from the Ethical Committee of Tongji Hospital of Tongji University (K-W-2021-006). Informed consent was obtained from all individual participants included in the study.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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