Research Square

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Dynamics of Bone Turnover Markers Across the Menopausal Transition: A Retrospective Analysis

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Research Article

Keywords: Menopause, Bone Turnover Markers, women health

Posted Date: June 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9776620/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

The transition from pre-menopause to post-menopause is characterized by drastic hormonal shifts that impact bone metabolism.

Methods

A retrospective study of 309 women was conducted, categorized into pre-menopausal (n = 56), peri-menopausal (n = 187), and post-menopausal (n = 66) three groups. Serum levels of N-MID OC, P1NP, and the P1NP/β-CTx ratio were analyzed.

Results

Post-menopausal women exhibited significantly higher levels of N-MID OC (19.73 ± 6.80 ng/mL), P1NP (62.41 ± 25.15 ng/mL), and β-CTx (0.4488 ± 0.2407 ng/mL) compared to the pre-menopausal group ($P < 0.05$). Notably, the P1NP/ β-CTx ratio remained stable across all groups ($P = 0.4607$). Strong correlations were observed between P1NP and N-OC (r = 0.80).

Conclusion

Bone turnover accelerates significantly after menopause, but the coupling between formation and resorption remains balanced at a higher set point.

Introduction

Menopause is a critical physiological milestone associated with an increased risk of osteoporosis due to estrogen deficiency(1, 2). Estrogen plays a pivotal role in inhibiting bone resorption; its decline leads to an imbalance in bone remodeling(3, 4). While Bone Turnover Markers (BTMs) like P1NP (formation) and β-CTx (resorption) are used to monitor bone health, their specific dynamic changes during the peri-menopausal transition are often less emphasized than in established post-menopausal osteoporosis(5, 6). This study aims to quantify these shifts and evaluate the coupling balance between bone formation and resorption(7).

Materials and Methods

Study Design

A retrospective cross-sectional analysis of 309 female subjects.

Grouping: Subjects were divided based on menopausal status: Pre-menopausal (Pre-M), Peri-menopausal (Peri-M), and Post-menopausal (Post-M).

Markers

Serum N-MID Osteocalcin (N-OC), Procollagen type I N-terminal propeptide (P1NP), and β-isomerized C-terminal telopeptide of type I collagen (β-CTx) were measured.

Statistical Analysis

Normality was assessed via Shapiro-Wilk test. Differences were analyzed using Kruskal-Wallis or Brown-Forsythe ANOVA followed by Dunn's or Sidak's multiple comparisons. Correlation was analyzed using a heatmap.

Results

1.1 Distribution and Descriptive Statistics

Most BTMs showed non-normal distribution ($P < 0.05$ in Shapiro-Wilk tests for most groups). The descriptive data summarized in Table 1 shows a clear upward trend in marker concentration following menopause.

[Insert Table 1 **here]**

Table 1
Serum levels of bone turnover markers according to menopausal status

Variable	Pre-menopausal (n = 56)	Peri-menopausal (n = 187)	Post-menopausal (n = 66)	*P* value
N-MID OC (ng/mL)	16.17 ± 6.43	16.26 ± 5.70	19.73 ± 6.80[ab]	*0.0086*
P1NP (ng/mL)	49.08 ± 21.15	51.28 ± 21.79	62.41 ± 25.15[a]	*0.0201*
β-CTx (ng/mL)	0.3252 ± 0.1903	0.3537 ± 0.1952	0.4488 ± 0.2407[a]	*0.0088*
P1NP/β-CTx ratio	177.1 ± 87.17	167.7 ± 74.23	158.8 ± 59.32	*0.4607*

Data are presented as Mean±Standard Deviation (SD). *P* values were determined by Kruskal-Wallis test or Brown-Forsythe ANOVA. [a]$P < 0.05$ versus Pre-menopausal group. [b]$P < 0.05$ versus Peri-menopausal group.

1.2 Comparison of Bone Markers

Bone Formation (P1NP & N-OC)

Post-M women had significantly higher N-OC compared to both Pre-M and Peri-M groups ($P < 0.05$). P1NP followed a similar trend, being significantly elevated in the Post-M group (62.41 ng/mL) vs Pre-M (49.08 ng/mL).

Bone Resorption (β-CTx)

β-CTx levels increased significantly in Post-M women (0.4488 ng/mL) compared to Pre-M women (0.3252 ng/mL).

Coupling Balance

The P1NP/ β-CTx ratio showed no statistically significant difference across the three stages ($P = 0.4607$). **(**Fig. 1**)**

[Insert Fig. 1 **here]**

3.3 Correlation Analysis

Heatmap analysis revealed a robust and consistent positive correlation between N-MID OC and P1NP is maintained throughout the menopausal transition (Pre: r = 0.73, Peri: r = 0.81, Post: r = 0.82). **(**Fig. 2**)** β-CTx exhibits strong positive correlations with both P1NP (r = 0.75) and N-MID OC (r = 0.80) in the post-menopausal group, reflecting the high-turnover coupling mechanism typical of early estrogen deficiency. Age showed weak correlations with specific markers (r = 0.02 to 0.16).(5)

[Insert Fig. 2 **here]**

The matrix displays the Spearman correlation coefficients (r) between various bone turnover markers (BTMs) and the P1NP/β-CTx ratio within the Pre-menopausal, Peri-menopausal, and post-menopausal groups. **Color-coded Correlation**: Blue squares indicate a positive correlation, while red squares indicate a negative correlation; the intensity of the color corresponds to the strength of the association (r value).

Discussion

Our results confirm that the post-menopausal state is characterized by a marked 'acceleration' of bone turnover. While bone metabolism remains relatively stable during the peri-menopausal transition, a significant upward shift occurs after the final menstrual period.

A pivotal finding in this study is the stability of the P1NP/β-CTx ratio across all cohorts ($P = 0.4607$). This stability suggests that despite the increased absolute rate of remodeling units triggered by estrogen deficiency, the intrinsic 'coupling' between bone formation and resorption is preserved during the early post-menopausal years.

Furthermore, the exceptionally strong correlation between P1NP and N-MID OC (r = 0.82) in post-menopausal women presents a significant opportunity for clinical optimization. Given that P1NP exhibits

lower biological variation and is less affected by renal function than Osteocalcin, our data supports a more cost-effective screening approach: prioritizing P1NP and β-CTx to monitor bone health during the menopausal transition. This simplification could reduce diagnostic costs without compromising the ability to detect rapid bone loss. (8) (9).

Limitations

We acknowledge several limitations in this study. First, the cross-sectional design prevents us from tracking individual longitudinal changes. Second, due to the retrospective nature of the database, data on BMI, serum Vitamin D, and PTH levels were not recorded for this cohort.

While these factors are important modulators of bone metabolism, our study focused on characterizing the dominant impact of the menopausal transition on bone turnover markers in a large, real-world healthy screening population (n = 309). The clear stage-specific trends observed across three distinct groups provide robust evidence of metabolic shifts, even in the absence of these secondary variables. Future studies incorporating longitudinal BMD measurements and comprehensive endocrine profiles are recommended.

Conclusion

In conclusion, menopause triggers a synchronized acceleration of bone turnover, yet the formation-resorption balance remains coupled at a higher set point. The high synchronicity between N-OC and P1NP indicates that monitoring a single formation marker alongside β-CTx is sufficient for early metabolic assessment. These findings provide clinicians with a streamlined tool for early intervention during the menopausal transition, potentially before significant bone density loss occurs.

Abbreviations

BTMs
Bone turnover markers
N-MID OC
N-MID osteocalcin
P1NP
Procollagen type 1 N-terminal propeptide
β-CTx
β-crosslaps of type I collagen.

Declarations

Declarations Funding:

This study was supported by National Natural Science Foundation of China, No. 8250062894 and Guangzhou Municipal Health Commission, No. 2023A04J1251.

Competing interests:

The authors declare no competing interests.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. Due to the retrospective nature of this study utilizing de-identified clinical data, the requirement for informed consent was waived by the Ethics Committee of Guangzhou Women and Children's Medical Center.(No.[2022] 146B00)

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 8250062894).

Author Contribution

Siqin Duan wrote the main manuscript text and wenzheng li prepared data. All authors reviewed the manuscript.

Acknowledgements

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

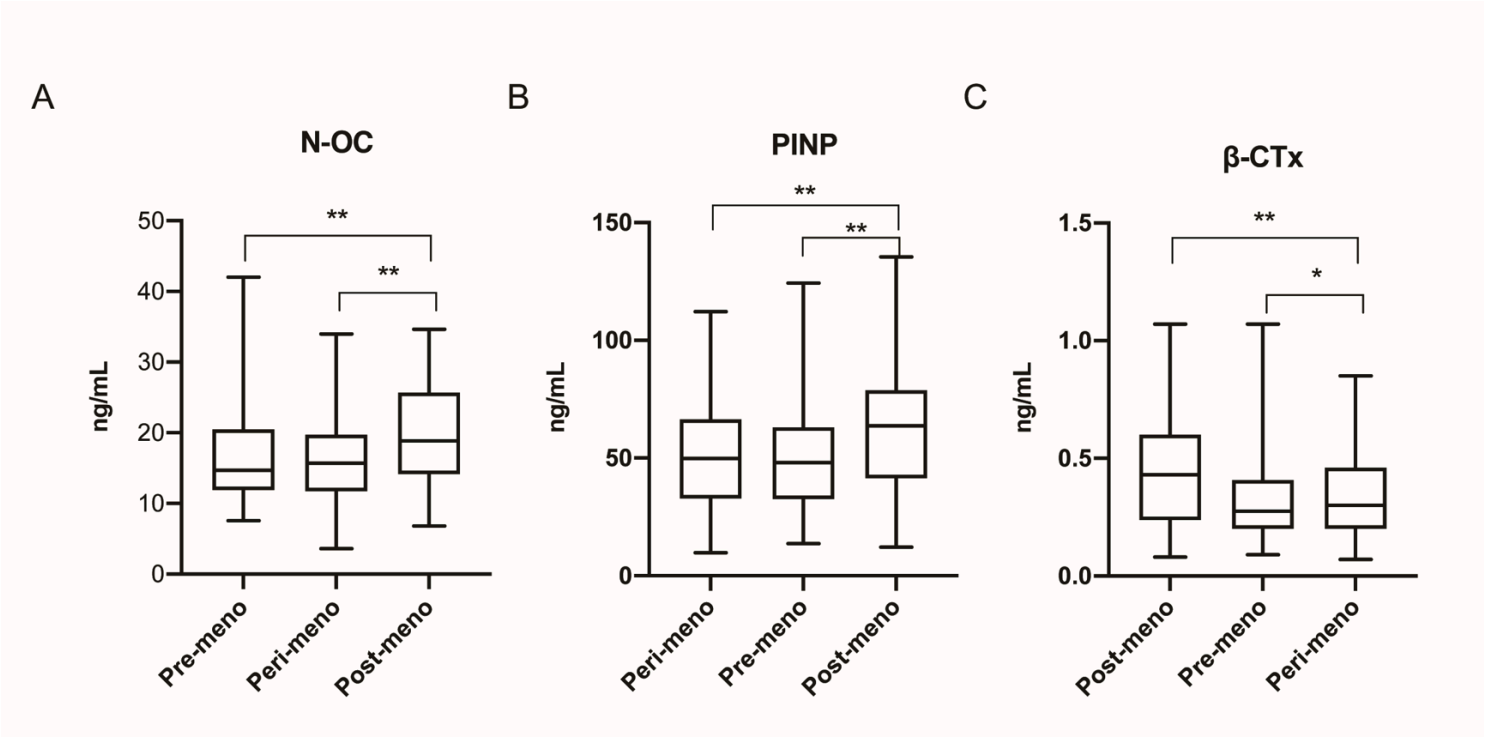


Figure 1

Comparison of bone turnover markers (BTMs) across different menopausal stages.

(A) Serum N-MID Osteocalcin (N-OC) levels: Box plots show a significant increase in N-OC concentrations in the post-menopausal group compared to both pre-menopausal and peri-menopausal groups. **(B) Serum Procollagen type I N-terminal propeptide (P1NP) levels:**P1NP levels remain stable between pre- and peri-menopause but rise significantly upon reaching the post-menopausal stage. **(C) Serum β-isomerized C-terminal telopeptide of type I collagen (β-CTx) levels:** A marked elevation in bone resorption activity is observed in post-menopausal women. Data are presented as medians with interquartile ranges. Significant differences ($P < 0.05$) are indicated by asterisks based on Dunn's multiple comparisons test.

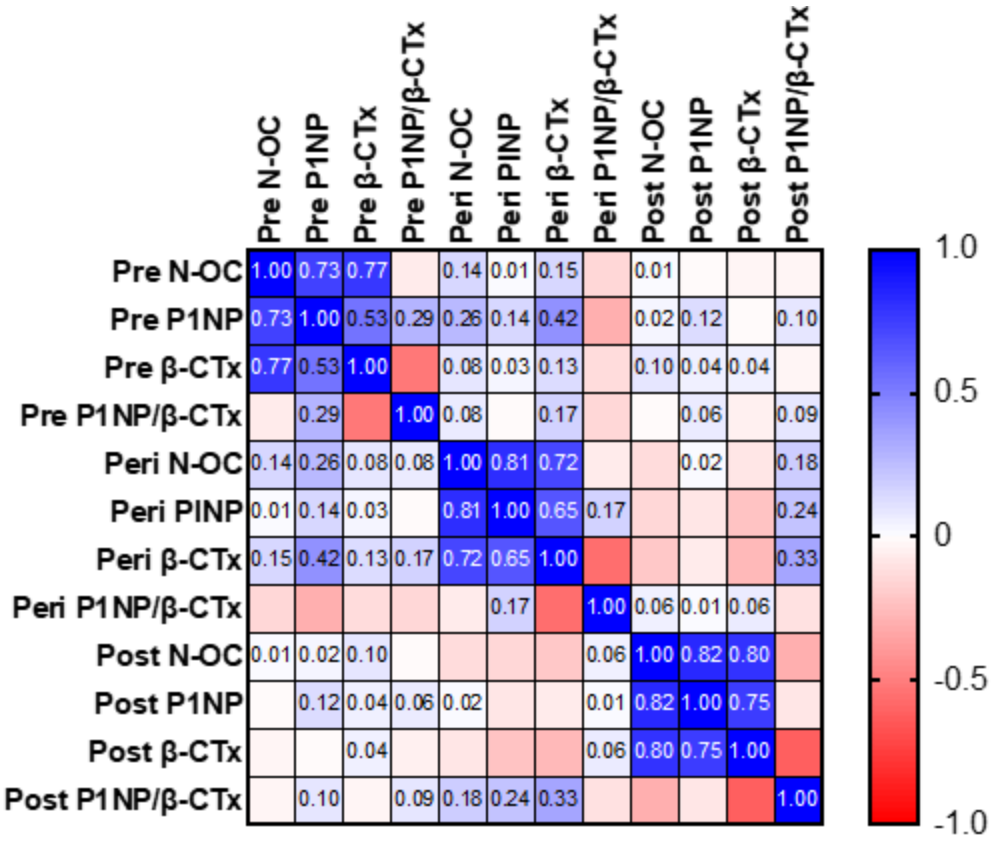


Figure 2

Comparative correlation matrices of bone turnover markers across menopausal stages.