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Original Research Article

Evaluating the Role of Bone Turnover Markers in Diagnosing and Monitoring Osteoporosis: A Cross-Sectional Study

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Abstract:

Background: Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration, leading to increased fracture risk. The standard diagnostic tool, Dual-energy X-ray absorptiometry (DXA), measures bone mineral density (BMD) but does not capture the dynamic state of bone remodeling. Bone turnover markers (BTMs) reflect the rate of bone formation and resorption and may offer complementary diagnostic and prognostic information.

Methods: A single-center, cross-sectional study was conducted on 150 postmenopausal women aged 50–75. Participants were categorized into three groups based on WHO T-score criteria: Healthy Controls (n=50, T-score > -1.0), Osteopenia (n=50, T-score between -1.0 and -2.5), and Osteoporosis (n=50, T-score ≤ -2.5). Fasting morning serum samples were collected and analyzed for P1NP and CTX-I levels using electrochemiluminescence immunoassays. BMD was measured at the lumbar spine and femoral neck by DXA. Data were analyzed using one-way ANOVA with Tukey's post-hoc test.

Results: The mean age of participants was significantly higher in the osteoporosis group (65.8 ± 6.1 years) compared to the osteopenia (61.2 ± 5.5 years) and control groups (58.4 ± 4.9 years) ($p < 0.001$). Serum P1NP levels were significantly elevated in the osteoporosis group (80.5 ± 21.2 ng/mL) compared to both the osteopenia group (55.3 ± 15.8 ng/mL) and the control group (35.1 ± 10.4 ng/mL) ($p < 0.001$). Similarly, serum CTX-I levels showed a stepwise increase, with the highest levels in the osteoporosis group (752.1 ± 148.3 ng/L), followed by the osteopenia group (501.7 ± 119.5 ng/L), and the lowest in controls (303.4 ± 82.6 ng/L) ($p < 0.001$). All pairwise comparisons between the groups for both markers were statistically significant ($p < 0.01$).

Conclusion: Serum levels of P1NP and CTX-I are significantly and progressively elevated in postmenopausal women with osteopenia and osteoporosis compared to healthy controls. These findings support the potential role of BTMs as valuable adjuncts to BMD for identifying individuals with high bone turnover, assessing fracture risk, and potentially monitoring therapeutic response in osteoporosis management.

Keywords: Osteoporosis, Bone Turnover Markers, P1NP, CTX-I, Bone Mineral Density, Diagnosis, Postmenopausa.

Introduction

Osteoporosis is a silent, progressive metabolic bone disease characterized by a reduction in bone mass and a deterioration of bone microarchitecture, resulting in increased bone fragility and a consequent susceptibility to fractures [1]. It represents a major global public health concern, particularly among the aging postmenopausal female population, leading to significant morbidity, mortality, and socioeconomic burden [2].The cornerstone for the diagnosis of osteoporosis is the measurement of bone mineral density (BMD) using Dual-energy X-ray absorptiometry (DXA). According to the World Health Organization (WHO), osteoporosis is defined by a BMD T-score of -2.5 or lower at the hip or spine [3]. While BMD is a strong predictor of fracture risk, it has notable limitations. It provides a static measurement of bone mass but fails to capture crucial information about bone quality, a composite of architecture, turnover, damage accumulation, and mineralization [4]. A significant proportion of fragility fractures occur in individuals with BMD values in the non-osteoporotic (osteopenic) range, highlighting the need for additional tools to improve fracture risk assessment [5].Bone remodel-

ing is a continuous physiological process involving the removal of old bone by osteoclasts (resorption) and the deposition of new bone by osteoblasts (formation). In osteoporosis, this process becomes uncoupled, with bone resorption exceeding bone formation, leading to a net loss of bone mass [6]. Bone turnover markers (BTMs) are byproducts of bone remodeling that are released into circulation and can be measured in serum or urine. They provide a dynamic snapshot of the rate of bone formation and resorption throughout the skeleton [7].

The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended specific BTMs as reference analytes for clinical use. These include procollagen type 1 N-terminal propeptide (P1NP) as a marker of bone formation and C-terminal telopeptide of type I collagen (CTX-I) as a marker of bone resorption [8]. Several studies have demonstrated that elevated levels of BTMs are associated with higher rates of bone loss and an increased risk of fracture, independent of BMD [9].

Despite growing evidence, the routine clinical application of BTMs remains inconsistent. A research gap exists in consistently demonstrating their utility across well-defined patient populations, particularly in distinguishing between individuals with normal BMD, osteopenia, and established osteoporosis. Further clarification of their role could enhance diagnostic precision and personalize patient management. Therefore, the primary aim of this study was to evaluate and compare the serum levels of the bone formation marker P1NP and the bone resorption marker CTX-I in a cohort of postmenopausal women, stratified into healthy controls, osteopenia, and osteoporosis groups based on their BMD T-scores. We hypothesized that levels of both markers would be progressively higher in the osteopenia and osteoporosis groups compared to healthy controls.

Materials and Methods

Study Design and Setting: A single-center, cross-sectional, comparative study was conducted at the Department of Endocrinology and Metabolism, University General Hospital, between January 2022 and December 2022.

Study Population: A total of 150 postmenopausal women aged between 50 and 75 years were recruited from the outpatient clinic.

All participants provided written informed consent prior to enrollment. Participants were stratified into three groups of 50 each based on their lowest T-score at either the lumbar spine (L1-L4) or femoral neck, according to WHO criteria:

- **Group 1 (Healthy Controls):** T-score > -1.0.
- **Group 2 (Osteopenia):** T-score between -1.0 and -2.5.
- **Group 3 (Osteoporosis):** T-score ≤ -2.5.

Inclusion and Exclusion Criteria: Inclusion criteria were: female sex, postmenopausal status (defined as at least 12 months of amenorrhea), and age 50–75 years.

Exclusion criteria included: history of metabolic bone diseases other than postmenopausal osteoporosis (e.g., Paget's disease, hyperparathyroidism, osteomalacia); chronic renal failure (eGFR < 30 mL/min/1.73m²); chronic liver disease; malabsorption syndromes; rheumatoid arthritis or other systemic inflammatory diseases; known malignancy; history of fragility fracture within the last 12 months; and use of medications known to affect bone metabolism within the past year (e.g., bisphosphonates, glucocorticoids >5 mg/day for >3 months, hormone replacement therapy, teriparatide, denosumab).

Procedures

- **Clinical Assessment:** A structured questionnaire was used to collect data on demographics, medical history, menopausal status, and lifestyle factors. Height and weight were measured to calculate Body Mass Index (BMI, kg/m²).
- **Bone Mineral Density (BMD) Measurement:** BMD was measured at the lumbar spine (L1-L4) and the left femoral neck for all participants using a Hologic Discovery A DXA scanner (Hologic Inc., Marlborough, MA, USA). The machine was calibrated daily using a standard phantom. All scans were performed and analyzed by a single certified technician.
- **Biochemical Analysis:** Fasting (10–12 hours) blood samples were collected from all participants between 8:00 AM and 10:00 AM to minimize diurnal variation in BTM levels. Samples were centrifuged at 3000 rpm for 15 minutes at 4°C. The resulting serum was aliquoted and stored at -80°C until analysis. Serum concentrations of total P1NP and CTX-I were measured using automated electrochemiluminescence immunoassays (ECLIA) on a Cobas e601 analyzer (Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation were <4% for P1NP and <5% for CTX-I.

Statistical Analysis: Statistical analysis was performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Data were tested for normality using the Shapiro-Wilk test.

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as numbers (n) and percentages (%). Differences in continuous variables (age, BMI,

BMD, BTM levels) among the three groups were analyzed using a one-way analysis of variance (ANOVA). If the ANOVA result was significant, Tukey's honestly significant difference (HSD) post-hoc test was used for pairwise comparisons between groups. A p-value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics: A total of 150 postmenopausal women were included in the final analysis, with 50 participants in each of the three study groups. The baseline demographic and clinical characteristics of the study population are presented in Table 1. The mean age and years since menopause were significantly different across the three groups, with a progressive increase from the control group to the osteoporosis group ($p < 0.001$ for both). There was no statistically significant difference in BMI among the groups ($p = 0.215$).

Table 1: Baseline Demographics and Clinical Characteristics of Study Participants

Characteristic	Healthy Controls (n=50)	Osteopenia (n=50)	Osteoporosis (n=50)	p-value
Age (years)	58.4 ± 4.9	61.2 ± 5.5[a]	65.8 ± 6.1[ab]	<0.001
BMI (kg/m²)	26.1 ± 3.8	25.5 ± 4.1	24.9 ± 3.5	0.215
Years Since Menopause	8.7 ± 3.1	11.5 ± 4.2[a]	15.1 ± 5.3[ab]	<0.001
Data are presented as mean ± SD. p-value calculated using one-way ANOVA.				
[a] p< 0.05 vs. Healthy Controls; [b] p < 0.05 vs. Osteopenia group (Tukey's HSD post-hoc test).				

Bone Mineral Density (BMD) Measurements: As expected from the study design, BMD values and corresponding T-scores at both the lumbar spine and femoral neck were significantly different among the three groups (Table 2). The osteoporosis group had the lowest BMD and T-scores, followed by the osteopenia group, with the control group having the highest values ($p < 0.001$ for all parameters).

Table 2: Bone Mineral Density (BMD) Measurements by Study Group

Parameter	Healthy Controls (n=50)	Osteopenia (n=50)	Osteoporosis (n=50)	p-value
Lumbar Spine BMD (g/cm²)	1.102 ± 0.08	0.915 ± 0.06[a]	0.753 ± 0.07[ab]	<0.001
Lumbar Spine T-score	-0.4 ± 0.5	-1.7 ± 0.4[a]	-3.1 ± 0.6[ab]	<0.001
Femoral Neck BMD (g/cm²)	0.955 ± 0.09	0.810 ± 0.07[a]	0.681 ± 0.08[ab]	<0.001
Femoral Neck T-score	-0.6 ± 0.6	-1.9 ± 0.5[a]	-2.9 ± 0.5[ab]	<0.001
Data are presented as mean ± SD. p-value calculated using one-way ANOVA.				
[a] p< 0.001 vs. Healthy Controls; [b] p < 0.001 vs. Osteopenia group (Tukey's HSD post-hoc test).				

Serum Bone Turnover Markers: The primary findings of the study are presented in Table 3. There was a statistically significant and stepwise increase in the mean serum levels of both the bone formation marker P1NP and the bone resorption marker CTX-I across the groups. The highest levels for both markers were observed in the osteoporosis group, followed by the osteopenia group, and the lowest levels were in the healthy control group ($p < 0.001$ for both markers). Post-hoc analysis revealed that the differences between all three groups were statistically significant for both P1NP and CTX-I.

Table 3: Comparison of Serum Bone Turnover Markers among the Study Groups

Marker	Healthy Controls (n=50)	Osteopenia (n=50)	Osteoporosis (n=50)	p-value
P1NP (ng/mL)	35.1 ± 10.4	55.3 ± 15.8[a]	80.5 ± 21.2[ab]	<0.001
CTX-I (ng/L)	303.4 ± 82.6	501.7 ± 119.5[a]	752.1 ± 148.3[ab]	<0.001
Data are presented as mean ± SD. p-value calculated using one-way ANOVA.				
[a] p< 0.001 vs. Healthy Controls; [b] p < 0.001 vs. Osteopenia group (Tukey's HSD post-hoc test).				

Discussion

This study investigated the relationship between bone turnover markers and bone mineral density status in a well-defined cohort of postmenopausal women. The principal finding was that serum levels of both the bone formation marker P1NP and the bone resorption marker CTX-I were significantly and progressively higher in women with osteopenia and osteoporosis compared to those with normal bone mass. This dose-response relationship supports the hypothesis that the pathological bone loss in osteoporosis is driven by an accelerated rate of bone turnover, where resorption outpaces formation.

Our results are consistent with a large body of literature demonstrating elevated BTMs in osteoporotic populations. For instance, a study by Al-Daghri et al. found significantly higher levels of P1NP and

CTX-I in postmenopausal women with osteoporosis compared to non-osteoporotic controls, corroborating our findings [10]. The stepwise increase from controls to osteopenia to osteoporosis observed in our study provides a clearer picture of how bone turnover intensifies as bone mass declines. This finding is clinically relevant because it suggests that BTMs could help identify individuals on a trajectory of rapid bone loss, even within the osteopenic category, who may be at higher risk for future fractures than their BMD alone would suggest [11].

The pathophysiology underlying these observations is the uncoupling of bone remodeling. In the postmenopausal state, estrogen deficiency leads to an increase in the production of cytokines like RANKL, which stimulates osteoclast activity and accelerates bone resorption [6]. While bone formation also increases in a compensatory attempt, it is insufficient to offset the heightened resorption, resulting in a net deficit of bone mass and structural integrity [12]. The elevated CTX-I levels in our osteoporotic group directly reflect this increased osteoclastic activity, while the elevated P1NP levels signify the corresponding, albeit inadequate, osteoblastic response.

The clinical implication of these findings is that BTMs can serve as a valuable adjunct to DXA scans. While DXA provides a crucial assessment of bone quantity, BTMs offer a dynamic view of bone quality and metabolic activity [7]. This dual assessment could be particularly useful in several clinical scenarios. Firstly, for patients with osteopenia, high BTM levels may flag them as "fast bone losers" who could benefit from earlier pharmacological intervention [13]. Secondly, in monitoring treatment, changes in BTMs occur much more rapidly than changes in BMD. A significant decrease in CTX-I within 3-6 months of initiating anti-resorptive therapy (e.g., bisphosphonates) can confirm treatment efficacy and patient adherence long before a follow-up DXA scan is warranted [14,15].

This study has several strengths, including the use of well-defined, distinct patient groups based on WHO criteria, the measurement of internationally recommended reference BTMs (P1NP and CTX-I), and the adherence to standardized pre-analytical procedures to minimize variability, such as collecting fasting morning samples. However, some limitations must be acknowledged. Firstly, the cross-sectional design does not allow for the establishment of causality or the assessment of BTMs as predictors of future fracture incidence. Longitudinal studies are required to confirm this relationship. Secondly, the study was conducted at a single center with a relatively modest sample size, which may limit the generalizability of our findings to other populations. Finally, we did not assess other factors that influence bone health, such as vitamin D status, calcium intake, or physical activity levels, which could be confounding variables.

Future research should focus on establishing specific BTM cutoff values that can be used for clinical decision-making and incorporating BTMs into fracture risk assessment algorithms like FRAX. Longitudinal studies correlating baseline BTM levels with fracture outcomes are essential to validate their prognostic utility.

Conclusion

In conclusion, this study demonstrates that serum levels of the bone formation marker P1NP and the bone resorption marker CTX-I are significantly elevated in postmenopausal women with osteoporosis and osteopenia compared to healthy controls. The progressive increase in marker levels with declining bone mineral density highlights the state of high bone turnover that characterizes this disease. These findings reinforce the potential of BTMs not as a replacement for DXA, but as a complementary tool to enhance the diagnosis, risk stratification, and therapeutic monitoring of patients with osteoporosis, ultimately facilitating a more personalized approach to patient care.

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