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Research Article

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Study of Procollagen Type 1 N-terminal Propeptide as a Biomarker of Bone Health in Postmenopausal Women of Uttarakhand

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ABSTRACT

Background: An estimated 200 million people worldwide have osteoporosis, which causes 8.9 million fractures. Menopausal estrogen insufficiency promotes bone resorption. Bone mineral density (BMD) is measured by DXA, which does not detect skeletal activity. Bone turnover markers (BTMs) like PINP improve prognosis and therapy monitoring. Due to its stability and sensitivity, the IOF/IFCC recommends using the PINP test to evaluate bone development.

Methods: This observational study was conducted in the Department of Biochemistry, Govt Doon Medical College & Hospital, in collaboration with the Orthopaedics department, Govt Doon Medical College & Hospital. A total of 172 postmenopausal women from Uttrakhand were included in this study, and the duration was 24 months to evaluate P1NP, osteocalcin, and BMD levels. The women were without menstruation and >40 UI/L FSH. P1NP blood samples were collected within a two-week timeframe after DXA testing. Dual-energy X-ray absorptiometry (DXA) was used to assess BMD at different locations. Results suggested bone turnover indicators might be used clinically alongside BMD.

Results: Quarterlies of postmenopausal serum P1NP concentrations: 38.1 to 54.0 ng/mL in the 1st quartile, 30.2 to 54.1 in the 4th. Negative s-P1NP-BMD normalized correlation coefficients at various sites. Comparison of P1NP levels in postmenopausal women with osteoporosis and healthy controls, categorized by demographic factors. Compare s-P1NP levels across BMD quartiles and study and control groups. Sensitivity analysis compares P1NP levels across groups and conditions.

Conclusion: The study has concluded that increased s-P1NP concentrations are associated with reduced BMD.

Key-words: Bone mineral density, P1NP, BTMs, s-P1NP, DXA, Postmenopausal women

INTRODUCTION

Osteoporosis, a prevalent worldwide ailment, is characterized by a decline in BMD, which increases the brittleness of the bone and causes fractures. Globally, an estimated 200 million individuals are impacted by osteoporosis, leading to about 8.9 million fractures caused by the fragility of bones. Screening for osteoporosis in females sixty years of age and above is advised because of the substantial morbidity and mortality associated with this condition. The global rise in life expectancy, along with the rising prevalence of osteoporosis, has rendered it a significant health concern [1,2].

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Oestrogen deficiency disrupts the normal bone turnover cycle during menopause. The observed phenomenon could be attributed to oestrogen receptors in multinucleated osteoclasts and osteoclast progenitor cells. An increase in osteoclastic resorption activity has been noted, accompanied by a decrease in osteoblastic activity. Consequently, the quantity of bone that has been resorbed is greater than the amount implanted, leading to a net decrease in bone mass. The observed rise in total bone resorption can be attributed to a diminished inhibitory impact resulting from the decreased availability of oestrogen, which affects osteoclastogenesis and osteoclast activity [3].

BMD is mainly assessed by dual-energy X-ray absorptiometry (DXA) to determine the osteoporotic state, the risk for fragility fractures, and the treatment of osteoporosis following menopause. DXA-based BMD provides a set evaluation of bone health: a momentary glimpse into the combined impact of various factors on the evaluated skeletal location over time [3]. However, it does not provide a skeletal activity dynamic estimate, which might offer an understanding of potential future changes in the skeleton. Bone is an organ that exhibits dynamic and metabolic activity, undergoing two ongoing processes: resorption and formation. These activities are together referred to as remodeling or turnover of bone. BMD changes become apparent later on DEXA, where they are largely unchangeable [4].

The dynamic nature of bone results in the continuous release of bone turnover biomarkers into the bloodstream, which offer dynamic information about bone status. The release of circulating bone turnover markers (BTMs) during the remodeling process might be helpful in the treatment of osteoporosis following menopause. These markers offer dynamic information about the skeletal status, which is distinct from and often complements measurements of BMD. Creation and absorption are typically closely interconnected in terms of space and time. Consequently, any marker indicating this connection appropriately represents the total bone turnover [5,6].

Bone turnover markers encompass two categories: bone formation markers, such as the Bone alkaline phosphatase (B-ALP) and procollagen type I N-terminal propeptide (PINP), and indicators of bone resorption, such as type I collagen carboxy-terminally cross-linked telopeptides and type I collagen amino-terminally cross-linked telopeptides (NTX) [7].

These biomarkers indicate that initial alterations in BMD can be replicated at frequent intervals. They can be advantageous for evaluating the prognosis of osteoporosis, particularly in determining the duration of drug breaks during bisphosphonate therapy. Moreover, they offer enhanced accessibility for bedridden patients suffering from terminal illnesses. Due to biological and analytical variability, it is necessary to evaluate their diagnostic accuracy [6,7].

Fibroblasts and osteoblasts are responsible for the synthesis of procollagen type 1. While turning procollagen into collagen, some proteases remove the N- and C-terminal extension of procollagen type 1 [8]. The bone matrix is subsequently conjugated with procollagen type 1, which consists of P1CP and P1NP. P1NP, a biomarker for bone development, is a unique sign of the deposition of type 1 collagen. The release of P1NP occurs in the interior of cells throughout the process of type 1 collagen synthesis and is found in the bloodstream. The release of P1NP typically occurs in a trimeric structure that originates from the structure of trimeric collagen. Subsequently, it undergoes rapid transformation into a monomeric form due to the influence of thermal degradation effects [9].

Serum P1NP has emerged as a potentially valuable biomarker for assessing bone formation in osteoporosis. The monitoring of serum P1NP is clinically significant due to its relatively low sensitivity to changes in meal intake and circadian rhythm variability. Furthermore, under typical ambient conditions, it exhibits a reasonable level of stability. The International Osteoporosis Foundation (IOF) & the International Federation of Clinical Chemistry (IFCC) suggest PINP as the ideal biomarker for bone development after publishing an extensive examination of bone morphology markers (BTMs). P1NP antibodies are used to detect P1NP's trimeric structure through enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay techniques [9,10].

MATERIALS AND METHODS

Research Design- This cross-sectional study was conducted among postmenopausal women referred by their primary care provider for osteoporosis screening at our hospital in Uttrakhand. This study was conducted from Jan 2022 to Dec 2023.

Postmenopausal women with osteoporosis often require BMD as the primary modality of investigation, but many cases may be missed. Measurements of these Bone turnover markers in the blood, such as Procollagen type 1 N-propeptide (PINP) and Osteocalcin, may provide clinically helpful aid to optimize the management of these patients. Postmenopause was defined as 18 months without menstruation and increased serum FSH (>40 UI/L). Predict P1NP and osteocalcin levels in postmenopausal women attending GDMC Dehradun Orthopaedics. To examine P1NP, osteocalcin, and BMD in these patients. Participants who self-reported diabetes, breast cancer, or endocrinopathies associated with secondary osteoporosis were suspected after laboratory tests. To determine P1NP, osteocalcin, and BMD correlation in postmenopausal women. These indicators provided clinically valuable skeletal state information independent of and even additive to BMD assessment. This study was divided into two groups: the study and control groups. The study group included 172 postmenopausal women up to 60 with menopause lasting at least 1 year. The control group included 172 sample calculations and used a two-sided test at a 5% significance level (a=0.05) and 80% power (B=0.2) and (r=-0.116).

Anthropometric measurements- Height and weight were taken in indoor clothes, and no shoes were used. Using a wall-mounted stadiometer, height was measured to 0.5 cm. The seca digital scale measured weight to the closest 0.1 kg. The BMI formula was weight (kg) divided by height (m). BMI values of 19-25 kg/m^2 were deemed normal, while BMI ≥25 kg/m^2 and ≥30 kg/m^2 were termed overweight and obese, respectively.

P1NP measurement- Blood samples were taken within two weeks of bone mineral density testing. The tube was immediately placed on ice and cooled until serum separation for P1NP measurement. This test detects monometric and trimetric P1NP. This approach refers to P1NP levels to 16.27-73.87 ng/mL.

DXA measurement- The hospital's Clinics for Radiology assessed bone mineral density using Hologic QDR 4500 DXA. BMC and areal BMD (g/cm^2) are transformed into T- and Z-scores. The L1–L4 lumbar spine, whole hip, femoral neck, trochanter, and intertrochanteric shaft bone mineral density was assessed. Hip measurements were usually taken on the left unless the hip was broken or replaced. Precision coefficients of variation for hip and lumbar spine are 1% and neck and trochanter 2.5%.

Statistical Analysis- Statistical analysis was done by using SPSS 27. A T-test was applied to test the significance of the two groups. The Spearman or Pearsons test was applied for correlation testing to compare subgroup P1NP levels. At p<0.05, differences were deemed significant. The sensitivity, specificity, and positive and negative predictive values of P1NP were computed with multiple cut-off levels. We controlled age, BMI, and years after menopause in multiple regression analyses of P1NP and BMD.

Ethical Consideration- Our hospital approved this study, and informed consent was obtained from each subject.

RESULTS

Table 1 shows quartile postmenopausal serum procollagen type 1 N-terminal propeptide (s-P1NP) concentrations. Every quartile represents a portion of the dataset, starting with the lowest 25%, then the next 25%, etc. The minimum and maximum s-P1NP concentrations in each quartile are shown. The 1st quartile is 38.1 to 54.0 ng/mL, the 2nd 40.1 to 59.8 ng/mL, the 3rd 29.8 to 39.8 ng/mL, and the 4th 30.2 to 54.1 ng/mL. This breakdown reveals the postmenopausal cohort's s-P1NP concentration distribution.

Table 1: s-P1NP concentration in postmenopausal

	1st quartile	2nd quartile	3rd quartile	4th quartile
P1NP(ng/mL)	38.1-54.0	40.1-59.8	29.8-39.8	30.2-54.1

P1NP (Procollagen type 1 N-terminal propeptide)

Serum procollagen type 1 N-terminal propeptide (s-P1NP) and BMD at the femoral neck, whole hip, and lumbar spine are correlated in Table 2. These coefficients show the intensity and direction of the linear association between s-P1NP and BMD. The negative data suggest that increased s-P1NP concentrations reduce BMD. Standardized coefficients enable comparisons of correlation strength and BMD measurement. S-P1NP and lumbar spine BMD have a moderate to severe negative connection, with adjusted and unadjusted correlation coefficients ranging from -0.22 to -0.24. Both adjusted and uncorrected coefficients range from -0.16 to -0.239 for femoral neck and total hip BMD, showing a negative connection between s-P1NP levels and BMD.

Table 2: Standardized correlation coefficients between s-P1NP and BMD

	Femoral neck BMD		**Total hip BMD**		**Lumbar spine BMD**	
	Not adjusted	Adjusted	Not adjusted	Adjusted	Not adjusted	Adjusted
s-P1NP	-0.201**	-0.16*	-0.22**	-0.205**	-0.239**	-0.24

Femoral neck BMD (Bone Mineral Density); Total hip BMD (Bone Mineral Density); Lumbar spine BMD (Bone Mineral Density); s-P1NP (Procollagen type 1 N-terminal propeptide)

Table 3 compares serum procollagen type 1 N-terminal propeptide (P1NP) levels in postmenopausal women with osteoporosis (study group, N=172) and healthy controls (control group, N=172) across demographic and clinical categories. The table groups participants by BMI (<25, 25-30, ≥30 kg/m²), age (≤55, 56-63, ≥64 years), and years since menopause (≤10, 11-20, ≥20 years) and provides median P1NP levels with interquartile ranges. The study found higher P1NP levels in persons with BMI ≥30 kg/m² than those with BMI <25 and 25-30 kg/m², suggesting a link between obesity and accelerated bone turnover. In the study, younger postmenopausal women (≤55 years) had higher P1NP levels than older age groups (56-63 and ≥64 years), suggesting an age-related impact on bone turnover. A study found that those ≤10 years since menopause had increased P1NP levels compared to those with longer durations, suggesting that menopausal length may impact bone metabolism. The table shows that postmenopausal women with osteoporosis and healthy controls have varied P1NP levels throughout age, BMI, and menopausal length, suggesting complicated interactions between these variables and bone metabolism.

Table 3: Postmenopausal women with osteoporosis and healthy controls had varied P1NP levels by age, BMI, and years since menopause

Parameters	**Study group (N=172)**	**Control group (N=172)**
BMI (kg/m²)		
<25	49.4(39.2-60.1)	48.2 (37.9-58.6)
25-30	44.5(35.2-56.1)	45.2 (37.3-59.7)
≥ 30	55.2(39.6-59.1)	54.8 (39.5-61.2)
Age (yr)		
≤55	49.1(39.6-70.2)	50.5 (42.3-70.2)
56-63	52.4(35.7-59.8)	54.8 (36.2-59.2)
≥ 64	45.8(30.2-54.2)	47.2 (29.8-49.2)
Years since menopause		
≤ 10	56.2(45.8-69.2)	54.2 (44.2-55.2)*
11-20	41.2(36.2-54.2)	41.5(29.5-44.7)
≥ 20	50.2(23.2-59.2)	48.2(6.88-59.2)*

Fig. 1 may show serum procollagen type 1 N-terminal propeptide (s-P1NP) concentration throughout BMD quartiles at the lumbar spine, whole hip, and femoral neck. Quarter 1 has the lowest BMD levels, and quartile 4 has the highest. The picture compares s-P1NP concentrations within each quartile across the three skeletal sites to examine the association between bone turnover markers and bone density. It may show how s-P1NP concentrations change when BMD grows or declines across quartiles, revealing bone metabolism and turnover rates at distinct anatomical regions. This comparison helps measure bone health and osteoporosis risk by understanding the relationship between bone density and turnover markers.

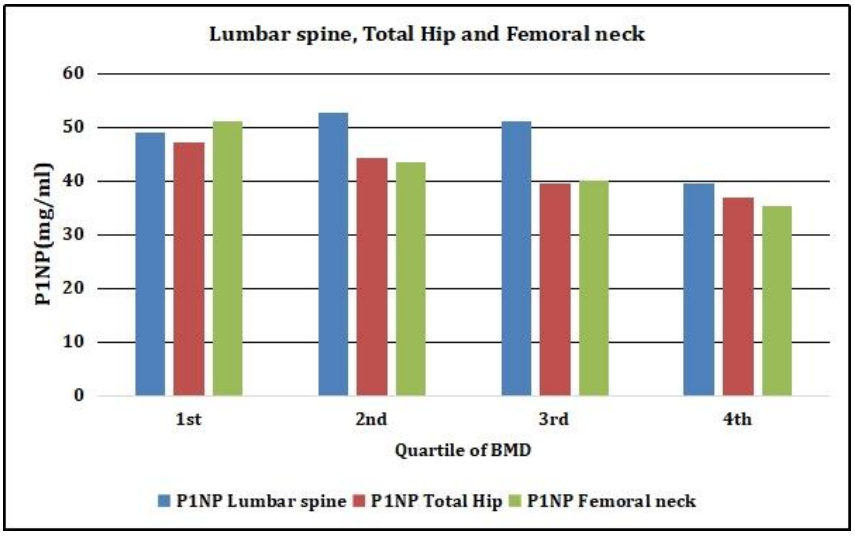

Fig. 1: s-P1NP concentration in lmbar spine, whole hip, and femoral neck quartiles.

Fig. 2 shows the study and control groups' serum procollagen type 1 N-terminal propeptide (s-P1NP) concentrations in quartiles over the lumbar spine, entire hip, and femoral neck. The dataset's lowest 25% is in quartile 1, the next 25% in quartile 2, and so on. The figure may compare s-P1NP concentrations between the study and control groups at various skeletal locations. It may reveal how s-P1NP concentrations fluctuate within each quartile across skeletal sites, revealing how bone turnover markers affect bone health at specific anatomical places. Comparing the study and control groups' s-P1NP concentrations across quartiles can help explain bone metabolism and osteoporosis in the study population.

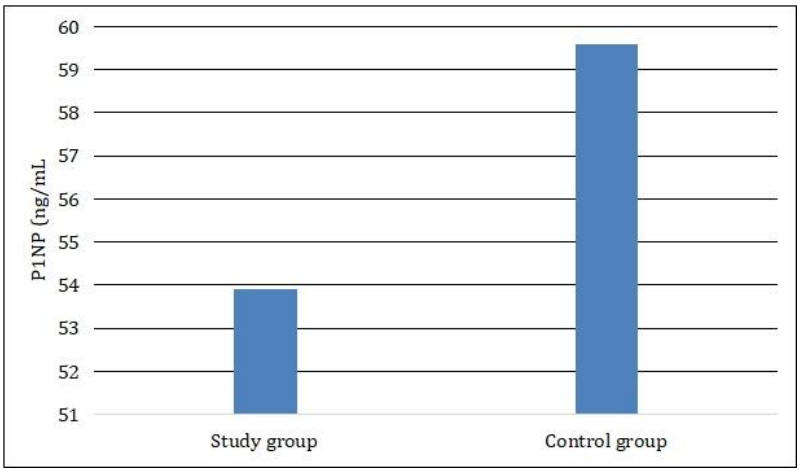

Fig. 2: Study and control group postmenopausal women's serum P1NP levels

Fig. 3 may show the sensitivity analysis of serum procollagen type 1 N-terminal propeptide (P1NP) levels in postmenopausal women compared to the control group. Sensitivity analysis examines how changes in one variable (sensitivity) affect P1NP levels while holding other factors constant. The sensitivity values (1 to 0)

represent different scenarios or conditions, and the research and control groups' P1NP levels show how these vary. At a sensitivity value of 1, P1NP levels in the study group are 0, while in the control group, they are 0.0011. This comparison shows the research and control groups' varied effects on P1NP levels under different sensitivity values. This investigation shows the biomarker's robustness in postmenopausal women across multiple circumstances, revealing its clinical reliability and prognostic utility."

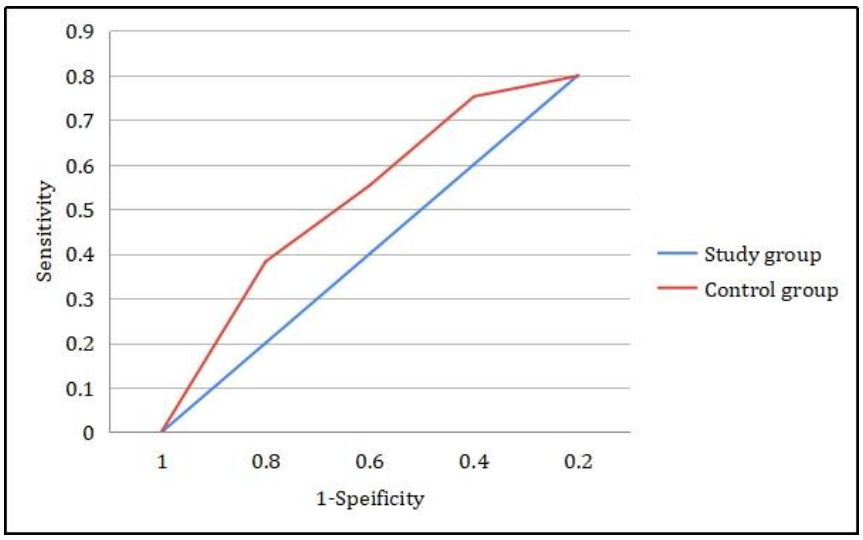

Fig. 3: Postmenopausal women with osteoporosis and healthy controls

DISCUSSION

Teriparatide, a bone anabolic drug, may be necessary for postmenopausal women suffering from severe osteoporosis. Although alterations in BMD can indicate a reply, it is crucial to remember that observing measurable changes in BMD typically necessitates a minimum of one year. The biochemical indicators of bone turnover undergo alterations within 1 to 3 months following the start of osteoporosis therapy. Keeping an eye on the amounts of PINP, a procollagen type I N propeptide protein derived from osteoblasts, during the treatment with teriparatide can offer valuable clinical insights for treating individuals who have osteoporosis. The observation of PINP has the potential to offer additional information to BMD monitoring, thereby serving as a useful instrument for treating people with anabolic osteoporosis treatment. This is analogous to the utility of biological indicators of bone resorption for tracking antiresorptive medication [11].

A research investigation was undertaken to assess the accuracy of P1NP's diagnosis when considering osteoporosis and osteopenia. The research findings indicate that P1NP can be a trustworthy diagnostic biomarker in detecting postmenopausal spinal osteoporosis [12].

Biochemical indicators of bone turnover have the potential to offer prognostic insights into the likelihood of fractures. They could be valuable in assessing the effectiveness of antiresorptive and anabolic treatments in individuals with osteoporosis. An empirical investigation was undertaken using a fully automated test to assess the efficacy of detecting total serum N-terminal propeptide for type I collagen (P1NP), a marker of bone development. The automated assay for total serum P1NP demonstrates a high level of precision and sensitivity, enabling the detection of changes that surpass the lower serum concentration (LSC) in a considerable percentage of postmenopausal women after a three-month course of therapy regimen involving PTH 1-84 or alendronate. Due to its convenient nature and efficient processing capabilities, this bone formation marker exhibits potential utility in surveilling individuals who have osteoporosis [13].

A research investigation was undertaken to ascertain the reference ranges for Thai women's blood levels of Procollagen type I N-propeptide (PINP), an essential marker of bone development between the ages of 40 and 70. The study examined the levels of PINP in Thai women of all ages and phases of their menstrual cycles. PINP average in the postmenopausal women cohort exhibited a greater magnitude than the premenopausal

cohort, substantiating the notion that postmenopausal women experience a higher rate of bone turnover [14].

The research aimed to determine reference intervals for P1NP levels in postmenopausal females who were either healthy or osteoporotic. The study aimed to stratify the participants based on body mass index, age, and menopause length. The study additionally sought to assess the relationship between BMD and P1NP. It demonstrated a negative correlation between P1NP and BMD, even when accounting for years since menopause, age, and BMI. Although postmenopausal women with osteoporosis had much higher P1NP levels than postmenopausal women with intact bone density, the test's low specificity makes it ineffective for diagnosing osteoporosis [15].

A research investigation evaluated the relationship between postmenopausal women's bone mineral density and P1NP undergoing teriparatide treatment. P1NP levels may indicate the risk of osteoporosis, but they are not associated with bone strength. P1NP levels should be routinely monitored at baseline and every three months during osteoporosis therapy, as these changes may provide insight into the following BMD response. In addition, monitoring serum levels during treatment can potentially enhance medication adherence [16].

CONCLUSIONS

A study concluded a negative connection between s-P1NP levels and BMD in multiple skeletal locations, suggesting that higher levels lower BMD. P1NP is reliable as a biomarker in several situations, highlighting its clinical relevance. S-P1NP concentrations and BMD in postmenopausal women highlight the complex link between bone turnover and health. Quartile distribution of s-P1NP concentrations shows bone metabolism changes, whereas negative correlations with BMD show higher levels affect bone density. Age, BMI, and postmenopausal duration affect P1NP levels, which may indicate fast bone turnover and osteoporosis risk. This work highlights the association between s-P1NP concentrations and BMD in postmenopausal women from Uttarakhand, however, the molecular routes linking P1NP to bone turnover in this group are unknown. Further research could examine the molecular pathways linking P1NP to bone metabolism and osteoporosis risk in postmenopausal women. Longitudinal studies recording P1NP levels and bone health outcomes may reveal disease development and advise preventative and therapeutic actions.

CONTRIBUTION OF AUTHORS

Research concept- Anil Joshi, Sunita D Singh, Indira Yadav

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Supervision- Anil Joshi, Sunita D Singh, Indira Yadav

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Data collection- Sunita D Singh, Chandra Shekhar

Data analysis and Interpretation- Devanshi Singh, Indira Yadav

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Critical review- Anil Joshi, Chandra Shekhar

Article editing- Sunita D Singh, Indira Yadav, Chandra Shekhar

Final approval- Anil Joshi

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