



Original Article

Association of Serum P1NP and β -CTX-I with Calcaneal Quantitative Ultrasound Parameters in Postmenopausal Women

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ABSTRACT

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Background: Bone turnover markers reflect skeletal remodelling, whereas calcaneal quantitative ultrasound (QUS) assesses heel skeletal status. This study examined serum procollagen type I N-terminal propeptide (P1NP) and beta-isomerised C-terminal telopeptide of type I collagen (β -CTX-I) in relation to calcaneal QUS in Indian postmenopausal women.

Methods: A hospital-based analytical cross-sectional study included 170 naturally postmenopausal women aged 50–70 years. Device-derived QUS categories comprised Group I, QUS-normal (n=50); Group II, QUS-low (n=70); and Group III, QUS-markedly low (n=50). Serum markers and biochemical variables were assessed. Spearman correlation, adjusted linear regression and exploratory receiver operating characteristic (ROC) analyses examined marker–QUS relationships.

Results: Median P1NP concentrations were 40.8, 45.8 and 53.3 ng/mL across Groups I–III (p=0.004); corresponding β -CTX-I concentrations were 0.3185, 0.3693 and 0.5008 ng/mL (p<0.001). P1NP (ρ =−0.241, p=0.002) and β -CTX-I (ρ =−0.471, p<0.001) correlated inversely with QUS T-score. In the joint adjusted model, β -CTX-I remained associated with QUS T-score (β =−0.669 per doubling; p<0.001), whereas P1NP did not (p=0.370). Exploratory AUCs were 0.661 (95% CI 0.573–0.745) for P1NP and 0.785 (95% CI 0.708–0.857) for β -CTX-I. The combined-marker AUC was 0.801.

Conclusion: Higher marker concentrations were associated with poorer QUS-defined skeletal status, with a stronger observed association for β -CTX-I. These markers may provide complementary information but cannot establish osteoporosis. Central dual-energy X-ray absorptiometry (DXA) was not performed, and device-derived QUS categories are not equivalent to DXA diagnostic categories.

Keywords: Postmenopause; bone turnover markers; P1NP; β -CTX-I; quantitative ultrasound.

INTRODUCTION

Bone strength depends on bone quantity, matrix composition and skeletal architecture. Type I collagen and hydroxyapatite form its principal structural components, while coordinated osteoclast-mediated resorption and osteoblast-mediated formation maintain the skeleton through remodelling.¹ RANK/RANKL signaling regulates osteoclast activity,² and osteocytes respond to mechanical loading and help coordinate skeletal adaptation.³ After menopause, declining oestrogen increases remodeling, with resorption exceeding replacement and contributing to progressive bone loss.

Osteoporosis increases susceptibility to fragility fracture. Its densitometric classification uses a central DXA T-score of ≤ -2.5 at an accepted skeletal site.⁴ Age, previous fragility fracture, low body mass index, inactivity and secondary causes also influence clinical risk.⁵ DXA remains the reference investigation for densitometric assessment; device-derived heel

QUS T-scores cannot be substituted for central DXA diagnostic thresholds.⁶ Although widely used, DXA measures areal rather than volumetric density and access may be limited in some settings.⁷

Bone turnover markers (BTMs) describe current remodeling activity rather than accumulated bone mass.⁸ P1NP and β -CTX-I are recommended reference markers of formation and resorption, respectively.⁹ Their interpretation requires attention to sampling and storage.¹⁰ P1NP is released during collagen synthesis, and hepatic endothelial cells participate in propeptide clearance.¹¹ Its molecular forms influence assay behaviour,¹² so results from total and intact P1NP assays are not necessarily interchangeable.¹³ β -CTX-I reflects collagen degradation.¹⁴ Its circadian and feeding-related variation makes fasting morning collection particularly important.^{15,16}

Calcaneal QUS offers a portable, radiation-free assessment of ultrasound propagation through heel bone. Its measurements provide information on skeletal status but do not directly measure central bone mineral density. Studying BTMs alongside QUS may help characterise the relationship between active remodeling and peripheral skeletal measurements where DXA access is limited. This study assessed associations of serum P1NP and β -CTX-I with device-derived QUS categories and QUS T-score in postmenopausal women. Secondary objectives examined clinical and biochemical correlates and exploratory discrimination of markedly low QUS status.

METHODS

Study design and participants: This analytical cross-sectional study was conducted from 30 December 2024 to 30 December 2025 at JLN Medical College and Associated Group of Hospitals, Ajmer, jointly by the Departments of Physical Medicine and Rehabilitation (PMR), Orthopaedics and Biochemistry. Institutional Ethics Committee approval was obtained before recruitment (no. 10248-55/Acad-III/MCA/2024; 2 May 2024). Women attending PMR and Orthopaedics outpatient services were recruited using consecutive non-probability sampling. Laboratory analyses were performed in Biochemistry and the Multi-Disciplinary Research Unit. The sample included 170 women aged 50–70 years with natural menopause for at least 12 months. All provided written informed consent before enrolment and underwent technically satisfactory QUS assessment. A feasibility-based sample size reflected eligible participant availability and resources for clinical, QUS and biochemical assessment; no formal a priori sample-size calculation was performed.

Women with surgical menopause, secondary or other metabolic bone disease, significant endocrine, renal, hepatic, gastrointestinal, inflammatory, haematological or malignant disorders, Paget disease, malabsorption, prolonged immobilisation, or recent major/healing fracture were excluded. Additional exclusions were medications or therapeutic calcium/vitamin D supplementation affecting bone metabolism and excessive alcohol consumption. These restrictions reduced potential influences on marker concentrations but also limit applicability to women with comorbidities or ongoing treatment.

QUS assessment: The SONOST 3000 system (OsteoSys, Republic of Korea) measured calcaneal speed of sound and broadband ultrasound attenuation and generated a Bone Quality Index and T-score. Measurements followed the manufacturer-recommended procedure. Participants were classified as Group I, QUS-normal ($n=50$); Group II, QUS-low ($n=70$); or Group III, QUS-markedly low ($n=50$). These labels describe device-derived skeletal status and do not represent DXA-confirmed normality, osteopenia or osteoporosis.

Clinical assessment: A structured proforma recorded demographics, reproductive and medication histories, anthropometry and fracture-related factors. BMI was calculated as weight/height² (kg/m²). Previous fragility fracture meant spontaneous fracture or low-energy trauma equivalent to a fall from standing height or less. Recurrent falls meant at least two falls in the preceding year. Family history referred to osteoporosis or hip fracture in a first-degree relative. These histories were participant reported.

Low physical activity was defined in the study as not meeting 150 minutes/week of moderate-intensity activity or 75 minutes/week of vigorous-intensity activity, or an equivalent combination. Dietary calcium intake was estimated from reported frequency and usual portion size; intake <1000 mg/day was classified as low. Low sunlight exposure meant <30 minutes/day of direct exposure between 10:00 a.m. and 3:00 p.m. with the face, neck, arms or forearms exposed. These operational categories should be distinguished from validated measurements of habitual intake or vitamin D synthesis.

Laboratory assessment: Venous blood (approximately 5–10 mL) was collected after an overnight fast of at least eight hours between 7:30 and 10:00 a.m. Participants avoided strenuous activity for 24 hours and reported recent illness, fracture and medication use. Serum P1NP, β -CTX-I, 25-hydroxyvitamin D, total calcium, alkaline phosphatase and creatinine were analysed. P1NP and CTX-I were measured using GENLISA ELISA kits (KRISHGEN BioSystems; KBH3601, version 2.2, and KBH1352, version 1.1, respectively). The CTX-I result is termed β -CTX-I here as reported in the study dataset.

Blood was allowed to clot at room temperature for 10–20 minutes and centrifuged at 2000–3000 rpm for 20 minutes. Separated serum was analysed promptly or stored at -20°C . Grossly haemolysed samples were excluded, repeated freeze–thaw cycles were avoided, and results were accepted when quality-control values met predefined limits. The study's assay

description reports CTX-I absorbance measurement at 450 nm, a calibration range of 0.16–10 ng/mL and a quantification limit of 0.1 ng/mL. Manufacturer-reported intra-assay and inter-assay coefficients of variation were <15% and <18%, respectively. Standardised morning collection reduced, but could not eliminate, biological and pre-analytical variability.

Statistical analysis: Data were entered in Microsoft Excel and analysed with IBM SPSS Statistics 25.0. Continuous variables were summarised as mean $\pm$ SD or median (interquartile range) according to distribution, assessed by the Shapiro–Wilk test. One-way ANOVA or Kruskal–Wallis tests compared groups; categorical comparisons used chi-square or Fisher’s exact tests. Significant overall comparisons were followed by Bonferroni-adjusted pairwise tests. Spearman correlations assessed marker relationships; secondary correlations were exploratory and unadjusted for multiplicity.

Linear regression assessed marker associations with QUS T-score, adjusting for age, BMI, vitamin D, serum calcium, low physical activity, low dietary calcium and previous fragility fracture. P1NP was analysed per 10 ng/mL and β -CTX-I per doubling after $\log_2$ transformation. Separate and joint marker models were fitted. Because age and duration since menopause were strongly correlated, sensitivity analyses replaced age with menopausal duration. Exploratory ROC analyses compared Group III with Groups I/II combined. Cut-offs were not diagnostic thresholds. Two-sided $p < 0.05$ indicated statistical significance.

For interpretation, the primary skeletal outcome was the continuous device-derived QUS T-score. The categorical comparisons assessed whether marker concentrations differed across the three reported QUS groups, while ROC analysis assessed separation of the lowest-status category. These analyses address different questions: a continuous association may be present even when concentrations overlap across categories. Regression coefficients represent adjusted differences in QUS T-score for the specified marker increments, rather than probabilities of osteoporosis or fracture. The present analyses did not evaluate incident fracture outcomes or changes in markers during treatment.

RESULTS

The sample comprised 50, 70 and 50 women in Groups I–III. These hospital-based proportions do not estimate community prevalence. Mean age increased from 58.81 ± 4.24 to 60.14 ± 3.61 and 61.84 ± 4.27 years ($p = 0.001$; Table 1). Educational status, socioeconomic category and occupation showed no significant group differences ($p = 0.805$, 0.416 and 0.967 , respectively). Most participants were homemakers. Mean QUS T-scores were -0.39 ± 0.28 , -1.78 ± 0.33 and -3.03 ± 0.30 .

Table 1: Distribution by age

Age group	Group I (n=50)	Group II (n=70)	Group III (n=50)	Total, (n=170)
50–54 years	10 (20.0%)	4 (5.7%)	3 (6.0%)	17 (10.0%)
55–59 years	19 (38.0%)	33 (47.1%)	15 (30.0%)	67 (39.4%)
60–64 years	15 (30.0%)	22 (31.4%)	19 (38.0%)	56 (32.9%)
65–70 years	6 (12.0%)	11 (15.7%)	13 (26.0%)	30 (17.6%)
Mean age, years	58.81 ± 4.24	60.14 ± 3.61	61.84 ± 4.27	60.25 ± 4.14

Values are n (%) unless stated otherwise; group percentages use 50, 70 and 50 participants.

Duration since menopause increased across groups ($p = 0.002$). Vitamin D concentrations decreased ($p = 0.004$), whereas alkaline phosphatase increased ($p < 0.001$). Age at menopause, BMI, calcium and creatinine did not differ significantly (Table 2). Previous fragility fracture occurred in 0.0%, 4.3% and 12.0%; low activity in 36.0%, 45.7% and 62.0%; and low calcium intake in 40.0%, 52.9% and 66.0%. Family history, recurrent falls and low sunlight exposure did not differ significantly ($p = 0.177$, 0.079 and 0.460).

Table 2: Reproductive anthropometric and biochemical characteristics

Variable	Group I	Group II	Group III	p-value
Age at menopause, years	49.40 ± 2.45	49.43 ± 2.13	49.35 ± 2.02	0.977
Duration since menopause, years	9.41 ± 5.08	10.71 ± 3.81	12.50 ± 4.30	0.002
BMI, kg/m ²	24.43 ± 3.19	24.82 ± 2.80	24.38 ± 2.69	0.647
25-hydroxyvitamin D, ng/mL	22.74 ± 4.67	20.97 ± 4.42	19.70 ± 4.34	0.004
Serum calcium, mg/dL	9.27 ± 0.30	9.22 ± 0.36	9.13 ± 0.33	0.088
Alkaline phosphatase, U/L	84.35 ± 16.88	87.10 ± 14.45	98.76 ± 12.89	<0.001
Serum creatinine, mg/dL	0.79 ± 0.12	0.78 ± 0.10	0.78 ± 0.08	0.813

Values are mean $\pm$ SD. Group sizes: I=50, II=70, III=50.

Median P1NP and β -CTX-I increased across QUS categories (Table 3). Bonferroni-adjusted P1NP comparisons were significant for I versus III ($p=0.005$) and II versus III ($p=0.022$), but not I versus II ($p=1.000$). β -CTX-I differed for I versus III and II versus III (both $p<0.001$), but not I versus II ($p=0.289$).

Table 3: Serum marker concentrations by QUS category

Bone turnover marker	Group I	Group II	Group III	p-value
P1NP, ng/mL	40.8 (33.1–54.0)	45.8 (32.7–55.4)	53.3 (43.3–62.1)	0.004
β -CTX-I, ng/mL	0.3185 (0.2459–0.4259)	0.3693 (0.3018–0.4645)	0.5008 (0.4034–0.7082)	<0.001

Values are median (interquartile range). Group sizes: I=50, II=70, III=50.

Both markers correlated inversely with QUS T-score, more strongly for β -CTX-I (Table 4). P1NP correlated positively with menopausal duration and alkaline phosphatase. The markers correlated with each other ($\rho=0.315$, $p<0.001$). β -CTX-I also correlated with age ($\rho=0.240$, $p=0.002$), menopausal duration ($\rho=0.221$, $p=0.004$), alkaline phosphatase ($\rho=0.328$, $p<0.001$) and vitamin D ($\rho=-0.217$, $p=0.005$). Neither marker correlated significantly with BMI, calcium or creatinine.

Table 4: Spearman correlations with clinical biochemical and QUS variables

Variable	P1NP ρ	p-value	β -CTX-I ρ	p-value
Age	0.142	0.064	0.240	0.002
Duration since menopause	0.168	0.028	0.221	0.004
BMI	0.086	0.267	0.028	0.719
Vitamin D	-0.019	0.808	-0.217	0.005
Serum calcium	0.032	0.680	0.094	0.221
Alkaline phosphatase	0.394	<0.001	0.328	<0.001
Serum creatinine	-0.005	0.953	-0.109	0.157
Calcaneal QUS T-score	-0.241	0.002	-0.471	<0.001

ρ , Spearman correlation coefficient. Secondary correlation p-values are exploratory and unadjusted for multiple testing.

In exploratory ROC analysis, P1NP showed limited discrimination of QUS-markedly low skeletal status, with an AUC of 0.661 (95% CI 0.573–0.745). At an exploratory cut-off of 42.7 ng/mL, sensitivity was 80.0% and specificity was 50.0%. β -CTX-I showed better discrimination, with an AUC of 0.785 (95% CI 0.708–0.857); at a cut-off of 0.399 ng/mL, sensitivity was 80.0% and specificity was 63.3%. The combined P1NP and β -CTX-I model yielded the highest AUC of 0.801. In separate adjusted models, both markers were associated with lower QUS T-score. In the joint model, β -CTX-I remained associated, whereas P1NP was attenuated (Table 6). Replacing age with menopausal duration reportedly produced similar findings. Adjusted R^2 values were 0.164 for P1NP, 0.283 for β -CTX-I and 0.282 for the joint model.

Table 5: Exploratory discrimination of Group III from Groups I and II

Marker	AUC	95% CI	Exploratory cut-off	Sensitivity	Specificity
P1NP	0.661	0.573–0.745	42.7 ng/mL	80.0%	50.0%
β -CTX-I	0.785	0.708–0.857	0.399 ng/mL	80.0%	63.3%
Combined markers	0.801	Not reported	Not reported	Not reported	Not reported

AUC, area under the ROC curve; CI, confidence interval.

Table 6: Adjusted marker associations with QUS T-score

Model	Adjusted β	95% CI	p-value	Adjusted R^2
P1NP, per 10 ng/mL	-0.108	-0.203 to -0.014	0.024	0.164
β -CTX-I, per doubling	-0.703	-0.920 to -0.486	<0.001	0.283
Combined model: P1NP, per 10 ng/mL	-0.041	-0.131 to 0.049	0.37	0.282
Combined model: β -CTX-I, per doubling	-0.669	-0.898 to -0.439	<0.001	0.282

Models adjusted for age, BMI, vitamin D, calcium, low activity, low calcium intake and previous fragility fracture. β denotes regression coefficient.

DISCUSSION

Higher serum P1NP and β -CTX-I accompanied poorer QUS-defined skeletal status in this sample. β -CTX-I had the stronger observed inverse correlation and remained associated with QUS T-score when both markers entered the adjusted model. The results support a relationship between remodeling activity and heel skeletal measurements, but statistical association does not establish causation, future fracture risk or diagnostic accuracy for DXA-defined osteoporosis.

Age and menopausal duration increased across QUS groups. Li et al. reported relationships between calcaneal QUS and DXA measurements,¹⁷ but agreement across modalities cannot be inferred from group trends here. Sowers et al. described changes in resorption during the menopausal transition,¹⁸ while Garnero et al. related higher turnover to lower bone mass in late postmenopause.¹⁹ Those findings provide biological context; differences in study design, skeletal site and assays prevent direct comparison of absolute concentrations.

The formation and resorption markers were positively correlated, consistent with coupled remodeling. Nevertheless, significant differences between group medians do not establish reliable classification of individuals. Biver et al.'s systematic review found limited baseline diagnostic utility for BTMs.²⁰ Here, neither marker distinguished Groups I and II after pairwise adjustment, and P1NP lost significance in the joint regression model. This attenuation may reflect shared information between markers and should not be interpreted as evidence that formation is unimportant.

Lower vitamin D and higher alkaline phosphatase accompanied poorer QUS status. Although altered calcium–parathyroid hormone regulation could contribute, PTH was not measured systematically, so the mechanism remains uncertain. Total alkaline phosphatase is not specific to bone. Low activity and calcium intake were also more frequent in Group III. Aggarwal et al. identified exercise and dietary calcium as relevant factors in Indian peri- and postmenopausal women assessed by DXA.²¹ The direction of these findings is comparable, but differing populations and measurement methods preclude equivalence.

Previous fragility fracture was more frequent in Group III, but the numbers were small and fracture history was self-reported. Dobnig et al. examined ultrasound and biochemical markers prospectively in nursing-home patients.²² Their fracture-prediction setting differs substantially from this outpatient cross-sectional sample. Our data describe previous fracture history and cannot determine whether either marker or QUS measurement predicts subsequent fracture. Prospective follow-up would be needed to address that question.

QUS also requires cautious interpretation. Swinton et al. found limited validity of heel ultrasound relative to DXA in UK Biobank participants.²³ Consequently, the present categories describe device-derived heel measurements rather than densitometric diagnoses. Lorentzon et al. emphasised that BTMs cannot diagnose osteoporosis and require interpretation within the broader clinical assessment.²⁴ Combining turnover markers with QUS may describe complementary skeletal characteristics, but this study did not demonstrate that the combination improves clinical decisions or replaces central DXA. The ROC analyses showed limited discrimination for P1NP and greater numerical discrimination for β -CTX-I. However, their reference outcome was Group III QUS status, not confirmed osteoporosis. Both cut-offs were derived and assessed in the same sample, creating optimism in apparent performance. No external validation or formal comparison established superiority. These thresholds should therefore remain exploratory; a clinically useful test would need reproducible assays, independent validation and assessment against an appropriate reference outcome.

The hospital-based sample is susceptible to referral, selection and spectrum bias. Women attending musculoskeletal clinics may differ from asymptomatic community participants, and the group proportions cannot estimate population prevalence. The cross-sectional design prevents temporal inference. Excluding women with comorbidities or bone-active treatment restricts generalisability. Residual confounding remains possible despite adjustment, particularly because diet, activity, falls and fracture history were participant reported.

Other limitations include absent central DXA, single-time-point sampling and exploratory secondary testing without multiplicity correction. Marker concentrations also depend on analytical specificity and biological variation. Future studies should specify assay targets and device-specific classification rules, include central DXA and prospective fracture outcomes, and validate any cut-offs in an independent population before considering clinical application. The feasibility-based sample was not supported by an a priori sample-size calculation, so adequacy for the secondary analyses and adjusted models was not established prospectively.

The distinction between statistical significance and clinical usefulness is especially relevant to these findings. A small p-value indicates that an observed group difference is unlikely under the tested null hypothesis; it does not show that a marker has sufficient sensitivity, specificity or reproducibility for clinical classification. Likewise, adjustment for measured covariates does not remove selection bias or establish that elevated turnover preceded deterioration in QUS status. The

joint model suggests that β -CTX-I retained information about QUS T-score beyond PINP and the listed covariates, but the model has not been validated in another sample.

A further consideration is the anatomical difference between the calcaneus and the central skeletal sites commonly assessed by DXA. Heel ultrasound captures peripheral acoustic properties, whereas serum markers reflect turnover across the skeleton. An association between them is therefore plausible without close correspondence to hip or spine density. The study did not analyse marker relationships with speed of sound, broadband attenuation or Bone Quality Index separately, so its findings should be confined to the reported T-score and category analyses rather than generalised to every QUS parameter.

Replication should also examine the full distribution of marker concentrations rather than relying on group medians alone. Assay-specific reference intervals and repeated measurements would help distinguish between measurement variability and differences in skeletal turnover. Reporting recruitment and classification procedures in detail would allow readers to judge whether the observed separation reflects the broader outpatient population or the particular mix of QUS categories enrolled in this study.

CONCLUSION

PINP and β -CTX-I were higher in women with poorer calcaneal QUS-defined skeletal status and correlated inversely with QUS T-score. β -CTX-I showed the stronger observed association and remained significant in the joint adjusted model. These findings concern skeletal turnover and device-derived QUS status; they do not establish osteoporosis or validate a diagnostic threshold. The markers may offer complementary information alongside clinical assessment, with central DXA used when diagnostic classification is required.

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Ethics and consent: The Institutional Ethics Committee, JLN Medical College, Ajmer, approved the study (approval no. 10248-55/Acad-III/MCA/2024, dated 2 May 2024). Written informed consent was obtained from all participants before enrolment.

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Conflict of interest: The authors report no conflicts of interest.

Data availability: Deidentified survey data are available from the corresponding author on reasonable request, subject to institutional approval and protection of participant confidentiality.

Use of artificial intelligence: ChatGPT assisted with language revision, and reference formatting. Authors confirmed responsibility for the final manuscript.

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