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POPULATION-BASED REFERENCE INTERVALS FOR BONE TURNOVER MARKERS IN BLACK AFRICAN ADULTS AND INITIAL ASSESSMENT OF THE BONE BALANCE INDEX

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Abstract

Background: Bone turnover markers (BTMs) are increasingly used to assess bone remodeling and to monitor osteoporosis treatment. However, reference intervals remain largely undefined for African populations, limiting their clinical utility in these settings.

Methods: We established reference intervals for intact procollagen type I N-propeptide (iPINP) and C-terminal telopeptide of type I collagen (β-CTX-I) in a rigorously selected cohort of healthy adult Black African blood donors from Côte d'Ivoire. Participants were screened for factors affecting bone metabolism, including kidney function, vitamin D status, and infectious diseases. Serum samples were processed under standardized conditions and analyzed using the IDS iSYS platform. Reference intervals were determined according to the CLSI C28-A3 guideline using the bootstrap non-parametric method, complemented by a Box-Cox transformation to verify robustness. The Bone Balance Index (BBI), defined as the standardized difference between observed and expected β-CTX-I based on IPINP, was also explored in women >45 years.

Results: In men (*n* = 90), β-CTX-I concentrations showed reference interval of 181–610 ng/L (90 % CI: 168–196 / 480–745), and in women ≤45 years (*n* = 86), 167–378 ng/L (90 % CI: 166–166 / 343–413). For iPINP, the corresponding reference intervals were 30–169 µg/L (90 % CI: 19–41 / 151–187) in men and 28–142 µg/L (90 % CI: 24–33 / 107–176) in women ≤45 years. Box–Cox–based intervals were comparable, confirming the robustness of the bootstrap results. Compared to published data in non-African populations, β-CTX-I values were generally lower, while iPINP values, particularly in men, tended to be higher. Among 27 women > 45 years, BBI values ranged from − 1.36 to +8.59, with a median of 0.13; 20 (74 %) showed BBI > 0, suggesting a predominance of resorption, while 2 (7 %) had BBI < − 1.

Conclusions: This study provides the first rigorously derived reference intervals for β-CTX-I and iPINP in a sub-Saharan African population, enabling more accurate interpretation of BTMs in African clinical contexts. The BBI may further help characterize bone remodeling balance at the individual level, though its clinical significance warrants further study.

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Keywords

Reference intervals, Bone turnover markers, β-CTX-I, Intact PINP, Bone Balance Index, Sub-Saharan Africa, Côte d'Ivoire, Osteoporosis

1. Introduction

Osteoporosis, a systemic skeletal disorder characterized by reduced bone mass and microarchitectural deterioration, is a growing global public health concern [1,2]. Traditionally perceived as a disease predominantly affecting populations of European and Asian descent [3,4], osteoporosis is now increasingly recognized as a significant health challenge in Sub-Saharan Africa as well [5,6]. This shift in understanding is largely driven by demographic changes, including an aging population and urbanization, which together contribute to evolving risk profiles and changing patterns of bone health across the continent. Historically, it was believed that individuals of African ancestry were relatively protected against osteoporosis due to higher bone mineral density (BMD) and lower fracture incidence [7]. However, recent epidemiological data and fracture trends suggest a rising burden of osteoporosis and fragility fractures in African populations, challenging these long-held assumptions [8–10]. This emerging reality is compounded by limited access to diagnostic tools such as dual-energy X-ray absorptiometry (DEXA), restricted availability of advanced osteoporosis treatments, and a scarcity of trained specialists in bone health [11]. Collectively, these factors create substantial barriers to optimal osteoporosis care in Sub-Saharan Africa. In this context, bone turnover markers (BTMs) have gained prominence as valuable tools in the assessment and management of osteoporosis [12]. BTMs provide dynamic insights into bone remodeling processes, offering potential advantages over BMD measurements alone [13]. They are increasingly recognized for their role in predicting fracture risk, monitoring therapeutic efficacy, and guiding treatment decisions [14–16]. However, the interpretation of BTMs requires robust reference intervals derived from well-characterized populations [17]. To date, no studies have established reference intervals for BTMs in healthy Sub-Saharan African populations, a critical gap that hampers the clinical utility of these markers in the region [18].

In this study, conducted in Abidjan, Côte d'Ivoire, we address this gap by proposing, for the first time, reference intervals for key bone turnover markers in a healthy West African population. This work aims to provide a foundation for the integration of BTMs into osteoporosis care in Sub-Saharan Africa, contributing to more accurate diagnosis, risk stratification, and treatment monitoring for this increasingly prevalent disease [19]. In addition, we aimed to derive a population-specific coupling equation between iPINP and β-CTX-I, allowing the calculation of the Bone Balance Index (BBI) in postmenopausal women, a tool that allows the estimation of net bone formation relative to resorption [20], which has never been applied to African populations to date.

2. Materials and methods

The cohort consisted of healthy adult blood donors, recruited from the Centre National de Transfusion Sanguine in Abidjan. All participants provided informed consent prior to participation. The study was

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approved by the National Committee for Ethics and Research of the Ministry of Health of the Republic of Ivory Coast under the reference 072/MSHP/CNER-kp.

Participants were screened to exclude conditions known to influence bone metabolism, including hypertension, diabetes, liver disease, chronic kidney disease, and HIV or hepatitis B/C infections [21]. Blood samples were collected after an overnight fast and processed within 1.5 h by centrifugation. Serum and plasma aliquots were stored at − 80 °C in Abidjan and subsequently transported under temperature-controlled conditions by a specialized transporter to the Clinical Chemistry Department of the University Hospital of Liège, Belgium.

All analyses were performed using validated methods [22]. Bone turnover markers were measured on the IDS iSYS automated platform (Immunodiagnostic Systems, Boldon, UK), including intact procollagen type I N-propeptide (iPINP) and β-isomerized C-terminal telopeptide of type I collagen (β-CTX-I). Parathyroid hormone (PTH) and 25-hydroxyvitamin D (25-(OH)D) were measured using the Fujirebio Lumipulse G1200; all the tests are ISO 15189 accredited; serum calcium, phosphate, and creatinine were assessed in Abidjan with the Roche cobas analyzer (Mannheim, Germany). The integrity of the samples was maintained throughout, with all samples stored at − 80 °C and measured within one month of shipment to ensure preanalytical stability. Quality controls and calibrations were performed in accordance with manufacturers' instructions, and all assays demonstrated acceptable precision (CV <5 %). This study is an ancillary analysis of a previously published trial [23].

In 2024, IDS introduced a recalibration of its β-CTX-I assay to align with the Roche Elecsys method. All β-CTX-I concentrations reported in this study were recalibrated accordingly, using the manufacturer- provided equation: $CTX\,(recalibrated) = 141.6 + 0.8127\,CTX(measured)$.

These recalibrated values were used consistently for both reference interval estimation and further analyses, including the calculation of the BBI, which assesses the coupling between bone formation and resorption. The BBI is defined as the standardized difference between the observed β-CTX-I concentration and the expected β-CTX-I value derived from the individual's iPINP level [20]. $BBI = \frac{CTX\ observed - CTX\ expected}{SD\ of\ residuals\ from\ the\ regression}$

Expected β-CTX-I concentrations were estimated using a linear regression model established in the reference population (healthy women aged ≤ 45 years), with iPINP as the independent variable

CTX expected = a + b × PINP

where a and b are the intercept and slope of the model, respectively. The standard deviation of the residuals from the regression model was used for normalization.

All statistical analyses followed the CLSI C28-A3 guideline. Reference intervals were determined using both a bootstrap non-parametric approach (10,000 iterations) and a parametric Box-Cox transformation to confirm robustness. The Box-Cox procedure was applied to normalize skewed data before calculation of parametric limits (mean ± 1.96 X SD) on the transformed scale, followed by back-transformation to the original units. Consistency between both approaches was verified and differences were reported when relevant. Analyses were performed using MedCalc software (MedCalc Software Ltd., Ostend, Belgium) and Microsoft Excel (for Box-Cox computations). Distributional characteristics of bone turnover markers were assessed using visual inspection (histograms and Q–Q plots) and the Shapiro-Wilk test for normality. Skewness and kurtosis coefficients were reported when relevant. Outliers were identified using the Tukey method, defining "far-out" values as those exceeding three times the interquartile range (IQR). In accordance with CLSI C28-A3,

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flagged values were not excluded automatically but were individually reviewed. Exclusion was applied only when justified by a clear analytical or clinical anomaly (e.g., suspected assay interference).

3. Results

In the subgroup of healthy male participants (n = 90), the mean age was 36.3 ± 10.4 years (range: 20–71). Baseline biochemical parameters (mean ± SD) were within expected physiological ranges: serum creatinine of 1.12 ± 0.11 mg/dL (reference interval: 0.74–1.35 mg/dL, to convert in µmol/L, multiply by 88.4), phosphorus of 1.25 ± 0.19 mmol/ L (reference interval: 0.80–1.50 mmol/L), calcium 2.40 ± 0.09 mmol/L (reference interval: 2.15–2.60 mmol/L), PTH 14.7 ± 5.9 pg/mL (reference interval: 5,5–31,9 pg/mL; to convert in pmol/L, multiply by 0.105), and 25(OH)-D of 27.6 ± 6.4 µg/L (expected values: >20 µg/L; to convert in nmol/L, multiply by 2.5).

From the original cohort of 113 healthy women, we decided to exclude 27 subjects older than 45 years old, leaving 86 women that we considered arbitrarily as premenopausal since we did not have access to the information on their menopause status. In this subgroup, the mean age was 33.3 ± 6.7 years (range: 18–45). Serum creatinine was 0.81 ± 0.10 mg/dL (reference interval: 0.59–1.04 mg/dL), phosphorus 1.24 ± 0.20 mmol/L (reference interval: 0.80–1.50 mmol/L) and calcium 2.36 ± 0.09 mmol/L (reference interval: 2.15–2.60 mmol/L). PTH concentration was 16.8 ± 6.8 pg/mL (reference interval: 5,5–31,9 pg/mL) and 25(OH)-D concentration was 26.1 ± 5.6 µg/L (expected values: >20 µg/ L).

Bone turnover markers exhibited wide interindividual variability and non-normal distributions in both groups. For β-CTX-I (recalibrated), in men, concentrations ranged from 169 ng/L to 723 ng/L, with a median of 266 (IQR: 229–372) ng/L.

In women ≤ 45 years, concentrations ranged from 167 ng/L to 554 ng/L, with a median of 229 ng/L (IQR 191–258 ng/L).

Both distributions were right-skewed and non-Gaussian (Shapiro- Wilk, $P < 0.0001$). Reference intervals for recalibrated β-CTX-I were derived using both bootstrap non-parametric and Box-Cox transformed parametric methods. The bootstrap method yielded limits of 181–610 ng/L (90 % CI: 168–196 / 480–745) in men and 167–378 ng/L (90 % CI: 166–166 / 343–413) in women ≤45 years. The Box-Cox based limits were comparable, confirming robustness.

For iPINP, in men, a Tukey outlier analysis identified a far-out value of 416 µg/L in one subject. Upon review of the individual's biochemical profile, the result was deemed likely to reflect an analytical interference and was therefore excluded from the reference interval calculation. The remaining values ranged from 14 µg/L to 189 µg/L, with a median of 70 µg/L (IQR: 52–99 µg/L).

In women ≤ 45 years, iPINP ranged from 26 µg/L to 177 µg/L, with a median of 53 µg/L (IQR 40–78 µg/L). Both distributions were significantly right-skewed. Using the bootstrap non-parametric method, reference intervals were 30–169 µg/L (90 % CI: 19–41 / 151–187) in men and 28–142 µg/L (90 % CI: 24–33 / 107–176) in women ≤45 years. The Box-Cox based intervals showed similar limits. Age analysis suggested a gradual decline in bone turnover markers with advancing age.

Results are presented graphically in Fig. 1 and summarized in Table 1.

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A linear regression model was established in healthy women aged ≤ 45 years to predict β-CTX-I concentrations from iPINP values. The resulting equation was:

$$\beta\text{ - CTX− I } expected = 159\ (95\%CI : 133; 185) + 1.27(95\%CI : 0.90;1.64) \times iPINP$$

The residual standard deviation of the model was 53.6 ng/L.

This model was applied to women over 45 years of age (n = 27) to calculate the BBI. In this group, BBI values ranged from − 1.36 to + 8.59, with a median of 0.13. A total of 17 women (65 %) had a positive BBI, indicating predominant bone resorption, while 9 (35 %) had a negative BBI, suggesting a more balanced or formation-predominant profile. Using a threshold of ±1 to define a zone of indeterminate balance, 15 women (56 %) were classified within this grey zone. Ten women (37 %) had BBI values >1, consistent with a predominance of bone resorption and 2 women (7 %) had BBI values < − 1, suggesting a formation-predominant profile.

The distribution of BBI values is presented in Fig. 2. BBI correlated strongly with β-CTX-I concentrations (ρ = 0.90, $P < 0.0001$), but showed no significant correlation with iPINP, age, serum calcium, phosphate, PTH, creatinine, or 25-(OH)D levels

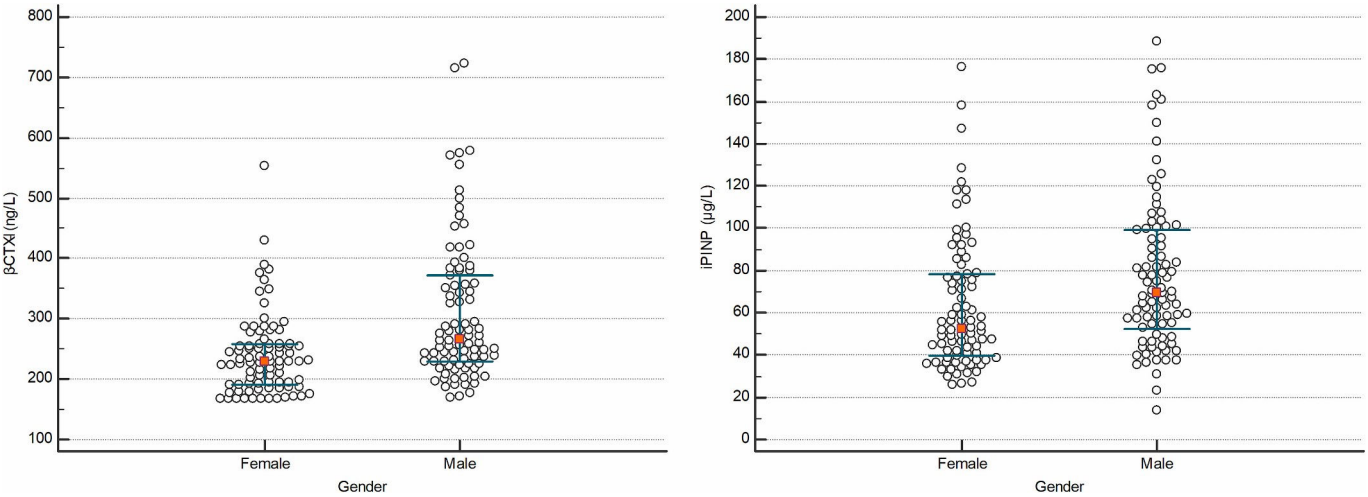

Fig. 1. Serum concentrations of β-CTX-I (left) and intact PINP (right) according to gender in a cohort of healthy blood donors from Côte d'Ivoire.
Each dot represents an individual. The red squares indicate the medians, and the green bars represent the 25–75 % interquartile range of the medians. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Reference intervals for bone turnover markers in healthy adults from Côte d'Ivoire (IDS iSYS platform).

Analyte	Group	N	Median (IQR)	Range	Reference interval (bootstrap, 90 % CI)	Reference interval (Box–Cox, 90 % CI)
β-CTX-I (ng/L, recalibrated)	Men	90	266 (229–372)	169–723	181 (168–196) – 610 (480–745)	187 (175–201) – 597 (482–716)
β-CTX-I (ng/L, recalibrated)	Women ≤45 y	86	229 (191–258)	167–554	167 (166–166) – 378 (343–413)	172 (168–176) – 370 (333–407)
iPINP (µg/L)	Men	89	70 (52–99)	14–189	30 (19–41) – 169 (151–187)	32 (21–44) – 165 (148–182)
iPINP (µg/L)	Women ≤45 y	86	53 (40–78)	26–177	28 (24–33) – 142 (107–176)	30 (25–35) – 138 (110–167)

Notes
Reference intervals were established according to CLSI C28-A3 using two complementary approaches

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(1) a bootstrap non-parametric method (10,000 iterations), and
(2) a parametric method after Box–Cox transformation, assuming normality on the transformed scale (confirmed by the Lilliefors test, $p > 0.1$)

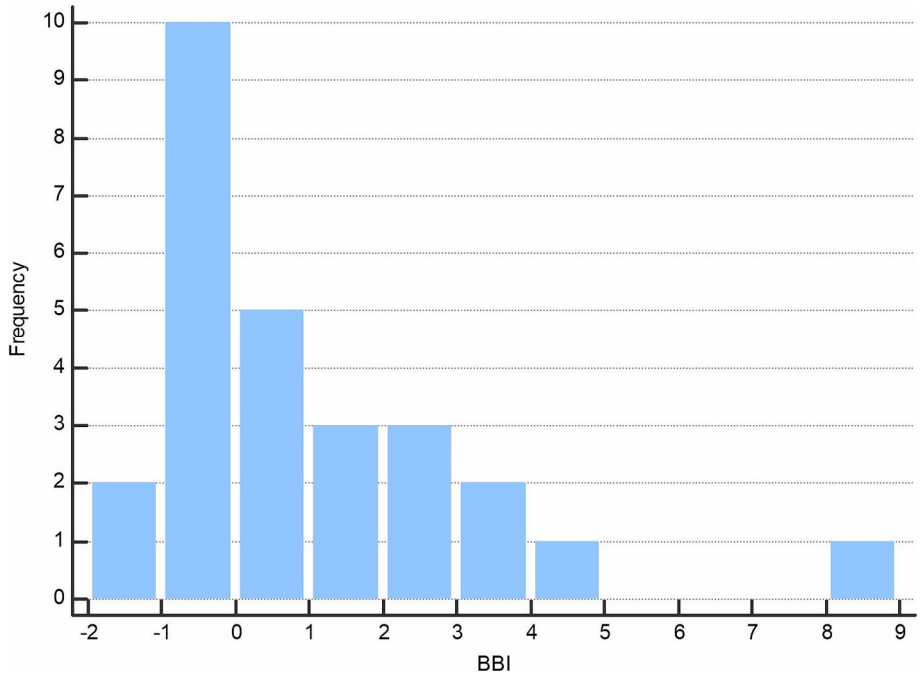

Fig. 2. Distribution of the Bone Balance Index (BBI) in women over 45 years of age (n = 26).
The BBI reflects the standardized difference between the observed β-CTX-I concentration and the value expected from the individual's PINP level, based on a regression model established in healthy women aged ≤ 45 years.

4. Discussion

Osteoporosis is a growing global health concern, and its burden in Africa is expected to rise steadily due to increased life expectancy, urbanization, and changing lifestyles [1]. Despite this trend, African populations remain largely underrepresented in studies that define diagnostic and monitoring tools, particularly for bone turnover markers (BTMs) [10,24]. This study addresses that gap by providing, for the first time, reference intervals for β-CTX-I and iPINP in a well-characterized cohort of healthy Black African individuals from Côte d'Ivoire.

Several methodological strengths distinguish our approach. All participants were rigorously screened to exclude common confounders of bone metabolism, including chronic kidney disease, HIV, hepatitis, and metabolic disorders [21]. Furthermore, all subjects had normal serum calcium, phosphate, PTH, creatinine, and 25-(OH)D levels, which is rarely confirmed in studies establishing BTM reference intervals [25–28]. Preanalytical conditions were tightly controlled: samples were processed promptly, stored at − 80 °C, and analyzed within one month using validated and standardized methods. All measurements were performed in a single central laboratory using the IDS iSYS platform, minimizing analytical variability.

Compared to published reference intervals in Caucasian and Asian populations [18,22], we observed that β-CTX-I concentrations in both men and premenopausal women from Côte d'Ivoire were slightly lower, while iPINP levels, especially in men, were higher. These findings highlight potential population-based differences in bone turnover and reinforce the importance of establishing region- and ethnicity-specific reference

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intervals to avoid misinterpretation when applying thresholds derived from non-African populations. To verify the robustness of these reference intervals, both non-parametric bootstrap and parametric Box–Cox approaches were applied. The Box–Cox transformation successfully normalized the data distributions (Lilliefors $p > 0.1$ for all), indicating that the observed asymmetry did not materially affect the derived limits. Both methods produced closely overlapping intervals, supporting the reliability of the reference estimates across different statistical frameworks.

To further explore the relationship between formation and resorption, we applied the Bone Balance Index (BBI) in women over 45 years of age. This index reflects the coupling status of bone turnover by comparing observed β-CTX-I levels to those expected from the individual's iPINP concentration. While designed primarily for longitudinal monitoring, we tested its value in a cross-sectional setting using a reference equation derived from healthy younger women. Although the BBI showed a strong correlation with β-CTX-I, as expected from its mathematical definition, it did not correlate with iPINP, age, or other biochemical parameters, suggesting it captures a specific imbalance between formation and resorption.

To enable practical interpretation, we proposed a provisional grey zone of ±1 SD around zero. Under this framework, most women fell within the grey zone, but a small subgroup (23 %) had markedly elevated BBI values, suggestive of disproportionate bone resorption. While this exploratory application of the BBI should be interpreted with caution, such individuals might benefit from further evaluation, especially in resource-limited settings where DXA is not readily available. These findings illustrate the potential of the BBI to complement traditional BTMs, but also underscore the need for longitudinal studies to define its prognostic and clinical relevance in diverse populations.

The main limitation of our study is the sample size, which did not meet the CLSI C28-A3 recommendation of 120 individuals per subgroup. Nevertheless, reference intervals were calculated using non-parametric methods appropriate for moderate-sized cohorts [29,30] and the robustness of our selection criteria, strict methodology, and internal consistency of the results contribute to the reliability of our findings. Another limitation is the lack of explicit information on menopausal status. To mitigate this, we excluded all women over the age of 45, assuming that most postmenopausal women fall within this age group.

Although a small number of perimenopausal women may have been included, their presence is unlikely to significantly affect the overall conclusions.

In conclusion, this study provides the first reference intervals for β-CTX-I and iPINP in a sub-Saharan African population. Given the increasing clinical use of BTMs to assess bone remodeling and monitor treatment efficacy [15,16,31], these findings offer an essential foundation for the appropriate interpretation of BTMs in African settings, especially in contexts where access to bone densitometry remains limited. Our results also call for further large-scale and harmonized studies to establish robust, population-specific guidelines for osteoporosis management across the continent.

CRediT authorship contribution statement

Etienne Cavalier: Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kadio A. Morel Kouakou:** Writing – review & editing. **Pierre Lukas:** Investigation, Data curation. **Carine Mireille Yao-Yapo:** Writing – review & editing. **Pierre Delanaye:** Writing – review & editing. **Eric Sagou Yayo:** Writing – review & editing, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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