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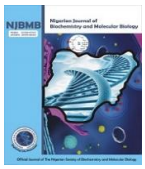

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Research Article

Elevated Alkaline Phosphatase: A Potential Marker of Bone Metabolism in Metabolic Syndrome

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ABSTRACT

Metabolic syndrome (MetS) is characterised by metabolic dysregulation, chronic inflammation, and increased cardiovascular risk, and may also impair bone remodelling. Alkaline phosphatase (ALP), a biomarker of bone formation, reflects skeletal turnover. This cross-sectional study at Igbinedion University Teaching Hospital, Edo State, Nigeria, assessed ALP in 75 MetS patients diagnosed using the Joint Interim Statement (JIS) criteria. Serum ALP was measured using the p-nitrophenyl phosphate (pNPP) assay, with values above the laboratory reference range (>120 U/L) considered elevated, indicative of subclinical skeletal remodelling abnormalities. Elevated ALP was observed in 34.7% of participants, suggesting that nearly one in three individuals with MetS may have subclinical skeletal changes. Among these, 21.3% were females ($p > 0.05$), indicating a possible gender trend. Body mass index (BMI) was significantly associated with ALP levels ($p = 0.009$), with 85.7% of obese participants exhibiting elevated ALP, highlighting adiposity as a potential driver of altered bone metabolism. These findings support the hypothesis that insulin resistance and chronic inflammation in MetS contribute to skeletal alterations, independent of bone mineral density (BMD). Routine ALP assessment in MetS, particularly in patients with extreme BMI, may facilitate early detection of bone health risks. Longitudinal studies are warranted to clarify causal relationships and guide integrated strategies for fracture prevention in MetS.

Keywords: *Metabolic syndrome, Alkaline phosphatase, Bone turnover, Orthopaedic Assessment, Bone mineral density*

INTRODUCTION

Metabolic syndrome (MetS) represents a constellation of interrelated cardiometabolic risk factors that predispose individuals to adverse health outcomes. These include central obesity, insulin resistance, hypertension, and dyslipidaemia, each contributing individually and synergistically to an increased risk of developing cardiovascular diseases and type 2 diabetes mellitus (Ibezim *et al*., 2025). As the global burden of MetS continues to rise, its multifaceted impact on various physiological systems is garnering increased scientific attention. While its association with cardiovascular and endocrine disorders is well-established, recent research has begun to unravel its systemic consequences, including those affecting skeletal integrity and bone health (Kinjo & Solomon, 2007).

Bone is a metabolically active tissue that undergoes continuous remodelling through tightly regulated processes of formation and resorption. This dynamic

equilibrium is mediated by osteoblasts and osteoclasts and is influenced by a range of hormonal, nutritional, mechanical, and inflammatory factors (Chen *et al*., 2016). Metabolic disruptions characteristic of MetS, such as chronic low-grade inflammation, insulin resistance, and oxidative stress, have the potential to interfere with this balance, thereby altering bone turnover and contributing to skeletal fragility. Moreover, the systemic inflammatory milieu associated with MetS may stimulate osteoclast activity while suppressing osteoblast function, further tipping the scales towards net bone loss.

Alkaline phosphatase (ALP), a hydrolase enzyme with isoforms expressed in several tissues, plays a central role in bone mineralisation. In the skeletal system, ALP is primarily secreted by osteoblasts and facilitates the hydrolysis of phosphate esters, promoting the deposition of calcium-phosphate complexes in the bone matrix (Magnusson & Farley, 2002). Traditionally, elevated serum ALP levels have been interpreted in the context of hepatic or biliary dysfunction. However, increasing evidence indicates that elevated ALP levels may also occur in individuals with metabolic disorders, including MetS, even in the absence of liver pathology (Liu *et al*., 2006; Khosla & Shane, 2016). This raises the intriguing possibility that ALP may serve not only as a hepatic marker but also as a surrogate indicator of increased bone turnover or altered bone remodelling in metabolic conditions.

Despite these insights, the relationship between MetS and bone metabolism remains underexplored, particularly in clinical settings where bone health is not routinely evaluated in patients with metabolic disease. Given the potential implications for fracture risk, orthopaedic complications, and long-term skeletal morbidity, there is a compelling need to elucidate this connection further. Investigating serum ALP levels in MetS patients may offer a practical and cost-effective means of assessing subclinical bone changes, thereby enabling early intervention and preventative strategies.

Therefore, this study aimed to evaluate the prevalence of elevated serum ALP among patients diagnosed with metabolic syndrome and to examine the clinical implications of such elevations in the context of bone health. By shedding light on this overlooked dimension of MetS, the research seeks to inform future screening protocols and therapeutic approaches that address not only cardiometabolic but also skeletal risks associated with the syndrome.

MATERIALS AND METHODS

Study design and location

This was a descriptive, hospital-based cross-sectional study designed to evaluate the prevalence of elevated serum ALP among patients with MetS. The study was conducted at the Igbinedion University Teaching Hospital (IUTH), Okada, Edo State, Nigeria. Data were collected from September 2024 to February 2025, covering a total period of five months. The study design allowed for an in-depth assessment of the biochemical and clinical parameters relevant to MetS and bone metabolism within a defined outpatient population.

Study Population

Seventy-five adult patients attending the medical outpatient clinic of Igbinedion University Teaching Hospital (IUTH), Okada, Edo State, Nigeria, were enrolled in this study. All participants were diagnosed with metabolic syndrome (MetS) according to the harmonised Joint Interim Statement (JIS) criteria (Alberti *et al.*, 2009). Diagnosis required the presence of at least three of the following components: central obesity, defined as waist circumference ≥94 cm in men or ≥80 cm in women; elevated triglycerides ≥150 mg/dL; reduced high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women; elevated blood pressure ≥130/85 mmHg or current use of antihypertensives; and fasting plasma glucose ≥100 mg/dL or current use of antidiabetic medications.

Inclusion criteria

Adults aged 18–70 years with MetS based on JIS criteria, who provided written informed consent and fasted for 8–12 hours before sample collection, were included in the study.

Exclusion criteria

Those with a history of chronic liver disease or active hepatobiliary disease, documented bone disorders (e.g., osteoporosis, Paget's disease, osteomalacia), recent fractures or orthopaedic surgeries within the past six months, current or recent (within three months) use of medications known to affect bone turnover (e.g., corticosteroids, bisphosphonates, anticonvulsants), pregnancy or lactation, and refusal to provide consent were excluded from the study.

Anthropometric measurement

General obesity was assessed using body mass index (BMI). Weight was measured to the nearest 0.1 kg using a calibrated digital scale with participants barefoot and wearing light clothing, while height was measured to the nearest 0.1 cm using a stadiometer with participants standing upright without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2) and participants were categorised as underweight (<18.5 kg/m^2), healthy weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2), according to World Health Organization (WHO)

guidelines (World Health Organization, 2000). Waist circumference was recorded using a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, to the nearest 0.1 cm.

Sample collection and biochemical analysis

Participants fasted overnight for 8–12 hours before sample collection. Upon arrival, patient identity was verified, and inclusion/exclusion criteria were reconfirmed. Venepuncture was performed aseptically on the antecubital vein, and 5 mL of venous blood was collected into plain vacutainer tubes without anticoagulant. Blood samples were allowed to clot at room temperature for 15–30 minutes, then centrifuged at 3,000 rpm for 10 minutes to obtain serum. The serum was aliquoted into cryovials and either analysed immediately or stored at −20°C for a maximum of 48 hours before analysis.

Serum ALP levels were measured using an enzymatic colorimetric method based on International Federation of Clinical Chemistry (IFCC) recommendations (Zerah *et al.*, 1993) on a Mindray BS-120 automated chemistry analyser. The assay involved hydrolysis of p-nitrophenyl phosphate (pNPP) to p-nitrophenol, producing a yellow colour measured at 405 nm (Burtis *et al.*, 2012). Calibration was performed using manufacturer-provided ALP calibrators (Clinical and Laboratory Standards Institute, 2012), and internal quality controls (low and high ALP) were run with each batch. All analyses were performed in duplicate, and the mean value was recorded. ALP levels >120 IU/L were considered elevated, according to the assay manufacturer's reference intervals and regional laboratory standards (Mindray Medical International Limited, 2021).

Data Analysis

Data were entered and analysed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviation, while categorical variables were presented as frequencies and percentages. Associations between ALP levels and demographic or clinical variables were evaluated using chi-square tests for categorical data. A p-value of less than or equal to 0.05 was considered statistically significant.

Ethical Considerations

Ethical approval for the study was obtained from the Ethics and Research Committee of Igbinedion University Teaching Hospital (IUTH/R.20/VOL.1/152). All participants were informed of the purpose, procedures, potential risks, and benefits of the study. Written informed consent was obtained before enrollment. Confidentiality of personal and medical information was strictly maintained. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 Revision) regarding research involving human subjects (World Medical Association, 2013).

RESULTS

Demographics and ALP Levels of Patients Diagnosed with MetS

Among the 75 MetS patients diagnosed with Metabolic Syndrome (MetS), the mean age was 54.3 ± 10.6 years, indicating a predominance of middle-aged individuals (40-60 years). Of this cohort, 44 were females, accounting for 58.7% of the study population, while 31 were males, representing 41.3%.

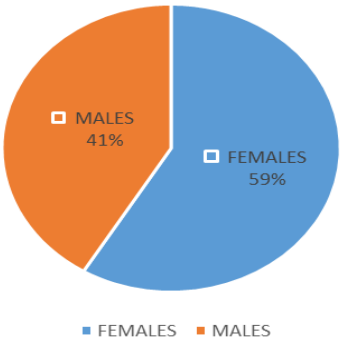

Figure 1: Gender Distribution of Patients with MetS

Elevated serum alkaline phosphatase (ALP) levels were observed in 26 out of the 75 participants, accounting for 34.7% of the total study population. Among those with elevated ALP, 16 were females (21.3% of the total sample) while 10 were males (13.3%). Although a higher proportion of females exhibited elevated ALP levels compared to their male counterparts, this gender difference did not reach statistical significance, as indicated by the Chi-square test (x^2= 0.235, df = 1, P = 0.615). This finding suggests that, within the context of this cohort, gender may not be a major determinant of ALP elevation among individuals with Metabolic Syndrome. Nonetheless, the notable prevalence in over one-third of the population shows the potential clinical relevance of this biomarker in the metabolic profile of affected individuals.

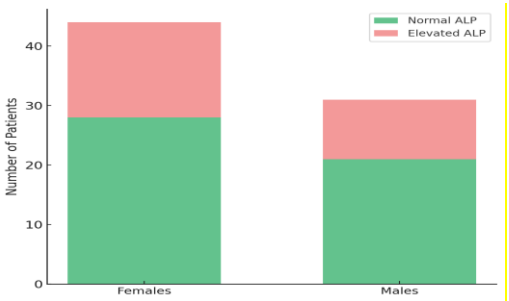

Figure 2: ALP Levels by Gender among Patients with MetS

Elevated ALP: >120 IU/L

Association between BMI and ALP Levels

A chi-square test was conducted to examine the association between BMI categories and serum ALP levels. The association was statistically significant (χ^2 = 11.652, df = 3, p = 0.009), indicating that BMI classification has a significant influence on ALP status in this cohort. Among obese participants, 6 out of 7 (85.7%) had elevated ALP levels, whereas only 6 out of 30 participants (20%) in the healthy weight group exhibited elevated ALP. Additionally, 10 out of 24 (41.7%) overweight individuals had elevated ALP. Interestingly, four underweight participants also showed elevated ALP levels, suggesting a U-shaped relationship between BMI and ALP levels in this sample. The linear-by-linear association test (value = 6.999, p = 0.008) further supported a significant trend across ordered BMI groups, with increasing BMI associated with a higher prevalence of elevated ALP. These findings suggest that both extremes of body composition, underweight and obesity, may be associated with metabolic alterations in bone turnover.

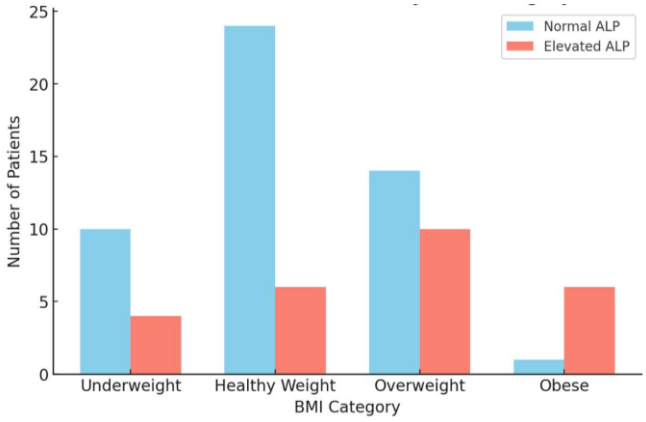

Figure 3: Distribution of ALP Status by BMI Category among Patients with MetS
Elevated ALP: >120 IU/L, Underweight (<18.5kg/m²) Healthy Weight (18.5–24.9 kg/m²), Overweight (25.0–29.9 kg/m²), Obese (≥30.0 kg/m²)
(χ^2 = 11.652, df = 3, p = 0.009)

DISCUSSION

This study found that approximately one in three individuals with MetS had elevated serum ALP levels, indicating a potential biochemical link between metabolic dysregulation and bone turnover. These findings align with emerging literature that highlights an association between MetS and skeletal alterations, independent of bone mineral density (Yoshimura *et al*., 2010; Rianon *et al*., 2010). Alkaline phosphatase (ALP) is a known membrane-bound protein with enzymatic activity. It is secreted by the liver and by osteoblasts, with the latter being a reflection of bone metabolic activity (Åkesson, 1995). Serum total ALP has often been used as a marker of bone formation (Eastell & Hannon, 2007), and 95% of Total ALP activity in serum reflects bone and liver ALP in almost equal amounts, and in the absence of liver disease, a rise in total ALP is thought to correspond to Bone ALP activity (Sardiwal *et al*., 2013).

In this study, although the proportion of females with elevated ALP was numerically higher than that of males, this difference did not reach statistical significance. This apparent lack of significant gender disparity may be influenced by underlying hormonal differences, particularly the influence of estrogen on both metabolic and skeletal homeostasis. Estrogen plays a dual regulatory role in glucose and lipid metabolism, where it improves insulin sensitivity and modulates fat distribution, and bone metabolism, where it promotes osteoblast activity and inhibits osteoclast-mediated bone resorption. Following menopause, estrogen levels decline sharply, which contributes to both increased metabolic syndrome risk and accelerated bone loss in women. This hormonal decline can potentially explain the higher frequency of ALP elevation observed among postmenopausal females, as ALP is a surrogate marker of bone turnover, and turnover rates typically rise in estrogen-deficient states. However, the absence of statistically significant gender differences in this study might suggest that other factors, such as inflammation, insulin resistance, or obesity, may have a more dominant influence on ALP levels in MetS patients, regardless of sex. This supports the concept that MetS induces systemic changes that affect skeletal metabolism beyond hormonal differences alone (Van der Velde *et al*., 2013). Kim *et al.* (2013) reported that men with MetS had a significantly increased risk of developing osteopenia or osteoporosis, challenging the long-standing assumption that bone fragility is predominantly a postmenopausal female issue. Their findings suggest that in males, a pro-inflammatory state, accompanied by reduced testosterone, increased visceral adiposity, and insulin resistance, can independently compromise bone quality and density. In contrast, some studies have paradoxically shown that BMD is preserved or even higher in women with MetS, likely due to mechanical loading from increased body mass and adipose-derived estrogen. Yet, this apparent protective effect in females may be misleading. Bone mineral density (BMD) alone does not account for bone quality, which includes microarchitecture and turnover. It is plausible that while BMD is preserved or increased in obese MetS females, the bone may still be structurally compromised, leading to a "silent" risk of fragility fractures, a pattern not captured by ALP alone.

The statistically significant association between BMI and ALP levels observed in this study exposes the role of body composition in modulating bone metabolism in MetS. Notably, obese individuals were substantially more likely to exhibit elevated ALP (85.7%), suggesting enhanced bone turnover in this group. This may be attributed to the pro-inflammatory cytokine environment and altered hormonal

signalling associated with adiposity, which promote osteoclast activation and impair osteoblast function (Zhao *et al*., 2007; Cao, 2011). Interestingly, elevated ALP was also observed in 4 underweight participants, pointing to the possibility of a U-shaped association, where both low and high BMI contribute to skeletal fragility through different mechanisms. This biphasic pattern aligns with literature suggesting that while obesity drives mechanical stress and inflammation, undernutrition may impair bone matrix formation and mineralisation. Given these observations, routine ALP screening in MetS patients, particularly at BMI extremes, may aid in the early detection of metabolic bone disease (Compston, 2001).

Insulin resistance and chronic inflammation, central features of metabolic syndrome, have been shown to negatively affect bone formation by impairing osteoblast function. Hyperinsulinemia downregulates osteoblastogenesis by interfering with the Wnt/β-catenin signalling pathway, a crucial regulator of osteoblast differentiation and activity (Fulzele *et al*., 2010). Additionally, pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 promote osteoclastogenesis while inhibiting osteoblast maturation, shifting the balance toward bone resorption (Hofbauer *et al*., 2007; Wei *et al*., 2015). This inflammatory milieu not only impairs bone formation but also increases oxidative stress within the bone microenvironment, thereby further suppressing osteoblast proliferation and survival (Wauguier *et al*., 2009). Consequently, elevated ALP levels in MetS patients could reflect a compensatory increase in bone turnover triggered by these metabolic and inflammatory insults.

Recent meta-analyses have explored the complex relationship between MetS and bone health, with a focus on biochemical markers including ALP. A 2023 systematic review confined to adult men found that although bone mineral density (BMD) at the femoral neck and lumbar spine was largely preserved in MetS, the heterogeneity of the data underlined the potential role of altered bone turnover in certain subgroups (Ryl *et al*., 2023). Conversely, a 2021 meta-analysis of MetS and osteoporosis noted an inverse association in men, suggesting that MetS-related metabolic derangements, such as insulin resistance and inflammation, may impair bone-forming processes, potentially raising ALP as a compensatory bone turnover marker (Liu *et al*., 2021). Another 2024 review highlighted that bone-specific ALP and total ALP were elevated in type 2 diabetes mellitus (a core component of MetS), even while other bone formation markers like osteocalcin were reduced, indicating dysregulated bone formation in a metabolic context (Yang *et al*., 2024). Together, these findings support our hypothesis that elevated ALP in MetS reflects subclinical disruptions in osteoblastic activity and bone remodelling.

In clinical settings, measuring ALP in patients with MetS can provide valuable insight into subclinical bone remodelling abnormalities that may not be apparent through routine assessments. Elevated ALP levels, particularly in the absence of liver pathology, may suggest increased bone turnover and should prompt further investigations, such as bone-specific ALP assays or imaging techniques like dual-energy X-ray absorptiometry (DEXA), to assess bone mineral density and microarchitectural integrity (Biver *et al*., 2012). This is particularly relevant in postmenopausal women and older men with MetS, where inflammatory and metabolic disturbances increase fragility fracture risk despite preserved BMD (Napoli *et al*., 2017). Incorporating ALP screening into routine metabolic evaluations in primary care, especially when MetS is accompanied by risk factors such as age >50 years, history of fractures, or reduced physical activity, could enable early identification of patients who may benefit from preventive bone health strategies. Structured protocols may include periodic ALP testing every 12–24 months, with follow-up DEXA scanning in individuals with persistent elevations or additional risk markers (Vasikaran *et al*., 2011). This multidisciplinary approach could help address the often-overlooked skeletal consequences of metabolic disorders.

CONCLUSION

Chronic inflammation and oxidative stress, hallmarks of Metabolic Syndrome (MetS) such as obesity, are known to impair osteoblast differentiation and stimulate osteoclast activity, potentially resulting in higher alkaline phosphatase (ALP) levels as a compensatory response. Orthopaedic perspectives show that elevated ALP, while not diagnostic of bone disease, may signal increased turnover, which could predispose to microarchitectural fragility and increased fracture risk. Hence, routine metabolic screening in MetS patients should be complemented by skeletal assessments to ensure early detection of potential complications. Incorporating ALP screening into routine MetS management may facilitate early detection of bone-related complications and enhance preventive care strategies. While causality cannot be established, these findings warrant a multidisciplinary approach involving metabolic and orthopaedic evaluation to mitigate overlooked skeletal risks. Longitudinal studies incorporating bone mineral density (BMD) and fracture incidence are recommended to validate these findings.

AUTHORS' CONTRIBUTIONS

IHU: Conceptualisation, Methodology, Data Curation and Writing original draft. OB: Conceptualisation, Orthopaedic Insights, Literature Review. IOE: Methodology, Literature Review and Editing. HKN: Supervision and Methodology. JOO: Supervision and Investigation. VM: Orthopaedic Insights, Proofreading and Validation.

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CONFLICT OF INTEREST

The authors declared no conflict of interest

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