Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 12.09.2026 | Accepted 14.09.2026 | Online 19.09.2026

УЎК: 616.441+ 616.12-008.318

COMPREHENSIVE ANALYTICAL EVALUATION OF THE INTERRELATIONSHIPS BETWEEN THE FGF-23/α-KLOTHO SYSTEM, MINERAL METABOLISM BIOMARKERS, AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

G'ulomova Sh. Q.
Department of Fundamental Medicine, Asia International University
gulomovashahrinoz@gmail.com
ORCID: 0009-0002-4838-6793

Abstract

Postmenopausal osteoporosis is a major metabolic bone disorder characterized by progressive reduction in bone mineral density (BMD) and increased fracture risk. Although estrogen deficiency is considered a central determinant of postmenopausal bone loss, increasing evidence indicates that systemic regulators of mineral metabolism may also influence skeletal health. Fibroblast growth factor 23 (FGF-23) and α-Klotho constitute an important endocrine signaling system involved in phosphate homeostasis, vitamin D metabolism, and bone-mineral regulation. FGF-23, predominantly produced by osteocytes and osteoblast-lineage cells, reduces renal phosphate reabsorption and suppresses renal production of 1,25-dihydroxyvitamin D. α-Klotho acts as an essential co-receptor for canonical FGF-23 signaling, particularly in the kidney. The interaction between FGF-23, α-Klotho, parathyroid hormone (PTH), calcium, phosphate, and vitamin D forms a complex regulatory network rather than an isolated hormonal pathway. Existing studies investigating the relationship between FGF-23, α-Klotho, and BMD in postmenopausal women have produced heterogeneous findings. Some studies have reported higher FGF-23 concentrations in women with osteoporosis, whereas others have found no independent association between FGF-23 and BMD. In contrast, several studies suggest that higher circulating α-Klotho concentrations may be associated with greater BMD and a lower probability of osteoporosis. These discrepancies may be explained by differences in renal function, age, vitamin D status, assay methodology, menopausal duration, body composition, and other confounding factors. This review summarizes current evidence concerning the FGF-23/α-Klotho system, mineral metabolism biomarkers, and BMD in postmenopausal women and proposes a comprehensive biomarker and statistical framework for future clinical research.

Keywords: FGF-23; α-Klotho; postmenopausal women; osteoporosis; bone mineral density; calcium; phosphate; vitamin D; PTH; mineral metabolism.

Introduction

Postmenopausal osteoporosis is one of the most important metabolic skeletal disorders affecting women after menopause. The decline in estrogen concentrations following

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

menopause accelerates bone remodeling, increases bone resorption, and progressively reduces bone mineral density (BMD), particularly at trabecular-rich skeletal sites such as the lumbar spine [14,11]. The clinical consequence is an increased risk of vertebral, hip, and other fragility fractures.

The pathogenesis of osteoporosis is multifactorial. In addition to estrogen deficiency, age, body composition, physical activity, nutritional status, calcium and vitamin D availability, renal function, endocrine abnormalities, medication exposure, and genetic factors may contribute to skeletal deterioration [14,15]. Therefore, evaluation of bone health solely on the basis of BMD may not completely characterize the biological mechanisms underlying bone loss.

Mineral metabolism is regulated by a complex endocrine network involving fibroblast growth factor 23 (FGF-23), α-Klotho, parathyroid hormone (PTH), vitamin D metabolites, calcium, and phosphate [8,16]. FGF-23 is primarily synthesized by osteocytes and osteoblast-lineage cells and functions as an endocrine regulator of phosphate homeostasis. Its major physiological actions include reduction of renal phosphate reabsorption and suppression of renal 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] production [8,3].

α-Klotho is a transmembrane protein that functions as an essential co-receptor for canonical FGF-23 signaling. The interaction between FGF-23, fibroblast growth factor receptors (FGFRs), and α-Klotho is particularly important in the kidney, where it regulates phosphate handling and vitamin D metabolism [3,4,21]. Klotho also exists in soluble forms that may have biological actions independent of classical FGF-23 receptor signaling, although the physiological importance of these additional effects remains incompletely defined [12,13].

The potential relationship between the FGF-23/α-Klotho system and osteoporosis is of increasing interest. Experimental evidence suggests that FGF-23 and Klotho participate in pathways linking bone, kidney, and mineral metabolism [6,19]. However, clinical studies in postmenopausal women have reported inconsistent associations between circulating FGF-23 or Klotho concentrations and BMD [1,7,10,18].

The purpose of this review is to summarize current knowledge regarding the FGF-23/α-Klotho system, its interaction with conventional mineral metabolism biomarkers, and its possible relationship with BMD in postmenopausal women. Particular attention is given to the methodological limitations of existing evidence and to the design of future original clinical research.

Materials and Methods

This article was designed as a narrative literature review. Relevant scientific literature concerning FGF-23, α-Klotho, mineral metabolism, osteoporosis, postmenopausal bone loss, and BMD was considered.

Priority was given to peer-reviewed clinical and experimental studies, systematic or narrative reviews, and authoritative clinical recommendations. Particular attention was paid to studies involving postmenopausal women and to publications evaluating circulating FGF-23 or Klotho in relation to BMD or osteoporosis.

The reviewed literature was conceptually grouped into several domains: biological characteristics of FGF-23; α-Klotho and FGF-23 signaling; regulation of calcium-

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

phosphate metabolism; effects of estrogen deficiency on bone remodeling; clinical studies of FGF-23 and Klotho in postmenopausal women; and methodological considerations related to biomarker assessment and DXA-based BMD evaluation.
Because the author's original clinical investigation is at an early stage, no original patient numbers, statistical results, or clinical outcomes are presented in this review.

Results

FGF-23 is a member of the fibroblast growth factor family and functions primarily as an endocrine regulator of phosphate metabolism. Osteocytes are considered the major physiological source of circulating FGF-23, although osteoblast-lineage cells can also contribute to its production [8,6].
FGF-23 acts predominantly through FGFRs in tissues expressing α-Klotho. The kidney represents a major target organ. Activation of FGF-23 signaling decreases expression of sodium-phosphate cotransporters in the renal proximal tubule, thereby reducing phosphate reabsorption and increasing urinary phosphate excretion [3,4].
A second important action of FGF-23 is suppression of renal 1α-hydroxylase activity and stimulation of vitamin D catabolism. Consequently, FGF-23 decreases circulating $1,25(OH)_2D$ concentrations and limits intestinal phosphate absorption [8,3]. Through these mechanisms, FGF-23 maintains systemic phosphate balance.
FGF-23 production itself is regulated by multiple factors. Phosphate availability, vitamin D signaling, PTH, calcium, iron metabolism, inflammation, and bone-derived signaling molecules may influence FGF-23 secretion [8,16,17]. This complex regulation indicates that serum FGF-23 should not be interpreted as an isolated marker of bone metabolism.
α-Klotho as an FGF-23 Co-Receptor and Independent Regulator
α-Klotho is essential for the classical endocrine actions of FGF-23. The discovery that Klotho converts conventional FGFRs into receptors capable of responding specifically to FGF-23 provided an important mechanistic explanation for the tissue selectivity of FGF-23 signaling [21].
The FGF-23–Klotho complex activates intracellular signaling pathways that regulate renal phosphate handling and vitamin D metabolism [3,4]. The kidney is particularly rich in membrane-bound α-Klotho and represents one of the principal physiological targets of FGF-23.
Klotho biology, however, extends beyond FGF-23 signaling. Soluble Klotho has been proposed to influence ion transport, oxidative stress, cellular signaling, and aging-related processes [12,13]. These broader effects have generated interest in Klotho as a potential biomarker of systemic biological aging and skeletal health.
Nevertheless, the interpretation of serum Klotho measurements requires caution. Circulating Klotho concentrations may be influenced by renal function, age, metabolic status, and methodological differences among assays. Therefore, an observed association between serum Klotho and BMD cannot automatically be interpreted as evidence of a direct causal effect on bone.
FGF-23/Klotho Integrated Mineral Metabolism Network
The FGF-23/α-Klotho axis functions within an integrated network that includes PTH, vitamin D, calcium, and phosphate [8,16].

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

An increase in phosphate availability can stimulate FGF-23 production. Increased FGF-23 then promotes renal phosphate excretion and reduces $1,25(OH)_2D$ production. Reduced active vitamin D limits intestinal phosphate and calcium absorption, creating feedback within the system [8,16].

PTH interacts with this network as well. PTH increases renal phosphate excretion and stimulates renal vitamin D activation, whereas FGF-23 suppresses vitamin D activation. Therefore, simultaneous measurement of FGF-23, PTH, calcium, phosphate, and vitamin D may provide substantially more information than assessment of any single biomarker [16].

This network perspective is particularly important in postmenopausal women because age-related changes in renal function, dietary intake, vitamin D status, and skeletal remodeling may alter several components of the system simultaneously.

Estrogen deficiency is a fundamental driver of postmenopausal bone loss. Estrogen normally suppresses excessive osteoclast activity and helps maintain a balanced relationship between bone resorption and bone formation [11,14].

Following menopause, reduced estrogen signaling leads to increased osteoclastogenesis and enhanced bone resorption. Cytokines and receptor activator of nuclear factor-κB ligand (RANKL)-related pathways contribute to this remodeling imbalance [14].

The early postmenopausal period is characterized by particularly rapid bone loss, after which skeletal decline generally continues at a slower rate with aging [11,14]. The resulting reduction in BMD is most clinically important when it progresses to osteoporosis.

Because FGF-23 is produced predominantly by osteocytes, which are embedded within the mineralized bone matrix, changes in bone remodeling may potentially influence FGF-23 production. Conversely, alterations in systemic mineral metabolism may affect the bone microenvironment [6,19]. This provides a biological rationale for studying FGF-23 together with conventional bone turnover markers and DXA-derived BMD.

FGF-23 should not be regarded simply as a renal hormone because its principal source is bone. Osteocytes act as endocrine cells capable of sensing and responding to changes in mineral metabolism [6,19].

Experimental studies indicate that FGF-23 participates in communication between bone and kidney. However, the direct effects of FGF-23 on bone mineralization are complex and may depend on the cellular context, receptor expression, Klotho availability, phosphate concentration, vitamin D status, and other factors [6,19].

Some experimental findings have suggested that excessive FGF-23 signaling can be associated with impaired mineralization, whereas other evidence indicates that FGF-23 may represent a compensatory response to disturbances in phosphate metabolism rather than a primary cause of skeletal disease [19].

Therefore, a high circulating FGF-23 concentration in a patient with low BMD should not automatically be interpreted as proof that FGF-23 caused osteoporosis. The direction of causality remains an important unresolved issue.

Relationship Between FGF-23 and Low Bone Mass in Postmenopausal Women

Clinical studies specifically examining postmenopausal women provide evidence both for and against an association between FGF-23 and skeletal status.

Shen et al. evaluated 180 women divided into premenopausal, early postmenopausal, and late postmenopausal groups. The investigators measured BMD and several biochemical parameters, including calcium, phosphate, $25(OH)D_3$, intact PTH, osteocalcin, CTX-I,

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

PINP, and FGF-23. Their findings suggested a relationship between serum FGF-23 and low bone mass in postmenopausal women [18].

Celik et al. also investigated postmenopausal women with osteoporosis, osteopenia, and normal bone status. FGF-23 concentrations were higher in the osteoporosis group, while lumbar and femoral BMD values were lower [1]. These findings support the hypothesis that FGF-23 may be associated with skeletal deterioration in some postmenopausal populations.

However, these observations should be interpreted in the context of other mineral metabolism parameters. FGF-23 is closely related to phosphate and vitamin D metabolism, and therefore an apparent relationship with BMD may partly reflect other physiological variables.

Evidence Against a Simple FGF-23–BMD Relationship

Not all clinical studies have demonstrated a significant relationship between FGF-23 and BMD.

Han et al. examined 355 northern Chinese postmenopausal women and evaluated the relationships among serum FGF-23, Klotho, and lumbar spine BMD. After adjustment for relevant covariates, serum Klotho was positively associated with lumbar spine BMD, whereas FGF-23 did not demonstrate a statistically significant independent association with lumbar spine BMD [7].

These findings are important because they indicate that the FGF-23 concentration alone may be insufficient to explain skeletal status. FGF-23 activity depends on receptor availability and Klotho expression, and its biological interpretation may therefore depend on the broader endocrine environment.

Differences among study populations may also explain conflicting findings. Age, ethnicity, renal function, vitamin D status, body mass index, calcium intake, physical activity, menopausal duration, and osteoporosis treatment may all modify observed associations.

Compared with FGF-23, circulating Klotho has increasingly attracted attention as a potential biomarker of skeletal health.

Han et al. reported a positive association between serum Klotho and lumbar spine BMD among northern Chinese postmenopausal women after adjustment for relevant variables [7]. This observation suggests that higher circulating Klotho may be associated with better skeletal status.

Further evidence was provided by Jiang et al., who analyzed data from 871 postmenopausal women participating in NHANES. Higher serum Klotho concentrations were associated with a lower probability of osteoporosis, supporting a potential relationship between Klotho and skeletal health [10].

The biological explanation for this relationship remains uncertain. Klotho may influence bone indirectly through phosphate and vitamin D metabolism, renal function, oxidative stress, and cellular signaling [12,13]. Consequently, the observed association may reflect a combination of direct and indirect mechanisms.

Importantly, serum Klotho should currently be considered a promising research biomarker rather than an established clinical diagnostic test for osteoporosis.

Calcium and phosphate are fundamental components of bone mineral. Their serum concentrations are tightly regulated by PTH, vitamin D, FGF-23, renal function, and intestinal absorption [8,16].

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

Despite their importance, serum calcium is often maintained within a relatively narrow physiological range even when skeletal calcium stores are changing. Consequently, a normal serum calcium concentration does not exclude osteoporosis.

Phosphate is similarly regulated by multiple hormonal mechanisms. FGF-23 is a major phosphaturic hormone, while PTH also increases renal phosphate excretion [8,16].

For future studies of the FGF-23/α-Klotho system, simultaneous measurement of serum calcium and phosphate is therefore essential. These measurements allow interpretation of FGF-23 and Klotho concentrations within their physiological context.

Vitamin D metabolism is closely interconnected with FGF-23. Circulating 25-hydroxyvitamin D [25(OH)D] is the principal indicator of vitamin D status, whereas $1,25(OH)_2D$ represents the active hormonal form.

FGF-23 suppresses renal production of $1,25(OH)_2D$ and promotes its catabolism [3,8]. Conversely, vitamin D signaling can stimulate FGF-23 production, creating an endocrine feedback loop.

Vitamin D deficiency is common among older adults and may contribute to impaired calcium absorption, secondary hyperparathyroidism, and adverse skeletal outcomes. Therefore, 25(OH)D should be included in clinical studies evaluating the relationship between FGF-23/Klotho and BMD.

PTH is one of the principal regulators of calcium and phosphate homeostasis. Its actions overlap with those of FGF-23 in renal phosphate handling but differ in their effects on vitamin D metabolism [16].

PTH stimulates renal 1α-hydroxylase and increases $1,25(OH)_2D$ production, whereas FGF-23 suppresses it. The interaction between these hormones therefore creates a complex regulatory system.

In postmenopausal women, vitamin D insufficiency and reduced calcium intake may increase PTH concentrations. Secondary hyperparathyroidism may then contribute to increased bone turnover. Consequently, measurement of PTH is important when assessing whether an association between FGF-23 or Klotho and BMD represents an independent skeletal relationship or is partly mediated by altered calcium-vitamin D-PTH physiology.

Bone turnover markers provide information that is complementary to BMD.

Procollagen type 1 N-terminal propeptide (P1NP) is widely used as a marker of bone formation, while β-C-terminal telopeptide of type I collagen (β-CTX) reflects bone resorption. Osteocalcin may also be used as a marker of osteoblast-related activity.

Increased bone turnover is characteristic of the early postmenopausal period [11,14]. Therefore, incorporating P1NP and β-CTX into FGF-23/Klotho studies may help determine whether these endocrine biomarkers are associated with the dynamic process of bone remodeling rather than simply with accumulated changes in BMD.

A comprehensive analysis combining FGF-23, Klotho, PTH, vitamin D, mineral concentrations, bone turnover markers, and BMD may therefore provide a more informative biological model.

3.13. DXA and Bone Mineral Density

Dual-energy X-ray absorptiometry (DXA) remains the principal clinical method for evaluating BMD and diagnosing osteoporosis.

According to the International Society for Clinical Densitometry (ISCD), T-scores are preferred for the classification of BMD in postmenopausal women. A T-score of ≤ -2.5 at

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

the lumbar spine, total hip, or femoral neck is consistent with densitometric osteoporosis when measured appropriately [9].
However, BMD is a surrogate measure of bone strength rather than a direct measure of fracture resistance. Bone microarchitecture, cortical porosity, bone turnover, fall risk, and other clinical factors also contribute to fracture risk.
For research purposes, both absolute BMD values and T-scores should be recorded. Lumbar spine, total hip, and femoral neck should preferably be evaluated separately because the association between systemic biomarkers and BMD may differ according to skeletal site.

Discussion

The available evidence supports the concept that FGF-23 and α-Klotho participate in a complex endocrine network connecting bone, kidney, and mineral metabolism. Nevertheless, the relationship between these biomarkers and osteoporosis in postmenopausal women remains incompletely defined.
One important explanation for the heterogeneous clinical findings is that FGF-23 concentration does not necessarily represent FGF-23 biological activity. Canonical FGF-23 signaling requires the presence of α-Klotho and an appropriate FGFR. Thus, two individuals with similar FGF-23 concentrations may have different biological responses depending on Klotho availability and renal function [3,4].
A second explanation is the influence of kidney function. The kidney is a major target organ of FGF-23 and an important site of α-Klotho expression. Changes in renal function can alter both mineral metabolism and Klotho biology [3,4]. Even relatively mild differences in estimated glomerular filtration rate (eGFR) may therefore represent an important confounding factor in observational studies.
A third factor is vitamin D status. Because FGF-23 suppresses active vitamin D production and vitamin D can stimulate FGF-23 expression, the two systems are biologically interdependent [8,16]. Failure to adjust for 25(OH)D may consequently distort the observed association between
The postmenopausal state itself also introduces substantial biological heterogeneity. Women shortly after menopause may have a higher rate of bone turnover than women who are many years beyond menopause. Menopause duration should therefore be considered in statistical analyses.
The available evidence concerning Klotho may be particularly interesting. The positive association between circulating Klotho and lumbar BMD reported by Han et al. [7], together with the lower probability of osteoporosis among women with higher Klotho concentrations in the NHANES analysis by Jiang et al. [10], suggests that Klotho deserves further investigation.
However, these studies are observational and cannot establish causality. It remains uncertain whether reduced Klotho contributes directly to bone loss, reflects biological aging, is influenced by renal function, or represents a marker of broader metabolic health.
Renal function is a critical variable in studies of FGF-23 and Klotho.
FGF-23 signaling is strongly connected with renal phosphate excretion and vitamin D metabolism [3,4]. α-Klotho is highly expressed in the kidney, and renal impairment is

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

associated with alterations in Klotho biology.
For this reason, serum creatinine and eGFR should be included in any clinical study evaluating FGF-23/Klotho and BMD. Failure to account for renal function may lead to misleading conclusions.
In statistical analyses, eGFR can be included as a covariate. In larger studies, stratified analyses according to renal function may also be appropriate.
An important methodological issue is that different laboratory assays measure different forms of FGF-23.
Commercial assays may measure intact FGF-23 or C-terminal FGF-23 fragments. These assays are not interchangeable and can produce substantially different numerical concentrations [5,20,23].
Pre - analytical handling is also important. FGF-23 may be unstable under certain storage and temperature conditions, and sample handling can influence measured concentrations [20,23].
Therefore, future clinical studies should report:
the exact FGF-23 assay used;
whether intact or C-terminal FGF-23 was measured;
sample collection and processing conditions;
storage temperature and duration;
assay manufacturer;
analytical sensitivity and intra-/inter-assay variability.
These details are necessary for reproducibility and meaningful comparison between studies.
An exploratory concept for future research is assessment of the relationship between FGF-23 and α-Klotho rather than analyzing either biomarker independently.
A theoretical FGF-23/α-Klotho ratio could potentially reflect the balance between ligand availability and co-receptor availability. However, this ratio is not currently an established clinical biomarker and should not be presented as a validated diagnostic indicator.
Its value could be investigated prospectively by determining whether it improves the prediction of low BMD or osteoporosis beyond conventional clinical variables and individual biomarker concentrations.
Such analysis should be considered exploratory and hypothesis-generating.
Based on the reviewed evidence, a comprehensive future study in postmenopausal women could include the following variables.
Primary endocrine/mineral biomarkers: FGF-23, α-Klotho, PTH, 25(OH)D.
Mineral parameters: serum calcium, phosphate, magnesium, alkaline phosphatase.
Bone turnover markers: P1NP, β-CTX, osteocalcin.
Renal parameters: serum creatinine, eGFR.
Skeletal parameters:lumbar spine BMD, total hip BMD, femoral neck BMD, T-scores.
Clinical covariates: age, BMI, duration since menopause, physical activity, dietary calcium intake, vitamin D intake/supplementation, smoking, alcohol consumption, medications affecting bone metabolism, history of fragility fracture.
This comprehensive panel would allow the independent contribution of FGF-23 and Klotho to be evaluated while accounting for major biological confounders.
The statistical strategy should be defined before analysis.
First, descriptive statistics should be used to characterize the study population and

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 12.09.2026 Accepted 14.09.2026 Online 19.09.2026

distribution of biomarker concentrations.
Second, Pearson or Spearman correlation analysis can be used to assess relationships between FGF-23, α-Klotho, mineral metabolism markers, bone turnover markers, and BMD.
Third, multivariable linear regression can evaluate whether FGF-23 or Klotho independently predicts continuous BMD values after adjustment for age, BMI, menopause duration, vitamin D status, PTH, eGFR, calcium, phosphate, and other relevant covariates.
Fourth, logistic regression can be used when osteoporosis is treated as a binary outcome.
Fifth, receiver operating characteristic (ROC) analysis can explore the ability of individual biomarkers or combinations of biomarkers to discriminate women with osteoporosis from those without osteoporosis.
A combined model including FGF-23, α-Klotho, PTH, 25(OH)D, calcium, phosphate, eGFR, and clinical factors may be compared with conventional clinical models.
Importantly, statistical association should not be interpreted as proof of causality. Longitudinal studies will be required to determine whether baseline FGF-23 or Klotho predicts subsequent BMD decline or incident fracture.
Several limitations should be considered when interpreting the available literature.
First, most clinical studies are cross-sectional. Consequently, temporal relationships between biomarker changes and BMD loss cannot be established.
Second, studies differ considerably in participant characteristics, including age, ethnicity, menopausal duration, vitamin D status, BMI, and renal function.
Third, FGF-23 assays are heterogeneous. Intact and C-terminal assays measure different molecular forms and should not be directly compared without appropriate consideration [5,20,23].
Fourth, serum Klotho measurement is also affected by methodological considerations, and the biological interpretation of circulating soluble Klotho remains under investigation.
Fifth, BMD reflects accumulated skeletal changes but does not directly measure bone turnover or microarchitecture.
Finally, many studies have limited sample sizes and may not adequately control for all potential confounders.
The FGF-23/α-Klotho system represents a potentially important link between mineral metabolism and skeletal health.
From a clinical perspective, measurement of these biomarkers is not currently a substitute for DXA-based BMD assessment or established osteoporosis risk evaluation. Instead, their primary value at present is scientific and investigational.
From a research perspective, simultaneous assessment of FGF-23 and α-Klotho may provide a more complete picture of mineral metabolism than measurement of FGF-23 alone. Integration with PTH, vitamin D, calcium, phosphate, renal function, bone turnover markers, and DXA may help identify biologically distinct phenotypes of postmenopausal bone loss.
Future longitudinal research could determine whether FGF-23 or Klotho predicts changes in BMD, development of osteoporosis, or fragility fractures. Such studies could also clarify whether changes in the FGF-23/Klotho system are consequences of aging and bone loss or active contributors to skeletal deterioration.

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 12.09.2026 | Accepted 14.09.2026 | Online 19.09.2026

Conclusion

The FGF-23/α-Klotho system is an important component of the endocrine regulation of phosphate and vitamin D metabolism and represents a biologically plausible pathway linking bone, kidney, and systemic mineral homeostasis.

Current evidence suggests that the relationship between FGF-23 and BMD in postmenopausal women is complex and inconsistent. Some studies have reported higher FGF-23 concentrations in women with osteoporosis or low bone mass, whereas other studies have not identified an independent association after adjustment for relevant factors [1,7,18].

In contrast, circulating α-Klotho has shown a potentially more consistent positive relationship with BMD and a possible inverse association with osteoporosis risk in observational studies [7,10]. Nevertheless, these findings require confirmation in larger, longitudinal, and methodologically standardized studies.

Future original research should therefore evaluate FGF-23 and α-Klotho together with PTH, 25(OH)D, calcium, phosphate, magnesium, bone turnover markers, renal function, and DXA-derived BMD. An exploratory FGF-23/α-Klotho ratio may also be investigated, but it should currently be regarded as a research hypothesis rather than a validated clinical marker.

A comprehensive analytical approach may ultimately clarify whether the FGF-23/α-Klotho system represents merely a marker of altered mineral metabolism or an important biological pathway contributing to postmenopausal skeletal deterioration.

References

1. Celik E, Guzel S, Abali R, Guzelant AY, Celik Guzel E, Kuçukyalcin V. The relationship between fibroblast growth factor 23 and osteoporosis in postmenopausal women. Minerva Med. 2013;104(5):497–504.
2. Determination of fibroblast growth factor 23. Ann Clin Biochem. 2009. doi:10.1258/acb.2009.009066.
3. Erben RG. Update on FGF23 and Klotho signaling. Mol Cell Endocrinol. 2016;432:56–65. doi:10.1016/j.mce.2016.05.008.
4. Erben RG, Andrukhova O. FGF23-Klotho signaling axis in the kidney. Bone. 2017;100:62–68. doi:10.1016/j.bone.2016.09.010.
5. Fauconnier C, Roy T, Gillerot G, Roy C, Pouleur AC, Gruson D. FGF23: Clinical usefulness and analytical evolution. Clin Biochem. 2019. doi:10.1016/j.clinbiochem.2019.03.002.
6. Fukumoto S. FGF23/Klotho and bone metabolism. Clin Calcium. 2009;19(7):945–950.
7. Han W, Bai XJ, Han LL, Sun XF, Chen XM. The relationship between serum fibroblast growth factor 23, Klotho, and lumbar spine bone mineral density in northern Chinese postmenopausal women. Menopause. 2019;26(5):546–553. doi:10.1097/GME.0000000000001276.
8. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 12.09.2026 | Accepted 14.09.2026 | Online 19.09.2026

Rev Physiol. 2013;75:503–533. doi:10.1146/annurev-physiol-030212-183727. [11.09.2026 11:06]
9. International Society for Clinical Densitometry. 2023 ISCD Official Positions—Adult. ISCD Official Positions. 2023.
10. Jiang J, Liu Q, Mao Y, Wang N, Lin W, Li L, et al. Klotho reduces the risk of osteoporosis in postmenopausal women: a cross-sectional study of the National Health and Nutrition Examination Survey (NHANES). BMC Endocr Disord. 2023;23:151. doi:10.1186/s12902-023-01380-9.
11. Kato S. Hormones and osteoporosis update. Estrogen and bone remodeling. Clin Calcium. 2009;19(7):951–956.
12. Kuro-o M. Klotho as a regulator of oxidative stress and aging. Biol Chem. 2008;389(3):233–241.
13. Kuro-o M. Klotho and aging. Biochim Biophys Acta. 2009;1790(10):1049–1058.
14. Lerner UH. Bone remodeling in post-menopausal osteoporosis. J Dent Res. 2006;85(7):584–595. doi:10.1177/154405910608500703.
15. McNamara LM. Osteocytes and estrogen deficiency. Curr Osteoporos Rep. 2022. doi:10.1007/s11914-021-00702-x.
16. Portales-Castillo I, Simic P. PTH, FGF-23, Klotho and Vitamin D as regulators of calcium and phosphorus: genetics, epigenetics and beyond. Front Endocrinol (Lausanne). 2022;13:992666. doi:10.3389/fendo.2022.992666.
17. Razzaque MS. The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis. Nat Rev Endocrinol. 2009;5:611–619.
18. Shen J, Fu S, Song Y. Relationship of Fibroblast Growth Factor 23 (FGF-23) Serum Levels With Low Bone Mass in Postmenopausal Women. J Cell Biochem. 2017;118(12):4454–4459. doi:10.1002/jcb.26101.
19. Sirikul W, Siri-Angkul N, Chattipakorn N, Chattipakorn SC. Fibroblast Growth Factor 23 and Osteoporosis: Evidence from Bench to Bedside. Int J Mol Sci. 2022;23(5):2500. doi:10.3390/ijms23052500.
20. Stability and degradation of fibroblast growth factor 23 (FGF23): the effect of time and temperature and assay type. Osteoporos Int. 2016. doi:10.1007/s00198-016-3543-5.
21. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006;444:770–774.