Al-Kindy College Medical Journal (KCMJ)

Review Article

Emerging Markers in Osteoporosis, A Review

Wassan Nori [1*], Mohammed Jaffer Jawad [2], Munaf Jarallah Yaseen [3], Mufeed Akram Taha [4], Reia Jaber [5]

[1] Department of Obstetrics and Gynecology, College of Medicine, Mustansiriyah University, Baghdad, Iraq
[2] Department of Orthopedic Surgery Mustansiriyah University, College of Medicine, Baghdad, Iraq
[3] Department of pediatrics, College of medicine, University of Baghdad, Baghdad, Iraq.
[4] Department of Medicine, College of Medicine, University of Kirkuk, Azadi Teaching Hospital, Kirkuk, Iraq.
[5] Orlando Health/ Department of Infection Prevention & Control, Florida, United States of America
* Corresponding author's email: Dr.wassan76@uomustansiriyah.edu.iq

Article history:
Received 10 April 2026
Accepted 16 July 2026
Available online 1 August 2026

DOI: 10.47723/y86mr443

Keywords: Osteoporosis; bone turnover markers; endocrine markers; inflammatory biomarkers; multiomics; combined biomarker panels; performance; cost.

ABSTRACT

Osteoporosis is a global health concern with bone frailty and high fracture risk. Existing diagnostic paradigms largely rely on bone scanning and bone mineral density evaluation which are hindered by the delayed prediction of fractures, especially in high-risk groups. This review assesses existing and novel Osteoporosis biomarkers, their mechanisms, clinical efficacy, drawbacks, and discusses the best biomarkers in Osteoporosis risk stratification and management, to convert them into better patient care. An online search was conducted, including PubMed, Web of Science, Embase, and Google Scholar up to June 2026. Passed studies were reviewed critically and organized biomarkers into five different panels: traditional and bone turnover markers, mineral metabolism and endocrine regulators, inflammatory and immune mediators, novel metabolic and multi-omics biomarkers, and combined biomarkers panels. The traditional markers are still useful in therapeutic monitoring although they have a natural biological variability that cannot be used to achieve optimum diagnostic use. Combined and inflammatory mediator panels showed greater discriminative ability, with Net Reclassification Index of improvements of 0.15-0.23, which appropriately reclassified 15-23 percent of intermediate-risk patients who were misidentified using traditional screening. The highest performance acquisition was experienced in diabetic cohorts where density-based measurements often miss. The management of osteoporosis should be changed to precision medicine with multi-dimensional biochemical profiling. The clinical utility and cost-effectiveness of the integrated approach in biomarkers make them a mandatory complement to imaging and a crucial point in holistic patient care for improved prognosis.

Introduction

Osteoporosis [OP] is a metabolic disease characterized by reduced bony mass and microarchitectural deterioration. It ultimately leads to substantial morbidity and fragility, factored by reduced quality of life. The overall burden of the disease is globally rising with increased life expectancy and risk factors, including genetic factors, and early menopause. OP and osteopenia prevalence based on recent WHO criteria is around 19.8%. OP is a disease that is better prevented than treated [1,2].

For a long time, radiological prediction has been the gold standard for prediction. However, significant gaps still hinder the reliable detection [3].

Radiological diagnosis of OP by dual-energy X-ray absorptiometry [DXA-Scan] has limitations. One is that it provides a statistical

measure of bone mineral density [BMD] without offering insight into the bone's internal environment, including quality and turnover [4].

Consequently, many patients experience fractures despite having BMD values above the OP threshold. Several clinical risk tools, such as FRAX [Fracture Risk Assessment Tool], were proposed to enhance predictive value [5]. However, The utility or application of FRAX was limitedby their variability across different populations and the lack of biological and molecular insight into the bone internal environment. Taken together, these limitations led to missed opportunities for timely intervention [6].

Giant leaps in molecular biology, high-throughput platforms, and integrative analytics have made biological markers a promising option for OP prediction. Biological markers reflect the dynamic metabolic environment of the bone and systemic influences, distinguishing early skeletal bony changes before structural deterioration occurs, which are captured by imaging [7,8].

The advancement presented by biomarkers enables stratification of population risk, implementation of personalized therapy, and monitoring of disease progression [9,10].

The current review critically discusses the current and emerging OP biomarkers by exploring their underlying mechanism, advantages, limitations, and performance in clinical practice. We aim to highlight how biological markers are reshaping OP prediction, risk stratification, and management. Our goal is to provide evidence-based reference for clinicians with a comprehensive, integrated overview that can be translated into improved patient care.

Understanding osteoporosis

Bone health is maintained throughout a process called bone remodeling, a continuous process that keeps the bone integrity intact. The process of bone formation and resorption is maintained in a delicate balance among healthy individuals [11]. Should that balance get disturbed, the net will be progressive structural fragility, microarchitecture bone damage that ultimately ends with OP [12]. To keep that equilibrium valid, 3-cell types are involved: osteoblast, osteoclast, and osteocytes.

Osteoclasts are hematopoietic cell precursors that reabsorb old or damaged bone. Later, they undergo apoptosis, triggering signaling factors that initiate the bone formation phase. Osteoblast cells [Mesenchymal stem cell–derived] migrate to the resorption pit, depositing new matrix to restore bone volume [13]. Part of these osteoblasts will be encased in the mineralized matrix to become the most abundant bony cell type, i.e., the osteocytes. The latter serves as the central remodeling regulator; they behave as mechanosensors. Once there is mechanical bone strain and microdamage, osteocytes release molecular signals that orchestrate osteoblast and osteoclast activity [14]. Peri-lacunar remodeling allows osteocytes to modify the surrounding bone directly [15].

There are multiple factors that tilt the balance inside the bone toward excessive bone resorption and inadequate bone formation, for instance, hormonal factors, nutritional deficiencies, inflammation, and genetic predisposition [16-18].

Once the balance is tilted, the result will be apparently normal bone, but it is structurally

weakened. A deeper insight into this dynamic cellular-interplay enhances our understanding of the limitations of conventional diagnostic tools and deepens our appreciation for advanced biomarkers in OP, highlighting the necessity for improvement [19].

Subjects and Methods

Review design and literature search strategy

This mini review adopted online search throughout electronic databases like PubMed, WOS, Embase and Google Scholar to cover publications up to November 2025. A combination of MeSH terms and free text keywords was used [osteoporosis, bone turn over markers, endocrine markers, inflammatory biomarkers, multiomics, combined biomarkers panels, advantage, performance, cost.

Inclusion criteria: Peer reviewed human studies, including controlled trials, systematic reviews, meta-analyses, observational studies published in English up to June 2026. Studies focusing on OP biomarkers and their diagnostic or predictive role were prioritized. All studies involving adult human aged≥ 18 years. We did not start time restriction for inclusion however we include studies published in electronic databases mentioned earlier with no lower date restriction and with an upper limit of June 2026.

Exclusion Criteria: Case reports, editorials, letters to the editor, conference abstracts, in vitro, animal studies and non-English publications, given the review's primary focus was on clinical applicability. Studies lacking sufficient methodological details and performance, such as sensitivity, specificity, and AUC were all excluded.

The selection of studies was performed according to a two-stage process, with initial screening based on title and abstract, and a second stage involving a full-text assessment. Both stages were carried out separately by two researchers, with any discrepancies resolved through a consensus process, with a third researcher acting as a mediator in any disputes. All studies meeting the predetermined selection criteria were included, with no studies excluded based on the nature of their findings in order to avoid any potential selection bias. The Extracted data were synthesized to provide a structural overview regarding the biological basis, clinical applicability, limitations, and future potential, see Fig 1.

Markers were categorized into five panels.

- Traditional Bone Turnover Markers
- Mineral Metabolism & Endocrine Markers
- Inflammatory & Immune Markers
- Novel Metabolic & Multi-Omics Markers
- Combined Biomarker Panels

Results

Traditional bone turnover markers [BTM]

The bone is not a static tissue; it is in a delicate balance of bone formation [by the osteoblast] and bone resorption [by the osteoclast]. This balance is called bone remodeling. Makers of bone remodeling can reflect the bone internal environment and are measured in serum or urine [20,21].

If these markers increase, it indicates that bone turnover is elevated, underscoring deterioration in bone health and an increased risk of fragility. These makers are categorized into:

- bone formation markers [total and bone-specific alkaline phosphatase [ALP], procollagen type 1 N-propeptide [P1NP], osteocalcin, and procollagen type 1 C-propeptide [P1CP] [22,23].
- bone resorption makers [pyridinoline, tartrate-resistant acid phosphatase 5b, deoxypyridinoline, the carboxy-terminal cross-linked telopeptide of type 1 collagen [CTX-1], and the amino-terminal cross-linked telopeptide of type 1 collagen [NTX-1] [24,25]

What is special about these markers is their sensitivity to the changes in bone turnover rates, which makes them recommended to check adherence and response to treatment [26] .The most recommended markers by the International Osteoporosis Society for predicting fracture risk and OP therapy are [P1NP and CTX-1] for bone formation and resorption, respectively [27]. One of their limitations is that they do not specify the affected bone, but rather reflect overall bone turnover. For that, they are recommended as an adjuvant tool rather than a sole detection tool alongside DXA [28], see **Table 1.**

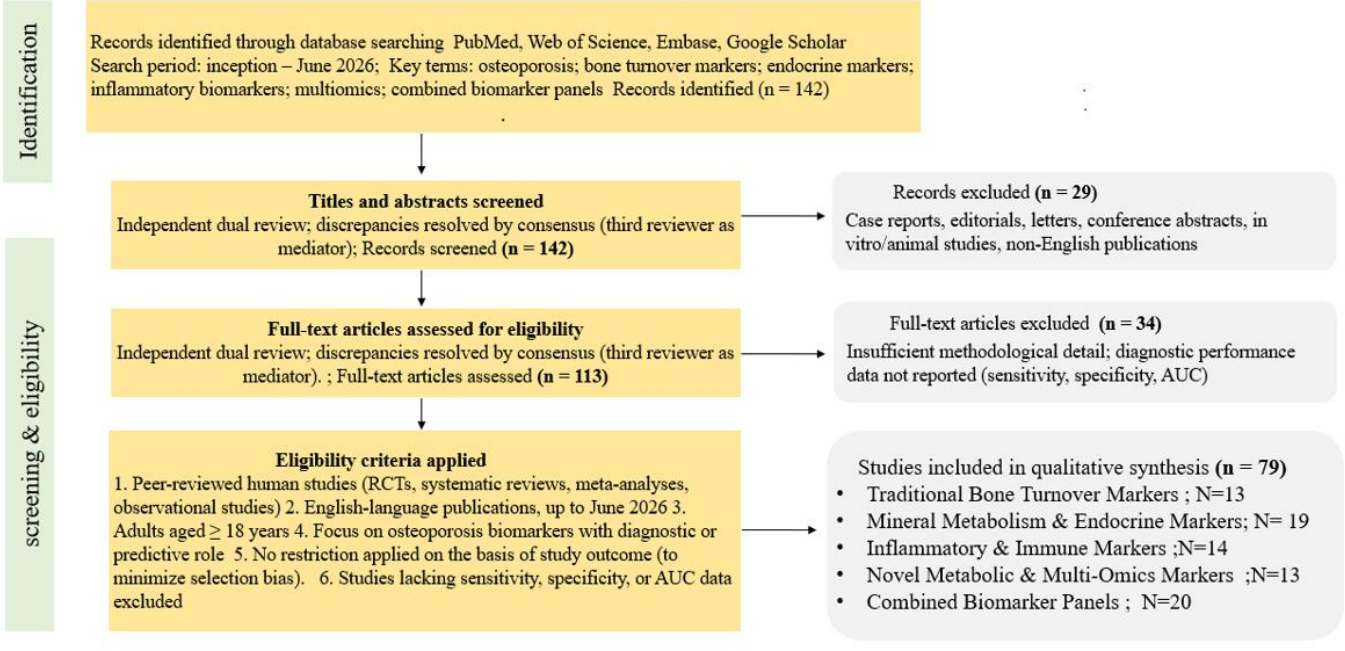

Fig 1: study flow chart showing how studies were included and excluded

Table 1 summarizes the most common BTM, their methods, sampling specimen advantages, limitations, and performance.

Biomarkers	Method/ sample used	Mechanism of action	Advantage	Limitation	Performance	reference
PINP [Procollagen Type I N-terminal Propeptide]	Immune assay; ELISA, ECLIA; Serum/Plasma;	They mirror osteoblast activity & bone formation. High levels mean rapid bone turnover.	FDA-approved for monitoring It has Low diurnal variation Sit is stable in serum Strong fracture prediction [HR 1.2–1.6]	Affected by liver disease & has Renal clearance issues Limited population data • The test is Expensive	**Good** AUC: 0.65–0.75 Sensitivity: 65–75%	29
BSAP [Bone-Specific Alkaline Phosphatase]	ELISA, IRMA; Serum sample	It measures the Enzyme released during bone formation, i.e., it reflects bone-forming activity [osteoblast]	Long clinical history & is widely available The assay is Heat-stable	The results may show cross-reactivity with liver ALP The test showed Age-dependent variation & has limited specificity	Fair AUC: 0.55–0.68 Sensitivity: 50–60%	30

				There is poor assay standardization		
Osteocalcin [Total & Undercarboxylated]	ELISA, RIA; Serum; Cost: $30–40	Marker of osteoblast function & vitamin K status. Undercarboxylated form = poor bone quality.	• Bone-specific protein • Reflects vitamin K status • Related to fracture geometry • Metabolic insights	• Very unstable • Multiple isoforms • Temperature sensitive • Difficult interpret	Poor AUC: 0.50–0.63 Sensitivity: 45–55%	31
CTX-I [C-terminal Telopeptide] [resorption biomarker]	Immune assay ; ECLIA, ELISA; fasting Serum samples	It measures collagen degradation, i.e., reflects bone resorption [osteoclast activity]. High levels mean increased bone resorption.	Gold standard as a resorption biomarker Extensive available clinical data Licensed for treatment monitoring & has a Rapid therapy response	It has a severe diurnal variation [~50%]. The patient should fast The renal function test should be good. It has poor fracture prediction alone.	Fair AUC: 0.60–0.70 Sensitivity: 55–65%	32
TRACP 5b tartrate-resistant acid phosphatase 5b [resorption biomarker]	Its measured using monoclonal antibody-based immunoassay [ELISA], ELISA; done on Serum samples	It reflects osteoclastic enzyme directly and is not cleared renal system for that	it has the advantage of giving reading when CTX reading become unreliable in renal failure cases can monitor anti resorptive treatment	Limited availability , not yet validated for fracture prediction nor OP.	It showed moderate performance in practice and has association with long term risk of fracture	33

ELISA: Enzyme-Linked Immunosorbent Assay, ECLIA: Electrochemiluminescence Immunoassay, IRMA: Immunoradiometric Assay; RIA: Radioimmunoassay, AUC; Area Under the Curve

The data displaced in Table 1 unveil an interesting pattern: while P1NP stands out as the marker with most favorable performance [AUC 0.65–0.75, sensitivity 65–75%] and showing a low diurnal variability, the gold-standard CTX-I — as resorption marker — is severely constrained by diurnal variation of up to 50%, demanding mandatory fasting morning samples to be clinically valid [29,32].

Osteocalcin showed poorest performance across studies [AUC 0.50–0.63], owing to thermal instability in addition to multiple isoforms that complicate assay standardization [31]. Collectively, the tabulated evidence confirms that no single BTM reaches diagnostic-grade performance in isolation, which imply that these markers are adjunctive rather than primary tools [20,28].

Mineral metabolism and endocrine markers

Here we have bone markers involved in calcium and phosphates hemostasis as well as the hormones that govern bone metabolism. These markers gives insight into systemic factors that affect bone health by reflecting the underlying mechanisms of bone loss such as endocrine dysfunction and nutritional deficiency [34,35]

Some of these key factors [include Parathyroid Hormone [PTH], Vitamin D, Calcium, Phosphate, Fibroblast Growth Factor 23 [FGF23], and Estradiol [17β-Estradiol]. PTH is one of these hormones that critically regulate calcium and phosphate levels and indirectly impact bone remodeling [36-38].

for example, PTH once increased, can cause bone resorption; where is vitamin D deficiency is an another risk factor for OP. Calcium and phosphate levels reflects the overall mineral balance, and abnormal levels underscore systemic illness that impact bone health [39].

Evaluation of these biomarkers aids in the diagnosis and management of OP and other related bone diseases; moreover, monitoring changes in their levels can help assess response to therapy, especially among cases receiving supplement or pharmacological therapy [40,41].

Typically, these markers are used in connection with bone density measurement in the diagnosis of OP. It is worth noting that the interplay of these hormones and minerals is quite complex, and the interpretation of a single marker can be challenging. The levels of these markers can be influenced by diet, kidney function, drugs, and other medical comorbidities; thus, careful evaluation is required [42].

Table 2 shows a comparison of the most researched mineral metabolism and endocrine markers.

As shown in **Table 2,** Vitamin D exhibits the broadest evidence base between endocrine markers [AUC 0.68–0.78], however the threshold controversy — with sufficient levels inconsistently defined between 20 and 50 nmol/L across enrolled studies — hinders direct clinical translation [36, 43, 44]. PTH present a more limited and indirect predictive performance . PTH value is focused on identifying secondary OP causes rather than primary fracture prediction, a distinction that carries direct implications in clinical practice [45]. Despite that FGF-23 is ,mechanistically sound among CKD populations, the current evidence remains preliminary with no validated clinical threshold in daily practice cut-off established [53].

Inflammatory & Immune Markers in Osteoporosis

The delicate balance between bone formation and bone resorption can be influenced by various inflammatory and autoimmune processes that ultimately affect bone remodeling [55]. Imbalance in these biomarkers can increase bone resorption and reduce bone formation. Moreover, pro-inflammatory cytokines can promote osteoclast differentiation, leading to suppressed osteoblast formation and differentiation, and shifting the balance for bone resorption, which contributes to bone loss and increased fracture risk [56,57.]

Furthermore, the chemokines that recruit immune cells may indirectly impact bone remodeling [58]. Many novel inflammatory markers are being examined for their potential in predicting low BMD or OP risk, aiming for a newer approach in preventing, diagnosing, and treating OP [see Table 3]. It is worth noting that these markers are not currently used as standalone diagnostic biomarkers; they hold promise for stratification of the fracture risk, monitoring disease progression, and assessing therapeutic targets. One of the limitations of these biomarkers is their non-specificity, as they may rise in various inflammatory conditions other than OP [59].

Taken together data in Table 3 reveals that RANKL/OPG ratio surpassed individual cytokine measurement [AUC 0.62–0.74 vs 0.53–0.62 for IL-6], which reinforces the mechanistic view that osteoclast activators and inhibitors interplay — rather than a solitary signaling pathway is what drives bone resorption [60]. Still , as the SII data from the postmenopausal cohort by Di et al [63], discussed that inflammatory mediators derived from routine blood counts has pragmatic clinical advantage added to their accessibility making them appealing option over RANKL/OPG and TNF-α that are hindered by technical complexity and inter assay variability.

Novel Metabolic and Multi-Omics Markers in Osteoporosis

This category represents an advanced approach aimed at understanding the complex pathology of OP. These categories provide a holistic approach for OP understanding by integrating more than one pathway [genomics, transcriptomics, proteomics, and metabolomics] to leverage our understanding beyond traditional BTM [64] .

In proteomics, researchers tend to analyse large-scale protein profiling and identify candidates to mitigate their risk, improving diagnostic accuracy and giving mechanistic insight [64,65]. Metabolomics involves analyzing small metabolites to provide a snapshot of cellular activity. For instance, alanine can serve as a potential biomarker in post-meal conditions, particularly in cases of Type 2 diabetes [66]. MicroRNA [miRNA], also known as osteomiRs, regulates gene expression, acting as serum-based biomarkers [67].

Multi-omics integration unveils a complex interaction, like a genetic variant, that guides bone metabolism and pathway [i.e., MAPK/TGF-β, ans WNT/β-catenin]. These markers hold promise in personalized medicine via early diagnosis, risk stratification, and disease progression; these markers may guide personalized treatment and serve as independent diagnostic markers [68].

One of the promising biomarkers is sclerostin [bone formation inhibitor] which showed potential of therapeutic as well as predictive value for OP. Romosozumab ; an anti-sclerostin inhibiter showed strong efficacy in reducing vertebral fractures by 70 % , still the studies are conflicting and needs further validation [69]. These markers are hindered by cost, data complexity, and need for validation; [see Table 4]. Additionally, the causal association needs rigorous studies and advanced bioinformatics instruments.

The above table clarify the negative relationship between mechanistic complexity and clinical applicability in this category. Metabolomic panels and miRNA signatures accomplish the best discriminative performance [AUC 0.80–0.93], yet both are limited to research settings owing to cost, technical difficulty, and lack of multicenter validation [71, 73]. Sclerostin has a clinically unique place: its AUC of 0.67–0.76 is modest compared to multi-omics panels, still its dual role as a predictive biomarker and therapeutic target for Romosozumab making it the most promising candidate for clinical translation among this panel [67, 72]. On the other hand AGEs demonstrate a meaningful performance especially in diabetic subgroups [70], which confirms its value as a disease specific biomarker

The Combined Biomarker Panels

Owing to the multifactorial nature of osteoporosis, a single biomarker cannot capture the whole picture. By integrating combined biomarker panels from multiple categories, such as BTM, mineral/endocrine biomarkers, inflammatory mediators, and omics-driven biomarkers, along with clinical risk factors, we aim to improve diagnostic accuracy, better stratify risk, and monitor therapeutic response [64].

This approach collects diverse biological signals to provide a deeper insight into the inner bone health environment—for instance, combining clinical risk factors and hip BMD improves risk score prediction by 30% [74]. Through multi-omics integration, we will gain a deeper understanding of genetic variants and pathways that impact bone metabolism [75, 76]. Machine learning, on the other hand, enables the interpretation of complex datasets, yielding optimal marker combinations with the highest predictive accuracy for osteoporosis [77,78].

This panel holds promise for earlier prediction, more accurate diagnosis, and better response follow-up, especially in cases with borderline bone density or unclear pathology. It also holds promise for high-risk individuals by enabling precision health options. One of the significant challenges of their application in practice is the complexity of interpreting the data, as there are no standardized panels to compare to [79]; see **Table 5.** Since most of them are in the research phase, they suffer high costs and need validation to be translated into clinical practice.

The compound panel give the best evidence for the core argument of this review. The panels incorporating BTM, inflammatory and metabolic markers reliably yielded improvements in NRI of 0.15–0.23 over traditional screening in the validation cohorts — corresponding to correctly reclassifying between 15% and 23% of intermediate-risk patients [99,100]. The figures for the diabetic cohort [NRI 0.31] are noteworthy: this is precisely the population for which BMD-based tools perform poorest, and alongside where biomarker panels provide highest additive benefit [101,102]. Optimization of panel using machine-learning yielded a further improvement [AUC was increased up to 0.83 in recent works] [77,78] which open the path for future implementation in practice.

Table 2: Mineral Metabolism and endocrine markers comparison with respect to the mechanism of action, advantages, limitations, and performance in OP prediction

Biomarkers	Method/ sample used	Mechanism of action	Advantage	Limitation	Performance	reference
25[OH]D [25-hydroxyvitamin D]	LCMS, CLIA; Serum samples	vitamin D status influences calcium absorption & bone mineralization. Reduced levels predict high fracture risk.	• Routinely used in clinical practice, widely accepted, and cost-effective • has a strong fracture association and serves as a treatable target	The assay has strong seasonal variation [40–60%] & standardization issues. There are threshold controversies. & population differences There are confounding Lifestyle factors.	Good AUC: 0.68–0.78 Sensitivity: 60–75% OR: 1.5–2.2 per SD	43, 44
PTH [Parathyroid Hormone]	ECLIA, IRMA; Serum samples	Secondary hyperparathyroidism is a response of the body to low vitamin D or calcium. Chronic elevation causes bone resorption.	Well-established clinical marker that gives mechanistic insight into mineral metabolism useful biomarker in treatment monitoring	An indirect bone marker that has weak fracture prediction. The assay levels are affected by age-related changes, among other factors . Moreover, there are sample stability issues.	Fair AUC: 0.58–0.67 Sensitivity: 50–65%	45,46
Estradiol [17β-Estradiol]	Immune assay ; ELCA, RIA, Serum sample	Low estrogen levels in menopausal women cause bone loss Very low levels are a good predictor of rapid bone loss	It has strong biological and mechanical insight into OP. It is associated with menopause timing and has a clear therapeutic target.	It has assay sensitivity limits; its levels are very low in postmenopausal women. It showed wide interpersonal variation Expensive test with limited clinical utility	Fair AUC: 0.60–0.72 Sensitivity: 55–70% Best in severe deficiency	47,48
AMH [Anti-Müllerian Hormone]	Immune assay ELISA, SERUM samples	Reflects the ovarian reservoir in women. Low levels were associated with increased fracture risk and fragility fractures	Non-invasive, gives early insight into OP risk	Limited data in practice, it needs validation Show variability across the population	Good Sensitivity:85% & specificity 60%	49,50
Adipokines ; such as : Adiponectin, leptin	Serum samples are analyzed by ELISA	Adipokines interact with bone health via regulating energy, bone remodeling and their effect on inflammatory pathways. Adiponectin is linked with vertebral fracture risk , while leptin is linked to long bone fracture risk	Easily measured and gives insight about the systemic metabolic statues and highlight site specific fracture risk	It showed population diversity Their levels are affected by metabolic syndrome , obesity and other co-morbidities	Independent risk factors for site specific- OP fractures	51,52
FGF23 [Fibroblast Growth Factor 23]	ELISA, SERUM, and plasma samples	Guide phosphate and vitamin D metabolism Disturbed levels affect mineralization	It gives mechanical insight as it links phosphate & mineral metabolism. It has a novel research application with a potential therapeutic target	Limited clinical data; only in research, and it is expensive. Complex regulation with no standard threshold	Currently exploratory	53,54 .

ELISA: Enzyme-Linked Immunosorbent Assay, ECLIA: Electrochemiluminescence Immunoassay, IRMA: Immunoradiometric Assay; RIA: Radioimmunoassay, AUC; Area Under the Curve, LCMS: Liquid Chromatography-Mass Spectrometry; CLIA: Chemiluminescence Immunoassay

Table 3: shows a comparison of Inflammatory & Immune Markers in Osteoporosis with respect to sample used, the mechanism of action, advantages, limitations, and performance in OP prediction.

Biomarkers	Method/ sample used	Mechanism of action	Advantage	Limitation	Performance	Ref
RANKL/OPG Ratio [Receptor Activator of NF-κB Ligand / Osteoprotegerin]	Immune assay ELISA; Serum sample	It mirrors the central pathway of bone makeover. A high ratio means increased osteoclast activity and bone fragility.	It has direct mechanical insight with a strong biological rationale. It has a novel research application with a potential therapeutic target	It has a high cost, is used in research, and has technical difficulty Only with limited clinical application	**Fair** AUC: 0.62–0.74 Mostly research-based evidence	60
IL-6 [Interleukin-6]	ELISA, ECLIA; Serum sample	Pro-inflammatory cytokines stimulate osteoclastogenesis, and chronic elevation is linked to bone loss.	Well-established inflammatory marker with available assays that have biological plausibility Mechanistic association between inflammation & bone	It is a marker of systemic inflammation, which confounds its level;i.e, it lacks specificity. Additionally, it has acute-phase variability. It has limited value as a standalone test, owing to low fracture prediction.	Poor AUC: 0.53–0.62 Non-specific predictor	61
TNF-α [Tumor Necrosis Factor-α]	ELISA, Serum samples	It governs cytokines, leading to bone resorption	Widely used marker in research as an inflammatory factor with mechanistic insight and a promising therapeutic target.	Sample instability and technical challenges with poor reproducibility Highly variable levels with weak predictive power	Poor AUC: 0.50–0.60 Research use only	62
Systemic Immune-Inflammation Index [SII]	Whole blood [hematology testing] – postmenopausal women [n = 238, mean age 60.5 ± 8.1 years]	Composite index derived from platelets, neutrophils, and lymphocytes; reflects systemic inflammatory status that contributes to bone resorption and osteoporosis	Simple, inexpensive, routinely available from standard blood counts	Non-specific marker; influenced by infections, chronic inflammation, and comorbidities	High SII associated with increased risk of osteoporosis and osteoporotic fractures in postmenopausal women	63

ELISA: Enzyme-Linked Immunosorbent Assay, ECLIA: Electrochemiluminescence Immunoassay, IRMA: Immunoradiometric Assay; RIA: Radioimmunoassay, AUC; Area Under the Curve, LCMS: Liquid Chromatography-Mass Spectrometry; CLIA: Chemiluminescence Immunoassay

Table 4: Comparison of Novel Metabolic and Multi-Omics Biomarkers in Osteoporosis with Respect to Sample Used, Mechanism of Action, Advantages, Limitations, and Performance in Osteoporosis Prediction.

Biomarkers	Method/ sample used	Mechanism of action	Advantage	Limitation	Performance	Ref
AGEs [Advanced Glycation End-products]	HPLC, Fluorescence; the samples are : Serum/Tissue	Reflect on the relationship between collagen cross-linking & bone quality deterioration, particularly among diabetic cases.	Assesses bone quality with a strong diabetes–bone link They offer novel mechanistic insights & have strong research potential	It has a high cost, is used in research, and has technical difficulty Only with limited clinical application	Fair AUC: 0.63–0.71 Diabetes subgroup only	70
Metabolomic Panel [Multi-metabolite Signatures]	LCMS/MS; samples include Serum/Urine;	They offer an integrated metabolic profile for bone-related pathways in addition to personalized risk signatures.	They give a systemic biological approach reflected by pathway insight It showed high discrimination power strengthened by personalized signature	It has a very high cost, is used in research, and has technical difficulty Only with limited clinical application	Excellent* AUC: 0.82–0.93 *Proof-of-concept stage	71
Sclerostin [SOST Gene Product]	ELISA; Serum	It is a direct Wnt pathway inhibitor. Increased levels predict bone loss.	Being a direct Wnt signaling inhibitor offers a Novel mechanistic pathway it is refered as independent predictor of Osteoporotic fractures independent of BMD and classical BTMs. early data showed a promising therapeutic target as anti-sclerostin mAbs [romosozumab]	Inconsistent results with age-dependent variability & has technical difficulty It has a high cost, used in research, only not yet approved for clinical practice There was raised metabolic and cardiovascular Complication	Good AUC: 0.67–0.76 Emerging clinical evidence	72
miRNA Panel [MicroRNA Signatures]	qRT-PCR, Array; serum samples	serum mirror bone cell activity & fracture risk by multi-target regulation.	As a multi-target regulator it reflect a potential high specificity. it has therapeutic potential, especially in personalized medicine.	Hindered by high cost, limited to research, and has technical difficulty	Excellent* AUC: 0.80–0.90 *Research settings only	73

HPLC: High-Performance Liquid Chromatography; LC-MS/MS: Liquid Chromatography with Tandem Mass Spectrometry; ELISA: Enzyme-Linked Immunosorbent Assay; qRT-PCR: Quantitative Reverse Transcription Polymerase Chain Reaction

Table 5: Comparison of Combined Biomarker Panels in Osteoporosis with Respect to Components, Mechanism, Advantages, Limitations, and Predictive Performance.

Biomarkers	Method/ sample used	Mechanism of action	Advantage	Limitation	Performance	Ref
Basic BTM Panel [PINP + CTX + 25[OH]D]	This panel has three markers as Standard assays.	It presents an integrative panel that provides data regarding bone formation, resorption, and mineral bone metabolism markers.	They are clinically feasible & acceptable. They have established assays of moderate cost.	They are hindered by diurnal variation, require skilled personnel, they have limited population data. They have moderate performance.	Good AUC: 0.72–0.80 Better than single markers	80-82
Extended Panel [BTMs + Hormones + Inflammatory]	It contains 8–10 markers collected as Mixed assays	by combining multi-pathway risk assessment [bone turnover markers, hormones, and inflammation]	has improved predictive ability via strong mechanistic insight has Strong research applications	has a high cost, is used in research, and has limited clinical validation.	Good AUC: 0.75–0.82 Research-level validation	83,84
AI-Enhanced Panel [Machine Learning Integration]	variable biomarkers are included , with AI algorithms	AI associate multiple biomarkers with clinical and/or demographic data to predict OP risk .	They showed the highest predictive accuracy. have personalized risk stratification as well as adaptive models. with an optimistic future-ready approach	Limited by High cost, implementation barriers & no regulatory approval The decision-making process is challenging to explain to patient. Limited to research	Excellent* AUC: 0.83-0.92 *Experimental validation	85-87
Serotonin+ fat soluble vitamin + BTM[E2, TP1NP, PTH, Osteocalcin, BMI]	serum	Serotonin controls the bone formation and resorption; vitamins A, D3, K as bone control variables; indicators of bone turnover are evidence of dynamic Bony remodeling.	Combines several biochemical and hormonal predictors; is a better predictor of the diagnosis than BMD.	small samples size; external validity is not yet available.	Osteoporosis was detected in 85.7%; Total = 79.8%. Accuracy of internal validation 72.5%. Serotonin and vitamin K had the best predictive roles.	84

Discussion

Summary of Study Finding

The current work had systematically evaluated biochemical markers [five different panel] to predict osteoporosis; including traditional bone turnover markers, mineral metabolism and endocrine markers, inflammatory and immune markers, novel metabolic and multi-omics markers, and combined biomarker panels. The combined panels were found to be substantially better than bone mineral density and FRAX in reclassifying fracture-risk, and thus, fill crucial diagnostic gaps where traditional imaging is not effective, especially in high-risk groups [i.e. renal kidney cases, individuals with hyperlipidemia and patients with type 2 diabetes] [88-90].

The latter have normal or increased BMD but they show paradoxically high rates of fractures because of deteriorated bone quality and microarchitecture [12].

Comparative performance of biomarkers across panels

The conventional bone turnover markers especially s-CTX and s-P1NP remain to be the standards in monitoring therapeutic response but due to their high biological variability, cannot be used as diagnostic tools for osteoporosis; on their own [91,92].

Endocrine markers are specific to detect secondary osteoporosis causes, but have no specificity in fracture prediction as they lack specificity [93,94].

The appearance of new biomarkers provides mechanistic understanding of bone quality: Lecithin-Cholesterol Acyltransferase has diagnostic capability with an Area Under the Curve of 0.822 and a sensitivity of 75.9% and is better than vitamin D screening due to its

dual regulation activity that favors osteoblast differentiation and inhibits osteoclast maturation [95,96.]

Importantly, some markers as sclerostin do not serve as a predictive biomarker, but also a diagnostic indicator. High levels of sclerostin discriminate candidate eligible for to anabolic treatment with Romosozumab, a sclerostin inhibitor, and, therefore, guide therapeutic choice. It is worth noting that sclerostin based requirement for selecting cases and therapeutic strategies to use are still lacking [97,98].

The combination of panels with CTX, P1NP, LCAT, sclerostin, and inflammatory markers and metabolic signatures had better performance, with an improved Net Reclassification Index [NRI] by 0.15-0.23 in validation cohorts, which is equivalent to 15-23 percent of patients with intermediate risks; who were obscured by traditional screening being reclassified appropriately [99,100]. Interestingly, the enhancement achieved by combined panels is highest in diabetic populations (NRI 0.31) where conventional instruments display the worst performance, which is translated to more than half a billion people in the world at high risk of fracture without reduced bone density [101].

It is especially applicable in type 2 diabetes where advanced glycation end product interferes with collagen cross-linking and osteoblast glycolysis with a net effect of inhibiting bone formation despite maintained density measurements [102].

Likewise, the multi-marker evaluation of bone turnover dynamics is beneficial to glucocorticoid-treated patients, chronic kidney disease, and cases suffering mineral metabolism disorders; all of these groups are not visible or captured on static routine imaging [103,104].

See comparative Table 6 .

In summary, this review finding supports a stratified diagnostic paradigm; the classical markers for monitoring therapeutic response; endocrine markers for etiological characterization; multi-omics panels combined for risk reclassification in populations where imaging-based screening performs least well, and there is the most unmet clinical need [88,103,104]. The worth of the panel is in not substituting DEXA as the first-line screening, but properly reclassifying intermediate-risk patients to actionable high-risk or true low-risk groups, to optimize intervention strategies.

Notably, this diagnostic paradigm does not imply the simultaneous application of the five categories in every patient encounter. Rather, it supports the context-driven selection of these five markers based on the patient's phenotypic characteristics. For example, the biochemical profile of a postmenopausal woman with borderline bone density differs from that of a patient receiving glucocorticoids or one with type 2 diabetes and normal bone density [88,103,104]. Standardization of pre-analytical variables, such as fasting morning blood samples for CTX-I, and harmonization of the LCAT and sclerostin assays, remain the main obstacles to the translation of this tiered model into clinical guidelines. As these prerequisites are addressed, the application of multi-dimensional biomarker profiling in combination with traditional densitometry is the only model with any real promise to achieve precision fracture risk assessment—and to bridge the diagnostic gap for millions of high-risk patients, including those with diabetes and glucocorticoid-induced osteoporosis, currently not identified by standard-of-care imaging approaches [101,106].

Clinical implication in practice

The implementation pathway in clinical practice involves consideration of three priorities. To start with, potential validation studies need to define population-specific cutoff points and demonstrate an improvement in the Net Reclassification Index [NRI] across a variety of cohorts. This includes postmenopausal women and patients with diabetes and osteosarcopenia , whereby a simultaneous decrease in muscle mass increases the risk of fractures. 12,105 to become part of the clinical practice instructions, regulatory agreement through standardized panels, parallel to how the lipid panel was developed as a research instrument to be used to screen cardiovascular risk, would be needed. Additionally, they should be approved by worldwide osteoporosis groups to create payment streams [106].

Second, rigid pre-analytical harmonization procedures need to curb CTX diurnal variability, for example by using fasting and morning-only samples, since biological averaging of combined markers does not overcome assay limitations [9].

Third, new biological indicators can be incorporated into treatment strategies. Especially metabolites that are associated with the gut - bacterial- imbalance that favor bone erosion, in addition to biomarkers that remain detectable during anti-resorptive therapy [such as individuals on denosumab] [107,108].

Cost effectiveness and consideration in practice

The health economic value proposition is not similar to mere cost comparison. Though multi-marker panel assessment is more expensive than a single DEXA scan, the cost is reasonable given the prevention of fractures in high-risk groups , where the imaging is not reliable .In fact one fracture of the hip costs healthcare as much as $40,000-80,000; so a small fraction of the fracture in diabetic or glucocorticoid-treated cohorts when prevented via better risk stratification will result in a significant long-term savings [109,110].Also, continuous monitoring of biomarkers enables prompt intervention, which would enable clinicians to take appropriate action to correct metabolic abnormalities before bone is damaged irretrievably. This helps in the administration of treatment in its most effective state [94]. Equally, diagnostic sclerostin measurements are used to select the best candidates to receive Romosozumab, making the most of the costly anabolic regimens to the most likely responder [98].

Strengths and Weaknesses of the Study

The main strength of the present research is in the comprehensive assessment of mechanistically different biomarkers, which combine the novel markers with theragnostic potential. The biomarkers act as a retrospective lens which discloses the longitudinal history of bone metabolic health which provides a granular perspective of bone physiological integrity which is not possible with simple imaging.

Their range is constantly growing besides increasing their diagnostic accuracy which allow screening, stratifying risks, early identifying complications and tracking treatment effectiveness.

These panels are not set to replace the existing imaging; instead, they are poised to complement conventional densitometry [111,112,113]. Their capability to detect subtle variations in the bone microarchitecture even before such changes can be detected through the use of imaging techniques, qualifies them as the promising tools of improved OP

care. Nevertheless, the path is not yet flawless. There are critical issues to address [105]. In spite of being a promising option , there are barriers to clinical translation of OP biomarkers, including a wide range of pre-analytical and data gaps, and the lack of results validation [114].

For that, larger and multicenter cohorts should be used to standardize assay procedures and establish population-specific thresholds, which are needed by the hard and fast requirements of calibration of such markers as CTX [100,111]. Moreover, longitudinal data that follow biomarker patterns during the treatment process is lacking, and prospective studies that measure the health-economic benefit of fracture prevention are also lacking [112-115].To break the existing barriers on standardization, implementing multi-marker panels should be adopted. These panels are the future of osteoporosis treatment, as they enable a shift towards generalized, reactive care and active precision medicine, which is based on personal metabolic signatures.

Table 6 : Comparative landscape of OP biomarkers performance in practice with advantages and limitations

Parameter	Bone Turnover Markers (BTMs)	Mineral Metabolism & Endocrine Markers	Inflammatory & Immune Markers	Multi-Omics Markers	Combined Panels
Advantages	Non-invasive assessment Detects high-turnover before BMD changes Monitors anti-resorptive efficacy	Diagnoses secondary osteoporosis Guides specific interventions (Vit D, hormone therapy) Cost-effective for targeted populations	Links systemic inflammation to bone loss May identify therapy responders	Identifies molecular subtypes Potential for precision medicine Discovers novel drug targets	Higher discrimination than single markers May refine FRAX® predictions
Critical Limitations	High preanalytical variability (±30%) Requires fasting/standardized timing Lacks fracture-specific thresholds Inconsistent reference ranges	Low specificity for fracture risk Seasonal/diurnal variation Does not assess bone quality Weak independent fracture association	No validated assays or cut-points Non-specific (elevated in multiple conditions) No RCT evidence for clinical utility Confounding by comorbidities	Prohibitive cost ($500–$5000+) No clinical-grade standardization Lacks outcome validation Significant confounding/ethical concerns	Increased cost and complexity No consensus panel composition Regulatory/reimbursement barriers Limited head-to-head trials vs. standard care
Evidence Level (1-5)	4/5	4/5	4/5	1/5	2/5
Clinical Readiness	Ready for clinical use	Ready for clinical use	Ready for clinical use	Research-stage	Research-stage
Cost	Moderate	low	ModeraT	High	High
Special notes	Their use is limited to therapy monitoring; insufficient as a standalone fracture predictor	Useful for excluding secondary causes per clinical guidelines. Not recommended for primary fracture risk assessment.	Theoretical only; they requires prospective fracture outcome studies before clinical implementation.	Still in research stage ; they need validation, replication, and demonstrated superiority to FRAX®/BMD	Theoratical only ; Requires demonstration of net reclassification improvement and cost-effectiveness.

Conclusion

Treatment of osteoporosis should be changed towards a density-focused paradigm to a precision medicine paradigm based on combined biochemical profiling. This change is essential in mitigating the diagnostic blindness of DEXA especially in Type 2 diabetes whereby fracture risk is not a result of reduced bone density but a result of impaired bone quality. The diagnostic potential of such markers as sclerostin can help us precisely direct the anabolic therapies to those who will respond the best. Even though the standardization demands strict compliance with the protocols, health economic benefits of fracture prevention among high-risk and density-preserved populations justify the investment in multi-marker strategies as a complementary measure to the standard imaging.

Funding

This work was self-funded

Conflict of Interest

All authors declare that they have no conflict of interest.

Author Contributions

All authors contributed equally to the manuscripts with respect to conception, literature search, writing, editing, and revising. All authors have read and agreed on the final version.

ORCID

Wassan Nori	0000-0002-8749-2444
Mohammed Jawad	0000-0002-4837-498X
Munaf Yaseen	0009-0000-3636-3514
Mufeed Taha	0000-0001-5726-0733
Reia Jaber	0009-0003-0250-8262

References

[1] Xiao PL, Cui AY, Hsu CJ, Peng R, Jiang N, Xu XH, et al. Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis. Osteoporos Int [Internet]. 2022 Oct 1 [cited 2026 Jan 15];33[10]:2137–53. https://doi.org/10.1007/s00198-022-06454-3

[2] Patel D, Saxena B. Decoding osteoporosis: Understanding the disease, exploring current and new therapies and emerging targets. Journal of Orthopaedic Reports [Internet]. 2025 Dec 1 [cited 2026 Jan 15];4[4]:100472. https://doi.org/10.1016/j.jorep.2024.100472

[3] Asadipooya K, Greene LW. Bone mineral density assessment by DXA in disease-associated osteoporosis: the limitations. Frontiers in Endocrinology. 2026 Mar 9;17:1768509. https://doi.org/10.1155/2015/832127

[4] Dimai HP. Use of dual-energy X-ray absorptiometry [DXA] for diagnosis and fracture risk assessment; WHO-criteria, T- and Z-score, and reference databases. Bone [Internet]. 2017 Nov 1 [cited 2026 Jan 15];104:39–43. https://doi.org/10.1016/j.bone.2016.12.016

[5] Whittier DE, Samelson EJ, Hannan MT, Burt LA, Hanley DA, Biver E, et al. A Fracture Risk Assessment Tool for High Resolution Peripheral Quantitative Computed Tomography. J Bone Miner Res [Internet]. 2023 Sep 1 [cited 2026 Jan 15];38[9]:1234–44. Available from: https://doi.org/10.1002/jbmr.4808

[6] El Miedany Y. FRAX: re-adjust or re-think. Arch Osteoporos [Internet]. 2020 Dec 1 [cited 2026 Jan 15];15[1]. Available from: https://doi.org/10.1007/s11657-020-00827-z

[7] Tao R, Qiao MQ, Wang B, Fan JP, Gao F, Wang SJ, et al. Laboratory-based Biomarkers for Risk Prediction, Auxiliary Diagnosis and Post-operative Follow-up of Osteoporotic Fractures. Curr Osteoporos Rep [Internet]. 2025 Dec 1 [cited 2026 Jan 15];23[1]. https://doi.org/10.1007/s11914-025-00914-5

[8] Gao J, Zhang X, Ding J, Zhang H, Zhang X, Jiang J, et al. The characteristic expression of circulating MicroRNAs in osteoporosis: a systematic review and meta-analysis. Front Endocrinol [Lausanne] [Internet]. 2024 [cited 2026 Jan 15];15. https://doi.org/10.3389/fendo.2024.1481649

[9] Biomarkers of Bone Turnover: Molecular Approaches and Clinical Relevance | Bentham Science Publishers [Internet]. [cited 2026 Jan 15]. https://doi.org/10.2174/9781681084954117010l

[10] Li L, Lan X, Zeng W, Xu Y, Chen Q. Risk prediction models for postmenopausal osteoporosis: a systematic review and meta-analysis study. BMC Musculoskelet Disord [Internet]. 2026 Jan 8 ;27(1):12 25. https://doi.org/10.1186/s12891-025-09385-2

[11] Patel D, Wairkar S. Bone regeneration in osteoporosis: opportunities and challenges. Drug Deliv Transl Res [Internet]. 2023 Feb 1 [cited 2026 Jan 15];13[2]:419–32. https://doi.org/10.1007/s13346-022-01222-6

[12] Ahire JJ, Kumar V, Rohilla A. Understanding Osteoporosis: Human Bone Density, Genetic Mechanisms, Gut Microbiota, and Future Prospects. Probiotics Antimicrob Proteins. 2024 Jun;16(3):875-883. https://doi.org/10.1007/s12602-023-10185-0

[13] Föger-Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schindl K, Pietschmann P. Osteoporosis: Pathophysiology and therapeutic options. EXCLI J [Internet]. 2020 [cited 2026 Jan 15];19:1017–37. https://doi.org/10.17179/excli2020-2591

[14] Šromová V, Sobola D, Kaspar P. A Brief Review of Bone Cell Function and Importance. Cells [Internet]. 2023 Nov 1 [cited 2026 Jan 15];12[21]. https://doi.org/10.3390/cells12212576

[15] Evans H, Andrews R, Abedi FA, Sprules A, Trend J, Lovric G, et al. Evidence for peri-lacunar remodeling and altered osteocyte lacuno-canalicular network in mouse models of myeloma-induced bone disease. JBMR Plus [Internet]. 2024 Aug 4 [cited 2026 Jan 15];8[9]. https://dx.doi.org/10.1093/jbmrpl/ziae093

[16] Singh S, Sarma DK, Verma V, Nagpal R, Kumar M. From Cells to Environment: Exploring the Interplay between

Factors Shaping Bone Health and Disease. Medicina [Kaunas] [Internet]. 2023 Sep 1 [cited 2026 Jan 15];59[9]. https://pubmed.ncbi.nlm.nih.gov/37763665/

[17] Karimi SM, Abbaspour F, Tabatabaei-Malazy O, Qolami H, Fayyaz F, Ebrahimi Fana S, et al. Impact of medicinal plants on bone health; a systematic review and meta-analysis of clinical studies. J Agric Food Res [Internet]. 2025 Mar 1 [cited 2026 Jan 15];19:101545. https://doi.org/10.1016/j.jafr.2024.101545

[18] Zhong Y, Yang F, Chen W. Genetically predicted inflammatory cytokines and bone health outcomes: A 2-sample Mendelian randomization study. Medicine (Baltimore) [Internet]. 2026 Mar 6 [cited 2026 Jul6];105(10):e47939. https://doi.org/10.1097/MD.0000000000047939

[19] Na X, Yang Y, Yang H, Chen Z, Qu X, Zhang J, Chen M, Wang D, Breuille D, Yu K, Zhao A and Li Z (2025) The effect of non-pharmacological interventions on bone health among patients with low bone mass: a systematic review and meta-analysis. Front. Endocrinol. 16:1612739. https://doi.org/10.3389/fendo.2025.1612739

[20] Vasikaran SD, Miura M, Pikner R, Bhattoa HP, Cavalier E. Practical Considerations for the Clinical Application of Bone Turnover Markers in Osteoporosis. Calcif Tissue Int [Internet]. 2023 Feb 1 [cited 2026 Jan 16];112[2]:148–57. https://doi.org/10.1007/s00223-021-00930-4

[21] Morris HA, Eastell R, Jorgensen NR, Cavalier E, Vasikaran S, Chubb SAP, et al. Clinical usefulness of bone turnover marker concentrations in osteoporosis. Clin Chim Acta [Internet]. 2017 Apr 1 [cited 2026 Jan 16];467:34–41. https://doi.org/10.1016/j.cca.2016.06.036.

[22] Szulc P. Bone turnover: Biology and assessment tools. Best Pract Res Clin Endocrinol Metab [Internet]. 2018 Oct 1 [cited 2026 Jan 16];32[5]:725–38. https://doi.org/10.1016/j.beem.2018.05.003

[23] Roomi AB, Mahdi Salih AH, Noori SD, Nori W, Tariq S. Evaluation of Bone Mineral Density, Serum Osteocalcin, and Osteopontin Levels in Postmenopausal Women with Type 2 Diabetes Mellitus, with/without Osteoporosis. J Osteoporos [Internet]. 2022 [cited 2026 Jan 16];2022. https://doi.org/10.1155/2022/1437061

[24] Zhong Y, Li J, Luo J, Chen F. Advances in Bone Turnover Markers (PINP and CTX) in Optimizing Anti-resorptive and Anabolic Therapies Against Osteoporosis. Discov Med. 2021 Nov-Dec;32(167):149-154. PMID: 35221001. https://pubmed.ncbi.nlm.nih.gov/35221001/

[25] Chubb SAP, Chubb SAP, Vasikaran SD. Proposed common reference intervals for reference bone turnover markersin osteoporosis. Pathology [Internet]. 2025 Dec 11 [cited 2026 Jan 16];58(1):45-52]; https://doi.org/10.1016/j.pathol.2025.11.001.

[26] Burch J, Rice S, Yang H, Neilson A, Stirk L, Francis R, et al. Systematic review of the use of bone turnover markers for monitoring the response to osteoporosis treatment: the secondary prevention of fractures, and primary prevention of fractures in high-risk groups. Health Technol Assess [Internet]. 2014 Feb [cited 2026 Jan 16];18[11]:1–180. https://doi.org/10.3310/hta18110.

[27] Tao R, Qiao MQ, Wang B, Fan JP, Gao F, Wang SJ, et al. Laboratory-based Biomarkers for Risk Prediction, Auxiliary Diagnosis and Post-operative Follow-up of Osteoporotic Fractures. Current Osteoporosis Reports 2025 23:1 [Internet]. 2025 Apr 8 [cited 2026 Jan 16];23[1]:19-. https://doi.org/10.1007/s11914-025-00914-5

[28] Bhattoa HP, Vasikaran S, Trifonidi I, Kapoula G, Lombardi G, Jørgensen NR, et al. Update on the role of bone turnover markers in the diagnosis and management of osteoporosis: a consensus paper from The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [ESCEO], International…. Osteoporos Int [Internet]. 2025 Apr 1 [cited 2026 Jan 16];36[4]:579–608. https://doi.org/10.1007/s00198-025-07422-3

[29] Tian A, Ma J, Feng K, Liu Z, Chen L, Jia H, et al. Reference markers of bone turnover for prediction of fracture: a meta-analysis. Journal of Orthopaedic Surgery and Research 2019 14:1 [Internet]. 2019 Feb 28 [cited 2026 Jan 16];14[1]:68-. https://doi.org/10.1186/s13018-019-1100-6

[30] Mobasseri M, Tarverdizadeh N, Mirghafourvand M, Salehi-Pourmehr H, Ostadrahimi A, Farshbaf-Khalili A. The role of bone turnover markers in screening low bone mineral density and their relationship with fracture risk in the postmenopausal period. Journal of Research in Medical Sciences [Internet]. 2023 Jan 1 [cited 2026 Jan 16];28[1]:54. https://doi.org/10.4103/jrms.jrms_612_22

[31] Martiniakova M, Biro R, Kovacova V, Babikova M, Zemanova N, Mondockova V, et al. Current knowledge of bone-derived factor osteocalcin: its role in the management and treatment of diabetes mellitus, osteoporosis, osteopetrosis and inflammatory joint diseases. Journal of Molecular Medicine 2024 102:4 [Internet]. 2024 Feb 16 [cited 2026 Jan 16];102[4]:435–52. https://doi.org/10.1007/s00109-024-02418-8

[32] Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporosis International 2010 22:2 [Internet]. 2010 Dec 24 [cited 2026 Jan 16];22[2]:391–420. https://doi.org/10.1007/s00198-010-1501-1

[33] Brouwers P, Bouquegneau A, Cavalier E. Insight into the potential of bone turnover biomarkers: Integration in the management of osteoporosis and chronic kidney disease-associated osteoporosis. Curr Opin Endocrinol Diabetes Obes [Internet]. 2024 Aug 1 [cited 2026 Jan 16];31[4]:149–56. https://doi.org/10.1097/MED.0000000000000869

[34] Bonjour JP, Kohrt W, Levasseur R, Warren M, Whiting S, Kraenzlin M. Biochemical markers for assessment of calcium economy and bone metabolism: application in

clinical trials from pharmaceutical agents to nutritional products. Nutr Res Rev [Internet]. 2014 Nov 14 [cited 2026 Jan 16];27[2]:252–67.

[35] Renkema KY, Alexander RT, Bindels RJ, Hoenderop JG. Calcium and phosphate homeostasis: concerted interplay of new regulators. Ann Med. 2008;40(2):82-91. https://doi.org/10.1080/07853890701689645

[36] Chen X, Shen L, Gao C, Weng R, Fan Y, Xu S, Zhang Z, Hu W. Vitamin D status and its associations with bone mineral density, bone turnover markers, and parathyroid hormone in Chinese postmenopausal women with osteopenia and osteoporosis. Front Nutr. 2024 Jan 10;10:1307896. https://doi.org/10.3389/fnut.2023.1307896

[37] Nguyen VL, Lee KB, Moon YJ. Parathyroid Hormone as a Modulator of Skeletal Muscle: Insights into Bone–Muscle and Nerve–Muscle Interactions. International Journal of Molecular Sciences 2025, Vol 26, Page 7060 [Internet]. 2025 Jul 22 [cited 2026 Jan 16];26[15]:7060. Available from: https://doi.org/10.3390/ijms26157060

[38] Heijboer AC, Cavalier E. The Measurement and Interpretation of Fibroblast Growth Factor 23 [FGF23] Concentrations. Calcified Tissue International 2022 112:2 [Internet]. 2022 Jun 4 [cited 2026 Jan 16];112[2]:258–70. Available from: https://doi.org/10.1007/s00223-022-00987-9

[39] Liu Y, Wang W, Yang Y, Deng J, Zhang Z. Vitamin D and bone health: from physiological function to disease association. Nutrition & Metabolism 2025 22:1 [Internet]. 2025 Oct 2 [cited 2026 Jan 16];22[1]:113-. Available from: https://doi.org/10.1186/s12986-025-01011-1

[40] Migliorini F, Maffulli N, Spiezia F, Peretti GM, Tingart M, Giorgino R. Potential of biomarkers during pharmacological therapy setting for postmenopausal osteoporosis: a systematic review. Journal of Orthopaedic Surgery and Research 2021 16:1 [Internet]. 2021 May 31 [cited 2026 Jan 16];16[1]:351-. https://doi.org/10.1186/s13018-021-02497-0

[41] Romero Barco CM, Manrique Arija S, Rodríguez Pérez M. Biochemical Markers in Osteoporosis: Usefulness in Clinical Practice. Reumatología Clínica [English Edition] [Internet]. 2012 May 1 [cited 2026 Jan 16];8[3]:149–52. https://doi.org/10.1016/j.reumae.2011.05.004

[42] Yu D, Chen W, Zhang J, Wei L, Qin J, Lei M, et al. Effects of weight loss on bone turnover, inflammatory cytokines, and adipokines in Chinese overweight and obese adults. Journal of Endocrinological Investigation 2022 45:9 [Internet]. 2022 May 30 [cited 2026 Jan 16];45[9]:1757–67. Available from: doi.org/10.1007/s40618-022-01815-5

[43] Wang D, Yang Y. The Relationship Between Serum 25-Hydroxyvitamin D Levels and Osteoporosis in Postmenopausal Women. Clin Interv Aging [Internet]. 2023 [cited 2026 Jan 16];18:619–27. Available from: doi: 10.2147/CIA.S405317.

[44] Chen FP, Lin YC, Lin YJ, Huang MH, Chen JF, Lai PL, et al. Relationship Between Serum 25-Hydroxyvitamin D and Bone Mineral Density, Fracture Risk, and Bone Metabolism in Adults With Osteoporosis/Fractures. Endocrine Practice [Internet]. 2024 Jul 1 [cited 2026 Jan 16];30[7]:616–23. Available from: doi: 10.1016/j.eprac.2024.04.013.

[45] Qu Z, Yang F, Hong J, Wang W, Yan S. Parathyroid Hormone and Bone Mineral Density: A Mendelian Randomization Study. J Clin Endocrinol Metab [Internet]. 2020 Nov 1 [cited 2026 Jan 16];105[11]:e4038–45. https://dx.doi.org/10.1210/clinem/dgaa579

[46] Noh M, Che X, Jin X, Lee DK, Kim HJ, Park DR, et al. Dimeric R25CPTH[1-34] activates the parathyroid hormone-1 receptor in vitro and stimulates bone formation in osteoporotic female mice. Elife [Internet]. 2025 Mar 28 [cited 2026 Jan 16];13. https://doi.org/10.7554/eLife.97579

[47] Orwoll ES, Lapidus J, Wang PY, Vandenput L, Hoffman A, Fink HA, et al. The Limited Clinical Utility of Testosterone, Estradiol, and Sex Hormone Binding Globulin Measurements in the Prediction of Fracture Risk and Bone Loss in Older Men. J Bone Miner Res [Internet]. 2017 Mar 1 [cited 2026 Jan 16];32[3]:633–40. https://doi.org/10.1002/jbmr.3021

[48] Tian X, Zhang B. The association between sex hormones and bone mineral density in US females. Sci Rep [Internet]. 2025 Dec 1 [cited 2026 Jan 16];15[1]:5546. https://doi.org/10.1038/s41598-025-89985-z

[49] Kuriakose C, Cherian KE, Jebasingh F, Kapoor N, Asha HS, Jose A, et al. The prevalence of vertebral fractures among Indian perimenopausal women and its association with ovarian biomarkers. J Bone Miner Metab [Internet]. 2022 Jan 1 [cited 2026 Jan 16];40[1]:142–9. https://doi.org/10.1007/s00774-021-01266-7

[50] Wang S, Yu EW, Hivert MF, Rifas-Shiman SL, Shifren JL, Kazemi M, et al. Associations of AMH in Midreproductive Years with Bone Mineral Density and Turnover Markers in Midlife. J Clin Endocrinol Metab [Internet]. 2025 Jul 1 [cited 2026 Jan 16];110[7]:1836–45. https://doi.org/10.1210/clinem/dgae694

[51] Nakamura Y, Nakano M, Suzuki T, Sato J, Kato H, Takahashi J, et al. Two adipocytokines, leptin and adiponectin, independently predict osteoporotic fracture risk at different bone sites in postmenopausal women. Bone [Internet]. 2020 Aug 1 [cited 2026 Jan 16];137:115404. https://doi.org/10.1016/j.bone.2020.115404

[52] Wang XJ, Bai X, Miu Y, Chen P, Yan PJ, Jiang CX. The assessment value of pathological condition of serum adiponectin and amylin in primary osteoporosis and its correlation analysis with bone metabolism indexes. J Med Biochem [Internet]. 2023 [cited 2026 Jan 16];42[1]:86. https://doi.org/10.5937/jomb0-35877

[53] Liu D, Yang H, Liao Q, Chang B, Zhang W, Li X, et al. Circulating FGF-23 Is Associated With Increased Risk of Osteoporosis and Fractures in Hemodialysis Patients: A Prospective Observational Study. Int J Clin Pract [Internet]. 2024 Jan 1 [cited 2026 Jan 16];2024[1]:1070492.

https://doi.org/10.1155/2024/1070492

[54] Ramli FF, Chin KY. A Review of the Potential Application of Osteocyte-Related Biomarkers, Fibroblast Growth Factor-23, Sclerostin, and Dickkopf-1 in Predicting Osteoporosis and Fractures. Diagnostics 2020, Vol 10, Page 145 [Internet]. 2020 Mar 6 [cited 2026 Jan 16];10[3]:145. https://doi.org/10.3390/diagnostics10030145

[55] Zhao B. TNF and Bone Remodeling. Curr Osteoporos Rep [Internet]. 2017 Jun 1 [cited 2026 Jan 16];15[3]:126–34. https://doi.org/10.1007/s11914-017-0358-z

[56] Epsley S, Tadros S, Farid A, Kargilis D, Mehta S, Rajapakse CS. The Effect of Inflammation on Bone. Front Physiol. 2021 Jan 5;11:511799. https://doi.org/10.3389/fphys.2020.511799

[57] Messina OD, Vidal M, Adami G, Vidal LF, Clark P, Torres JAM, et al. Chronic arthritides and bone structure: focus on rheumatoid arthritis—an update. Aging Clinical and Experimental Research 2023 35:7 [Internet]. 2023 May 24 [cited 2026 Jan 16];35[7]:1405–16. https://doi.org/10.1007/s40520-023-02432-9

[58] Amarasekara DS, Yu J, Rho J. Bone Loss Triggered by the Cytokine Network in Inflammatory Autoimmune Diseases. J Immunol Res [Internet]. 2015 Jan 1 [cited 2026 Jan 16];2015[1]:832127. https://doi.org/10.1155/2015/832127

[59] Terkawi MA, Matsumae G, Shimizu T, Takahashi D, Kadoya K, Iwasaki N. Interplay between Inflammation and Pathological Bone Resorption: Insights into Recent Mechanisms and Pathways in Related Diseases for Future Perspectives. International Journal of Molecular Sciences 2022, Vol 23, Page 1786 [Internet]. 2022 Feb 4 [cited 2026 Jan 16];23[3]:1786. https://doi.org/10.3390/ijms23031786

[60] Zhang Y, Liang J, Liu P, Wang Q, Liu L, Zhao H. The RANK/RANKL/OPG system and tumor bone metastasis: Potential mechanisms and therapeutic strategies. Front Endocrinol (Lausanne). 2022 Dec 16;13:1063815. https://doi.org/10.3389/fendo.2022.1063815

[61] Shi X, Jiang J, Hong R, Xu F, Dai S. Circulating IGFBP-3 and Interleukin 6 as Predictors of Osteoporosis in Postmenopausal Women: A Cross-Sectional Study. Mediators Inflamm [Internet]. 2023 Jan 1 [cited 2026 Jan 16];2023[1]:2613766. https://doi.org/10.1155/2023/2613766

[62] Kitaura H, Marahleh A, Ohori F, Noguchi T, Nara Y, Pramusita A, et al. Role of the Interaction of Tumor Necrosis Factor-α and Tumor Necrosis Factor Receptors 1 and 2 in Bone-Related Cells. International Journal of Molecular Sciences 2022, Vol 23, Page 1481 [Internet]. 2022 Jan 27 [cited 2026 Jan 16];23[3]:1481. https://doi.org/10.3390/ijms23031481

[63] Di D, Zhou H, Cui Z, Zhang J, Liu Q, Yuan T, et al. Frailty phenotype as mediator between systemic inflammation and osteoporosis and fracture risks: A prospective study. J Cachexia Sarcopenia Muscle [Internet]. 2024 Jun 1 [cited 2026 Jan 16];15[3]:897–906. https://doi.org/10.1002/jcsm.13447

[64] Wang XY, Zhang RZ, Wang YK, Pan S, Yun SM, Li J jie, et al. An updated overview of the search for biomarkers of osteoporosis based on human proteomics. J Orthop Translat [Internet]. 2024 Nov 1 [cited 2026 Jan 16];49:37–48. https://doi.org/10.1016/j.jot.2024.08.015

[65] Wang J, Xue M, Hu Y, Li J, Li Z, Wang Y. Proteomic Insights into Osteoporosis: Unraveling Diagnostic Markers of and Therapeutic Targets for the Metabolic Bone Disease. Biomolecules 2024, Vol 14, Page 554 [Internet]. 2024 May 4 [cited 2026 Jan 16];14[5]:554. https://doi.org/10.3390/biom14050554

[66] Alshahrani A, Aleidi SM, Al Dubayee M, AlMalki R, Sebaa R, Zhra M, et al. Postprandial Metabolomic Profiling: Insights into Macronutrient-Specific Metabolic Responses in Healthy Individuals. Nutrients [Internet]. 2024 Nov 1 [cited 2026 Jan 16];16[21]:3783. https://doi.org/10.3390/nu16213783

[67] Daneshpour M, Ghadimi-Daresajini A. Overview of miR-106a Regulatory Roles: from Cancer to Aging. Bioengineering [Internet]. 2023 Aug 1 [cited 2026 Jan 16];10(8):892. https://doi.org/10.3390/bioengineering10080892

[68] Papadaki E, Kakkos I, Vlamos P, Petropoulou O, Miloulis ST, Palamas S, et al. Recent Web Platforms for Multi-Omics Integration Unlocking Biological Complexity. Applied Sciences 2025, Vol 15, Page 329 [Internet]. 2024 Dec 31 [cited 2026 Jan 16];15[1]:329. https://doi.org/10.3390/app15010329

[69] Chiu SH, Wu WT, Yao TK, Peng CH, Yeh KT. Sclerostin and Cardiovascular Risk: Evaluating the Cardiovascular Safety of Romosozumab in Osteoporosis Treatment. Biomedicines 2024, Vol 12, Page 2880 [Internet]. 2024 Dec 18 [cited 2026 Jan 16];12[12]:2880. https://doi.org/10.3390/biomedicines12122880

[70] Cavati G, Pirrotta F, Merlotti D, Ceccarelli E, Calabrese M, Gennari L, et al. Role of Advanced Glycation End-Products and Oxidative Stress in Type-2-Diabetes-Induced Bone Fragility and Implications on Fracture Risk Stratification. Antioxidants 2023, Vol 12, Page 928 [Internet]. 2023 Apr 14 [cited 2026 Jan 16];12[4]:928. https://doi.org/10.3390/antiox12040928

[71] Gong L, Bai Z. Association of genetically predicted blood metabolites with osteopenia in individuals over 60 years of age: A Mendelian randomization study. Jt Dis Relat Surg [Internet]. 2025 [cited 2026 Jan 16];36[2]:229. https://doi.org/10.52312/jdrs.2025.1991

[72] Ramli FF, Chin KY. A Review of the Potential Application of Osteocyte-Related Biomarkers, Fibroblast Growth Factor-23, Sclerostin, and Dickkopf-1 in Predicting Osteoporosis and Fractures. Diagnostics 2020, Vol 10, Page 145 [Internet]. 2020 Mar 6 [cited 2026 Jan 16];10[3]:145. https://doi.org/10.3390/diagnostics10030145

[73] Mandourah AY, Ranganath L, Barraclough R, Vinjamuri S, Hof RVT, Hamill S, et al. Circulating microRNAs as potential diagnostic biomarkers for osteoporosis. Scientific Reports 2018 8:1 [Internet]. 2018 May 30 [cited 2026 Jan 16];8[1]:8421-. Available from: do https://doi.org/10.1038/s41598-018-26525-y

[74] Luo Y. Hip Fractures: Clinical, Biomaterial and Biomechanical Insights into a Common Health Challenge. Bioengineering [Internet]. 2025 May 28 [cited 2026 Jan 16];12(6):580. https://doi.org/10.3390/bioengineering12060580

[75] Li Q, Wang J, Zhao C. From Genomics to Metabolomics: Molecular Insights into Osteoporosis for Enhanced Diagnostic and Therapeutic Approaches. Biomedicines [Internet]. 2024 Oct 1 [cited 2026 Jan 16];12[10]:2389. https://doi.org/10.3390/biomedicines12102389

[76] Nori W, Abdulqader SK, Akram NN, Al-Ani RM, Hassan QA, Pantazi AC. Unusual Presentation of Osteoid Osteoma with Exacerbating Pain during Menses. Sultan Qaboos Univ Med J [Internet]. 2021 Oct 31 [cited 2024 Nov 22];21(4):e600-605. https://doi.org/10.18295/squmj.10.2024.067

[77] Yasin P, Ding L, Mamat M, Guo W, Song X. Machine Learning-Based Interpretable Screening for Osteoporosis in Tuberculosis Spondylitis Patients Using Blood Test Data: Development and External Validation of a Novel Web-Based Risk Calculator with Explainable Artificial Intelligence [XAI]. Infect Drug Resist [Internet]. 2025 [cited 2026 Jan 16];18:2797–821. https://doi.org/10.2147/IDR.S520062

[78] Wei Q, Zhan J, Chen X, Huang Q, Li H, Guo W, et al. Development and validation of an interpretable machine learning model for osteoporosis prediction using routine blood tests: a retrospective cohort study. BMC Medical Informatics and Decision Making 2025 25:1 [Internet]. 2025 Nov 22 [cited 2026 Jan 16];25[1]:446-. https://doi.org/10.1186/s12911-025-03292-1

[79] Zheng Z, Zhang X, Oh BK, Kim KY. Identification of combined biomarkers for predicting the risk of osteoporosis using machine learning. Aging [Albany NY] [Internet]. 2022 [cited 2026 Jan 16];14[10]:4270. https://doi.org/10.18632/aging.204084

[80] Szulc P, Naylor K, Hoyle NR, Eastell R, Leary ET. Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporosis International 2017 28:9 [Internet]. 2017 Jun 19 [cited 2026 Jan 16];28[9]:2541–56. https://doi.org/10.1007/s00198-017-4082-4

[81] Brunetti A, Cellini M, Vitale V, Gentile LMS, Birtolo MF, Vescini F, et al. A practical use of bone turnover markers in management of patients with skeletal fragility. Endocrine 2025 89:2 [Internet]. 2025 May 29 [cited 2026 Jan 16];89[2]:356–64. Available from: d https://doi.org/10.1007/s12020-025-04275-y

[82] Omran S, Gamal Eldeen H, Abdellatif Z, M. Abdou D, Hamdy A Mohammed R, Gaber AA, et al. Assessment of bone health by bone turnover biomarkers in a cohort of Egyptian patients with inflammatory bowel disease: a cross-sectional analytical study. Egyptian Rheumatology and Rehabilitation 2025 52:1 [Internet]. 2025 Jun 3 [cited 2026 Jan 16];52[1]:39-. https://doi.org/10.1186/s43166-025-00332-6

[83] Tao R, Qiao MQ, Wang B, Fan JP, Gao F, Wang SJ, et al. Laboratory-based Biomarkers for Risk Prediction, Auxiliary Diagnosis and Post-operative Follow-up of Osteoporotic Fractures. Current Osteoporosis Reports 2025 23:1 [Internet]. 2025 Apr 8 [cited 2026 Jan 16];23[1]:19-. Available from https://doi.org/10.1007/s11914-025-00914-5

[84] Wang J, Shan L, Hang J, Li H, Meng Y, Cao W, et al. Development and validation of a novel prediction model for osteoporosis. Bone Joint Res. 2025 Feb 1;14[2]:111–23. https://doi.org/10.1302/2046-3758.142.BJR-2023-0409.R2

[85] Carvalho FR, Gavaia PJ. Enhancing osteoporosis risk prediction using machine learning: A holistic approach integrating biomarkers and clinical data. Comput Biol Med [Internet]. 2025 Jun 1 [cited 2026 Jan 16];192:110289. https://doi.org/10.1016/j.compbiomed.2025.110289

[86] Tu JB, Liao WJ, Liu WC, Gao XH. Using machine learning techniques to predict the risk of osteoporosis based on nationwide chronic disease data. Scientific Reports 2024 14:1 [Internet]. 2024 Mar 4 [cited 2026 Jan 16];14[1]:5245 https://doi.org/10.1038/s41598-024-56114-1

[87] Suh B, Yu H, Kim H, Lee S, Kong S, Kim JW, et al. Interpretable Deep-Learning Approaches for Osteoporosis Risk Screening and Individualized Feature Analysis Using Large Population-Based Data: Model Development and Performance Evaluation. J Med Internet Res [Internet]. 2023 Jan 13 [cited 2026 Jan 16];25[1]:e40179. https://doi.org/10.2196/40179

[88] Hsu CY, Chen LR, Chen KH. Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review. International Journal of Molecular Sciences 2020, Vol 21, Page 6846 [Internet]. 2020 Sep 18 [cited 2026 Jan 16];21[18]:6846. https://doi.org/10.3390/ijms21186846

[89] Bai Y, Lin Y, An N, Wang C, Deng Y, Chen R. Prevalence and risk factors of CKD-associated osteoporosis in maintenance hemodialysis patients aged over 50 years: a cross-sectional study. Sci Rep[Internet]. 2026 Jan 9 [cited 2026 Jul 6];16(1):4908. https://doi.org/10.1038/s41598-026-35136-x

[90] Mandal CC. High cholesterol deteriorates bone health: New insights into molecular mechanisms. Front Endocrinol [Lausanne] [Internet]. 2015 Oct 23 [cited 2026 Jan 16];6[OCT]:154102. D https://doi.org/10.3389/fendo.2015.00165

[91] Long G, Liu C, Liang T, Zhang Z, Qin Z, Zhan X. Predictors of osteoporotic fracture in postmenopausal women: a meta-

analysis. Journal of Orthopaedic Surgery and Research. 2023 Aug 5;18(1):574. https://doi.org/10.1186/s13018-023-04051-6

[92] Jiang C, Zhu S, Zhan W, Lou L, Li A, Cai J. Comparative analysis of bone turnover markers in bone marrow and peripheral blood: implications for osteoporosis. Journal of Orthopaedic Surgery and Research 2024 19:1 [Internet]. 2024 Mar 1 [cited 2026 Jan 16];19[1]:163-. https://doi.org/10.1186/s13018-024-04634-x

[93] Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P, Milat F. Secondary Osteoporosis. Endocr Rev [Internet]. 2022 Mar 9 [cited 2026 Jan 16];43[2]:240–313. https://dx.doi.org/10.1210/endrev/bnab028

[94] Kim BJ, Lee SH, Koh JM. Potential Biomarkers to Improve the Prediction of Osteoporotic Fractures. Endocrinology and Metabolism [Internet]. 2020 Mar 1 [cited 2026 Jan 16];35[1]:55–63. https://doi.org/10.3803/EnM.2020.35.1.55

[95] Wen Y, Cheng S, Gou L, Zhou W, Li Y, Wang R, et al. Serum LCAT as a Gender-Neutral Biomarker for Early Osteoporosis: A Multicenter Cohort Validation Study. Int J Gen Med [Internet]. 2025 Jul [cited 2026 Jan 16]; Volume 18:4131–45. https://doi.org/10.2147/IJGM.S536568

[96] Tripathi A, Ansari MS, Dandekar P, Jain R. Analytical methods for 25-hydroxyvitamin D: advantages and limitations of the existing assays. J Nutr Biochem [Internet]. 2022 Nov 1 [cited 2026 Jan 16];109:109123. https://doi.org/10.1016/j.jnutbio.2022.109123

[97] Li Y, Luo Y, Huang D, Peng L. Sclerostin as a new target of diabetes-induced osteoporosis. Front Endocrinol [Lausanne]. 2024 Dec 10;15:1491066. https://doi.org/10.3389/fendo.2024.1491066

[98] Rauner M, Taipaleenmäki H, Tsourdi E, Winter EM. Osteoporosis Treatment with Anti-Sclerostin Antibodies—Mechanisms of Action and Clinical Application. Journal of Clinical Medicine 2021, Vol 10, Page 787 [Internet]. 2021 Feb 16 [cited 2026 Jan 16];10[4]:787. https://doi.org/10.3390/jcm10040787

[99] Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med [Internet]. 2011 Jan 15 [cited 2026 Jan 16];30[1]:11–21. https://doi.org/10.1002/sim.4085

[100] Nagy EE, Nagy-Finna C, Popoviciu H, Kovács B. Soluble biomarkers of osteoporosis and osteoarthritis, from pathway mapping to clinical trials: An update. Clin Interv Aging [Internet]. 2020 [cited 2026 Jan 16];15:501–18 https://doi.org/10.2147/CIA.S242288

[101] Hofbauer LC, Busse B, Eastell R, Ferrari S, Frost M, Müller R, et al. Bone fragility in diabetes: novel concepts and clinical implications. Lancet Diabetes Endocrinol [Internet]. 2022 Mar 1 [cited 2026 Jan 16];10[3]:207–20. https://doi.org/10.1016/S2213-8587(21)00347-8

[102] Chu, W., Wu, M., Sun, J. et al. HALP score-adjusted FRAXplus tool effectively predicts hip fracture risk in elderly women with type 2 diabetes mellitus. BMC Endocr Disord (2026). https://doi.org/10.1186/s12902-026-02338-3.

[103] Fassio A, Adami G, Idolazzi L, Giollo A, Viapiana O, Vantaggiato E, et al. Wnt Inhibitors and Bone Turnover Markers in Patients With Polymyalgia Rheumatica and Acute Effects of Glucocorticoid Treatment. Front Med [Lausanne] [Internet]. 2020 Sep 9 [cited 2026 Jan 16];7:559278. https://doi.org/10.3389/fmed.2020.00551

[104] Srisuwarn P, Eastell R, Salam S. Clinical Utility of Bone Turnover Markers in Chronic Kidney Disease. J Bone Metab [Internet]. 2024 Nov 1 [cited 2026 Jan 16];31[4]:264. Available from: doi: 10.11005/jbm.24.789

[105] Di Vincenzo O, Piciocchi C, Muzzioli L, Poggiogalle E, Frigerio F, Minnetti M, et al. Osteosarcopenic obesity: A systematic review and a call for consensus on definitions and diagnostic criteria. Clinical Nutrition [Internet]. 2025 Aug 1 [cited 2026 Jan 16];51:146–60. https://doi.org/10.1016/j.clnu.2025.06.009

[106] Chandran M, Thiyagarajan JA, Alokail M, Bruyère O, Harvey NC, Rizzoli R, Veronese N, Reginster JY. WHO benchmarks for equitable hip-fracture care and osteoporosis treatment in older people. Nat Rev Rheumatol. 2026 Jan;22(1):62-70 https://doi.org/10.1038/s41584-025-01319-5

[107] Hidayat K, Zhu Y, Rizzoli R, Wei H, Shi BM, Qin LQ. Probiotic Supplementation and Bone Health Parameters in Adults: A Systematic Review and Meta-Analysis. Osteoporosis International 2025 [Internet]. 2025 Oct 31 [cited 2026 Jan 16];1–16 https://doi.org/10.1007/s00198-025-07691-y

[108] Hassan WNM, Al-kaabi MM, Akram NN, Kassim MAK, Pantazi AC. Probiotics for Inflammatory Bowel Disease; A Deep Dive into their Impact on Disease Course and Associated Health Risks. Curr Med Chem [Internet]. 2024 May 2 [cited 2026 Jan 16];31[30]:4807–25. https://doi.org/10.2174/0109298673314861240429072352

[109] Shahzad H, Bhatti NS, Phillips FM, Khan SN. Applications of Augmented Reality in Orthopaedic Spine Surgery. J Am Acad Orthop Surg. 2023 Sep 1;31(17):e601-e609. https://doi.org/10.5435/JAAOS-D-23-00023

[110] Nikitovic M, Wodchis WP, Krahn MD, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. Osteoporosis International 2012 24:2 [Internet]. 2012 Jun 27 [cited 2026 Jan 16];24[2]:659–69. https://doi.org/10.1007/s00198-012-2034-6

[111] Kuo TR, Chen CH. Bone biomarker for the clinical assessment of osteoporosis: recent developments and future perspectives. Biomarker Research 2017 5:1 [Internet]. 2017 May 18 [cited 2026 Jan 16];5[1]:18-.

https://doi.org/10.1186/s40364-017-0097-4

[112] Schäfer H, Lajmi N, Valente P, Pedrioli A, Cigoianu D, Hoehne B, et al. The Value of Clinical Decision Support in Healthcare: A Focus on Screening and Early Detection. Diagnostics 2025, Vol 15, Page 648 [Internet]. 2025 Mar 6 [cited 2026 Jan 16];15[5]:648. https://doi.org/10.3390/diagnostics15050648

[113] 113. Alosami MH, Adnan S, Hameed EK. Serum uric acid level and bone mineral density in Iraqi postmenopausal women. The Egyptian Rheumatologist. 2019 Jul 1;41(3):221-4. https://doi.org/10.1016/j.ejr.2018.07.009

[114] Marini S, Barone G, Masini A, Dallolio L, Bragonzoni L, Longobucco Y, et al. The Effect of Physical Activity on Bone Biomarkers in People With Osteoporosis: A Systematic Review. Front Endocrinol [Lausanne] [Internet]. 2020 Oct 23 [cited 2026 Jan 16];11:585689. https://doi.org/10.3389/fendo.2020.585689

[115] Abdulbari A, Jassim NA, Motlaq YH, Ismael HA, Al Ani WA, Nafai CK, Younis AA, Qaradaghi TA, Mahdi FJ, Rahmah AM, Alameri AH. Epidemiology of hip fracture in Iraq and development of a country-specific FRAX model. Archives of Osteoporosis. 2025 Dec;20[1]:145. https://doi.org/10.1007/s11657-025-01631-3