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Advances in Clinical Diagnosis and Monitoring of Postmenopausal Osteoporosis

Lijun Xie [1] and Yuan Wu [2, *]

[1] Hunan Normal University First Affiliated Hospital, Hunan Provincial People's Hospital, Changsha Hunan, 410005, China
[2] Department of General Practice, Hunan Normal University First Affiliated Hospital, Hunan Provincial People's Hospital, Changsha Hunan, 410005, China

*** Corresponding author:** Yuan Wu

Abstract: Postmenopausal osteoporosis is a major cause of fragility fracture, disability, and loss of independence in older women. Although dual-energy X-ray absorptiometry remains the diagnostic cornerstone, bone mineral density alone does not fully reflect bone quality, remodeling activity, treatment response, or short-term fracture probability. This review summarizes evidence published from 2021 to 2025 on major tools used in the diagnosis and monitoring of postmenopausal osteoporosis, including dual-energy X-ray absorptiometry, trabecular bone score, vertebral-fracture assessment, quantitative computed tomography, bone turnover markers, FRAX-based risk assessment, and emerging molecular approaches such as circulating microRNAs, extracellular vesicles, and cell-free DNA. Current evidence favors a multimodal strategy in which imaging remains foundational, biochemical markers are used mainly for biological contextualization and treatment monitoring, and molecular biomarkers are developed as complementary rather than replacement tools.

Keywords: Bone Fragility; Fracture Risk; Bone Mineral Density; Bone Turnover Markers; FRAX; Trabecular Bone Score; Cell-free DNA.

1. Introduction

Postmenopausal osteoporosis (PMOP) is a chronic skeletal disorder characterized by reduced bone mass, microarchitectural deterioration, and impaired bone strength, ultimately predisposing women to fragility fracture. Estrogen deficiency is the initiating biological event, but the clinical phenotype is also shaped by aging, low body weight, reduced physical activity, vitamin D insufficiency, endocrine disease, medication exposure, and frailty [1, 2]. Because fracture often represents the first clinically obvious manifestation, delayed diagnosis remains common.

The burden of PMOP extends beyond low bone mineral density (BMD). Vertebral and hip fractures are associated with chronic pain, functional decline, hospitalization, institutionalization, and excess mortality [3, 4]. The growing number of older women with osteopenia or osteoporosis has also increased demand for earlier identification and longitudinal monitoring [5, 6]. These realities have shifted clinical management from single-test diagnosis toward integrated assessment combining structural imaging, biological monitoring, and fracture-risk estimation [6, 7].

This review focuses on the principal methods currently used in clinical practice and near-term translation: DXA-based diagnosis, complementary imaging for bone quality, bone turnover markers (BTMs), FRAX-based fracture-risk assessment, and emerging liquid-biopsy approaches. The aim is to clarify the strengths, limitations, and most appropriate clinical role of each tool in contemporary PMOP management.

2. Imaging-Based Diagnostic Assessment

2.1. Dual-Energy X-Ray Absorptiometry as the Diagnostic Cornerstone

Dual-energy X-ray absorptiometry (DXA) remains the reference method for diagnosing osteoporosis because it is standardized, widely available, low in radiation exposure, and supported by guideline-based treatment thresholds [1, 8]. Measurements at the lumbar spine and hip provide the basis for BMD classification and remain central to screening, baseline risk assessment, and serial follow-up. In routine practice, DXA offers a common language for communicating skeletal status and therapeutic decisions [7, 9].

Important limitations should, however, be recognized. Areal BMD is a two-dimensional projection and may be affected by degenerative spinal change, osteophytes, vascular calcification, scoliosis, vertebral compression, prior surgery, or positioning differences [8, 10]. DXA also provides limited information on cortical porosity, trabecular connectivity, and remodeling activity. Consequently, women with similar T-scores may differ substantially in fracture risk or treatment response, especially in older age groups [2, 11].

For longitudinal use, DXA should ideally be repeated on the same instrument and interpreted with awareness of precision error and least significant change [8, 10]. Clinically, DXA is indispensable for diagnosis and long-term follow-up, but it is less suitable as an isolated marker of early therapeutic efficacy. When the fracture phenotype appears discordant with measured BMD, complementary tools are warranted [7, 12].

In screening pathways, the decision to obtain DXA should be guided by age, prior fragility fracture, menopausal duration, long-term glucocorticoid exposure, family history, low body weight, and coexisting disorders that accelerate bone loss [13, 14]. This is particularly relevant in general practice, where women may first present with back pain, height loss, fear of falling, or medication-related concerns rather than a known diagnosis of osteoporosis. A pragmatic imaging pathway therefore begins with clinical suspicion, proceeds to DXA when indicated, and expands to adjunctive assessment when fracture risk appears disproportionate to measured BMD.

2.2. Complementary Imaging for Bone Quality and Microarchitecture

Several adjunctive imaging methods attempt to capture aspects of bone quality not fully reflected by DXA. Quantitative computed tomography and high-resolution peripheral quantitative computed tomography can provide volumetric density and microarchitectural information, including cortical and trabecular compartment characteristics [11]. Their main value is in research and selected complex cases, because cost, access, radiation exposure, and the lack of universally accepted therapeutic thresholds limit routine use [8, 11].

Among clinically accessible adjuncts, trabecular bone score (TBS) has achieved the widest uptake. Derived from standard lumbar DXA images, TBS acts as an indirect surrogate for trabecular degradation and can improve fracture-risk stratification when interpreted together with BMD and clinical risk factors [12, 15]. Its practical attraction lies in the fact that it can often be generated from existing DXA acquisitions without additional radiation or substantial workflow disruption [12].

Vertebral-fracture assessment is another highly useful extension of imaging, particularly in older women, women with height loss, and women with symptoms or history suggestive of occult vertebral compression. Because vertebral fractures may be clinically silent but strongly increase future fracture probability, their detection can materially alter risk classification and treatment decisions [2, 7]. The most defensible current approach is therefore to use DXA as the diagnostic base and add TBS, vertebral-fracture assessment, or advanced imaging when clinical and densitometric findings are not fully concordant [8, 12].

3. Bone Turnover Markers in Longitudinal Monitoring

Bone turnover markers (BTMs) provide dynamic information about ongoing remodeling and therefore complement the structural perspective supplied by imaging. Formation markers such as procollagen type I N-terminal propeptide reflect osteoblastic activity, whereas resorption markers such as beta-cross-linked C-telopeptide reflect osteoclastic activity [16, 17]. In PMOP, where accelerated remodeling is central to disease biology, BTMs are most valuable for describing the tempo of skeletal change and for monitoring response to antiresorptive or anabolic therapy [16, 17].

Their principal advantage is temporal sensitivity. Changes in BTMs usually occur earlier than measurable changes in BMD, allowing clinicians to obtain supportive evidence of biological response within months rather than years [16, 17]. In practice, this can assist adherence counseling, reinforce persistence with long-term therapy, and help distinguish slow radiographic response from possible treatment failure [18]. BTMs may also help prioritize follow-up intensity in women with high baseline turnover or concerns about adherence [16].

Interpretation nonetheless requires caution. BTM concentrations are influenced by circadian rhythm, fasting status, recent food intake, renal function, acute illness, fracture healing, and analytical platform differences [16, 17]. For this reason, pre-analytical standardization and consistent laboratory methods are essential. Current evidence supports BTMs as complementary monitoring tools rather than stand-alone diagnostic substitutes for imaging [16, 17].

In general practice and nursing follow-up, BTMs may be especially useful when clinicians need to explain that biological improvement often precedes symptomatic change or measurable BMD gain. When integrated with DXA, fracture history, and medication review, they enrich interpretation of whether low bone mass is accompanied by active remodeling and whether therapy is moving in the expected direction [6, 16].

A further practical point is that BTMs should be matched to the clinical question. They are most informative when used to confirm expected biological response, support adherence discussions, or interpret discordance between symptoms, medication exposure, and slow-changing BMD results. Overuse without a clear monitoring purpose may increase cost while adding little clinical value. Their greatest contribution is therefore within structured follow-up rather than indiscriminate testing.

4. Fracture-Risk Assessment and Integrated Clinical Decision-Making

The ultimate goal of PMOP management is fracture prevention rather than BMD classification alone. For that reason, fracture-risk algorithms remain central to treatment decision-making. FRAX is the most widely used tool and estimates 10-year probability of major osteoporotic fracture and hip fracture from clinical risk factors with or without femoral-neck BMD [19, 20]. Its practical value lies in identifying women whose fracture risk may justify treatment even when BMD falls in the osteopenic rather than osteoporotic range [7, 21].

FRAX should, however, be understood as a decision-support tool rather than a complete summary of skeletal fragility. Falls risk, recent fracture, sarcopenia, frailty, glucocorticoid dose, and some secondary causes of bone loss may be incompletely captured [7, 19]. Recent evidence therefore favors combining FRAX with BMD, TBS, vertebral-fracture status, and clinical judgment instead of using any single estimator in isolation [19, 21]. A risk-based framework is particularly useful for selecting treatment thresholds, prioritizing monitoring, and communicating prognosis to patients [19].

Recent guidance also highlights that fracture risk is dynamic rather than static. A woman with recent vertebral fracture, recurrent falls, substantial frailty, or rapid health decline may warrant more intensive intervention than her baseline FRAX estimate alone suggests [19]. Conversely, lower-risk women may benefit more from lifestyle optimization, fall-prevention measures, calcium and vitamin D adequacy, and interval reassessment. In this sense, FRAX is most useful when embedded in a broader clinical conversation about imminence of fracture, competing comorbidity, life expectancy, and feasibility of long-term therapy.

5. Emerging Molecular and Liquid-Biopsy Approaches

5.1. Circulating MicroRNAs and Extracellular Vesicles

As osteoporosis research moves toward precision medicine, interest in circulating molecular markers has increased. MicroRNAs (miRNAs) are short non-coding RNAs involved in osteoblast differentiation, osteoclast activation, and

signaling pathways relevant to bone remodeling. Recent systematic review evidence suggests that panels of circulating miRNAs differ between women with osteoporosis and those with preserved bone mass, indicating potential diagnostic or stratification value [22]. However, candidate signatures remain heterogeneous across studies and are not yet standardized for routine care [22].

Extracellular vesicles and exosomes represent a related line of investigation. Because they transport proteins, lipids, and regulatory nucleic acids between cells, they may better reflect the biological microenvironment of bone remodeling than single circulating analytes. Recent osteoporosis-focused reviews suggest potential translational value as biomarkers and therapeutic carriers, but the current evidence base remains predominantly preclinical and not yet ready for routine clinical use [23]. At present, these approaches should be viewed as promising adjunctive biomarkers rather than clinically validated tests.

Despite this promise, translational barriers are substantial. Molecular studies often use small cohorts, differing specimen types, variable normalization strategies, and inconsistent case definitions, making it difficult to compare results across studies or to define clinically actionable thresholds [22, 23]. In addition, many proposed biomarkers are biologically plausible yet lack demonstration that they improve prediction beyond established tools such as DXA, FRAX, or BTMs. Routine implementation will therefore require analytical standardization, external validation, and proof of added value in real clinical pathways.

5.2. Cell-Free DNA and Epigenetic Liquid Biopsy

Cell-free DNA (cfDNA) extends the concept of liquid biopsy into non-neoplastic disorders. Derived from apoptosis, necrosis, and active cellular release, cfDNA can reflect tissue injury, inflammation, and altered cellular turnover. This may be relevant to PMOP because menopause-associated biological changes appear to influence circulating nucleic-acid profiles; a recent study reported higher plasma circulating DNA concentrations in postmenopausal than in pre- or perimenopausal women, providing a biologically plausible basis for further skeletal research [24]. Compared with conventional imaging, cfDNA-based testing is minimally invasive and potentially repeatable over short intervals.

Yet evidence specific to PMOP remains limited and should be interpreted cautiously. Current data do not establish cfDNA as a bone-specific diagnostic marker, and its eventual clinical value may depend less on absolute concentration alone than on fragment size, methylation patterns, or tissue-of-origin signals that better connect circulating DNA to skeletal biology [24]. For now, cfDNA is best regarded as an investigational complement rather than a routine monitoring tool.

A further challenge is biological specificity. Because circulating DNA reflects whole-body processes rather than bone alone, age-related inflammation, vascular disease, malignancy, and other comorbidities common in older women may contribute to cfDNA variation and complicate osteoporosis-specific inference [24]. Future work should therefore focus on skeletal specificity, longitudinal responsiveness, and whether cfDNA can improve decision-making when combined with established diagnostic and monitoring tools.

5.3. Toward Multimodal Precision Monitoring

These emerging biomarkers are most useful when conceptualized as additions to, not replacements for, established assessment. The likely future direction is multimodal precision monitoring in which DXA defines structural status, BTMs describe remodeling activity, and FRAX estimates clinical fracture probability [16, 19]. Data on microRNAs and extracellular vesicles support this general direction, although clinical translation remains incomplete [22, 23]. CfDNA research suggests a related but even earlier-stage opportunity for phenotypic refinement [24].

Digital health tools and analytic modeling may further support this approach by combining repeated imaging, laboratory trends, medication exposure, and patient-level clinical characteristics into more personalized risk trajectories. The challenge is to ensure that these models remain clinically interpretable and outcome-oriented rather than technologically sophisticated but operationally impractical.

6. Current Challenges and Future Directions

Several barriers still limit optimal implementation of modern PMOP monitoring. First, diagnostic and monitoring tools are unevenly available across healthcare settings. Advanced imaging and frequent BTM testing may be feasible in tertiary centers but less practical in many community or primary-care environments [7, 16]. Molecular assays face an additional access gap because they remain largely research-based. Because most women are first recognized outside specialist services, scalability and workflow simplicity remain crucial.

Second, standardization remains a recurring challenge. This is obvious for BTMs and molecular assays, but even imaging requires attention to precision, machine consistency, and appropriate follow-up intervals [8, 16]. Third, much of the literature emphasizes diagnostic association rather than hard outcomes such as incident fracture, functional decline, or sustained treatment response. Future studies should therefore prioritize prospective validation, clinically meaningful endpoints, and integration strategies that are feasible for real-world care [19, 24].

The service-delivery context also deserves attention. PMOP management is multidisciplinary and commonly involves primary-care physicians, endocrinologists, rheumatologists, orthopedic specialists, nurses, rehabilitation teams, and laboratory services. Monitoring strategies should therefore be chosen not only for scientific sophistication but also for accessibility, interpretability, and their ability to support adherence, fall prevention, and long-term continuity of care. Methods that cannot be implemented consistently are unlikely to improve outcomes even if they appear promising in research settings.

7. Conclusion

Clinical diagnosis and monitoring of PMOP have evolved from a one-dimensional dependence on BMD toward a more integrated strategy. DXA remains the diagnostic foundation, while TBS, vertebral-fracture assessment, and selected advanced imaging help clarify bone quality and discordant cases. BTMs contribute dynamic information that is particularly useful for treatment monitoring, and FRAX supports risk-based decision-making. Emerging biomarkers

such as circulating miRNAs, extracellular vesicles, and cfDNA show translational promise, but they currently serve as complementary rather than replacement tools. The most practical future model is a multimodal framework that combines structural, biochemical, clinical, and molecular information to improve fracture prevention and individualized follow-up.

Conflict of Interest

No conflict of interest was reported by all authors.

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