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Advances in Osteoporosis Diagnosis: A Comprehensive Review of Conventional and Emerging Methods

Ghufran M. Ismael [1*], Rana I. Mahmood[1] and Samar A. Jaber[1]

[1]*Department of Biomedical Engineering, College of Engineering, Al-Nahrain University, Jadriya, Baghdad, Iraq*
**Corresponding author E-mail*: ghufran.mohammed.msc2023@ced.nahrainuniv.edu.iq

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Abstract: Osteoporosis is a common, chronic, and progressive metabolic bone disorder that is characterized by low bone mass and degeneration of the microarchitecture of the skeleton which predisposes individuals to an increased risk of fractures, particularly among postmenopausal women and elderly individuals. In this review, commonly used and newly developed techniques for the diagnosis of osteoporosis are reviewed. Dual-energy X-ray absorptiometry (DXA) is still the clinical application of choice to date for bone mineral density (BMD) measurement in view of its utility and convenience, whereas quantitative computed tomography (QCT) affords a three-dimensional structural assessment and sensitive probes for trabecular degradation. Magnetic Resonance Imaging (MRI) is an excellent modality for assessing bone microarchitecture and marrow composition, while quantitative ultrasound (QUS) offers a low-cost radiation-free screening solution. Biochemical markers (procollagen type I N-terminal propeptide [P1NP], bone-specific alkaline phosphatase [B-ALP], osteocalcin [OC], C-telopeptide of type I collagen [CTX] have also proven to be useful for the evaluation of bone turnover and treatment response. Digital tools, such as Artificial Intelligence (AI) models and mobile health (mHealth) applications based on emerging digital technologies, are changing our diagnostic paths with increased prediction accuracy, patient involvement, and remote surveillance. However, despite these achievements, diagnostic issues remain due to biological variations as well as the lack of consensus and widespread clinical validation. Combining imaging modalities, biochemical markers, and AI-based analytics appears the most hopeful route toward early, personalized, yet affordable osteoporosis detection.

Keywords: Osteoporosis; Bone Mineral Density (BMD); Dual-Energy X-ray Absorptiometry (DXA); Artificial Intelligence (AI); Bone Turnover; mHealth

1. Introduction

Osteoporosis is a predominant reason for decline in bone mass and breakdown of bone microarchitecture leading to increased risk of fragility fractures. In the year 2000, nine million new osteoporotic fractures would have to be occurred worldwide. One of these was hip fracture (n=1.6 million) 2 years' forearm fractures (n=1.7 million), and clinically diagnosed vertebral fracture (n=1.4) [1]. Although osteoporosis can affect both men and women, it is more prevalent among women, particularly after menopause. This condition is considered more serious in the elderly and postmenopausal women [2][3]. According to the U.S. Preventive Services Task Force (USPSTF), recommends routine osteoporosis screening for women aged 65 years and older and for postmenopausal women younger than 65 years who have increased fracture risk based on clinical risk factors. For men, current evidence is considered insufficient to recommend routine population-based screening, and assessment should be guided by individual risk profiles and clinical judgment (Figure 1) [4]. The primary cause of osteoporosis is bone loss resulting from a decrease in estrogen levels, particularly after menopause. Several modifiable biological factors are associated with reduced BMD, including nicotine use, excessive consumption of caffeine and alcoholic beverages, a sedentary lifestyle, deficiencies in calcium and vitamin D, and prolonged use of certain medications such as corticosteroids [5][6][7].

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An increasingly useful, noninvasive approach for comparing bone turnover and circumstance in a lot of metabolic bone issues is using biochemical signs for bone formation and resorption [8].

Decreased bone mass, diminished structural strength, and increased risk of fractures are key characteristics of osteoporosis, which often remains undiagnosed until a fracture occurs. Because they reflect the underlying mechanisms in conditions such as osteoporosis, inflammation, and bone cancer, bone biomarkers are essential for early detection. Among these biomarkers, collagen is one of the most extensively studied indicators of bone formation, as it is primarily produced by periosteal osteoblasts and osteocytes [9] [10]. If osteoporosis is not identified and managed early, bones gradually become more fragile and prone to breaking under minor stress. Fractures commonly occur in the hip, spine, and wrist, and their impact often extends well beyond the initial injury. Many patients experience long-term pain, difficulty with movement, and a loss of independence in daily activities. Hip and spinal fractures are particularly serious, as they are frequently associated with prolonged disability and an increased risk of mortality in older individuals. These outcomes underscore why timely detection and appropriate treatment of osteoporosis are essential rather than optional [11]. The management of osteoporosis focuses on reducing fracture risk through both lifestyle measures and pharmacological therapy. Adequate calcium and vitamin D intake, regular weight-bearing exercise, and fall-prevention strategies are recommended for all patients. In individuals at increased fracture risk, pharmacological treatment—most commonly antiresorptive agents such as bisphosphonates or denosumab, and anabolic therapies in selected high-risk cases—is advised to improve bone strength and prevent fractures (figure 2) [12].

Population	Recommendation	Grade
Women 65 years or older	The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in women 65 years or older. See the Practice Considerations section for more information on screening tests.	B
Postmenopausal women younger than 65 years with 1 or more risk factors for osteoporosis	The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk for an osteoporotic fracture as estimated by clinical risk assessment. See the Practice Considerations section for more information on risk assessment and screening tests.	B
Men	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men. See the Practice Considerations section for suggestions for practice regarding the I statement.	I

Fig. 1. USPSTF recommendations for osteoporosis screening by age and risk group [4].

Effective treatment depends on timely and accurate diagnosis, underscoring the importance of reliable screening and diagnostic tools, according to the National Institutes of Health (NIH), a biomarker is defined as a measurable and objectively evaluated indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [13]. BMD and marking the osteoporosis diagnosis, is a non-invasive procedure and utilized DXA technique fast, easy-adapted, and

highly accurate. DXA is the most accurate method of measurement of bone density according to World Health Organization (WHO) [14]. Biomechanical bone sensors work in real time, as opposed to conventional approaches which do not allow for an instantaneous evaluation of the biomechanics of bone. This advantage is what makes biomechanical sensors different than other technologies that only can detect or diagnose problems as they occur [15]. Yet, radiomics may also analyze quantitatively characteristics of a lesion on medical images, which can offer information concerning variations in lesion morphological features and parameters at unobserved levels. Such a measurement is in stark contrast to that provided by standard imaging methods, which generally yield qualitative or semi-quantitative information. Radiomics has been widely used in disease diagnosis, prognosis prediction, treatment response evaluation and a number of other clinical domains [16]. Instead of overtaking doctors, AI is augmenting their capacity and changing the way of healthcare. Surfacing fractures Forget Osteoporosis-Related fractures are identified instantly in AI assisted radiology and before a radiologist has had a chance to read the report. Early detection of these fractures is important because an absence of estrogen is the main reason for osteoporosis. One subfield of AI called machine learning (ML) is amongst others already making a change in the healthcare domain, with diagnostic imaging, genetic testing, electrodiagnosis and optimized treatment planning. ML derives Hounsfield Units (HU) from computed tomography (CT) scans to categorize vertebrae and measure lumbar spine results T- scores, which is helpful in diagnosing osteoporosis. AI in medical diagnosis helps to reduce the risk of osteoporosis through better early detection and intervention [17] [18].

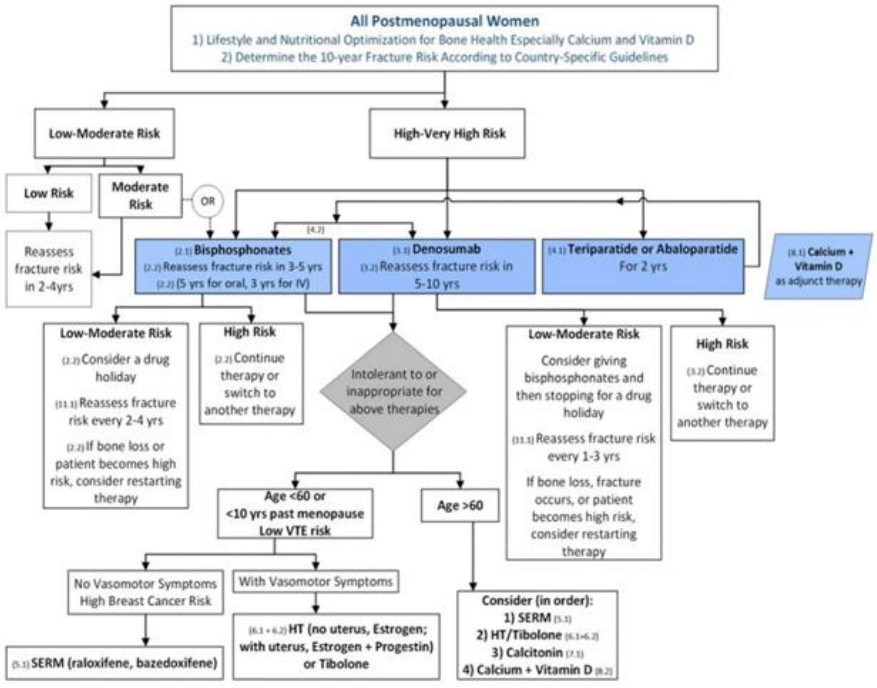

Fig. 2. Risk-based treatment pathway for osteoporosis management in postmenopausal women [12].

2. Methodology

This review was conducted as a narrative synthesis of the current literature on osteoporosis detection and diagnostic approaches. Relevant publications were identified through searches of major scientific

databases, including PubMed, ScienceDirect, and Google Scholar, with a focus on peer-reviewed studies, guidelines, and authoritative reviews addressing imaging modalities, biochemical markers of bone turnover, and emerging digital technologies for osteoporosis diagnosis.

The literature was reviewed with a targeted approach aimed at identifying clinically meaningful and methodologically representative studies rather than attempting an exhaustive survey of all published work. To enhance clarity and enable structured comparison, two summary tables were incorporated. Table 1 summarizes the key studies included in this review, outlining the diagnostic techniques employed and their principal findings. Table 2 compares the major osteoporosis diagnostic methods by outlining their respective advantages and limitations, thereby supporting evaluation of their clinical applicability.

This narrative review framework enables the integration of diagnostic principles, clinical relevance, and recent technological developments across different assessment modalities, providing a focused and coherent overview of current approaches to osteoporosis detection.

Table 1. Summary of Key Reviewed Articles on Osteoporosis Diagnosis (2015–2025)

Author (Year)	Diagnostic Focus	Technology	Sample	Main Findings
Liu et al. (2022)	Imaging	ML on CT + clinical data	n = 540 patients	ML improved diagnostic accuracy vs. DXA alone [31]
D. Luzhbin et al. (2023)	Imaging	QCT vs. DXA comparison	n = 120	QCT provided higher volumetric BMD precision [41]
Ramaraj et al. (2023)	Ultrasound	QUS vs. DXA	n = 121	QUS showed strong correlation with BMD (r = 0.91) [43]
Iftikhar et al. (2020)	Biomarkers	P1NP assay	n = 267	Sensitivity 83%, specificity 72% [55]
Suwan et al. (2024)	Biomarkers	CTX + P1NP monitoring	n = 60	Bone turnover reduced after risedronate [64]
Qiu et al. (2024)	AI	Deep neural network on clinical data	n = 350	AUC = 0.89 for osteoporosis prediction [73]
Bendtsen et al. (2024)	mHealth	App-based self-management	n = 120	Improved patient engagement, reduced clinic visits [77]

Table 2. Advantages and Disadvantages of Osteoporosis Diagnostic Methods.

Diagnostic Method	Advantages	Disadvantages
DXA	• Gold-standard technique with WHO T-score–based diagnostic criteria [4, 29, 30] • Low radiation dose and high measurement reproducibility [29, 30]	• Measures areal BMD only and does not assess bone microarchitecture [29, 36] • Susceptible to artifacts from degenerative changes and vascular calcifications [29, 33]
QCT	• Provides volumetric BMD and selective assessment of trabecular bone [36, 37, 41] • Improved fracture risk stratification compared with areal BMD in selected populations [29, 35]	• Higher radiation dose compared with DXA [36] • Higher cost and limited availability in routine clinical practice [36, 40]
HR-pQCT	• Enables high-resolution three-dimensional evaluation of cortical and trabecular bone microarchitecture [40]	• Limited to peripheral skeletal sites and primarily used in research settings [40]
MRI	• Radiation-free assessment of bone quality, marrow composition, and microarchitecture [48, 49, 51]	• Lack of standardized diagnostic thresholds for osteoporosis [48] • High cost and limited clinical accessibility [49, 50]
QUS	• Radiation-free, low-cost, and portable technique suitable for screening [42, 44, 45]	• Lower precision than DXA and strong site dependency [43, 46]

Biochemical Markers	• Useful for monitoring bone turnover and treatment response [12, 53, 54, 60]	• High biological variability and limited diagnostic specificity for standalone diagnosis [8, 65, 67]
AI-Based Methods	• Improved diagnostic accuracy and support for opportunistic osteoporosis screening [17, 31, 73, 74]	• Limited external validation and lack of standardized clinical implementation [73, 74]
mHealth & Portable Devices	• Enhance patient engagement, self-management, and remote monitoring [77, 78, 79, 80]	• Limited diagnostic capability and dependence on user compliance and digital literacy [77, 79]

3. Pathophysiology of osteoporosis

Post-traumatic osteoporosis is a multifactorial condition, often triggered by physiological stressors such as severe burns or musculoskeletal trauma (Figure 3) [19][20]. However, disruption of the biomineralization process occurs in many disorders through similar mechanisms at both cellular and molecular levels [21]. The dynamic process of biomineralization, where osteoblasts form new bone while osteoclasts resorb existing bone, is tightly regulated by cytokines and hormones within the bone microenvironment. Polytrauma has been linked to elevated levels of interleukin (IL)-1β and IL-8 cytokines, along with an increased IL-6/IL-10 ratio. IL-8 significantly impacts osteoclast formation and additionally stimulates nuclear factor of activated T cells 1 (NFATc1) activation via the receptor activator of nuclear factor kappa-B (RANK) pathway [22][23][24]. A recent study revealed that 76% of patients with conditions such as polytrauma and neurologic injuries in an inpatient rehabilitation facility had deficient vitamin D levels (<30 ng/mL) [25]. Compared to the osteotomy control group, delayed fracture healing and significantly reduced bone volume fraction were observed in the injury site of a polytrauma mouse model combining skeletal trauma and burn injuries [26].

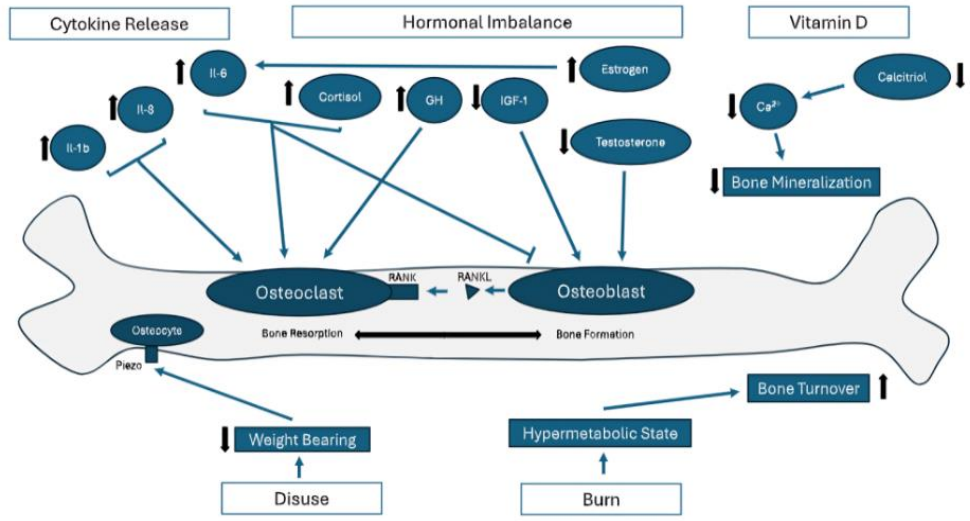

Fig.3. An illustrates how various factors disrupt the process of bone remodeling. Inflammation (cytokines), hormonal derangements, vitamin D deficiency, lack of weight bearing activity (disuse) and hypermetabolic states (e.g., burns) augment osteoclast activity and osteoblast function. Consequently bone resorption exceeds bone formation and loss of bone and osteoporosis ensues [27].

4. Traditional Diagnostic Methods

4.1 Dual-Energy X-ray Absorptiometry (DXA)

The clinical assessment of bone mineral density evolved from earlier photon-based absorptiometry methods, leading to the introduction of dual-energy X-ray absorptiometry in the late 1980s. Although the fundamental principle of dual-energy attenuation has remained unchanged, technological advances have improved detector performance, calibration accuracy, radiation dose optimization, and expanded clinical applications such as vertebral fracture assessment and trabecular bone score. Bone mineral density is quantified by measuring the differential attenuation of two X-ray beams at different energy levels as they pass through bone and soft tissue, enabling calculation of areal bone mineral density and standardized T-scores [28].DXA is the clinical standard for diagnosing osteoporosis because it directly measures bone mineral density by comparing how two different X-ray energy levels are absorbed by bone and soft tissue, allowing accurate quantification of bone mass. In contrast, conventional single-energy radiography (standard X-ray) produces qualitative images that show bone structure but does not provide reliable numerical measurement of bone mineral density. As a result, significant bone loss (often around 30–40% of bone mineral) must occur before it becomes visible on a regular X-ray, making it unsuitable for early osteoporosis detection or diagnosis. DXA's ability to generate standardized bone density measures (such as T-scores) and fracture risk estimations is reflected in international osteoporosis guidelines, which do not recommend routine diagnosis based on conventional X-ray alone [28][29] . DXA uses low-energy X-rays to measure BMD, this approach is standard practice for diagnosis and treatment of osteoporosis. Its success is based on strict quality control, accurate positioning protocols and uniform interpretation of the results. Recent advances such as the introduction of Vertebral Fracture Assessment (VFA) and Trabecular Bone Score (TBS) have improved its ability to assess bone health and fracture risk [30][31]. Normal DXA bone density results were detected in approximately 1 of 4 (24.54%), with osteopenia (mild loss) and osteoporosis identified in, respectively, 45.75% and 29.69% of the harvesting volunteers ages 30 to 60 years. Osteopenia was the most common diagnosis, being identified in 27 [26.2%] subjects [32]. As demonstrated in (Figure 4), when using the OSTA in conjunction with an anteroposterior radiograph of the hip, it is possible to accurately screen for osteoporosis in patients who have undergone hip arthroplasty. According to the study, a total prevalence of osteoporosis was 38.5% and it was highest in the lumbar spine (38.7%) and forearm (38.4%), showing gender-independent susceptibility levels. Bone density was measured in 384 participants using DXA. The results reveal how OSTA, DXA measurements and radiographic evaluation were in concordance of one another as illustrated from the graphical data in the study [33][34].

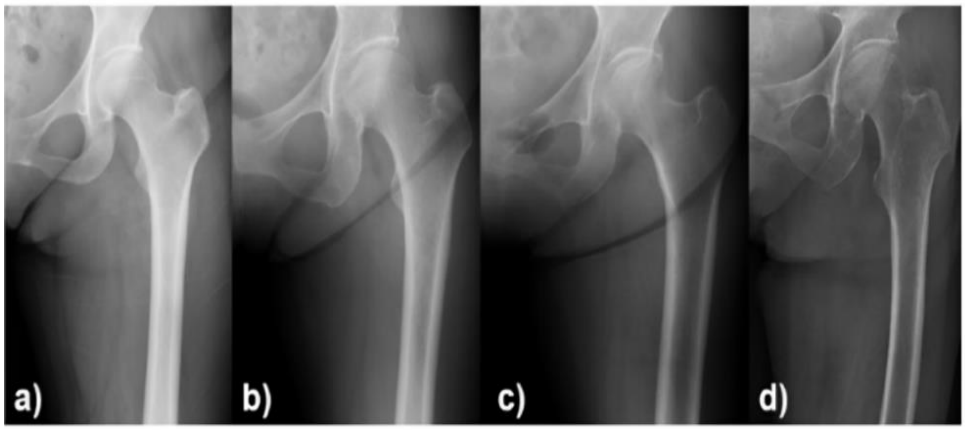

Fig. 4. Four X-ray examples that are used to categorize the risk of osteoporosis, 15 surgeons for these cases were a: very unlikely, b: unlikely, c: suspicious, and d: very suspicious [34].

4.2 Quantitative Computed Tomography (QCT)

Bone density is assessed using calibrated computed tomography images to measure X-ray attenuation values (Hounsfield units) within trabecular and cortical bone, which are converted into volumetric bone mineral density through the use of reference phantoms [35].Three-dimensional assessment of bone density was initially developed in the 1980s to overcome the limitations of two-dimensional measurements, particularly for evaluating trabecular bone. Early implementation was constrained by higher radiation exposure and cost; however, advances in CT technology, calibration techniques, and image analysis have led to renewed interest and improved clinical applicability in recent years [36].The susceptibility to osteoporosis is accessed by the use of QCT – a 3-dimensional image that can measure BMD, and which is particularly suited for measuring trabecular bone. QCT Long-term precision the simultaneous versus asynchronous calibration was judged by the study of BMD measurements with QCT over an 18-month period. The conclusion from the studies is that when exposed to sequential and asynchronous mode calibration, enhanced accuracy and precision were observed for measurements of trabecular (and cortical bone, showing potential application in BMD assessments in clinical care[37][38]. The clinical relevance of QCT measurement of bone mineral content (BMC) in the assessment of BMD and its relation to hip fracture risk were studied. It showed the distinct advantages that QCT offers with respect to complete assessment of cortical and trabecular bone structure. The findings demonstrated that QCT provides accurate measurement of bone mineral density and meaningful prediction of fracture risk, supporting its potential role as a complementary tool in osteoporosis assessment [24]. Recent technological developments have further strengthened the clinical value of QCT by enabling precise quantification of volumetric bone mineral density and improving fracture risk estimation through advanced segmentation and analytical techniques. Also, both trabecular and cortical bones can be better evaluated with QCT when compared to conventional means, which is essential for osteoporosis diagnosis and fracture risk evaluation [36][39]**.** Within the broader category of QCT, high-resolution techniques have further expanded the ability to characterize bone quality at the microstructural level. For QCT analysis, a mid-vertebral cross-sectional image was selected in the sagittal plane, and a region of interest encompassing trabecular bone was delineated while excluding cortical bone (Figure 5). High-resolution peripheral quantitative computed tomography represents an advanced extension of conventional QCT, providing ultra–high-resolution three-dimensional imaging of bone microarchitecture at peripheral skeletal sites such as the distal radius and tibia. Similar to standard QCT, it operates by measuring X-ray attenuation and converting these values into volumetric bone mineral density; however, its substantially higher spatial resolution enables separate evaluation of trabecular and cortical compartments and direct assessment of microstructural parameters, including trabecular thickness, number, and cortical porosity. These capabilities make HR-pQCT particularly valuable for research applications and enhanced fracture risk assessment beyond areal BMD, although its clinical use remains limited by high cost, restricted availability, longer acquisition times, and confinement to peripheral sites, preventing assessment of the spine and hip and positioning it as a complementary rather than routine diagnostic tool in clinical practice [36][40].

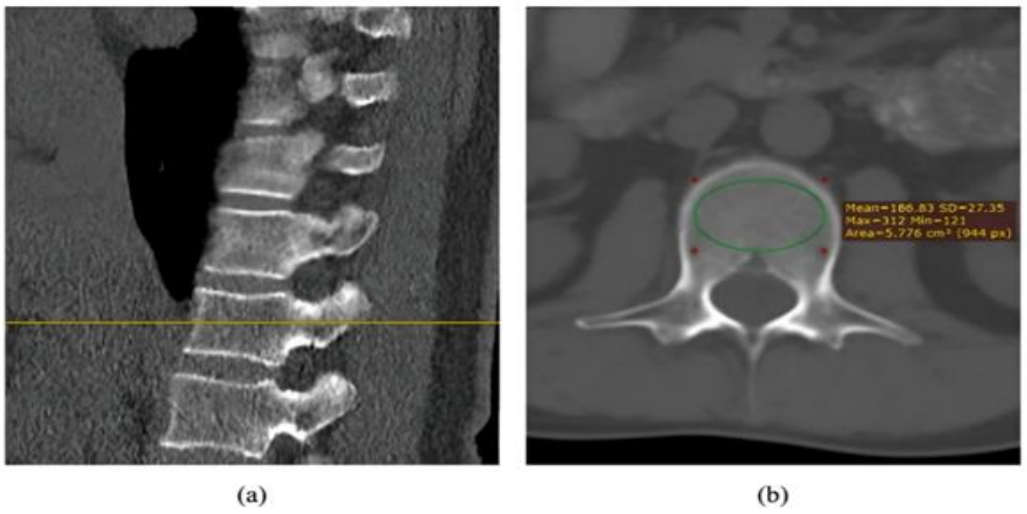

Fig. 5. (a) Identification of the cross-sectional image through the mid-portion of the vertebral body in the sagittal plane. (b) Manual delineation of the region of interest (ROI) on the selected slice to include trabecular bone while excluding the cortical shell [41].

4.3 Ultrasound

Bone properties are evaluated by transmitting ultrasound waves through peripheral skeletal sites and analyzing parameters such as speed of sound and broadband ultrasound attenuation, which reflect bone density and elasticity and allow assessment of bone health and fracture risk. Radiation-free ultrasound-based approaches to osteoporosis evaluation emerged in the 1990s as an alternative for population-level screening, particularly at peripheral skeletal sites. Although the fundamental principles of ultrasound-based bone assessment have remained largely unchanged, advances in signal processing and device portability have improved reproducibility and expanded their use in both clinical practice and screening settings [42]. Phalanx US (sensitivity 80-100% in this study) is easily available (and less expensive) as a method to screen for osteoporosis. Besides that, it can diagnose the early bone quality loss already starting in the premenopausal period in a female person, it gives age-related reference values and establishes the pathological risk thresholds. i.e. phalanxs US phalanx offers a useful GRA(Good Reproducibility and Accuracy) for early diagnosis and the screening of osteoporosis compared to DXA [43][44]**.** Bone mass in attend was assessed by QUS including Speed of Sound (SOS), Broadband Ultrasound Attenuation (BUA), Bone Quality Index (BQI), T-score, and Z-score. The humans were of normal bone mass between the ages of 21 and 40, the assistants between the ages of 41 and 60 had osteopenia, and to the bound of 71 to 80, the groups also exhibited osteoporosis. There was good linearity between two points Z-scores and SOS (R = 0.916), but BUA had a relatively significant association with BMI. QUS was also a safe, low-cost noninterfering modality for early stage of osteoporosis and monitoring bone condition [45][46]. The efficacy of the QUS Sonometer for the diagnosis of bone mineral loss and the risk of suffering from osteoporosis was checked in 121 subjects (menopausal and pre-menopausal). The subjects were divided into three groups as normal, osteopenic, and osteoporotic by the values on the calcaneus including the measurement of Speed of Sound (SOS), BUA, and T-score. Results: Postmenopausal women were the group with higher prevalence of postmenopausal osteoporosis (20%); 32.23% of the patients presented with normal bone mass, 58.67% with osteopenia, and 9.09% with osteoporosis. The present study verifies that QUS is a reliable, radiation-free, non-invasive and cost-effective method with early diagnosis value for osteoporosis, especially in high-risk population (such as postmenopausal women) [43].

4.4 Magnetic Resonance Imaging (MRI)

Bone quality is indirectly assessed using magnetic resonance techniques by exploiting differences in signal characteristics of bone marrow and trabecular structure, allowing evaluation of bone microarchitecture and marrow composition without exposure to ionizing radiation. Initially applied mainly for structural musculoskeletal imaging, magnetic resonance imaging has progressively expanded to include assessment of bone quality, with recent advances in high-resolution imaging and quantitative analysis enhancing its ability to non-invasively evaluate trabecular structure and marrow composition relevant to osteoporosis [47]. In osteoporosis, MRI assesses bone microarchitecture and quality through detection of changes in marrow composition and structural integrity of bone. The study aimed to assess the value of radiomics in distinguishing osteoporotic from healthy lumbar spine received multiparametric MR images using T1- and T2-weighted images with DXA. T1WI, T2WI, T1WI+T2WI radiomic features were processed by LASSO regression analysis, Courtesy of MRI bone imaging schematic showing macro- to molecular-level techniques (figure 6). Model performance was assessed using ROC curve and selection curve analyses. The combined T1WI+T2WI model demonstrated superior diagnostic performance compared to single-sequence models, achieving Area under the curve (AUC) values of 0.839 and 0.860 in the validation and training cohorts respectively. This strategy allows the development of a non-invasive osteoporosis-predicting tool that can help decrease reliance on DXA, and alleviates the need for unnecessary testing [48]. Recent studies highlight that MRI is superior to DXA in the diagnosis of osteoporotic fractures. While DXA primarily quantifies bone mineral density as a surrogate marker of fracture risk, magnetic resonance imaging provides a broader assessment of bone health by capturing changes in microarchitecture, geometry, and adjacent soft tissues. Using advanced sequences such as proton density–weighted, T1-weighted, and T2-weighted imaging, MRI enables detection of early structural alterations, bone marrow edema, and occult fractures that may not be evident on DXA. Consequently, MRI shows considerable potential for early identification of osteoporosis, improved fracture risk stratification, and more individualized therapeutic planning [47][49].

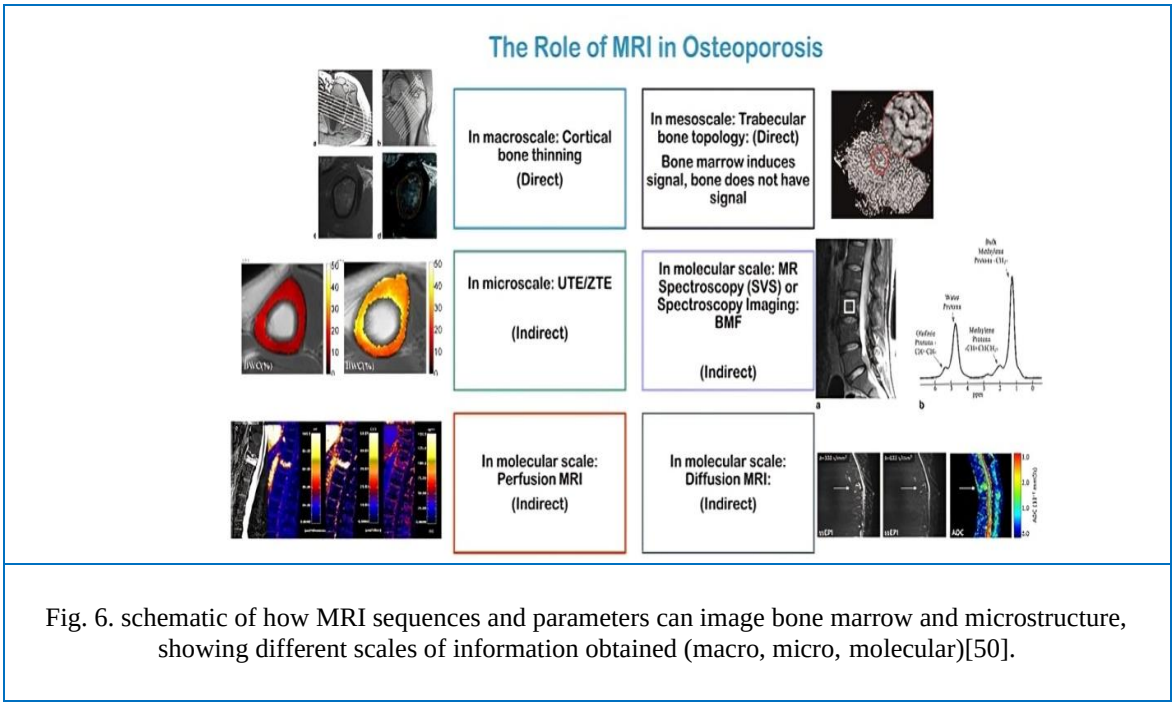

Fig. 6. schematic of how MRI sequences and parameters can image bone marrow and microstructure, showing different scales of information obtained (macro, micro, molecular)[50].

5. Biochemical Markers

Studies on bone turnover markers have developed continuously from their first application in the 1980s. Early assays suffered from lack of specificity and substantial analytical variability, which limited their clinical utility. But a better immunoassay technology and international standardization now give them an improved reliability, so their use has shifted nowadays for monitoring bone metabolism and therapy effect instead of being diagnostic methods alone [8]. These markers are an important means of learning about skeletal remodeling through the measurement of the circulation molecules released when bone is formed and resorbed, and thus they mirror osteoblastic and/or osteoclastic activity at a molecular level. As a result, they provide dynamic information in addition to structural imaging methods. Bone formation markers represent osteoblastic collagen synthesis, and (P1NP) is most commonly recommended because of its high specificity and reproducibility. On the other hand, bone resorption markers reflect osteoclast cell-mediated breakdown of bone matrix (CTX is usually used as a marker for this process) in order to measure level of resorption and assess response to osteoporosis therapy [51][52].

5.1 Formation Markers:

5.1.1 Procollagen Type I N-terminal Propeptide (P1NP)

P1NP is a biomarker of bone formation with extensive evidence, which greatly reflects osteoblastic collagen synthesis, and has a particular relationship with postmenopausal osteoporosis in clinic. Evidence from clinical studies suggests that serum P1NP concentration is significantly correlated with BMD, and elevated concentrations seem to indicate a higher rate of bone turnover in those with lower BMD. In populations of postmenopausal women, P1NP has favorable diagnostic performance for the early detection of osteoporosis in the spine with higher sensitivity and overall accuracy compared to DXA in the identification of metabolically active bone. Crucially, the relationship between P1NP and BMD was observed to be independent of key confounders such as age, BMI, and years since menopause. Because of its non-invasive evaluation, sensitivity to acute metabolic changes and a reliable response to anti-osteoporotic therapy, P1NP is recommended as reference marker for monitoring bone formation in osteoporosis by international guidelines [53] [52] [54].

5.1.2 Bone-Specific Alkaline Phosphatase (B-ALP)

B-ALP are an osteoblast enzyme secreted during bone matrix production and mineralization, and is thus considered to be a formation marker of the bone. There have been several articles in the literature reporting that levels of B-ALP are high in bone turnover states and independently correlated with changes in bone mineral density, a fact which may make it suitable as a tool for evaluation of metabolic activity in osteoporosis. In addition to serum levels, non-invasive methods including salivary B-ALP have been directly associated with skeletal maturation and bone growth and might be useful tools in certain clinical and research settings. While B-ALP does not possess the necessary specificity to be used as a sole diagnostic marker, it provides an important added information on osteoblastic activity and is often measured in conjunction with P1NP for assessment of bone formation dynamics and follow-up of treatment response [52][55]. Recent studies, both at diagnosis and post-COVID19 era, have supported even more the key role of B-ALP –based biomarkers in the clinical context and the synergistic correlation between B-ALP with bone formation in various age-specific groups or clinical categories “active disease or in remission”, when imaging is not easily accessible. Overall, there is supporting evidence to use B-ALP as an additional marker to assess bone turnover and osteoporosis risk rather than a stand-alone diagnostic tool [56].

5.1.3 Osteocalcin (OC)

OC has been widely investigated as a marker of bone turnover in postmenopausal women. Clinical studies have shown that serum OC levels are higher during the early postmenopausal period, reflecting increased bone remodeling activity shortly after menopause. This elevation is often accompanied by increased levels of other formation markers, such as ALP, supporting the concept of accelerated bone turnover during this stage. As OC is released during bone matrix formation, it serves as an indicator of osteoblastic activity; however, its clinical interpretation is limited by biological variability and the influence of non-skeletal factors, which restricts its use as a standalone diagnostic marker [57]. The investigation would prompt a biomaterial with woven architecture to confront bone loss progressively from OC to OP with OC being valuable biomarker in OP screening [58]. Studies conducted in postmenopausal Chinese women have demonstrated that osteocalcin–related biomarkers in serum and urine are associated with multiple aspects of skeletal health. Specifically, osteocalcin levels have been shown to correlate with bone mineral density, trabecular bone score, and indicators of bone microarchitecture, suggesting a link between bone turnover activity and both bone quantity and quality. The combined use of DXA-derived parameters and high-resolution peripheral quantitative computed tomography further supports the role of osteocalcin as a complementary marker reflecting skeletal remodeling rather than a standalone diagnostic indicator [59].

5.2 Resorption Markers:

5.2.1 C-Telopeptide of Type I Collagen (CTX)

The biochemical marker of bone resorption is CTX as show in (figure7). It is used for estimating bone turnover and following both the development and treatment of osteoporosis. Its relevance was supported by a study as a predictor of patients with osteoarthritis (OA) at risk of undergoing joint replacement, underscoring the utility of this measure in relation to the disease development and therapeutic choices. Higher serum CTX value was associated with the probability of joint failure and requirement of surgery ,especially the β-isomerized form measured in blood, is widely used to assess bone resorption and correlates negatively with bone mineral density [57][60]. A single-arm clinical trial was conducted at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand in postmenopausal women with osteoporosis aged 45 to 75 years. Subjects received a weekly oral 35 mg generic of risedronate for 52 weeks. The BMD was assessed at baseline and at end of study, in addition measurement of the serum BTMs, CTX and P1NP, at screening visit, baseline, week 12, week 24, and week 52. The objective of the trial was to determine the therapeutic effect of risedronate on bone turnover rates and changes in BMD over time[61]. In addition to peptide-based resorption markers, pyridinoline (PYD) and deoxypyridinoline (DPD) are collagen cross-linking compounds released during the degradation of mature type I collagen and excreted in urine. Both markers reflect osteoclastic bone resorption and have been widely used to assess bone turnover, particularly in metabolic bone diseases. Deoxypyridinoline is considered more bone-specific than pyridinoline, as it is less influenced by cartilage turnover. Although urinary PYD and DPD provide valuable information on resorptive activity, their clinical use has declined due to biological variability, pre-analytical limitations, and the need for urine collection, leading to preference for serum-based markers such as CTX in routine practice [62][52].

Fig. 7. This image illustrates the equilibrium between bone reabsorption and bone formation. When an increase in CTX-1 (bone resorption marker) and a decrease in OC (bone formation marker) occur, mineral density of bones decreases and the bones become weak. So, when you have greater OC and less CTX-1, that's when the bones are winning over bone formation, effectively making your bone stronger [63].

5.2.2 N-Telopeptide of Type I Collagen (NTX)

This biochemistry marker serves to assess the loss of bone (NTX) and is extensively utilized as a tool for following-up on bone metabolism and osteoporosis development. One study on patients showed that serum NTX is significantly correlated with low BMD, so a tight connection with osteoporosis can be presumed. provides insight into collagen degradation, although its use in routine clinical practice is generally supported by broader marker panels [64]. These observations emphasize the value of NTX in early determination and assessment of bone, particularly in conditions such as Crohn's disease whereby bone resorption is often expedited [65]. Experimental design Forty-nine-month-old virgin female Wistar rats were bilaterally ovariectomized. Serum leptin, OC and NTx were evaluated before, 20th postoperative day, 40th and the 60th days of ovariectomy. BMD was evaluated by pQCT before and after surgery. This was advantageous in that it allowed investigation of the interrelationship between serum leptin levels and BTMs at the onset of osteoporosis in ovariectomized rats [66].

5.2.3 Tartrate-Resistant Acid Phosphatase 5b (TRACP-5b)

As an indicator of bone breakdown, TRACP-5b reflects osteoclast activity and is important for diagnosing and monitoring osteoporosis. Comparisons with the Nittobo TRACP-5b assay have shown that it is applicable to a variety of clinical cases due to its analytical stability, reliability, and non-dependency on renal function. Its strong agreement with the Immunodiagnostic Systems (IDS) iSYS platform indicated that the assay had the possibility of being harmonized for general clinical use for measuring bone turnover [67][68].

Four hundred twenty-one postmenopausal women with osteopenia were treated for 3 months with bazedoxifene (20 mg daily) in combination with estradiol (1 mg daily). All subjects were determined for serum bone specific ALP and tartrate-resistant acid phosphatase 5b (TRACP 5b) which are markers for bone formation and bone resorption, respectively. BMD of the lumbar spine were predicted by the TRACP-5b/BAP ratio three months after treatment initiation for the change from baseline to one year of therapy [69].

6. Emerging Technologies

6.1 Artificial Intelligence and Machine Learning in Osteoporosis Detection

Osteoporosis risk can be estimated by applying machine learning algorithms to imaging data and clinical variables, enabling automated identification of patterns associated with low bone density and increased fracture risk. Advances in computational power and data availability over the past decade have driven the development of artificial intelligence–based approaches for osteoporosis detection, which continue to evolve rapidly and show promise for risk prediction and opportunistic screening; however, most remain under investigation and require further clinical validation before routine clinical implementation [70]. The AI-ML can analyze large clinical, demographic data for prediction of stepwise risk, early diagnosis, prevention approaches. Among the multi-dimensional AI models compared, the DNN (a deep neural network) exhibited better performance regarding accuracy, with the ability to use less input vectors and fewer samples than traditional machine-learning methods and regression techniques. These results further support the increasing importance of AI and ML to aid clinicians in their decision-making process, and to detect important risk factors linked with osteoporosis. AI has been more and more utilized for osteoporosis detection, fracture risk prediction in recent years, especially with ML and deep learning models. Most of these applications are developed for the analysis of imaging data that includes DXA scans, X-ray pictures and opportunistic CT images so as to facilitate an automatic estimation of bone mineral density and case identifying high fracture risk individuals. Newer strategies combine imaging features with clinical parameters and biochemistry, thereby evolving into a personalized and broadly based approach to risk stratification. Despite the promising results, incorporation of AI in routine care of osteoporosis is still at a nascent stage. The available studies are mostly retrospective, from single-center cohorts, without external validation, thus their reproducibility and generalizability for routine use is questioned. Variation in imaging protocols, patient demographics and outcome definitions also complicate pooling across studies. Thus, current evidence, indicates the application of AI as an adjunctive technique, to potentially enhance the efficiency of screening and enable opportunistic case finding and not as a replacement for established diagnostic modalities like DXA. More prospective studies and regulatory approval are required before the use of AI as a standalone diagnostic tool [71].Deep learning has the potential to serve as a valuable and cost-effective adjunct to DXA screening, particularly in healthcare settings with limited access to DXA equipment. Table 3 presents the sample characteristics along with feature descriptions and relevant information [72][73].

Table 3. Sample Data with Description and Attributes[72]

Age	Height (cm)	Weight (kg)	BMI	C.Width (mm)	C.FD	Tr. thick (mm)	Tr. FD	Tr. Numb	Tr. separa (mm)
62	153	55.15	23.4	1.73	0.87	0.13	0.22	2.14	0.71
60	182	76.82	23.13	3.76	0.54	0.22	0.15	2.05	0.5
72	152	68.94	29.75	2.32	0.87	0.2	0.3	2.18	0.61
65	183	72.85	21.59	4.19	0.38	0.18	0.44	2.44	0.53
80	152	80.2	34.68	3.08	0.59	0.13	0.17	2.38	0.26
60	150	75.11	33.06	3.9	0.46	0.23	0.33	2.14	0.55
65	177	76.99	24.33	4.44	0.62	0.09	0.11	2.17	0.28
57	189	74.32	20.61	4.02	0.4	0.1	0.59	1.39	0.52
53	185	70.45	20.39	4.1	0.8	0.15	0.18	1.33	0.67
89	173	88.59	29.59	2.72	0.81	0.1	0.27	1.94	0.66
53	186	50.61	14.52	3.16	0.87	0.24	0.11	1.22	0.73
74	150	79.92	35.42	2.26	0.39	0.22	0.36	1.83	0.28
52	189	78.28	21.91	2.09	0.67	0.12	0.6	1.47	0.72
81	169	85.81	29.82	3.02	0.58	0.18	0.34	1.65	0.45

6.2 Portable Devices

Portable technologies for osteoporosis management, such as limited diagnostic devices and mHealth apps, are convenient approaches to bone health monitoring and promotion. These tools track bone density readings, offer educational materials and promote lifestyle changes with features like calcium intake calculators. Studies on mHealth tools like the “My Bones” app is showing a high level of acceptability and usability with potential to reduce hospital visits, increase patient engagement who are taking their treatment into their own hands and in turn improve health outcomes in osteoporosis care [74].

For BMD, DXA was performed at a BMD but not fracture prior time point and the presence of osteoporosis was a case in the study. A participatory design approach was employed to develop a mobile health (mHealth) application that provides personalized information and support for women with osteoporosis. These findings highlight the growing role of AL and ML in improving clinical management and in identifying key risk factors associated with osteoporosis [75]. Deep learning may become an inexpensive added value to DXA screening, especially in situations with limited availability of DXA. Sample characteristics, feature descriptions, and summary information Table 2 shows the sample characteristics as well as description of features and relevant details [75][76]. The differences in eHealth literacy between the different demographic groups and the validity of the eHealth Literacy Questionnaire (eHLQ) were examined using a Bayesian mediated Multiple Indicators Multiple Causes (MIMIC) model. It was found that age, education and level of ICT use had a strong effect. These findings validate the eHLQ as being able to identify individuals’ needs in digital health literacy correctly [77].

7. Discussion

Osteoporosis detection remains a multifactorial challenge, as bone strength varies across skeletal sites and diagnostic techniques differ in their underlying measurement principles. The results of this review emphasize the continuous development in osteoporosis diagnostics from classical imaging to integrated, technology improved diagnostic models. DXA is the most commonly used diagnostic tool with validated clinical thresholds, reproducibility and availability [28][29]. The optimal anatomical sites for bone density assessment vary across diagnostic techniques, and measurements are not directly interchangeable between sites or modalities, as summarized in Table 4.

Table 4. Optimal anatomical sites for osteoporosis assessment across diagnostic techniques

Technique	Optimal anatomical sites	Clinical rationale	cross-modality comparability	Key references
DXA	Lumbar spine, total hip, femoral neck; distal forearm (alternative)	High fracture risk sites with validated diagnostic thresholds	Site-specific; measurements are not interchangeable across sites	[28, 29, 30]
QCT	Lumbar spine	Selective trabecular bone assessment using volumetric BMD (vBMD)	Not directly comparable to DXA due to vBMD vs aBMD	[36]
HR-pQCT	Distal radius, distal tibia	High-resolution assessment of cortical and trabecular microarchitecture	Research-focused; complementary to clinical imaging	[40]
QUS	Calcaneus	High trabecular content and ease of accessibility for screening	Site-specific; suitable for screening only	[44, 45]
MRI	Lumbar spine	Assessment of bone quality and marrow composition without ionizing radiation	No standardized diagnostic thresholds for osteoporosis	[48, 49, 51]
Biochemical markers	Systemic (blood / urine)	Reflect whole-skeleton bone turnover dynamics	Cannot localize site-specific bone loss	[8, 52, 54]
AI-based methods	Depends on input modality	Opportunistic osteoporosis risk prediction using imaging and clinical data	Dependent on underlying data source and modality	[73, 74]

Dual-energy X-ray absorptiometry remains the clinical reference standard, with the lumbar spine and proximal femur considered optimal sites due to their strong association with fragility fracture risk and the availability of validated diagnostic thresholds. However, degenerative changes, vascular calcifications, or prior fractures may affect spinal measurements, necessitating alternative sites such as the distal forearm in selected patients [30]. In contrast, quantitative computed tomography is most commonly applied to the lumbar spine, where selective assessment of trabecular bone allows volumetric bone mineral density measurement, although these values are not directly comparable to DXA-derived areal measurements [34]. QCT provides volumetric evaluation and greater sensitivity for identifying trabecular degeneration, yielding more accurate fracture prediction, High-resolution peripheral quantitative computed tomography further extends QCT capabilities by enabling detailed evaluation of trabecular and cortical microarchitecture at peripheral sites such as the distal radius and tibia. however, the clinical use of QCT is restricted by expense, radiation exposure, and access [36]. MRI also offers non-ionizing microarchitectural analysis and bone marrow composition assessment, and is therefore appropriate for early disease detection and follow-up [47]. However, so far simple MRI systems do not provide established diagnostic cutoffs for osteoporosis, and the realizability of the method is limited by expensive examinations as well as low incidence of devices. Ultrasound-based examination with QUS has been

developed for use in the general population as an effective and radiation-free alternative screening tool, particularly in low-resource areas [41]. Nevertheless, DXA is more reproducible in the diagnosis of osteoporosis compared to QUS because site variability and operator dependence introduce diagnostic limitations.

Biochemical markers play an important complementary role in the dynamic assessment of bone metabolism. Markers of formation, including the (P1NP) and that for (B-ALP), reflect osteoblastic activity and have been shown to relate to the rate of bone turnover and response to treatment [53][54]. On the other hand, resorption markers (e.g., CTX and NTX) reflect osteoclastic activities and are informative for the assessment of therapeutic effects [63][65]. Nevertheless, these markers are also characterized by remarkable inter-individual differences that vary according to circadian rhythm, diet and renal function, which hinders the low diagnostic specificity of each when used alone. Thus, while biochemical markers contribute to metabolic interpretation, they remain unable to act as diagnostic instruments alone.

Recent developments show a hopeful move towards digital diagnostics and AI-powered screening. Trabecular patterns and Hounsfield units from the vertebrae have been analyzed on routine CT scans by ML models for osteoporosis detection which allows opportunistic screening without added radiation doses to be possible [71][73]. (mHealth) applications also enable remote risk estimation and patient follow-up, thus enabling earlier intervention and better compliance [76]. Yet, it is not clear that these new methods will significantly improve the efficiency of scanning due to lack of standardized validation, reliance on high-quality datasets and lack of regulatory integration in clinical work flow.

In general, the current evidence indicates that no single diagnosis can adequately cope with the complexities of osteoporosis. Considering the possible combination of imaging metrics, biochemical markers and AI-enhanced risk prediction in a multimodal diagnostic framework, that tool could potentially allow early diagnosis, personalized monitoring and focused fracture risk stratification. Nevertheless, additional comprehensive longitudinal studies are needed to confirm these integrative models in different populations. Limitations of this review include its narrative format and dependence on published reports, which could induce referral bias or may not allow the possibility for a quantitative meta-analysis representation of diagnostic accuracy. Future research should focus on standardized diagnostic procedures and on harmonization of cut-off levels in order to improve clinical decision making and addressing doubts for diagnosis.

8. Conclusions

- Osteoporosis continues to be an important public health issue worldwide with its asymptomatic nature, and strong relationship with fragility fracture especially common in postmenopausalwomen and old people.
- Conclusions Although DXA is the clinical reference standard for osteoporosis diagnosis, due to its standardized thresholds, reproducibility and wide-spread availability but does not assessbone microarchitecture, there is a need for complementary diagnostic techniques.
- QCT and HR-pQCT offer valuable volumetric and microstructure of trabecular and cortical bone but have restricted clinical use due to higher cost, higher radiation does, and limited availability.
- MRI provides a radiation-free alternative to evaluate bone quality and marrow composition and adds valuable complementary information, but is not widely available in clinical implementation due to cost and the absence of standardized diagnostic thresholds.
- QUS provides a convenient low cost and radiation-free screening measure in the context of population surveys or resource-poor settings, with less precision compared to DXA.
- Biochemical measurements of bone turnover posted by P1NP, B-ALP, OC, CTX, NTX TRACP-5b and urinary collagen cross-links allow to obtain the dynamic information about skeletal metabolism and treatment response but their specificity is not high enough in order to assume a role as diagnostic tool alone.

- Emerging digital technologies, including AI-based models and mobile health apps show increasing promise for opportunistic screening, individual risk stratification, and remote patient monitoring; however current clinical adoption remains hindered by a lack of external validation, standardization issues and regulatory hurdles.
- Overall, available evidence suggests that any single diagnostic modality does not adequately capture the multimodal nature of osteoporosis. A multi-Med diagnostic concept including imaging, biochemical markers, and AI augmented analytics seems to represent the most complete approach for primary prevention of hip fractures.
- Longitudinal validation of new efforts is needed, as is harmonization of diagnostic criteria and integration of new technologies into clinical flow to further improve the accuracy, accessibility and global contribution that osteoporosis detection and treatment can bring.

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