Chapter

Advances in Clinical Application of Bone Mineral Density and Bone Turnover Markers

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Abstract

Bone mineral density is the main basis for the diagnosis of osteoporosis. The measurement methods of bone mineral density include dual X-ray absorptiometry (DXA), quantitative computer tomography (QCT), quantitative ultrasound (QUS), magnetic resonance imaging (MRI) and so on. Currently, bone mineral density measured by dual-energy X-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis. Bone turnover markers (BTMs) are biochemical products that reflect the activity of bone cells and the metabolic level of bone matrix, and they reflect the dynamic changes of bone tissue in the whole body earlier than bone mineral-density, procollagen type 1 N-terminal propeptide (PINP) and carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX) is sensitive BTMs, widely used in clinical practice, and can predict the occurrence of fractures. Some new markers such as Periostin, AGEs/RAGE, Gelsolin, and Annexin A2 provide new clues for exploring the mechanism of osteoporosis. The combination of the two can better carry out the diagnosis and differential diagnosis of multiple metabolic bone diseases, evaluate the therapeutic response of anti-osteoporotic medicines, and predict fracture risk.

Keywords: osteoporosis, bone mineral density, bone turnover markers, Periostin

1. Introduction

Osteoporosis (OP) is a systemic bone disease characterized by low bone mass and damage to the microstructure of bone tissue, causing increased bone fragility and susceptibility to fractures [1]. With the aggravation of the global population aging, the prevalence of osteoporosis and the associated fractures is increasing year by year [2]. The medical care and nursing produced by that require a lot of human, material and financial investment, rising serious consequences for families and society such as the huge economic burden and social pressure [3]. Therefore, osteoporosis has become an important public health problem around the world, and early diagnosis is of critical significance for the prevention and treatment of osteoporosis [4, 5]. The diagnosis of osteoporosis is frequently based on bone mineral density, while bone turnover markers were used for differential diagnosis, observation of curative effect and treatment follow-up.

2. Advanced imaging assessments of bone mineral density

Bone mineral density refers to the amount of bone contained in a unit volume (volume density) or a unit area (area density). There are many methods of bone mineral density measurement, and different methods have different roles in the diagnosis of osteoporosis, monitoring of curative effect and assessment of fracture risk. Plain film absorptiometry (RA) and single-energy X-ray absorptiometry (single x-ray absorptiometry. SXA) two detection methods have been rarely used in clinical practice. X-ray plain film can evaluate changes in bone mineral density, but its sensitivity and accuracy are not high. It's difficult to make a positive diagnosis when bone mineral loss is less than 20%.Only when the bone mass is reduced by more than 30%, or even more than 50%, there are abnormal manifestations [6], thus it is generally not used as a tool for routine evaluation of bone mineral density. Presently, the commonly used bone mineral density measurement methods in clinical and scientific research include dual energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS) and MRI, etc.

2.1 DXA

Dual X-ray Absorptiometry (DXA) measures two-dimensional bone mineral density (areal BMD), namely the measured bone mineral content (bone mineral content, BMC) divided by the measured bone projection area. DXA bone mineral density measurement is the most commonly used method for bone mineral density measurement in clinical and scientific research. The main measurement site is the axial bone, including: lumbar spine and proximal femur. Lumbar BMD can sensitively reflect the changes of bone metabolism and therapeutic effect, while femoral BMD is one of the most reasonable indicators for predicting femoral fractures. Anterior and posterior lumbar spine measurements are generally selected for lumbar BMD examination, and the region of interest includes the vertebral body and its posterior appendages. The regions of interest for proximal femur measurement were the BMD of the femoral neck, greater trochanter, total hip and Wards triangle, and the regions of interest for the diagnosis of osteoporosis were the femoral neck and total hip. If the measurement of the lumbar spine and proximal femur is limited, especially when secondary osteoporosis (e.g., hyperparathyroidism) is considered, the non-dominant distal forearm third (33%) can be selected. The distal forearm measurement can obtain the bone mass parameters of the radius, ulna, and radius plus ulna at the super-distal end, the distal mid-segment, the distal 1/3, and the total distal part, totaling 12 different regions [7].

BMD measured by DXA is currently a common diagnostic index for osteoporosis. For postmenopausal women and men aged 50 and over, the BMD value according to the diagnostic criteria recommended by WHO is lower than the peak bone value of healthy adults of the same sex and race. The patients with T value less than 1 are considered as healthy; the T value ranging from 1 and 2.5 as osteopenia (or low bone mass); the T value equal to or more than 2.5 are diagnosed as osteoporosis, the patients with severe osteoporosis usually have one or more fragility fractures simultaneously (**Table 1**). Bone mineral density is usually expressed by T-Score, T-value = (measured value - peak bone mineral density in normal young people of the same race and sex)/standard deviation of peak bone mineral density in normal young people of the same race and sex. For children, premenopausal women and men under the age of 50, it is recommended to use the Z value of the same race to judge the level of bone mineral density, z-value = (bone mineral density measurement value - the

Disease state	T value
normal	T Value ≥ -1.0SD
osteopenia	-2.5SD < T value <−1.0SD
osteoporosis	T value ≤ -2.5SD
Severe osteoporosis	T value ≤ -2.5SD combined with a fragility fracture

Table 1.
The diagnostic criteria for osteoporosis based on DXA, BMD, and T values.

mean bone mineral density of the same race and the same sex and the same age) /the same race and the same age. The standard deviation of bone mineral density among sex peers, z-values below −2.0 were considered as "low cohort expected range" or low bone mass.

The lumbar spine BMD examination generally chooses the anterior and posterior lumbar spine measurement, and the area of interest includes the vertebral body and its posterior appendage structures, so the measurement results are affected by the degenerative changes of the lumbar spine (such as bone hyperplasia and sclerosis of the vertebral body and vertebral facet joints, etc.), abdominal Aortic calcification, intervertebral disc calcification, schmorl node, etc. Literature studies suggested that the choice of lateral lumbar spine BMD measurement can avoid the interference of the above factors [8]. At the same time, about 60% of the vertebral body is cancellous bone, which is also a site prone to osteoporotic compression fractures, while the spinous process, transverse process and pedicle of the posterior 1/3 of the spine are rich in cortical bone, which can be difficult for osteoporotic compression fractures and not play an important role in fractures. Lateral measurement of the lumbar spine can exclude the posterior 1/3 of the spine and detect early vertebral bone loss. In addition, with aging, the bone loss of cortical bone and cancellous bone is different. During a person's lifetime, BMD of the anterior vertebral body decreases by about 50%, while the posterior decreases by about 25%. Therefore, the lateral BMD measurement of the vertebral body can better reflect the actual changes of the spongy bone and the bone mass of the vertebral body itself. The lateral lumbar spine bone mass measurement is paired (accompanied) with the anterior and posterior lumbar spine, that is, combined with the lateral scan measurement on the basis of the anterior and posterior scan measurements, so that the estimated volumetric bone mineral density (vBMD) of the lumbar two-dimensional scan can be obtained at the same time. Also known as width-adjusted BMD (WA-BMD), the bone mass parameters of each vertebral body and the entire vertebral body can be obtained. It also avoids some interference factors and improves the ability of early detection of bone loss, thereby improving the diagnosis of bone loss and susceptibility to loose tissue. The lateral thoracolumbar vertebral images collected by the DXA measuring instrument can also be used for vertebral morphological assessment and vertebral fracture assessment (VFA), but the repeatability of DXA lateral lumbar spine measurement is not as good as the anteroposterior one.

Although BMD measured by DXA is currently recognized as the gold standard for the diagnosis of osteoporosis, there are still some limitations. DXA has the characteristics of high specificity and low sensitivity for the prediction of fracture, and depends on the choice of diagnostic point. A large number of studies have shown that BMD only partially reflects bone strength and cannot effectively evaluate the effect of anti-osteoporosis treatment. It only partially reflects changes in bone structure during aging, metabolic disorders or treatment. More scholars began to pay attention

to how to expand the DXA measurement function: 1) Trabecular bone score (TBS) is a measurement index for evaluating bone microstructure by analyzing image pixels of lumbar spine DXA [9]. 2) Hip structure analysis (HSA) is to evaluate the bone strength by computer analysis of the geometric data obtained from the DXA scan image of the proximal femur [10]. 3) Finite element analysis (FEA) is a two-dimensional model for evaluating femoral strength parameters, which can be used as a hip fracture risk assessment [11]. 4) Body composition measurement, which can be used for the evaluation of body composition, and can provide information on BMC, bone density, lean mass and fat content in different regions of the body, but the whole body bone density cannot be used for diagnosis of osteoporosis [12]. 5) Bone density assessment around the prosthesis, DXA can evaluate the stability of the prosthesis by measuring the bone density around the prosthesis [13].

DXA is a currently widely used technology with low radiation dose, and highly recognized as bone mineral density measurement method, while there are still many deficiencies. The regional BMD measured by DXA is a comprehensive measurement of cancellous bone and cortical bone, and the measurement results cannot reflect the early changes in BMD. At the same time, due to the principle of DXA plane projection imaging technology, the area BMD measured by DXA is affected by weight, scoliosis, bone hyperplasia, vertebral fractures and vascular calcification and then reduce the accuracy of BMD measurement. Testing in pregnant women is not yet recommended. As development of osteoporosis percentage increasing and the research of DXA new function in the elderly, further improvement of DXA fan beam scanning technology and application of multidetector, the scope of the application of the low radiation dose DXA is expanding in the assessment of human body bone mineral density measurement. But in addition to the DXA bone mineral density measurement, body composition analysis and evaluation are relatively mature, other functions (such as HAS, TBS, FEA detection, peripheral bone mineral density measurement, etc.) are mostly limited to the preliminary clinical application or the research phase of the trial.

2.2 Quantitative ultrasound (QUS)

QUS is a non-ionizing technology for BMD detection using acoustic waves, which uses different parameters to reflect the situation of bone mass indirectly [14]. Since Longton et al. (2008) first used QUS to measure bone tissue in 1984.The theory, methods, and instruments for measuring BMD with QUS have been greatly developed [15]. There are four types of US transmissions: trabecular transverse transmission, cortical transverse transmission, cortical axial transmission, and pulse-echo measuring devices [16–18]. Among them, Trabecular Transverse Transmission is mainly used to measure cancellous bone and the detection site is calcaneus. Cortical Axial Transmission is used for cortical bone detection and detection site is Radius [19]. Other measurements sites of QUS devices are finger phalanges, tibia, less common femur, posterior processes of the spine and ulna. Through QUS, two parameters are mainly obtained: Broadband Ultrasound Attenuation (BUA) and Speed of Sound (SOS). In theory, the two QUS principal variables are both related not only to BMD but also to trabeculae orientation, the proportion of trabecular and cortical bone, the composition of organic and inorganic components, bone elasticity damage and fatigue [20]. But currently the extent of its impact on BUA and SOS is unknown. The correlation between QUS parameters and DXA-BMD is good. It can distinguish patients with osteoporosis from normal people, but the false negative rate is high. At present, there is no uniform standard for the diagnosis of osteoporosis

by ultrasonography. It is not appropriate to apply the WHO diagnostic standard of $T \leq -2.5SD$, and its sensitivity and specificity are not ideal. Trimpou_ et al. (2019) pointed out that QUS quantitative ultrasound measurement is mainly attenuation of ultrasonic signals caused by reflection and absorption of sound waves by structures in the region of interest (including soft tissue, bone tissue, and bone marrow tissue).

QUS measurements are not only correlated with bone mineral density, but also provide information about bone stress, structure and more. It is currently mainly used for screening of osteoporotic risk populations and risk assessment of osteoporotic fractures in clinical routine. Several studies of original, review or meta-analyses settings demonstrated that heel QUS parameters are strong predictors of osteoporotic fractures [21–25]. The ultimate clinical use of heel QUS parameters to assess the fracture risk will have to be based and further validated in currently widely used approaches such as FRAX.

QUS has some advantages like simplicity, no radiation damage, high repeatability, low price, and easy handling, etc., Also, QUS can be used in children and pregnant women for primary osteoporosis screening and fragility fracture prediction. Especially in medical facilities where DXA or QCT is deficient, bone density measured by quantitative ultrasound is not true for bone mineral content. It cannot yet be used for the diagnosis of osteoporosis and the judgment of drug efficacy. At present, there is no unified QUS screening judgment standard and it can be referred to the information provided by QUS equipment manufacturers. In addition, horizontal comparison of equipment from different manufacturers cannot be carried out. If the results were suspected for osteoporosis, further DXA measurements should be performed. In conclusion, although QUS currently has recognized limitations in clinical practice, it has also been widely used, especially in the field of pediatrics, township health centers, and physical examination and screening structures. Besides, substantial progress has been made [26]. The parameters of the device for evaluating bone quality are a good supplement to DXA, and it needs to be further standardized before it can be promoted clinically [14, 27].

2.3 Quantitative computer tomography (QCT)

QCT is a method of bone mineral density measurement based on CT scan data after QCT phantom calibration and professional software analysis [14]. QCT uses CT three-dimensional volume data for analysis, and measures the true volumetric bone mineral density (vBMD), which can more sensitively reflect changes in bone BMD. Compared with DXA, QCT measurement is not affected by spinal hyperplasia and regression. The influence of factors such as changes and vascular calcification can avoid the false negative results of planar projection bone mineral density measurement technology caused by the above factors [28]. At the same time, the raw data of QCT can also be used for complex image processing to analyze and study bone changes and structural features [29].QCT includes central QCT, peripheral QCT and high-resolution peripheral bone quantitative CT (HR-pQCT), and micro-CT.

2.3.1 Central QCT (central computed quantitative tomography, cQCT)

cQCT is a pattern that uses multiple two-dimensional slices, the central delineation area of the pattern is the lumbar spine (especially the L1–3 vertebral bodies), the proximal femur, and central QCT also provides a measure of muscle mass [30]. Compared with DXA, central QCT is a measure of mean volumetric BMD (mg/cm3), which

improves the sensitivity and accuracy of BMD measurement and can assess the biological properties of interosseous BMD, bone geometry, and bone strength [31]. However, its disadvantage is that it increases the load of ionizing radiation, and due to the fact that most scanners are single-energy devices, which will lead to the potential problem of bone marrow fat changes. Studies have shown that the sensitivity of lumbar spine QCT to determine BMD is better than that of lumbar spine and hip DXA measurement, and it can more accurately reflect the changes in bone metabolism [32]. Clinical needs to choose to do spine or hip. Hip CT scans can be used for QCT, and the measured BMD results are equivalent to DXA areal BMD [33, 34]. According to the diagnostic criteria of the International Society for Clinical Bone Densitometry (ISCD) and the American College of Radiology (ACR), studies have found that QCT is more sensitive than DXA to detect osteoporosis [35]. This diagnostic criterion applies to postmenopausal women and older men. Lumbar vertebra QCT diagnostic criteria for osteoporosis: taking the average value of cancellous BMD of 2 lumbar vertebrae (usually the first and second lumbar vertebrae), and using the absolute value of lumbar spine QCT BMD for diagnosis. The evidence of BMD larger than 120 mg/cm^3 usually is classified as normal, the absolute value of BMD in the range of 80–120 mg/cm^3 as the group of low bone mass, the absolute value of BMD less than 80 mg/cm^3 being considered as osteoporosis [36].

2.3.2 Peripheral quantitative computed tomography (pQCT)

The measurement sites of pQCT are the distal radius and tibia, and the measurement results at this site mainly reflect the cortical bone mineral density. With a low radiation burden compared to central QCT, this modality not only provides valuable data on volumetric BMD, interseptal BMD, bone geometry, and bone strength, but also provides data including cross-sectional area and muscle density, which can be used to assess the risk of hip fractures in postmenopausal women. Because there is no diagnostic standard at present, it cannot be used for the diagnosis of osteoporosis and the judgment of clinical drug efficacy.

2.3.3 High-resolution peripheral computed tomography (HR-pQCT)

HR-pQCT is newly developed QCT scanning modality, which can reconstruct multiple 2D slices (most commonly the radius or tibia) into a 3D virtual bone biopsy and provide enhanced spatial resolution beyond that provided by cQCT, pQCT or MRI [37]. The effective radiation dose of standard HR-pQCT in the distal radius or tibia is 3–5 μsv, which is considered to be a low radiation dose examination compared with other common medical imaging techniques [38]. HR-pQCT assessments have been performed in large epidemiological cohort studies such as the MrOs, OFELY, CaMos and Framingham Osteoporosis Study, which notably can be used for in vivo bone microstructural imaging at peripheral bone sites to understand the pathophysiology underlying bone fragility and improve fracture prediction. The pathophysiological is the basis of fragility and improve the prediction of fractures [39, 40]. And HR-pQCT is based on semi-automatic profiling and segmentation of tissue, which provides data from density, morphology, microstructure, and biomechanical (including stiffness and elastic modulus) measurements through finite element analysis. The clinical application and research of HR-pQCT in many other metabolic diseases exceeds osteoporosis, such as drug effects, rare bone diseases, hand joint imaging and fracture healing. It is used in rheumatoid arthritis to assess joint space width and bone erosion, in knee osteoarthritis and in some studies of fracture healing of the distal

radius [41, 42]. The unique advantage of HR-pQCT is the high spatial resolution in vivo, which enables the quantification of trabecular and cortical bone microstructure. HR-pQCT has high research value in bone quality, especially microstructure [43]. However, HR-pQCT is expensive and the imaging technology needs to be further standardized. Although recent recommendations for standardization in scanning, analysis, quality control, and result reporting have been given, the prospect of HR-pQCT in clinical practice still needs to be further studied [44].

There are some advantages and disadvantages for the QCT diagnostic measurements. The main advantages included the followings: ①The measurement of true volumetric bone mineral density is not affected by bone size and shape; ② Selective measurement of cancellous bone mineral density, more sensitive to reflect the changes of early bone mass; ③ The 3D geometric measurement parameters can be used to measure the bone mineral density of multiple sites and analyze the bone composition of cross sectional image; ④ It can be used in preoperative evaluation of orthopedics to guide the selection of clinical surgical methods and surgical sites. The disadvantage of DXA is not as common as DXA in clinical application because of its large size, expensive examination, larger dose of radiation received by patients and smaller application range than DXA.

In conclusion, QCT has been widely used in the clinical and health management of osteoporosis in recent years due to its advantages in imaging technology. Although QCT is more accurate in measuring volumetric bone density, it can measure cortical bone density separately bone and cancellous bone density, while the radiation is larger and there is a partial volume effect. In the vast majority of clinical cases, patients are undergoing CT scans for medical reasons, and the QCT bone mineral density analysis system is used to simultaneously scan the patients to obtain bone mineral density values, without additional radiation doses for patients. QCT can also measure intra-abdominal fat and liver fat content, and QCT combined with low-dose chest CT has a promising application in health management [45, 46].

2.4 Magnetic resonance imaging (MRI)

MRI uses strong magnetic fields and electromagnetic pulse sequences to obtain three-dimensional images. It has the advantages of sensitive signal display and rich post-processing. It can perform quantitative bone density examination, and can also perform bone microstructure imaging to understand the internal situation of bone structure, especially in judging osteoporotic fractures, it is superior to X-ray and CT examination, and there is no X-ray radiation. In recent years, various MR imaging techniques have gradually highlighted their advantages in the field of osteoporosis research, mainly including the followings [47, 48]. 1) Transverse relaxation time (T2*) measurement is a quantitative MRI that indirectly reflects the morphological structure of bone tissue through the T2* value of the bone marrow. Due to the difference in magnetic susceptibility between trabecular bone and bone marrow tissue, the magnetic field at the junction between the two is not uniform, and the morphological and structural changes of bone trabecular bone will affect the relaxation characteristics of the surrounding bone marrow. In the gradient echo sequence, the bone marrow T2* value changes. And it has a certain order of magnitude relationship with the number of trabecular bone. Studies have shown that MRI T2* values are moderately inversely correlated with quantitative computed tomography to assess bone mineral density in postmenopausal women with osteoporosis, and have certain potential in assessing the severity of lumbar osteoporosis [49]. A large number of studies have

confirmed that T2* is closely related to osteoporosis, but its sensitivity, specificity, random type, parameters and many other reasons are different [50]. Currently, there is no standard for the diagnosis of osteoporosis with T2*. 2) High resolution MR (HRMR) HRMR scanning has been widely used in recent years. The imaging is based on the signal difference between bone marrow and trabecular tissue. In the background of high signal in the bone marrow, trabecular bone appears as a black network structure. Studies have shown that the bone structure parameters of HRMR have a good correlation with the morphological structure parameters of tissue slices at the same site. The HRMR scanning matrix can reach the order of microns, which can better observe the trabecular bone microstructure and diagnose osteoporotic fractures [51–53]. The effect of HRMR in the detection of osteoporosis is positive, while MR examination time is relatively long, the price is high, and the evaluation is relatively complicated. There is still a lot of work to be done, such as sensitivity, specificity, accuracy, and standardized data processing. At present, it is not widely used in clinical practice, but is believed that with the deepening of research and the improvement of MR software and hardware. MR imaging will definitely play an important role in the diagnosis of osteoporosis. 3) Magnetic resonance spectroscopy (MRS) MRS can evaluate the organic matter, inorganic matter and bone matrix density of bone. Currently, there are phosphorus spectroscopy (13P-MRS) and hydrogen proton spectroscopy (^{1}H-MRS). Among them, phosphorus spectroscopy is to use the echo signal of ^{13}P in bone to determine the content of bone inorganic components [54]. ^{1}H-MRS uses chemical shift to detect bone marrow water and adipose tissue, analyze its biochemical composition and metabolic changes, and indirectly assess bone quality from the molecular level [55]. Due to high technical requirements and many influencing factors, MRS has not been widely used in clinical evaluation of osteoporosis. 4) Others diffusion-weighted imaging (DWI)reflects the early changes in bone marrow composition and can quantitatively assess bone marrow changes. The apparent diffusion coefficient (ADC) and signal-to-noise ratio (SIR) can better reflect the bone mineral density of vertebral bodies in patients with lumbar spine diseases, and can quantitatively evaluate them, which is important for the diagnosis of lumbar spine osteoporosis [56, 57]. Diffusion tensor imaging (DTI) characterizes the diffusion direction of water molecules, which is helpful in assessing fracture risk in patients with osteoporosis [58]. Perfusion-weighted imaging (PWI) uses paramagnetic contrast agents to induce transient changes in the local magnetic field of perivascular tissue, which can reflect the perfusion and hemodynamic changes in tissue microcirculation, and help to detect early abnormal blood supply in diseased tissue [58].

MRI has a good auxiliary role in the diagnosis and differential diagnosis of osteoporosis by taking advantage of its multi-sequence imaging. Tomography can be used to understand the internal situation of the bone structure, Bone quality can be evaluated quantitatively, noninvasively and without radiation. It can reflect the physiological and pathological changes of bone histologically, and better understand the physiological characteristics of bone, so as to make its diagnosis more early and accurate. Because the image analysis process and parameter thresholds of HR MR and quantitative magnetic resonance (QMR) examinations have not been unified, functional imaging such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) are very important for osteoporosis. The significance of the diagnosis is inconclusive, and the MRI examination is expensive and time-consuming. Therefore, QMR in the diagnosis of osteoporosis still needs further research. With the further maturity of MR imaging technology, the further improvement of coils and the

application of higher field strength MR machines, it will be possible to optimize the MR imaging of trabecular bone structure and make the technology of MRI evaluation of trabecular bone structure more mature.

2.5 Comparison of various imaging examination techniques

In conclusion, the above imaging techniques have their own emphasis: DXA has been widely used to evaluate BMD because of its economy, simplicity and low radiation. What's more, WHO has also recommended it as the "gold standard" for diagnosing OP. Although QCT is more accurate in measuring volume BMD, it can measure cortical bone and cancellous bone BMD respectively, but the radiation is larger. QUS is simple and radiation-free, which is mainly used as a screening tool for osteoporosis. MRS is radiation-free and can indirectly assess bone quality at the molecular level. On the premise of bone mineral density measurement, MR combined with QCT or QUS for the detection of osteoporosis, the combined application of multiple methods enhances our scientific understanding of bone microstructure, bone geometric properties and other biomechanics, and provides a basis for further exploration of osteoporosis. The pathophysiological process of the disease, sensitive clinical diagnosis, monitoring of disease changes and curative effects provide technical support (**Table 2**).

Project	Detection of parts	parameters	Clinical application
plain x-ray film	Vertebrae, wrist, metacarpal, calcaneus and tubular bone	—	The sensitivity and accuracy of bone mineral density evaluation are poor, but it can be used to locate the fracture
DXA	Spine, hips, distal forearm, whole body	Areal bone mineral density	It is currently recognized as the gold standard for the diagnosis of osteoporosis and can be used for body composition analysis
QUS	calcaneal、Radius、finger phalanges, tibia	BUA,SOS	It is mainly used for osteoporosis screening
QCT		Volumetric bone mineral density	It can distinguish cortical bone from cancellous bone and diagnose osteoporosis. It is more sensitive to fracture, especially fine fracture
cQCT	Lumbar vertebrae and proximal femur	Mainly cancellous bone mineral density	It can be used to diagnose osteoporosis
pQCT	Radius and tibia	Mainly cortical bone mineral density	To assess the risk of fracture
HR-pQCT	Radius and tibia	Mainly cortical bone mineral density	To quantify the bone microstructure and improve the prediction of fracture
MRI	Refer to QCT site	The related parameters of bone microstructure were evaluated indirectly	It can perform bone microstructure imaging, which is mainly used for differentiating microfracture, new fracture and bone tumor

Table 2.
Comparison of imaging techniques for various bone mineral density examinations.

3. Research progress in bone turnover markers

The diagnosis of osteoporosis also requires etiological diagnosis to further distinguish primary or secondary [59]. Bone turnover markers provide an important reference for clinical differential diagnosis and treatment follow-up. Bone tissue continuously undergoes bone modeling and bone remodeling to maintain bone growth and structural integrity. The microenvironment is characterized by continuous absorption of old bone to form new bone. This self-renewal process is called bone turnover (bone turnover). Bone turnover biomarkers (BTMs) are biochemical markers released in blood or urine during bone remodeling, which can reflect the dynamic changes of whole body bone tissue earlier than bone density. Including biochemical markers of bone formation and bone resorption, the former reflects the activity of osteoblasts and the state of bone formation, and the latter represents the activity of osteoclasts and the level of bone resorption. The determination of these markers is helpful for identifying primary and secondary osteoporosis, judging the type of bone turnover, predicting the rate of bone loss, assessing fracture risk, understanding disease progression, selecting interventions, monitoring drug efficacy and compliance, etc.

The common clinical biochemical markers of bone metabolism are shown in the table below (**Table 3**). Among the above markers, the International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry (IFCC) have recommended serum P1NP and CTX-1 as bone formation and resorption reference markers, which have the characteristics of good sensitivity, high specificity, good repeatability, and economical application. In recent years, with the deepening of research and the development of biotechnology, the research on bone metabolism markers has made great progress. New markers such as Periostin, advanced glycation end products/receptor for advanced glycation end products (AGEs/RAGE), gelsolin, annexin A2 etc. gradually emerged, which has potential advantages in reflecting the dynamic changes of the whole body bone tissue.

Bone formation markers	Bone resorption markers
alkaline phosphatase, ALP	tartrate-resistant acid phosphatase, TRACP
osteocalcin, OC	serum C-terminal telopeptide of type 1 collagen, S-CTX
bone alkaline phosphatase, BALP	urinary pyridinoline, Pyr
procollagen type 1 C-peptide, P1CP	urinary deoxypyridinoline, D-Pyr
procollagen type 1 N-peptide, P1NP	urinary C-terminal telopeptide of type 1 collagen, U-CTX
	urinary N-terminal telopeptide of type 1 collagen, U-NTX

Table 3.
Common clinical biochemical markers of bone turnover.

3.1 Procollagen type 1 N-peptide (P1NP)

Osteoblasts synthesize a large amount of type I procollagen, and its carboxyl and amino termini extend to both ends respectively to form the precursor of type I collagen. The propeptides extending toward the carboxyl end are C-propeptides. During bone formation, type I procollagen is secreted to the outside of the cell, and is cleaved 1: 1:1 into procollagen type I N-peptide (PINP), type I collagen and procollagen type I C-peptide (PICP), mature type I collagen mainly constitutes the main component of osteoid, while PINP and PICP enter into the blood and urine as metabolites, so the detection of PINP and PICP can reflect the level of bone

formation [60, 61]. Both P1NP and P1CP are metabolized in the liver. Because the half-life of serum PICP fluctuates greatly, the research evidence that P1NP reflects bone formation is more abundant than that of P1CP. Clinically, it is recommended to use PINP as an indicator of bone formation to reflect the synthesis rate of type I collagen and bone turnover [62].

Most studies suggest that elevated PINP can predict fractures. In postmenopausal osteoporotic patients, the P1NP of fracture patients is significantly higher than that of non-fracture groups, and PINP can be used as an important indicator to predict postmenopausal osteoporotic fractures [63]. A meta-analysis of postmenopausal women and men over 50 years of age showed that the hazard ratio (HR) of osteoporotic fractures was 1.18 for every one standard deviation increase in serum PINP [64]. Further studies have shown that high PINP is primarily associated with spine and hip fracture risk, predicting fractures with greater accuracy in the short term (5 years) than in the long term (10 years or more) [65]. After adjusting for BMI, smoking, frequency of falls, previous fracture history, vitamin D intake and other confounding factors, the Crandall study included 800 postmenopausal women with an average follow-up time of 7.13 years was found that serum PINP levels were not correlated with the risk of incidence of hip fractures [66]. Another Meta-analysis, with a total of 11,572 participants, showed that serum PINP levels were not significantly associated with fractures before confounding factors were adjusted. After adjusting for confounding factors (including age, BMI, previous fracture history and BMD, etc.) Raising one standard deviation level, the HR for fracture was 1.28. Whether PINP has a predictive effect on fracture occurrence is still inconsistent due to different statistical methods and different confounding factors in PINP research. At the same time, studies have found that PINP has a good predictive effect on the occurrence of fractures in non-diabetic patients, but has no predictive effect on the occurrence of fractures in patients with type 2 diabetes, suggesting that PINP will have different effects on fracture prediction under different health conditions [66]. Therefore, the correlation between PINP and osteoporotic fractures still needs to be further confirmed by large sample and prospective studies.

3.2 C-terminal telopeptide of type 1 collagen (CTX)

In the process of bone resorption, the mature type I collagen is cleaved and the C-terminal peptide and N-terminal peptide are removed. The common C-terminal peptides are α-CTX and β-CTX, which are isomers, and their production rate is equal to the degradation of type I collagen. CTX and NTX are released into the blood with the degradation of type 1 collagen molecules and can be excreted in the urine. Therefore, the concentrations of CTX and NTX in the blood and urine can specifically reflect the activity of osteoclasts and the level of bone resorption [67]. Since β-CTX has been studied more as a marker of bone resorption, it is clinically used as a sensitive and specific marker of bone resorption [68]. At the same time, CTX-I showed a circadian rhythm, and its concentration peaks usually appeared at night and early morning, and reached the lowest point in the afternoon [69]. And for the measurement of CTX-I, food intake has a greater impact on the results, so it is necessary to measure CTX-I in a fasting state [70].

A number of studies on women have suggested that elevated β-CTX is associated with fracture risk. Vilaca (2017) found that for each standard deviation increase in serum β-CTX, the risk of vertebral fractures increased by 1.4–2.2 times, and the risk of non-vertebral fractures increased by 1.8–2.5 times, and the results were basically

unchanged after adjusting for BMD, indicating that CTX has an independent predictive effect on fracture risk [66]. Fracture risk is better predicted if CTX is combined with BMD. The Swedish EPIDOS study showed that the 10-year fracture risk of postmenopausal women from high to low was as follows: ① Elevated serum β-CTX + history of fragility fracture; ② Elevated β-CTX + T value of BMD lower than - 2.5; ③ BMD Women with a T value below −2.5 + a history of fragility fracture; ④ elevated β-CTX or a history of fragility fracture; ⑤ BMD T value below −2.5 [66]. CTX may have a good application prospect in predicting the occurrence of osteoporotic fractures. However, it is still difficult to popularize and apply in clinical practice, and the results are still uncertain due to the high heterogeneity among different studies. Therefore, further large-sample, homogeneous prospective studies are still needed for detailed clarification in the future.

3.3 Periostin

Periostin is a newly discovered macromolecular glycoprotein. As a unique extracellular matrix protein, it is mainly expressed in the periosteum, also known as bone-specific factor 2 which is obtained from the osteoblast cell line MC3T3-E1 cDNA library by Takeshita et al. (1993). A bone adhesion have a molecular weight of 90-kDa [71]. Periostin mainly triggers signaling pathways such as NF-KB/STAT3, P13K/Akt and focal adhesion kinase (FAK) by binding to cell surface integrin receptors αvβ3 and αvβ5, and regulates the expression of downstream genes. It plays an important role in adhesion, tissue repairing and maintaining the integrity of connective tissue structure and function [72].

Basic research suggests that Periostin can regulate bone formation, promote bone development/remodeling, and increase bone strength. It is a key regulator of bone microstructure and plays a very important role in bone metabolism [73, 74]. Regarding the clinical study of periostin, Li et al. (2021) showed through cross-sectional observation in postmenopausal women that periostin has no significant correlation with the overall BMD [75], but is positively correlated with cortical bone density, negatively correlated with cortical bone porosity. Periostin is primarily responsible for periosteal metabolism, so it is more closely related to long bones covered by periosteum and can better reflect cortical bone loss [76]. Further studies suggested that periostin was not associated with baseline BMD and was significantly elevated in women with fractures [77–79]. Kim emphasized that it was primarily a risk factor for nonvertebral fractures [80]. Rousseau proposed that periostin is an independent risk factor for fractures in postmenopausal women, and microarray analysis suggested that periostin mRNA was up-regulated twice in the process of osteoporosis and fracture repairing [77].

In conclusion, periostin, as a new-generation biochemical marker of bone metabolism, is an independent risk factor for fractures among postmenopausal women. Combined with bone mineral density testing, it can better evaluate and predict the risk of osteoporosis and fracture in patients, and provide a theoretical basis for early intervention.

3.4 Advanced glycation end products/receptors for advanced glycation end products

Advanced glycation end products (AGEs) are a variety of compounds produced by non-enzymatic reactions between reducing sugars (such as glucose) and certain

metabolites (such as Methylglyoxal) and protein amino groups [81]. The receptor for advanced glycation end products (RAGE) can be expressed in osteoblasts, osteoclasts and osteocytes [82, 83]. In recent years, studies have found that AGEs/RAGE can cause essential changes in osteoblasts, osteoclasts, and osteocytes, resulting into imbalances in bone remodeling, decreased bone strength, and increased incidence of fractures, which may provide unique diagnosis and treatment ideas and molecular targets for the diagnosis and treatment of osteoporosis [84]. Clinical studies have found that the correlation between sRAGE and bone mineral density is controversial. Studies have found that serum sRAGE levels are significantly higher in postmenopausal women with osteoporosis and low bone mass than those with normal bone density, and sRAGE levels are associated with increased fracture risk [85]. RAGE was positively correlated with bone formation markers P1NP and osteocalcin in elderly men, and this correlation was more significant in men with diabetes [86]. However, there was no significant difference in RAGE levels between postmenopausal women with type 2 diabetes and the control group. There was no significant correlation between serum RAGE levels and bone mineral density, fracture prevalence, and bone turnover markers in the type 2 diabetes group [87]. The research and development of bone tissue engineering, it has been found that AGEs/RAGE can affect the structure and biomechanical properties of bone through various mechanisms. It may have a potential diagnostic role in monitoring osteoporosis, especially the progression of diabetic bone metabolism, but its clinical application is less studied, and its value in predicting fracture risk needs to be further studied [88].

3.5 Gelsolin (GSN)

Gelsolin is a calcium-dependent actin-binding protein that cleaves, caps, and nucleates actin to regulate cytoskeleton structure, cell movement and metabolic processes, and also participates in regulation of cell signal transduction and apoptosis [89]. As an actin-binding protein involved in the assembly and movement of osteoclast cell feet. GSN deficiency can hinder the assembly of osteoclast cell feet and increase bone mass and bone strength. Furthermore, GSN can hinder the assembly of osteoclasts to the bone matrix through integrins activation, thereby ultimately activating osteoclasts and promoting bone resorption [90]. Therefore, in different clinical studies, the relationship between GSN and BMD is not consistent. A Mexican study found that serum GSN levels were reduced in postmenopausal women with low bone mass and osteoporosis but the difference between groups was not statistically significant [90]. Peripheral blood mononuclear cells (PBMs), as precursors of osteoclasts, produce cytokines important for osteoclast development and play an important role in bone metabolism. A cytoplasmic proteomic analysis of PBMs from Caucasian men with very high and very low BMD found that GSN expression was significantly increased in patients with very low BMD [91]. The same study of more than 6000 subjects with very high and very low bone density samples found that there was no significant difference in plasma GSN between men with very high and very low bone density, but GSN levels in postmenopausal women were higher than the extremely low BMD group, and it was negatively correlated with hip BMD [92]. Deng et al. (2014) also found that GSN protein and mRNA levels in the PBM of subjects with low BMD were down-regulated, and SNP rs767770 was only significantly correlated with hip BMD in female Caucasians, suggesting that GSN is an important gene affecting hip BMD in female Caucasians [93]. A study on the correlation between GSN and BMD in Chinese postmenopausal women found that the GSN level in postmenopausal

women was significantly higher than that in premenopausal women, and compared with the normal BMD group, the plasma GSN level in the low bone mass or osteoporosis group was significantly higher. There is a negative correlation between plasma GSN and hip BMD in postmenopausal women, and GSN is an independent influencing factor of femoral neck and lumbar spine BMD [94]. In conclusion, the current research shows that plasma GSN may be used as a biochemical marker of bone resorption for the diagnosis of osteoporosis, but more in-depth and extensive research is still needed.

3.6 Annexin A2

Annexin A2 (ANXA2) is a calcium-dependent phospholipid-binding protein expressed on the surface of peripheral blood monocytes, which can stimulate monocytes migration across endothelial cells and osteoclasts formation. However, ANXA2's role in bone remodeling is not limited to osteoclast formation, but can also promote the proliferation and differentiation of bone precursor cells, thereby affecting bone formation [95]. Increased expression of ANXA2 was found in postmenopausal Caucasian women patients with low bone mass and osteoporosis. A recent study found that compared with patients without fractures, the expression of ANXA2 protein in the PBMs of patients with osteoporotic fractures was significantly increased and plasma ANXA2 were inversely related to hip BMD in older population, which are significantly higher in the patients with very low BMD than those in very high BMD [96]. These studies suggest that ANXA2 may be a potential biochemical marker for osteoporosis, but there are few clinical studies on ANXA2.Thus, further longitudinal studies are needed to determine whether plasma ANXA2 levels can predict osteoporosis.

4. Conclusion

In conclusion, bone mineral density has been always regarded as gold standard for the diagnosis of osteoporosis in the world. Biochemical markers of bone metabolism can reflect bone remodeling earlier and have the advantages of non-invasiveness and timeliness. The combination of them can be used for better diagnosis and differential diagnosis of metabolic diseases, drug development, and clinical monitoring of osteoporosis treatment efficacy. In recent years, with the research progress of imaging technology and biological science, it has provided technical support for further detection of bone microstructure, bone geometric properties, and bone strength, and provided a theoretical basis for exploring bone physiology and the pathogenesis of metabolic bone diseases. For the newly developed imaging technology and newly discovered bone metabolism markers, the clinical research evidence is limited, and its safety, specificity, sensitivity, stability and other characteristics in clinical application still need more in-depth and extensive research.

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