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Review Article

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Novel Imaging Modalities in The Diagnosis and Risk Stratification of Osteoporosis

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Abstract

Purpose of Review: Current clinical practices and guidelines rely on Dual-Energy X-Ray Absorptiometry (DXA) imaging for diagnosis and risk assessment of osteoporosis. In this review, we describe the latest research surrounding the conventional and novel imaging modalities in risk stratification and diagnosis of osteoporosis. Modalities including high-resolution Peripheral Quantitative Computed Tomography (hr-pQCT), peripheral Quantitative Computed Tomography (pQCT) and Magnetic Resonance Imaging (MRI) are reviewed in regard to their accuracy and precision in measuring various micro architectural parameters of bone, as well as the feasibility of clinical application.

Recent Findings: The World Health Organization defines osteoporosis through Dual-Energy X-Ray Absorptiometry (DXA) standardized measures of bone mineral density. Recent additions to these criteria have identified bone quality measures to be important factors in osteoporosis diagnosis and risk of fragility fractures. With the limited outcome parameters provided by DXA, other modalities such as hr-pQCT, pQCT and MRI have been emerging as research tools to assess macro and micro architectural bone changes. HR-pQCT yields unprecedented insight into micro structures of bone not yet achieved in the past decade. This modality provides high precision, reliability and reproducibility in highlighting key differences in gender- and age-related bone loss within both trabecular and cortical bone. Coupled with computer-based finite element analysis, hr-pQCT allows noninvasive assessment of bone strength. p-QCT has also been identified as a high precision imaging technique applied in research to provide three-dimensional bone quality measures, as well as insight into muscle and fat parameters that may present new information on assessing risk of bone strength and fragility fractures. Recent studies comparing hr-pQCT and p-QCT to MR imaging have identified the latter tool to be a less precise and reproducible, with minimal advantages over current DXA measures.

Summary: With the current limitations in DXA imaging, novel radiographic imaging is critical for accurate and timely assessment of osteoporosis risk and diagnosis. For research applications, hr-pQCT is ideally suited for quantifying micro architectural age- and sex-related trabecular and cortical bone parameters, as well as bone strength through finite element analysis. pQCT's functional measures of muscle and bone parameters can provide more detailed insights into bone fragility, and may present a more accessible modality with comparable precision and reliability to hr-pQCT bone parameters. When compared to the aforementioned modalities, MR imaging presents a feasible technique for bone quality measurement, however, reduced precision and reproducibility limit its potential as a reliable diagnostic tool. Future studies should elucidate the clinical applications of hr-pQCT and p-QCT in osteoporosis diagnosis and risk assessment.

Introduction

Osteoporosis is a skeletal disorder that is characterized by compromised bone strength which predisposes one to an increased risk of bone fracture [1]. This disorder is one of the greatest challenges faced by public health systems worldwide, as the annual incidence of fragility fractures substantially grows with the continued and rapid aging of the population [2]. With at least one in three women and one in five men suffering from an osteoporotic fracture during their lifetime, it is imperative that accurate diagnosis and fracture risk assessment be a priority for healthcare systems globally [2]. In 1993, the World Health Organization (WHO) defined osteoporosis as a "disease characterized by low bone mass

and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" [3]. Bone resorption and formation is a continual cycle dependent on osteoclast and osteoblast activity, respectively. In adulthood, several factors may contribute to imbalances to this cycle, causing progressive loss of trabecular and cortical bone, reduced Bone Mineral Density (BMD) and ultimately, increased fracture risk [1]. Most frequently associated with osteoporosis are hip, vertebral, and wrist fractures [3].

Currently, osteoporosis is clinically diagnosed based on BMD measurements that estimate bone strength, according to the WHO guidelines [1,3]. BMD is expressed in terms of standard deviation in T-scores that describe a patient's BMD compared to a standard population (sex matched individuals, 20-30 years of age) [4]. In clinical practice, areal BMD (aBMD; g/cm2) is measured non-invasively with the use of Dual-energy X-ray Absorptiometry (DXA), which is the current gold-standard technique for osteoporosis diagnosis [4]. Based on BMD assessments of lumbar spine (L1-L4), proximal femur (femoral neck and total hip) and forearm (distal) aBMD, the WHO has defined osteoporosis as a T-score ≤-2.5 for postmenopausal women and men ≥50 years of age [4,5]. To broaden the applicability of these guidelines, the International Society for Clinical Densitometry (ISCD) introduced Z scores that reflect BMD measures across age- and gender-matched reference populations; a Z score <-2 is defined as osteoporosis [6]. Although BMD, as measured with DXA, presents a well-standardized, cost-effective and low radiation technique with rapid measurement outcomes that explain approximately 70% of bone strength, its use as a diagnostic tool presents several limitations [7].

As a two-dimensional imaging modality, DXA overlooks critical information on the volumetric density of bone (vBMD) and the distinction between cortical and trabecular bone [7,8]. The measurement of areal BMD (aBMD) is also significantly affected by bone size, which results in systematic overestimation of density in larger bones and underestimation in smaller bones [8]. Further, spine and hip DXA measures are sensitive to degenerative changes which naturally increase areal density, thereby suggesting a lower fracture risk than is actually present [9]. DXA measures are also highly vulnerable to beam hardening artifact, in which high energy photons from incident polychromatic energy beams are over-represented, altering the observed density and composition of the measured material [10]. This hardening artifact results in inflation of measured aBMD in obese patients (BMI >25kg/m2), due to the superimposed soft tissue [11-13]. These shortcomings result in 50% of fractures occurring amongst individuals who would not be classified as osteoporotic based on DXA measured BMD [14]. Moreover, several pharmaceutical trials reported that increases in aBMD, as measured by DXA, did not entirely explain the observed reduction in fracture risk, presenting further challenges in monitoring bone responses to therapies [15].

To address the aforementioned limitations, in 2000, the U.S. National Institute of Health defined new ''quality'' criteria for the diagnosis of osteoporosis in addition to decreases in BMD [16]. These quality criteria, such as spatial distribution, cortical and trabecular micro architecture and bone turnover, as well as material properties, such as matrix mineralization, collagen polymorphisms, and micro-damage, cannot be evaluated by DXA [16]. Changes in bone quality differ with both age- and sex-related factors, with women experiencing greater trabecular perforation, cortical thinning and cortical porosity than men, as well as specific changes occurring within gender categories between age groups [17]. To better establish these micro architectural changes, new and innovative imaging techniques have been identified that can assess bone quality as an important biomarker for the risk stratification and diagnosis of osteoporosis beyond that provided by aBMD and DXA. The focus of this review is to report on novel imaging techniques that may better assess osteoporosis diagnosis and fracture risk, specifically, Peripheral Quantitative Computed Tomography (pQCT), High-Resolution Peripheral Quantitative Computed Tomography (hr-pQCT) and Magnetic Resonance Imaging (MRI).

High Resolution Peripheral Quantitative Computed Tomography (hr-pQCT)

HR-pQCT yields unprecedented three-dimensional insight into microstructures of bone never before achieved in the past decade [18]. Currently available for research use from a single manufacturer, (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland), it is a non-invasive, low-radiation method (effective dose of 3 uSv per measurement) for assessing bone microarchitecture and volumetric BMD (vBMD) in cortical and trabecular compartments of the ultradistal radius and distal tibia [18,19]. To obtain these measures, the system acquires a stack of parallel slices with a resolution of 82 μm [20], which provides substantially higher signal-to-noise ratios and spatial resolution compared with multidetector CT and MRI resolutions of 0.25-0.3 mm and 0.15-0.3 mm, respectively [7]. It is important to note, however that precision is ameliorated when hr-pQCT measures are performed at the tibia compared to the radius [21,22]. Nonetheless, hr-pQCT provides significantly higher signal-to-noise ratio and spatial resolution compared with multi-detector CT and MR-imaging [23].

This imaging modality also provides excellent precision for both density (<2%) and micro structural (<4%) measurements [24] for compartmental (total, cortical and trabecular) vBMDs, trabecular micro architecture [trabecular number (Tb.N), trabecular separation (Tb.Sp), heterogeneity of trabecular separation (Tb. SpSD), trabecular thickness (Tb.Th)] and cortical micro architecture [cortical thickness (Ct.Th) and cortical porosity (Ct.po)] [18]. Non-metric measures provide insight into the Structural Model Index (SMI) of bone, segmentation of trabecular bone structure into individual plates and rods, Degree of Anisotropy (DA), con-

nectivity density (Conn.D), extent of trabecular connectivity and cross-sectional moment of inertia [18] (Figure 1).

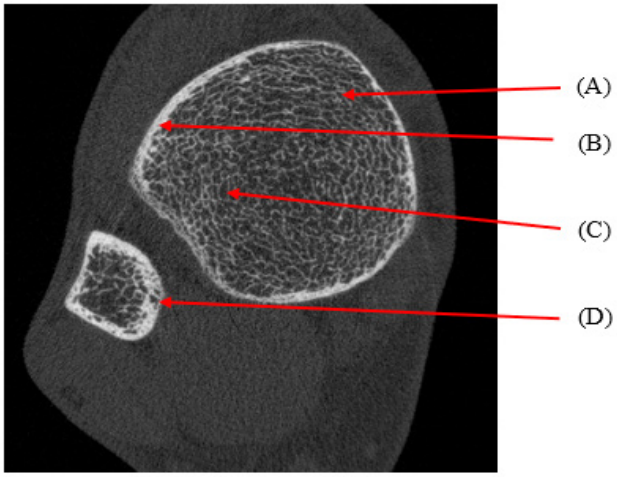

Figure 1: Cross-sectional image of tibia (right) and fibula (left) using hr-pQCT imaging. Trabecular (A) and cortical (B) bone compartments can be visualised. Separation of bone compartments allows for the measure of various micro architectural parameters such as trabecular separation (Tb. Sp), visualized here with black space between the white trabeculae (bone) (C) and cortical porosity (Co.Po) (D), the holes within the thicker cortex, amongst other measures.

Primary error sources for follow-up measurements of the aforementioned measures are cited as long scan times (2.8 min), motion artifact and difficulty in matching the analysis volume in repeat studies [25,26]. Further, partial volume effect, beam hardening, and assumptions in the calculations of all structural and densitometric measures, such as the structural model index, suggest proceeding with caution when interpreting hr-pQCT output measures [27].

Diagnosis

The use of hr-pQCT as a diagnostic tool has yet to be implemented into clinical practice and its primary application is in research as a high-resolution bone imaging modality. With less than 45 systems globally, both the limited accessibility and high cost of use remain large barriers that must be overcome prior to widespread clinical application. Nonetheless, with the development of normative databases to contextualize hr-pQCT outputs and the adaptation of fracture risk assessment tools to include hr-pQCT parameters, its use as a diagnostic tool may be a future possibility [18].

Risk Stratification

Currently, DXA measures are classified as both T and Z scores for comparison of individual results to mean BMDs of a standard population (20-30 years of age) and BMD measures across age- and gender-matched reference populations, respectively [3]. Both measures are critical as bone responds to aging through changes in aBMD, vBMD and micro architecture, and the mechanisms by which these changes occur vary between sexes and specific bone compartments. Thus, when assessing risk for individual osteoporosis status, it is imperative that these age- and sex-related changes are identified through accurate and reliable imaging. HR-pQCT is at the forefront of new advances in micro architectural bone imaging and provides essential measures for risk stratification. The development of normative databases for sex- and age-specific data has been an especially huge advance in providing a clinical context for individual hr-pQCT results [18]. Presently, three population-based hr-pQCT studies have described age- and sex-related variation in bone microarchitecture; the Calgary cohort of the Canadian Multicentre Osteoporosis Study (CaMOS) cohort, the Rochester, Minnesota cohort and the Cambridge, UK cohort [28-30].

Age and Gender

Numerous cross-sectional studies using hr-pQCT have provided consistent evidence towards trends in age- and sex-related bone loss, reporting general increases in cortical BMD [31-33], Tb.Th [34], Ct.Th [34,35], decreases in Ct.po [31,36] and overall increases in bone strength in both sexes during puberty [31,37]. Overall, hr-pQCT outputs from cross-sectional studies suggest that young males tend to have higher Tb.BV [33], Ct.Th [25], Tb.Nb [33,38,39], Tb.Th [33,38,39] and total cross sectional area (33% larger) [39] compared to age-matched females, owing to a greatly reduced fracture risk in adolescence [35,38,39]. Nonetheless, both genders experience reductions in these parameters during aging [35,38,39]. Throughout adulthood, hr-pQCT has identified that both women and men experience increases in Co.Po [25], with reductions in Ct.Th (52%, 38%, respectively) [33] and cortical BMD (22%, 16%, respectively) [33]. Moreover, hr-pQCT data suggests that changes in these cortical bone parameters occurs at a much faster rate in females compared to males [25,33]. Studies have reported that after accrual of peak BMD in males, bone loss remains steady until age 50 [40]. HR-pQCT was able to identify that this bone loss consists primarily of trabecular bone loss and reduced Tb.Th, decreasing total bone formation [33,39].

Contrastingly, bone loss in women tends to be associated with a loss in Tb.Nb associated with menopause and increased osteoclastic activity that disrupts the trabecular network [41]. This latter mechanism of bone loss is of a much greater magnitude and compromises bone strength much more than reductions in Tb.Th experienced in aging men [41,42]. HR-pQCT scans analyzed with Finite Element Analysis (FEA) further identified greater increases in load-to-strength ratios during aging in women (+27%) [39]. Therefore, hr-pQCT outcomes suggest that men achieve greater peak BMD, larger and denser bones, smaller decreases in the magnitude of age-related bone loss and less detrimental structural changes for total bone strength compared to women. Evidently, hr-pQCT is able to provide valuable information on critical bone

quality parameters that should be taken into account to reliably assess osteoporosis risk in reference to gender-and age-specific strata. Menopause Studies have shown that hr-pQCT is reliably able to differentiate micro architectural differences between osteopenic postmenopausal women with and without history of fracture [32]. This imaging modality identified decreased total BMD (-10%), trabecular BMD (-12.3%) and increased Tb.Sp (+25.6%) in women with a fracture history [25]. The application of FEA to hr-pQCT scans demonstrated bone strength to be associated with distal radius fractures in postmenopausal women, independent of aBMD [43]. This highlights the limitations of DXA analysis and the association between bone quality changes and increased fracture risk, independent of two-dimensional densitometric measures.

Specific changes in bone micro architecture during menopause have also been elucidated through research application of hr-pQCT. Measures performed at the distal radius have reported reductions in total BMD [25,35], cortical BMD [25,32,35], trabecular BMD [25], Ct.Th [25], Tb.Nb [25], Tb.Th [25] and increases in Ct.Po [32, 35,39] in postmenopausal women. These results elucidate rapid bone loss, largely in the trabecular bone compartment, which leads to trabecular perforation and loss of entire trabeculae in postmenopausal women [31]. Cortical bone loss is also accelerated throughout menopause, increasing intracortical and endocortical bone surface area [44]. As approximately 40% of all postmenopausal women will experience a fracture [45], these insights provide critical evidence for increased fracture risk with age, and specifically, onset of menopause in women. Understanding the impact of menopause as a confounding variable on fracture risk is imperative for proper risk assessment, diagnosis and monitoring of osteoporotic patients in pre-and post stages of menopause.

Overall, HR-pQCT results highlight age-specific variations in bone loss between and within sex-related age stratification. Elucidating key patterns of micro architectural changes such as increased rapid bone loss, more compromised bone strength due to reduced Tb.Nb and greater increases in Co.Po throughout menopause provide critical insight into increased fracture risk and osteoporotic risk for women at all ages compared to men. Moreover, the reliability provided by hr-pQCT imaging remains unmatched and could present a pivotal modality in assessing risk of fracture in vivo within clinical practice.

Peripheral Quantitative Computed Tomography (pQCT)

pQCT provides distinct obtainment of trabecular and cortical BMD values through an automatic x-ray scan analysis of the peripheral skeleton [46]. These images record various bone parameters, such as Cortical Cross-Sectional Area (CSA), cortical thickness (Co.Th) and both periosteal and endosteal circumference [15]. pQCT also provides critical insight into biomechanical bone parameters such as Cross-Sectional Moment of Inertia (CSMI), a measure of bending, polar moment of inertia, indicating bone strength in torsion, and Strength Strain Index (SSI), a surrogate measure of bone strength [15]. pQCT is performed on peripheral skeleton areas (radius, tibia, femur), with low-radiation doses (≈3 μSv per scan), yielding highly accurate and precise outcomes [47,48]. Scan locations of single-slice CT scanners are typically distal sites (4% of radius length), containing mainly trabecular bone (Figure 2), and a shaft location (15-65% of radius length) consisting predominantly of cortical bone [15,48]. The vBMD, micro architectural and biomechanical bone parameters provided by pQCT may present critical insight into clinical risk assessment of osteoporosis.

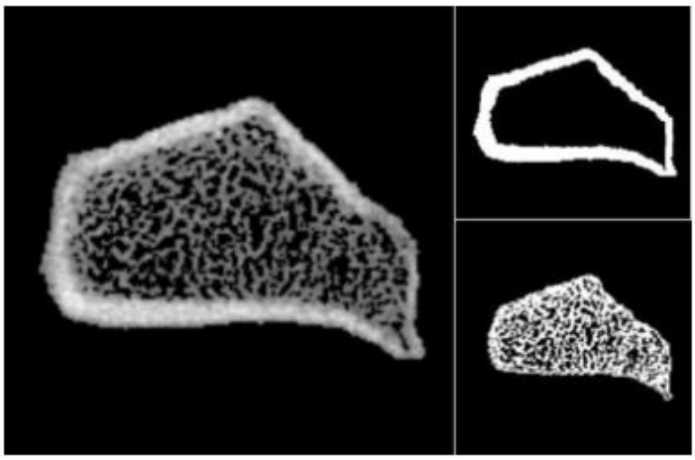

Figure 2: Cross-sectional slice of the ultradistal radius acquired using pQCT (left). The cortical (upper right) and trabecular (lower right) regions have been separated for analysis. It's evident that the resolution of pQCT is lower than hr-pQCT in Figure 1.

Diagnosis

Clinical routine absolute measurements of vBMD have been established to characterize fracture risk through pQCT measures (110-80 mg/cm^3 = mild increase in fracture risk, 80-50 mg/cm^3 = moderate increase in fracture risk, and 50 mg/ cm^3 = severe increase in fracture risk) [7]. These criteria allow the application of pQCT measures to fracture risk assessment and osteoporosis diagnosis. However, as the availability of pQCT is limited and mainly applied for research purposes, data from normative databases should be applied only in the centers in which it was developed [49,50]. Moreover, the studies from which these databases are formed report being underpowered due to small sample sizes, which reduces the applicability of the findings to larger patient populations of osteoporosis [49,50]. Thus, use of pQCT imaging in clinical settings, as of yet, is not recommended.

Risk Stratification

Age and Gender: A critical shortcoming of aBMD from DXA is the lack of insight into sex and age-related differences in micro

architectural changes throughout adulthood. pQCT has been established in research as a highly precise technique to evaluate differences across these strata. Specifically, pQCT has been shown to provide more precise data than DXA on increased fracture risk in aging populations and post-menopausal women [51,52]. To further assess pQCT precision and reliability relative to gold standard hr-pQCT, a study compared both modalities in measuring vBMD, as well as trabecular and cortical microstructure. The researchers concluded that pQCT is a feasible alternative to hr-pQCT for estimating trabecular and cortical bone microstructure and volumetric parameters across age- and gender-specific populations [53]. The short-term results demonstrated strong validity and reasonable reproducibility [53], and equally precise Tb.Sp measurements over one year follow-up [54]. Thus, pQCT presents a feasible substitute to hr-pQCT in assessing fracture risk in women and men across varying age groups. It is worth noting however, that pQCT has been reported to underestimate Ct.Th and Tb.Sp by 21.4% and 72.9%, respectively and overestimate Bone Volume to Total Volume (BV/TV) and cortical density (Ct.Den) by 265.8% and 13.1%, respectively [55]. Therefore, caution must be taken when evaluating pQCT measures as longer scan times may lead to motion artifact [53]. The use of a single, more distal slice is recommended to minimize this error [53].

An important advantage of pQCT is the functional evaluation of bone through muscle and fat measures. As muscle contracts on bone, micro strains are sensed by osteocytes, resulting in bone remodelling [15]. This muscle-bone functional unit has implications on bone strength as increased muscle mass per area is believed to be associated with increased bone strength [15,56-58]. To evaluate if bone strength is normally adapted to the muscle force and if the muscle force is adequate for body size, the ratio of Bone Mineral Content (BMC) to muscle Cross-Sectional Area (CSA) is measured from pQCT parameters [15]. Muscle Density (MD), an index of skeletal muscle fat content, has been proposed to predict changes in bone strength and density in young females and to be associated with increased risk of fracture [59,60]. pQCT measures have identified that muscular contractions during weight-bearing activities can site-specifically increase bone mass and strength in pre-pubertal or early pubertal children [61]. Some data in adolescents also showed significant correlations between muscle power, muscle CSA, and bone strength measured by SSI [62]. Thus, pQCT imaging may provide valuable insight into osteoporotic fracture risk dependent on MD measures.

When evaluating the 'muscle-bone unit', it is also critical to address the decline in number of Estrogen Receptor alpha (ER-a) observed in menopause [63]. This decline reduces the ability of mechanical loading to induce an osteogenic response [63]. This phenomenon is consistent with weaker correlations between muscle mass and BMD in women and lower attenuation of the effects of strenuous exercise on BMD with increasing age [64]. This suggests a mechanism by which women experience greater increases in fracture risk with onset of menopause, independent of MD measures from pQCT. Nonetheless, a comprehensive understanding of the effect of MD on bone strength has not yet been established. A study using pQCT found age to be a strong confounding factor in the relationship between MD and fracture risk, leading to complete attenuation of any correlation between the two when accounted for [65]. Thus, further research using pQCT measures of MD is required to better conclude its potential as a risk factor for fragility fractures and osteoporosis in both men and women.

Magnetic Resonance Imaging (MRI)

MR imaging is a non-ionizing modality that applies a magnetic field and radio-frequency pulses to produce three-dimensional images [66]. The lack of radiation associated with MR imaging makes it attractive in particular for scientific and clinical studies. This modality is generally applied to study trabecular architecture in the peripheral appendicular skeleton, particularly the distal radius and calcaneum [67]. MRI provides 2-3% reproducibility for two-dimensional structural parameters, and 3-9% reproducibility for three-dimensional parameters [67]. However, studies have claimed limited reproducibility for MRI parameters compared to both pQCT and hr-pQCT [53,54]. Moreover, the inability to provide densitometric outcome measures is a critical shortcoming of MR-imaging [68]. Several bone outcome parameters derived from MR imaging include; trabecular bone volume; mean trabecular width; mean trabecular spacing; mean intercept length as a function of angle; parameters such as 3D connectivity, as measured by the Euler number; the fabric tensor in 3 dimensions; and texture-related parameters, such as fractals [67].

A series of comprehensive studies were conducted by Wong et al. regarding validity and *in vivo* test-retest reliability of peripheral MRI (pMRI), using hr-pQCT as the gold-standard reference [53]. Concluded that pMRI is limited in achieving reliable values due to longer scan times and potential for greater motion artifact during imaging. Further, pMRI showed greatest long-term precision error, least significant change and standard error compared to both pQCT and hr-pQCT modalities *in vivo* [54, 69]. An important consideration for the reduced precision associated with MR imaging is its spatial resolution, which resides in the range of trabecular dimensions (in-plane resolution, 0.15-0.3 mm) [7]. Due to the accompanied long acquisition times, imaging is susceptible to motion artifacts, which can amplify the size of individual trabeculae [7, 68].

Diagnosis

Advances in MR imaging technology, such as 3T imaging and improved coil design, have allowed for greatly enhanced imaging of micro architectural bone structures [7]. The literature

provides substantial evidence for reliable outcome measures from MR imaging in identifying individuals with and without fragility fractures, independent of BMD [70-74]. However, the application of MR imaging as a sole imaging modality in the diagnosis of osteoporosis is not likely to be applied in clinical settings due to the considerable limitations of high costs and longer scan times [7,68].

Risk Stratification

5.2.1. Patient Populations: MR imaging provides several advantages to other imaging techniques in that it allows for measurement of physiological bone outcomes, such as marrow fat content, perfusion, and molecular diffusion [75]. These outcome measures can aid in risk stratification as MRI-based studies have identified decreases in cerebral marrow perfusion and increases in marrow fat content in osteoporotic patients in vertebral and femoral bone, compared to osteopenia subjects [75,76]. Further, subjects with osteopenia have decreased vertebral marrow perfusion and increased marrow fat compared with subjects with normal BMD [75,76]. The aforementioned results suggest that MR imaging may be beneficial in identifying preliminary risk factors in physiological bone parameters or preliminary identification of osteoporosis. MRI-based studies have further related reductions in spinal BMD, measured by DXA, to decreases in cerebral marrow perfusion, independent of the presence of any circulatory impairment [76]. Thus, marrow imaging through MRI may aid in identifying the severity of fracture risk in patients, in combination with BMD measures.

As previously discussed, the observation of various micro architectural changes can aid in identifying how fracture risk is stratified across age groups. Several studies have confirmed the ability of MR imaging to detect critical differences in trabecular structure depending on patient age, BMD, and osteoporotic status [77,78]. This allows MRI to be applied *in vivo* to assess risk of fracture through micro architectural bone parameters, but not independently of BMD and disease status. Beyond physiological and micro architectural measures, MRI provides insight into inter- and intra-muscular fat volume, which studies have recorded to be associated with prevalent fractures, prior to age adjustment [79]. A number of clinical studies have also demonstrated that MRI measures yield additional information to DXA measured BMD in differentiating individuals with fragility fractures from those without fragility fractures [70-74]. However, MRI presents several limitations. Wong et al. observed that model-dependent and model-independent MRI measures of Tb.Sp and Tb.N were underestimated, while bone volume fraction was overestimated, compared with hr-pQCT parameters in age-related women [53]. Similarly, MRI fat volume measurements remain limited by poor retesting precision [79]. Therefore, MRI presents a useful modality in identifying risk factors for osteoporosis through physiological and micro architectural bone measures, however, the literature does not suggest that MRI is the best candidate for reliable risk factor identification in clinical settings [80].

Conclusion

The use of accurate and precise imaging techniques is critical for both diagnosis and risk stratification of osteoporosis. Emerging evidence suggests that the limitations of DXA imaging, the current standard for clinical diagnosis of osteoporosis, suggest the use of novel imaging modalities that provide deeper insight into bone quality changes. There is clear emerging evidence that hr-pQCT is superior to DXA for assessing parameters of fracture risk, however all studies to date were cross-sectional. We highlight research that identifies hr-pQCT and pQCT as reliable tools in elucidating the differing patterns in macro and micro architectural bone loss between women and men throughout aging, as well as across cortical and trabecular compartments, which may help to explain the greater risk of osteoporosis in women than men. Overall, hr-pQCT and pQCT represent ideal candidates for quantifying bone outcomes for fracture risk assessment, while MRI measures present several limitations. Nonetheless, due to limited availability and high costs, additional steps are required until these modalities can be implemented as standardized diagnostic tools in clinical settings.

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