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Osteoporosis (A Lau, Section Editor)

Novel Imaging Modalities in Osteoporosis Diagnosis and Risk Stratification

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Abstract

Purpose of review Two hundred million individuals worldwide are diagnosed with osteoporosis, and every year, approximately 8.9 million experience a fracture. There is an opportunity with new diagnostic technology to enhance risk stratification of osteoporosis to improve patient outcomes. The current standard for osteoporosis diagnosis includes an areal bone mineral density (aBMD) T-score derived from a dual-energy X-ray absorptiometry (DXA) scan. However, aBMD does not account for bone quality, resulting in some individuals at risk for fracture not being identified. This review article will explore the potential of novel imaging technologies in osteoporosis diagnosis and risk stratification.

Recent findings Several novel imaging technologies have had success identifying those at risk for fracture and measuring treatment effectiveness. These include trabecular bone score (TBS), high-resolution peripheral quantitative computed tomography (HR-pQCT), peripheral quantitative computed tomography (pQCT), magnetic resonance imaging (MRI), and quantitative ultrasound (QUS). Recently, TBS has been incorporated into fracture risk prediction.

Summary While these imaging modalities show promise, further investigation is necessary to determine accuracy and reliability in osteoporosis diagnostics and fracture risk stratification before clinical integration is possible.

Introduction

Osteoporosis impacts an estimated 200 million men and women worldwide, burdening both individuals and healthcare systems alike [1]. Those with osteoporosis have increased fracture risk due to reduced bone strength because of decreased bone mineral density (BMD) and compromised trabecular and cortical bone microarchitecture [2, 3]. Increased susceptibility to fragility fractures contributes to poor overall health outcomes including increased chance of hospitalization, future fractures, mortality, and reduced quality of life [4].

The current standard for osteoporosis diagnosis is an areal bone mineral density (aBMD) T-score derived from a dual-energy X-ray absorptiometry (DXA) scan [5]. Osteoporosis is defined as a T-score 2.5 standard deviation (SD) or more below the average for sex-matched adults [3]. This criterion has been found to have low specificity and sensitivity, resulting in missed opportunities for treatment in some cases and unnecessary treatment in others [3]. The deficiency in the current diagnostic standard presents challenges for identifying and treating at-risk individuals.

Various factors influence fracture risk including age, sex, and prior fracture history. A major contributor underlying these risk factors is bone microarchitecture, an indicator of bone quality [5]. Bone quality includes aspects of bone composition and structure that contribute to bone strength independent of aBMD [3]. It is likely that the addition of quantitative bone microarchitecture data would be advantageous in predicting biomechanical properties of bone and potentially improving fracture risk stratification [6–8].

Since DXA-derived aBMD does not account for bone quality, researchers and clinicians have progressed towards exploring the use of imaging modalities that provide more comprehensive data [5]. These next-generation technologies include DXA-derived trabecular bone score (TBS), high-resolution peripheral quantitative computed tomography (HR-pQCT), peripheral quantitative computed tomography (pQCT), magnetic resonance imaging (MRI), and quantitative ultrasound (QUS). These imaging modalities aim to stratify fracture risk by introducing parameters associated with fragility fractures that may take into account aspects of bone quality. Recently, TBS has been incorporated into fracture risk prediction.

In this review, novel imaging modalities are briefly described, including their strengths, limitations, and potential for integration into osteoporosis diagnostics.

Novel imaging modalities

Trabecular bone score derived from DXA

TBS is a bone texture parameter yielded from DXA images through gray-level texture analyses [9]. TBS has been found to positively correlate with bone connectivity and the number of trabeculae such that a higher TBS score is associated with better bone microarchitecture and decreased fracture risk in older men and postmenopausal women [10].

TBS has been found to predict fracture occurrence independently of other measures, such as BMD [11]. A lower TBS is associated with increased fracture incidence and prevalence and aBMD at the proximal femur and lumbar spine [11]. Several cross-sectional and prospective studies have shown the predictive capabilities of TBS, as outlined by Harvey et al. [11]. A longitudinal study of 29,407 postmenopausal women demonstrated that lumbar spine aBMD and TBS predicted fracture risk equally well and actually performed better when used together [12]. Specifically, combining aBMD total hip with TBS spine was most accurate in predicting fractures over a 5-year period [12]. TBS can be used in fracture risk assessment with FRAX, an osteoporosis risk assessment tool that uses BMD and other individual clinical risk factors to estimate one's 10-year risk of hip and other major osteoporotic fractures [11]. A meta-analysis of 14

cohorts (including 17,809 men and women aged 40–90) assessed the predictive ability of FRAX and TBS in the occurrence of osteoporotic and hip fractures. They found that while both were predictive, TBS remained a significant predictor, independent of FRAX [13].

Due to TBSs' ability in predicting fractures, it has been integrated into fracture risk prediction with FRAX. It is currently uncertain how changes in TBS are associated with fracture risk reductions; however, its ability to assess the effectiveness of osteoporosis treatment is a subject of continuing investigation.

Computed tomography technologies

High-resolution peripheral quantitative tomography

Over the last 10 years, HR-pQCT techniques have been extensively tested (Fig. 1). Researchers are now directing investigation towards HR-pQCT's clinical utility [14–18]. HR-pQCT's effectiveness comes from its ability to directly quantify bone microarchitecture and measure volumetric BMD (vBMD) [15, 19]. HR-pQCT measures trabecular and cortical bone regions separately [19] at radiation doses of 3 μSv per scan, and it can measure three-dimensional bone microarchitecture in the distal radius and tibia [18, 19]. Several studies have reported a strong association between HR-pQCT-derived bone quality parameters, specifically trabecular separation and vBMD, and fracture incidence [20••].

Further, HR-pQCT provides an estimate of bone strength by building finite elemental analysis (FEA) models [19]. FEA is a computer-based technique that assesses structural stress and the structural characteristics of bones. FEA parameters are associated with fragility fractures of the radius and tibia in men and

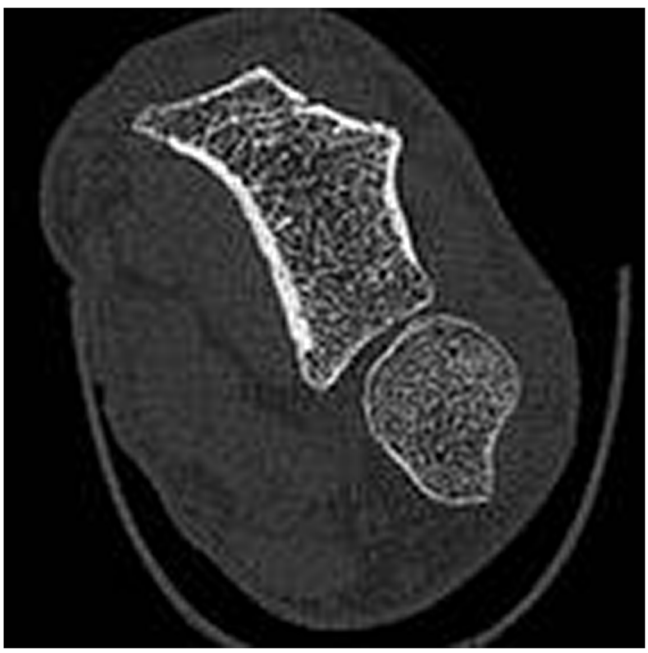

Fig. 1. HR-pQCT of wrist. Courtesy of Dr. A. Kin On Wong

women [20••, 21]. Using FEA, HR-pQCT has been shown to be an effective method of validating osteoporosis therapy in patients [22•]. For instance, HR-pQCT FEA analysis was used to determine the effectiveness of zoledronic acid in postmenopausal women with osteoporosis over an 18-month period [23].

With the insight into bone quality obtained by HR-pQCT, there is promise for future use of HR-pQCT in risk stratification of osteoporosis rather than use solely as a research tool. Ideally, it will be used as a surrogate measure of fracture risk and if accepted, it may be used to validate novel therapies aimed at fracture prevention.

Peripheral quantitative computed tomography

Studies have established the accuracy and reliability of pQCT in fracture discrimination by specifically associating fracture risk with bone parameters obtained by pQCT (Fig. 2) [20••]. Like HR-pQCT, pQCT is able to separately measure trabecular and cortical bone compartments in the distal tibia and radius at low radiation doses [18].

Several studies have examined the association between pQCT-derived bone outcomes and fracture risk [20••]. An interim analysis of data from the Canadian Multicenter Osteoporosis (CaMos) Bone Quality Study demonstrated higher associations among fracture risk and the following variables: cortical vBMD, tibial bone volume fraction, trabecular separation, and trabecular number [24]. There is a need for consolidation and comparison of pQCT measures in order to establish trends for at-risk population groups.

Muscle quality assessment

In osteoporosis, fracture risk is higher in those with muscle wasting [20••]. With weakened muscles, individuals are at higher risk for falls and have a decreased ability to protect oneself from falls [3].

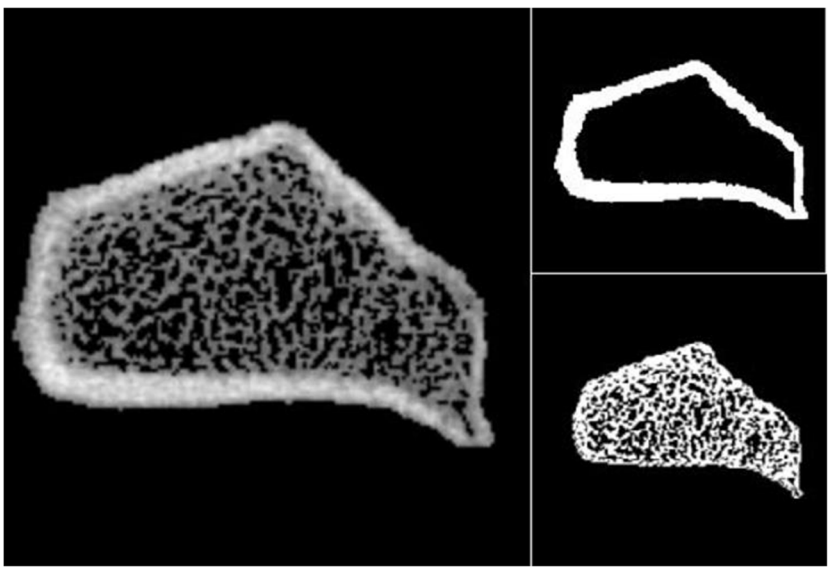

Fig. 2. pQCT of ulna highlighting cortical (top left) and trabecular (bottom right) regions. Courtesy of Dr. A. Kin On Wong

Using pQCT, a muscle cross-sectional area (MCSA) measure can be obtained and serve as an indicator of muscle quality [25, 26]. Additionally, MCSA can be used to derive muscle density as a surrogate for muscle adiposity [27]. Both muscle quality and muscle adiposity can influence bone quality and the subsequent risk of fractures. At least one study found an association between muscle quality and fracture risk [26]. In this cross-sectional study, associations were established between muscle density, fracture, and the degree of inter- and intramuscular fat content of muscles in postmenopausal women [26]. Currently, there is insufficient data to establish strong associations between these variables and prospective studies are needed [20••].

Challenges with HR-pQCT and pQCT

A significant challenge to HR-pQCT and pQCT serving as diagnostic tool for osteoporosis is segmentation [22•]. Scanned regions must be segmented in order to allow for evaluation of both the cortical and trabecular bone compartments [28]. However, it can be difficult to define clear borders between cortical and trabecular bone regions potentially compromising validity of associations between parameters and fracture risk [28]. Defining clear borders can be especially difficult when the cortical region is highly porous and seemingly trabecularized at the endosteal surface [28]. Though new methods have been proposed to address this issue [18], the accuracy and precision of these methods has yet to be established [22•]. Presently, there is contention as to whether the assessment of bone microarchitecture at the sites of distal radius and tibia assessed for HR-pQCT and pQCT would be sufficient to reflect strength of the axial bones [22•]. Most often, fractures of the hip, vertebrae, and wrist are associated with osteoporosis; however, an individual with osteoporosis and low bone mass has an elevated risk for almost all fracture types [29]. Lastly, due to high sensitivity to motion artifacts and a current lack of standardization of HR-pQCT and pQCT techniques, use of these techniques is somewhat limited [18].

Recommendations for HR-pQCT and pQCT

To date, the majority of studies relating fracture risk to HR-pQCT and pQCT parameters have been cross-sectional in design, which brings into question causal effect [20••]. Few prospective cohort studies found significant associations between bone quality parameters as measured by pQCT and incident fracture [20••]. A prospective study that assessed fracture incidence over a 6-year period found that cortical vBMD at the tibia and cortical thickness at the radius were significantly associated with incident fractures among women [30]. It is necessary to continue prospective studies to uncover which parameters are most appropriate for assessing fracture risk.

If HR-pQCT is to be integrated into clinical practice for the diagnosis and stratification of fracture risk in osteoporosis, it is likely necessary to establish normative databases of microarchitectural measures that can be compared to population data. Age- and sex- specific reference data are needed to aid with clinical interpretation of HR-pQCT. Similar to the method of using T-scores for

DXA scans, the development of normative databases can provide outcome measures to diagnose and assess fracture risk in at-risk patients [31]. To date, several studies have collected normative data with HR-pQCT measures in various age groups [31, 32].

Similarly to HR-pQCT, researchers could benefit from development of normative databases for pQCT bone parameters [33]. Presently, there are limitations with the use of HR-pQCT and pQCT due to the lack of large prospective studies assessing HR-pQCT and pQCT parameters as predictors for future fractures.

Magnetic resonance imaging

High-resolution MRI and peripheral MRI

High-resolution MRI (HR-MRI), like pQCT and HR-pQCT, analyzes cortical and trabecular bone microarchitecture [34]. Often, it is conducted at the distal radius and tibia but may also be performed at the proximal femur [34, 35]. MRI uses specific pulse sequences to generate high-resolution bone images [34]. The bone microstructural and microarchitectural parameters associated with fracture risk acquired by HR-MRI are comparable to those of HR-pQCT [34]. Like HR-pQCT, MRI can be used in conjunction with FEA modeling to use bone architecture in predicting bone mechanics [36].

Though there are similarities between MRI and HR-pQCT functionalities, unlike CT, MRI does not expose patients to ionizing radiation and thus allows for more frequent scanning [35, 37]. However, with MRI, there is lower spatial resolution, higher cost compared to HR-pQCT, and motion artifacts as a result of lengthy scan times [38, 39]. MRI also fails to provide a BMD measure [40]. Though MRI can enhance fracture risk prediction, its use in osteoporosis diagnostics is limited due to the aforementioned challenges.

HR-MRI, in conjunction with FEA modeling, is able to monitor alterations in bone microarchitecture parameters in response to treatment [41, 42]. A small cohort study of women between the ages of 50–75, representative of typical osteoporosis populations, demonstrated that structural and mechanical parameters measured at the distal radius show suitability in determining long-term treatment response [43]. In this study, peripheral MRI showed alterations in trabecular microarchitecture in participants undergoing bisphosphonate therapy [43]. Future studies should aim to include larger sample sizes and be prospective in design.

Quantitative ultrasound

Quantitative ultrasound (QUS) has showed potential in clarifying diagnosis and risk stratification of osteoporosis. QUS measures properties of ultrasound waves through bone tissue [44]. From measures of speed of sound and broadband ultrasound attenuation, bone tissue can be assessed, and these measures can be used to derive the stiffness index and the quantitative ultrasound index [45]. These measures characterize the elastic modulus and the compressive strength of the bone [46]. Several studies have reported that QUS measures can independently, and with DXA, serve as indicators of future fractures, while also being able to discriminate between those with and without fractures [47, 48]. Advantages of QUS include portability, no radiation, and low cost. Given these

properties, QUS may prove to be a promising screening tool, particularly in areas where DXA measurement is not available [49].

Conclusion

Shortcomings in the current osteoporosis diagnostic tools result in poor health outcomes for individuals at risk for fractures. Advances in imaging technologies show promise in improving osteoporosis diagnosis and risk stratification.

Due to TBSs' efficacy in predicting fractures, it has been integrated into fracture risk prediction with FRAX. While HR-pQCT, pQCT, MRI, and QUS show potential, there are limitations that hinder the present integration of these modalities into clinical practice. HR-pQCT and pQCT measures have demonstrated associations with fracture risk, but challenges including radiation exposure to patients, high sensitivity to motion artifacts, and inadequate standardization limit the use of these techniques [18]. Further, the use of pQCT in analyzing muscle quality and its association with fracture risk remains uncertain due to insufficient data [20••]. MRI technologies can enhance fracture risk prediction without radiation exposure but low spatial resolution, high cost, and motion artifacts as a result of lengthy scan times compromise utility [38, 39]. Further, larger prospective studies are necessary to determine the effectiveness of both CT and MRI modalities in osteoporosis treatment monitoring. Lastly, QUS appears promising for screening, but may not have a role as a diagnostic tool [49]. With further investigation using prospective studies with larger samples, stronger conclusions can be made as to the utility of these novel technologies in fracture risk prediction and risk stratification in individuals with osteoporosis.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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