High-resolution peripheral quantitative computed tomography - Towards clinical use for osteoporosis

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ABSTRACT

Dual X-ray absorptiometry (DXA) and the FRAX score lack sensitivity to identify postmenopausal women at high risk of fracture. To overcome this shortcoming, evaluation of bone microarchitecture using high-resolution peripheral quantitative computed tomography (HR-pQCT) has been suggested to improve fracture risk prediction.

In several prospective studies, bone microarchitectural parameters, evaluated using the finite element analysis (FEA) method, have provided better prediction of fracture risk than BMD alone, measured using DXA, or FRAX score. Most cohorts with prospective data have been combined in the Bone Microarchitecture International Consortium analysis, which confirmed on a large scale the improvement of fracture risk prediction, especially with FEA at the radius, but the magnitude of the improvement was not substantial. A recent study has shown that analyzing the microarchitecture to identify women to treat was cost-effective when using zoledronate. A deep learning model using only the images of the distal forearm, including both the bone and soft tissues, has also improved fracture risk prediction substantially.

The adoption of deep learning to analyze bone microarchitecture is likely to simplify and speed up the process of fracture risk evaluation. This will allow for adequate preventive therapy of a large proportion of postmenopausal women at high risk who are currently left untreated.

KEYWORDS

Osteoporosis, fracture, high-resolution peripheral quantitative computed tomography – HR, pQCT.

Introduction

Most women who will fracture are undetected by current methods, i.e., FRAX and bone mineral density (BMD) measurement. This shortcoming has fueled a considerable amount of research aimed at developing a variety of biomarkers of bone fragility, including imaging markers. It has been postulated that non-invasive evaluation of bone microarchitecture might improve fracture prediction and become a useful clinical tool. Thus, *in vivo* assessment of bone microstructure using high-resolution peripheral quantitative computed tomography (HR-pQCT) with the XTreme CT machine (Scanco, Bruttisellen, Switzerland) became available in the early 2000s. This narrative review focuses on the evidence obtained for its clinical use.

Technical aspects

This system uses a two-dimensional detector array in combination with a 0.08-mm point-focus X-ray tube, simultaneously acquiring a stack of parallel CT slices with a nominal resolution (voxel size) of 82 μm. One hundred and ten slices are obtained at the distal radius and tibia during a 3-minute scan, providing a three-dimensional representation of approximately 9 mm in the axial direction. The entire volume of interest is automatically segmented into cortical and trabecular regions using a threshold-based algorithm. The total, trabecular, and cortical volumetric bone densities are measured, along with the number and distribution of trabeculae and the cross-sectional area. Trabecular bone volume, thickness, and separation are calculated using the standard histomorphometry formulae [1]. Cortical porosity can also be assessed with several threshold- and non-threshold-based methods [2].

This technique has good reproducibility for microstructural parameters and excellent reproducibility for density measurements, with coefficients of variation of < 5% and < 1% respectively [3]. The precision of cortical bone microarchitecture measurement is also excellent with a least significant change for cortical porosity < 1%. The standard patient analysis allows direct measurement of the cortical and trabecular densities, trabecular number, and trabecular separation distribution, whereas trabecular bone volume, separation, and thickness are calculated using semi-derived methods. The extended cortical analysis is a dual-threshold segmentation technique that has been developed to overcome the segmentation variability in patients with thin or highly porous cortex [4].

Biomechanical properties can be assessed using a linear

finite element modeling technique that is installed by default using the voxel conversion approach and provides estimates of bone strength such as ultimate stress failure load and stiffness [5].

A second generation of the device (Xtreme CT II, Scanco Medical) has been developed that can provide either the same precision with a scan time two times shorter, or better precision also with a quicker scan time (60 instead of 82 µm voxel size; 2 min with high-resolution protocol, 168 slices). A wider and longer scan gantry provides a larger field of view and allows exploration of the knee and elbow joints.

Clinical application

Improvement of fracture discrimination and prediction

Prevalent fractures and bone microstructure
The first studies were case-control and cross-sectional studies. In a case-control analysis from the population-based OFELY cohort, women with osteopenia with prevalent fragility fracture also had lower trabecular density and more heterogeneous trabecular distribution than non-fractured women with the same areal BMD (aBMD) at the spine and hip [3]. In another analysis of subjects from the OFELY cohort, while all vertebral fractures were associated with low volumetric BMD and architectural alterations of both trabecular and cortical bone, severe and multiple vertebral fractures were associated with further alterations of cortical bone [6]. Most of these results observed in retrospective studies were obtained after adjustment for aBMD at the radius and hip for radius and tibia HR-pQCT measurements, respectively.

In microfinite element analyses (µFEA) performed with data from the OFELY cohort using linear models, the proportion of load carried by the cortical bone compared with that carried by the trabecular bone was associated with wrist fracture independently of aBMD and microarchitecture parameters [7]. However, non-linear models have also been implemented [4]. These non-linear models are more computer demanding than linear µFEA models. The linear µFEA parameters evaluated at the distal tibia and radius were also associated with all types of prevalent fractures, including vertebral ones [8]. The magnitude of this association was similar at the tibia and radius. So, the mechanical properties of the tibia and radius are relatively representative of those of other distant bone sites. The main limitations of µFEA are the need for engineering skills and access to powerful computers, and the duration of the analysis (around 30 min/bone site with a linear model on a regular computer station). With the rapid increase in computer performance and easier access to cloud computing, this duration can be reduced to a few minutes.

Prediction of incident fracture
The most important evidence has been obtained in prospective studies. Six individual studies demonstrated that HR-pQCT variables could predict incident fractures in postmenopausal women and older men [9-14]. In women, the strongest prediction was found for Tt.BMD and Tb.N at the distal radius [9-11]. In the three studies conducted in older men (mean age 74 to 84 years),

the strongest association was found for Tt.BMD and Tb.N at the radius [12-14] and for tibial Ct.Ar and mass [13].

The Bone Microarchitecture International Consortium (BoMIC) pooled HR-pQCT data of 7254 participants (66% women and 34% men, with a mean age of 69 years) from 8 cohorts assembled in the USA (Framingham, Mayo Clinic), France (QUALYOR, STRAMBO, OFELY), Switzerland (GERICO), Canada (CaMos), and Sweden (MrOS) for a combined prospective analysis of incident fracture risk [15]. All HR-pQCT data were obtained with the first-generation XtremeCT device. Within a mean follow-up of 4.6 years, 765 incident fractures occurred. After adjustment for age, sex, height, and cohort, Tt.BMD, Ct.BMD, Tb.BMD, and parameters of trabecular structure (Tb.N, Tb.Th, Tb.Sp) and cortical morphology (Ct.Ar, Ct.Th, Ct.Po) measured at the distal tibia or distal radius were significant predictors of incident fracture, with the exception of Ct.Po at the distal radius. Hazard ratios per 1 SD decrease were highest (up to 1.75) for Tt.BMD, Tb.BMD, and Ct.Ar, and varied from 1.12 to 1.58 for the other parameters.

Failure load calculated from µFEA at the distal radius and tibia also predicted the risk of fracture, with a HR of 2.13 and 2.40 per 1 SD decrease, respectively, but the confidence intervals were about 3 times greater than for the other parameters due to a smaller sample size for µFEA. In sex-stratified analyses, results for incident fracture were similar in women and men, although effect sizes were attenuated in men. Additional adjustment for femoral neck aBMD evaluated by DXA or by FRAX score reduced the HRs, but generally they remained

significant, with the exception of Ct.Th and Ct.Po measured at the tibia. These findings show that HR-pQCT measurements predict fracture risk independently of DXA-BMD of the hip. After adjustment for aBMD of the ultradistal radius by DXA, Tb.BMD (HR = 1.26) and Tb.N (HR = 1.18) still predicted incident fracture. The ultradistal aBMD adjustment eliminated the significance of all cortical parameters and even that of bone strength.

Ct.BMD, Tb.N, and Tb.Sp of the radius slightly but significantly improved AUC from 0.73 for DXA aBMD of the hip alone to 0.75, whereas at the tibia, cortical and trabecular HR-pQCT parameters did not further improve the AUC of 0.72 for DXA aBMD of the hip alone.

A more recent analysis from the QUALYOR and OFELY cohorts revealed that the structural fragility score, a non-thresholded approach to microstructure evaluation, predicts increased fracture risk irrespective of aBMD and FRAX in women ≥ 70 years of age [16]. Overall, the BoMIC study suggests that assessment of cortical and trabecular bone microarchitecture by HR-pQCT could improve overall fracture prediction in mostly normal or osteopenic elderly subjects beyond DXA hip aBMD, but the improvement provided in multivariate models was relatively small. When HRpQCT indices or failure load were compared with femoral neck aBMD, the overall net reclassification improvement value varied between 17 and 21% [15].

Thus, HR-pQCT may potentially be used for the differentiation of patients with severe microstructural deterioration, within osteopenic or osteoporotic BMD categories; this would have important implications for the decision on therapeutic interventions.

In fact, it has been reported that in women with osteopenia, it is cost-effective to treat those with microstructural deterioration [17].

Other diseases associated with bone fragility

Microstructural changes are also observed in metabolic bone diseases other than post-menopausal osteoporosis, such as diabetic bone disease [18] and bone fragility associated with chronic kidney disease or with active celiac disease [19]. The increased risk of non-hip non-vertebral fracture in obese women may stem from an inadequate adaptation of bone microarchitecture [19]. Decreased bone mass and increased bone fragility also characterize osteogenesis imperfecta, but the most prevalent subtype of this hereditary disorder has been shown to be associated with significant microarchitecture alterations compared with healthy controls.

Pitfalls

The bone imaging technology here described requires specialized scanners and currently the number of devices available is limited. Motion artifacts occurring during data acquisition sometimes challenge the validity of measurements at the radius, in some cases making it necessary to exclude analysis of microstructural parameters or order rescanning of patients.

Longitudinal assessment, serving to accurately evaluate therapeutic efficacy, requires control of the intrasubject image alignment but an automatic matching procedure has been proposed. In addition, significant heterogeneity in estimates of trabecular and volumetric density differences between fractured and non-fractured patients has been observed across centers in multicenter studies [4]. The investigation of central sites prone to fracture (vertebrae, hip) and of diaphyseal sites is not possible.

Treatment-related effects should be interpreted with caution due to some bone assessment assumptions and artifacts associated with beam hardening, X-ray scatter effects, and tissue mineralization changes observed with some treatments. Furthermore, it should be recognized that due to the limited resolution of HR-pQCT imaging, it is not possible to capture pores < 80μm.

Conclusion

HR-pQCT measures can improve the prediction of fracture over BMD and FRAX in men and women who have osteopenia. In this setting, newer approaches evaluating microstructure as a score combining both poor trabecular and cortical bone might further improve this prediction. Analyses using deep learning might also enhance the prediction and speed up the analysis. Such evolution of the technique may allow its use in clinical practice.

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