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Tri-Modality Comparison (Part III)

A Trimodality Comparison of Volumetric Bone Imaging Technologies. Part III: SD, SEE, LSC Association With Fragility Fractures

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Abstract

Part II of this 3-part series demonstrated 1-yr precision, standard error of the estimate, and 1-yr least significant change for volumetric bone outcomes determined using peripheral (p) quantitative computed tomography (QCT) and peripheral magnetic resonance imaging (pMRI) modalities in vivo. However, no clinically relevant outcomes have been linked to these measures of change. This study examined 97 women with mean age of 75 ± 9 yr and body mass index of 26.84 ± 4.77 kg/m^2, demonstrating a lack of association between fragility fractures and standard deviation, least significant change and standard error of the estimate-based unit differences in volumetric bone outcomes derived from both pMRI and pQCT. Only cortical volumetric bone mineral density and cortical thickness derived from high-resolution pQCT images were associated with an increased odds for fractures. The same measures obtained by pQCT erred toward significance. Despite the smaller 1-yr and short-term precision error for measures at the tibia vs the radius, the associations with fractures observed at the radius were larger than at the tibia for high-resolution pQCT. Unit differences in cortical thickness and cortical volumetric bone mineral density able to yield a 50% increase in odds for fractures were quantified here and suggested as a reference for future power computations.

Key Words: Clinical sensitivity; fragility fractures; least significant change; pMRI; pQCT.

Introduction

The previous reports in this 3-part trimodality comparison highlighted the acceptable short-term precision errors for volumetric bone outcomes derived from high-resolution (HR) peripheral quantitative computed tomography (pQCT) followed by pQCT, and then 1.0 T peripheral magnetic resonance images (pMRI) (REF1). In addition, the same pattern of long-term precision error was demonstrated, whereas exclusion of individuals with a history of fragility fractures or who were current antiresorptive users resulted in smaller long-term precision error for pQCT and pMRI (REF2). With the exception of trabecular number (Tb.N), all apparent trabecular microstructural measurements were shown to be valid as compared with HR-pQCT (REF1). However, the challenge associated with the measurements of change detectability (standard error of the estimate [SEE]) and clinically least significant change (LSC) is that there have been, so far, no associations drawn between these statistics and an actual clinical endpoint. Consequently, it remains unknown to what degree a given change in each volumetric outcome is associated with fragility fractures. The classical method of describing sensitivity involves the measurement of change in response per unit change in stimulus. This slope definition could be addressed by evaluating

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the association between given unit changes in each volumetric bone outcome and corresponding increases in the risk for fragility fractures. A base statistical model without any covariates would best describe this measurement. Although a number of studies have reported odds ratios (ORs) or hazard ratios (HRs) demonstrating the association between volumetric bone outcomes and fragility fractures, most studies targeted the goal of estimating fracture risk and not the goal of quantifying clinical sensitivity. An extrapolation of the magnitude of change in volumetric bone outcome required to achieve a standardized effect size (i.e., 50% increase in fracture risk) would be informative of the comparative clinical sensitivity across different techniques.

Most studies measuring odds and risks for fractures do not actually relate change in bone outcomes with fractures. Instead, the notion of change is represented by the associated increased odds or risks per unit difference in the outcome (interpreted as a hypothetical increase or decrease). Laib et al *(1)* demonstrated that each standard deviation (SD) increase in HR-pQCT-derived trabecular spacing (Tb.Sp), and decrease in Tb.N was associated with an age-adjusted increase of 1.85−2.03-fold in the odds for fractures. However, in a similar cross-sectional analysis, Melton et al *(2)* did not see any association between volumetric bone outcomes and prevalent fractures at the distal radius using HR-pQCT images. Although not examined in terms of changes in SDs, MacIntyre et al *(3)* showed that pQCT-derived mean intertrabecular hole area greater than 2 SDs from the mean translated to a 5.4-fold increase in the odds for fractures. One investigation by Boutry et al *(4)* reported a significantly increased odds for fractures per SD difference in 11 of 13 volumetric bone outcomes obtained from calcaneous scans on MRI. All the aforementioned studies only quantified bone at a single point in time and adjusted for a number of covariates.

The present study therefore juxtaposed the clinical sensitivity of volumetric bone outcomes derived from HR-pQCT, pQCT, and 1.0 T pMRI by quantifying the odds for fragility fractures associated with each unit decrease or increase in volumetric bone measure expressed as SD, LSC, or SEE units. This investigation also extrapolated these associations to determine the specific volumetric bone outcome values at which at least a 50% increase in the odds for fragility fractures would be observed.

This trimodality comparison is presented as the final component of a 3-part series discussing intermodality differences in technological limitations vs advantages in volumetric bone imaging.

Methods

This observational cohort study quantified volumetric bone outcome values derived from HR-pQCT, pQCT, and 1.0 T pMRI images, as well as retrospectively associated these outcomes with a history of fragility fractures. All study procedures were completed within 3.5 yr. Women 50 yr and older enrolled in the Canadian Multicentre Osteoporosis Study (CaMOS) and living within a 50 km radius of the Hamilton (Ontario, Canada) CaMOS site were considered eligible to participate (N = 340). CaMOS is an ongoing prospective cohort study of community-dwelling randomly selected women and men 25 yr and older at 9 major Canadian cities. The main CaMOS objectives, methodology, and sampling framework are described in detail elsewhere *(5)*. Participants were randomly selected from all eligible women from the Hamilton CaMOS cohort. Women with valid contraindications to MRI (pacemaker, insulin pumps) were excluded. Those participants weighing above 250 lbs were excluded from HR-pQCT and 1.0 T pMRI procedures because of the weight limit of the positioning chair. Women with self-reported tremors were also excluded to avoid significant motion artifact.

Participants volunteered in the completion of a pQCT, HR-pQCT, and 1.0 T pMRI ultradistal radius scan at baseline and at 1 yr follow-up. Repeated imaging was also performed at the ultradistal tibia for pQCT and HR-pQCT. One-yr repeats of these imaging procedures enabled the computation of long-term precision statistics with which fragility fractures were associated. Details of each imaging procedure have been reported in part I of this series. Because of limitations in the gantry diameter and depth, ultradistal tibia scans were not completed using pMRI. A complete list of current medications including dose, duration, and frequency, was collected at study visit. Information on medical conditions and ascertained incident fragility fractures from the last 15 yr was obtained from the CaMOS database. Fragility fractures were defined as nontraumatic fractures occurring as the result of a fall from standing height or less, excluding any fractures of the skull, fingers, and toes.

All study procedures were overseen and approved by the St. Joseph's Healthcare Research Ethics Board in Hamilton and the University Health Network in Toronto (Ontario, Canada).

High-Resolution Peripheral Quantitative Computed Tomography

Scans were performed at the ultradistal radius and tibia at the standard regions of interest (ROIs) using the same imaging parameters as previously described (REF1) for the HR-pQCT (XtremeCT v1; Scanco Medical AG, Bassersdorf, Switzerland). After acquiring 110 transaxial computed tomographic slices at an isotropic voxel resolution of 82 μm, acceptable quality images (grade 3 motion and below *(6)*) were semiautomatically segmented using Scanco software (Scanco Medical AG, Bassersdorf, Switzerland) and computed for apparent microstructural outcomes (bone volume/total volume [BV/TV], Tb.Sp, trabecular thickness [Tb.Th], Tb.N, cortical thickness [Ct.Th], integral, cortical, and trabecular volumetric bone mineral density [vBMD], subscripts: i, c, tr). Hydroxyapatite rod phantoms were scanned daily for quality control purposes.

Peripheral Quantitative Computed Tomography

Ultradistal radius and tibia scans were performed using an XCT2000 model pQCT (Stratec, Pforzheim, Germany) at an