A Trimodality Comparison of Volumetric Bone Imaging Technologies. Part II: 1-Yr Change, Long-Term Precision, and Least Significant Change

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Abstract

The previous article in this 3-part series demonstrated short-term precision and validity for volumetric bone outcome quantification using in vivo peripheral (p) quantitative computed tomography (pQCT) and magnetic resonance imaging (MRI) modalities at resolutions 200 μm or higher. However, 1-yr precision error and clinically significant references are yet to be reported for these modalities. This study examined 59 women with mean age of 75 ± 9 yr and body mass index of 26.84 ± 4.77 kg/m^2 , demonstrating the lowest 1-yr precision error, standard errors of the estimate, and least significant change values for high-resolution (hr) pQCT followed by pQCT, and 1.0-T pMRI for all volumetric bone outcomes except trabecular number. Like short-term precision, 1-yr statistics for trabecular separation were similar across modalities. Excluding individuals with a previous history of fragility fractures, or who were current users of antiresorptives reduced 1-yr change for bone outcomes derived from pQCT and pMR images, but not hr-pQCT images. In Part II of this 3-part series focused on trimodality comparisons of 1-yr changes, hr-pQCT was recommended to be the prime candidate for quantifying change where smaller effect sizes are expected, but pQCT was identified as a feasible alternative for studies expecting larger changes.

Keywords

least significant change; long-term precision; MRI; pQCT; segmentation; standard error of the estimate

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Introduction

The previous report in this 3-part trimodality comparison series has demonstrated a high degree of short-term precision for volumetric bone outcomes derived from high-resolution (hr)-peripheral quantitative computed tomography (pQCT), followed by pQCT, and by 1.0-T peripheral magnetic resonance imaging (pMRI). It was cautioned that a larger number of slices obtained by pMRI and a longer scan time resulted in increased motion artifact, and reduced the degree of reproducibility achievable. Scans obtained at the tibia were more reproducible than at the radius, and all volumetric bone outcome measures from pMRI and pQCT, with the exception of trabecular thickness (Tb.Th), were shown to be valid measurements as compared with hr-pQCT (REF). These 3 modalities demonstrated utility for quantifying interindividual differences suitable for cross-sectional analyses, but long-term precision information is required to assess their appropriateness for performing longitudinal studies examining intraindividual and cohort change over time.

There is currently a lack of studies that have quantified the long-term precision or the minimally detectable change for hr-pQCT, pQCT, and pMRI. Long-term precision data can be converted to least significant change (LSC) values, which putatively inform on the minimum change required to be considered clinically meaningful. The challenge with LSC values is their reliance on the properties of the cohort in which precision measures were obtained (1). In contrast, an appreciation of the long-term minimally detectable change independently of the expected biological variation could prove useful for assessing the analytical properties of the modality. To achieve this value, the standard error of the estimate (SEE) can be used—a statistical parameter that accounts for the biological correlation between the baseline and follow-up time points (2). Long-term precision of volumetric bone outcomes has been quantified from hr-pQCT scans repeated over an intermediate (5 mo) to longer durations (28 mo; 2.2%–3.4%) (3). One-yr long-term precision for 1.5-T MRI-derived bone volume/total volume (BV/TV), trabecular separation (Tb.Sp), and Tb.Th were between 3% and 6% (4), although LSC values have not been reported. No reports on the long-term precision of pQCT-derived bone structural or densitometric outcomes have been identified to date. Longitudinal studies have primarily been performed using hr-pQCT, examining changes owing to pharmaceutical intervention (5–7), disease states (8), and growth (9,10). Only 1 study used MRI for measuring change owing to intervention (11) or pQCT for characterizing adolescent bone growth patterns (12). The lack of studies using these modalities may in part be motivated by the absence of long-term precision data.

The report of 1-yr analytical properties for volumetric bone outcomes across the same time period for all modalities will enable a juxtaposition of these imaging tools' ability to quantify minimal change. More importantly, these values can guide future power analyses in the design of larger epidemiological studies and clinical trials measuring trajectories in volumetric bone outcomes. The present study therefore focused on comparing the long-term precision error, SEE, and LSC over a 1-yr period for individuals who are fracture and treatment naïve, and those who have sustained a previous fragility fracture or who have been on antiresorptive therapy.

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

Methods

This study was designed as a 1-yr longitudinal observational cohort study comparing the technical long-term precision and change detection limit of 3 technologies for imaging bone volumetrically. All study procedures were completed within 3.5 yr with each of baseline and follow-up period recruitment completed within 1.5 yr. Women aged 50 yr or 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). The CaMOS study is an ongoing, prospective cohort study of community-dwelling, randomly selected women and men aged 25 yr or older at 9 major Canadian cities. The main Ca-MOS objectives, methodology, and sampling framework are described in detail elsewhere (13). Participants were randomly selected from all eligible women from the Hamilton cohort of the CaMOS study. Women with valid contraindications to MRI (pacemaker or insulin pumps) were excluded from 1.0-T pMRI procedures. Those participants weighing more than 250 lbs were excluded from hr-pQCT and 1.0-T pMRI procedures owing to the weight limit of the 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. Details of each imaging procedure have been reported in Part I of this series (REF). Summarized descriptions of each are detailed below. Owing to the limitations of the gantry diameter and depth, ultradistal tibia scans were not completed using the pMRI, as this procedure would have required participants to sustain a plantar flexion position. 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 yrs 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 using the same imaging parameters as previously described (REF) for the hr-pQCT (XtremeCT v1; Scanco Medical AG, Bassersdorf, Switzerland). After acquiring 110 transaxial CT slices in the proximal direction at an isotropic voxel resolution of 82 μm , acceptable quality images [Grade 3 motion and below (14)] were semi-automatically segmented using Scanco software (Scanco Medical AG) and computed for apparent microstructural outcomes (BV/TV; Tb.Sp; Tb.Th; trabecular number [Tb.N]; cortical thickness [Ct.Th]; and 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 a region of interest coinciding with the 9.02 mm span volume from hr-pQCT. Two slices, each 2.5 ± 0.3 mm thick were obtained 11.5 and 16.5 mm proximal to the radial tilt midpoint; and 24.5 and 29.5 mm proximal to the tibial endplate plateau, at an in-plane resolution of 200 μm (REF). Hydroxyapatite phantoms were assessed on days in which the scans were obtained. Only images with no discontinuities in the cortical bone were accepted for image analyses. Densitometric ($v\text{BMD}_i$, $v\text{BMD}_c$, and $v\text{BMD}_{tr}$) measures were computed using Stratec v5.2.1 software; apparent trabecular microstructure (Tb.Sp, BV/TV, Tb.N, and Tb.Th) and Ct.Th were computed with custom software package, pQCT OsteoQ (In-glis Software Solutions, Inc., Hamilton, ON).

1.0-T Peripheral Magnetic Resonance Imaging

Ultradistal radius scans at the same 9.5 mm region of interest as hr-pQCT were performed on a 1.0-T pMRI OrthOne scanner (GE Healthcare, Pittsburgh, PA, USA). A series of 20 slices in tandem, each 1.0 mm thick, was prescribed perpendicular to the long axis of the radius using a T_1 -weighted spoiled 3-dimensional (3D) gradient recalled echo sequence (SPGR) yielding an in-plane resolution of 195 μm (REF). A geometric phantom was assessed on days in which scans were obtained. Only images that preserved sufficient sharpness and trabecular textural pattern were accepted for image analyses. Trabecular apparent structural outcomes (Tb.Sp, Tb.Sp standard deviation, BV/TV, Tb.N, and Tb.Th) were obtained from the central 18 slices using a custom designed software package, MRI OsteoQ (Inglis Software Solutions, Inc.) on a per-slice basis and averaged to yield a final measure.

Volumetric Bone Outcome Computation

All volumetric bone outcomes were derived from equations previously reported for hr-pQCT (15) and for histomorphometry. The latter was based on Parfitt's model of parallel plates and derived from single slices (16)—here on forward termed “model-dependent” outcomes. The former was not based on Parfitt's model but on equations assuming analysis of a volume.

Image Co-registration

Common volumes of interest in hr-pQCT images were automatically matched between baseline and follow-up acquisitions by assessing the percentage similarity in 2D periosteal cross-sectional areas (6,17). Manual co-registration for baseline and follow-up acquisitions of pMR images was achieved using an open source software package, 3D Slicer (v4.2.1, Boston, MA, USA) (18) by applying orthogonal translations and rotations within the axial image planes as previously described (REF). Commonly matched slices across all participant images were used in a second computation of volumetric bone outcomes for co-registered pMR images. Co-registration was not performed on baseline and follow-up pQCT images.

Data Analyses

Both root mean square coefficients of variation (RMSCV) and standard deviation (RMSSD) were computed as previously described by Gluer et al (19). The SEE was computed using a linear regression analysis between baseline (independent variable) and 1-yr follow-up (dependent variable) values for each volumetric bone outcome. The predicted dependent variable ($\hat{y}$) was determined by applying the derived linear equation to independent variable values. Equation 1 was then used to quantify SEE. The SEE represented the minimally detectable change independent of the biological correlation between baseline and 1-yr follow-up.

$$SEE = \sqrt{\frac{\sum_i^n (y_i - \hat{y}_i)^2}{n-2}} \quad (1)$$

Where $n - 2$ represents the estimated degrees of freedom.

The International Society for Clinical Densitometry has accepted the LSC as a measure of how large a difference is required for qualifying an outcome as clinically significant. For long-term test-retest measurement, the longitudinal LSC was calculated using Eq. 2.

$$LSC = Z(\text{Pr}) \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \text{ (in units of Pr)} \quad (2)$$

Where Z is the corresponding Z-score based on the confidence level desired (95% confidence interval = 1.96), Pr is the precision value in either relative (RMSCV) or absolute (RMSSD) terms, n_1 and n_2 are the number of baseline and follow-up measurements expected clinically, respectively (n_1 and $n_2 = 1$ for all volumetric bone measures obtained here) (20).

All statistical analyses were performed on SAS v9.3 (SAS Institute, Inc, Cary, NC). For simplicity, because results at the more proximal slice for pQCT were similar to the more distal slice, only data derived from the more distal pQCT slice were reported in tables and figures here.

Results

Of the 59 women (mean age: 74 ± 11 yr; BMI: 26.72 ± 6.12 kg/m²) who completed at least 1 set of baseline and follow-up procedures (Table 1), 30 completed the 1-yr longitudinal study for all 3 imaging techniques. Baseline and follow-up data were available for 48 individuals for pMRI, 40 for hr-pQCT, and 36 for pQCT. Anthropometrics for all study participants were similar across those individuals completing follow-up procedures for each modality. In total, 35 (59.3%) participants have sustained a fragility fracture within the last 15 yrs. In addition, 21 (35.6%) participants were on antiresorptive therapy. None of the

participants were on long-term glucocorticoid therapy, had undergone any organ transplantation, had primary or secondary hyper- or hypoparathyroidism, or had recently been immobilized owing to injury. The mean follow-up times for pMRI, pQCT, and hr-pQCT were: 1.20 ± 0.14 , 1.12 ± 0.12 , and 1.20 ± 0.15 yr, respectively.

One-yr Follow-Up Long-Term Precision

One-yr precision error was smallest for BV/TV, Tb.N, and Tb.Sp overall. For pQCT, the distal slice of the radius showed smaller 1-yr precision error in vBMD and Tb.Sp, but larger error in the overall amount of bone than the proximal slice. The same pattern was observed at the ultradistal tibia for all bone measures. One-yr precision error at the tibia was generally smaller than at the radius for pQCT (Table 2). However, for hr-pQCT, the opposite was true for several outcomes (Tb.Sp, Tb.Th, and Tb.N; Table 3). For both pQCT and hr-pQCT, integral vBMD showed smaller 1-yr precision error than both cortical and trabecular vBMD—these differential effects being more pronounced at the radius than at the tibia. One-yr precision error in radial bone measures from pMRI was similar to the distal pQCT slice of the radius (Table 4). For the most part, hr-pQCT bone outcomes exhibited smaller 1-yr precision error than those obtained on either pMRI or pQCT, except for Tb.N. One-yr precision error in Tb.Sp was similar across all modalities. By excluding individuals who have had a fragility fracture in the last 15 yrs or who were on antiresorptive therapy, the long-term precision was reduced for all volumetric bone measures derived from pQCT and pMR images, but not from hr-pQCT images. After co-registering baseline and follow-up pMR images, there was only a reduced precision error for Tb.Sp, Tb.Th, and Tb.N.

Detection Limits: SEE

The SEEs for apparent trabecular structure derived from pQCT radius images were smaller than for pMR images, but were comparable between the modalities after excluding individuals with a history of fragility fractures and those currently on antiresorptive therapy (Table 5). All hr-pQCT bone measures' SEEs were 2-fold smaller than both pQCT and pMRI, except for Tb.N. However, excluding those with fractures or on antiresorptives resulted in more comparable trabecular vBMD SEE values between hr-pQCT and pQCT at the radius. At the tibia, similar differences in SEE magnitudes can be described between hr-pQCT vs pQCT images. However, Tb.Sp measured on pQCT images of the tibia showed higher than 3-fold smaller SEEs compared with hr-pQCT (Table 6). In contrast to the radius, exclusion of women with fractures or who were on antiresorptive therapy did not make a considerable difference in the SEE values obtained at the tibia for either pQCT or hr-pQCT.

Clinical Sensitivity: LSC

The same intermodality differences were notable for LSC values as for RMSSD and SEE values. The pattern of differential vBMD changes over 1 yr for integral, cortical, and trabecular computations were consistent across LSC, RMSSD, and SEE values. Like SEEs, the LSC for model-independent Tb.Sp was comparable across modalities. In general, LSC values (Tables 2–4) were at least twice the magnitude of SEE values (Tables 5 and 6).

Discussion

Summary of Results

In the local cohort of women with mean age 75 ± 9 yr and BMI 26.84 ± 4.77 kg/m², pMRI 1-yr changes and long-term precision errors were larger for the radius than for the tibia, and smallest for hr-pQCT followed by pMRI and then pQCT for most variables, except for Tb.N which showed the opposite trend. One-yr precision in Tb.Sp was similar across the 3 modalities. Exclusion of individuals who were on antiresorptive therapy or who have had a fragility fracture in the last 15 yrs resulted in further decrease in 1-yr change for pQCT and pMRI, but not for hr-pQCT images. The LSC values were almost double the magnitude of SEE values but paralleled the same pattern of differences across modalities and across anatomical regions of interest. The degree of 1-yr change for integral, cortical, and trabecular vBMD were different, but generally showed a lower precision error for trabecular and integral vBMD compared with cortical vBMD.

One-yr Precision Error in Volumetric Bone Outcomes

Longitudinal computations were made within 3 mo of 1 yr from baseline measurements for all 3 modalities. The minor discrepancy in timing across modalities (1–3 mo) was not expected to translate significantly to any additional biological changes in bone measures. As a point of reference, 1-yr change in bone density for women in the CaMos study investigating antiresorptive therapy was less than 1.5% (21). It was logical that the larger 1-yr changes observed were mostly attributable to poorer retesting error as demonstrated in Part I of this series (REF). Long-term precision error in the more proximal slice of the ultradistal radius obtained from pQCT being larger than the more distal slice could be explained by the more heterogeneous trabecular structures at the proximal location. Small angulations in slice orientation may lead to larger differences in trabecular geometries at this region. The fact that 1-yr precision error in Tb.N measured from pQCT and pMR images was smaller than that derived from hr-pQCT images could be explained by the fact that Tb.N computed using the OsteoQ software for pQCT and pMRI relied on the calculation of bone perimeter (22), whereas hr-pQCT computed Tb.N as the inverse of Euclidean distances between trabecular ridges (15). With a lower image resolution, small differences in bone perimeters may not be immediately apparent, thus translating to similar Tb.N values both within and between the individuals. Although other variables also rely on bone perimeter or area, its variance component is buffered by other measures that reduce the overall effect of bone perimeter alone by arithmetic division. The fact that distal radius long-term precision errors were more pronounced than that of tibial bone could be explained by greater motion and the lack of weight bearing on the radius site. Without constant load applied to the radius, bone loss may not be as aggressively counteracted by load-induced bone formation (23).

The reduction in 1-yr precision error in most bone outcomes after exclusion of individuals with a history of fragility fractures may be justified by differences in bone turnover. High bone turnover is one of the etiologies of osteoporotic fractures (24). Thus, by excluding individuals with a previous fragility fracture, people with lower bone turnover will remain, explaining the smaller 1-yr biological change over time. In addition, exclusion of those who are currently on antiresorptive therapy could also modify the cohort's mean bone turnover

status—although the overall effect depends on the degree to which antiresorptives lowered the participants' bone turnover. While low bone turnover increases the time for mineral to accumulate, the rate of replacing old bone with new matrices is slowed, reducing bone formation (25,26). At this point, bone turnover markers were not measured in this cohort study.

In a study of women (age: 56 ± 4 yr) on alendronate therapy, Folkesson et al (11) showed that 3-T MRI-derived Tb.Th decreased by 0.49% in the treatment group vs a nonsignificant 0.24% decrease in the control group at the radius after 1 yr. These change values were well within the 7.1% 1-yr RMSCV for Tb.Th in individuals not on antiresorptive therapy shown here. In a randomized controlled trial of L-arginine vs placebo using pQCT, Baecker et al (27) showed that women (mean age: 54.5 ± 4.1 yr) in the placebo group decreased in trabecular (radius: 2.0%; tibia: 0.1%) and cortical vBMD (radius: 0.8%; tibia: 0.7%). The corresponding 1-yr precision errors in pQCT trabecular (radius: 2.7%; tibia: 1.2%) and cortical (radius: 12.7%; tibia: 3.1%) vBMD in the present study were also larger than those reported in this clinical trial. Although their regions of interest were slightly more distal, it is possible that there was inadequate power to observe treatment-induced changes over just 1 yr. In another RCT of 33 individuals on alendronate vs placebo, Burghardt et al (6) similarly showed that trabecular vBMD was the only bone outcome that demonstrated significant decrease by more than 2.25% at the radius and 1.75% at the tibia within 1 yr using hr-pQCT. In contrast to the L-arginine trial described above, the percentage decrease at the tibia was larger than the corresponding 1-yr RMSCV values (trabecular vBMD for tibia: 1.2%) reported in the present study, suggesting that the change may be biologically relevant.

Detection Limit and Long-Term Precision: SEE

The SEE values being smaller than LSC values suggest that biological changes over time would exceed SEE sooner than LSC, should the former be used as any reference of change. The SEE was previously described as a more appropriate measure for long-term precision compared with the standard deviation because it accounts for the expected correlation between time points and putative biological changes over time, thus reflecting only the intrinsic long-term precision of the measurement technique (2). However, the use of SEE in this study hinges on the assumption that changes in bone were linear. For the short-term, this approximation could remain valid (28), although even the precision of the bone imaging technique itself, independently of biological variation, can be precipitated by a greater amount of soft tissue and bone heterogeneity at the region of interest (29). There has so far been a lack of studies reporting 1-yr detection limits in volumetric bone outcomes using SEE. Few have only examined SEE in the context of dual-energy X-ray absorptiometry measurements over time (1,30).

Clinically Meaningful Detection Limit: LSC

It was logical that LSC values, just like SEE, were comparable for many bone outcomes between pQCT and pMRI because both used very similar in-plane resolutions. However, unlike SEE, LSC for Tb.Th measures were discrepant between the modalities, which could be explained by the biological change component factored in the LSC measurement. The amount of change required to be considered clinically significant for the LSC statistic can be

altered by reducing the uncertainty in the measurement through acquiring multiple baseline and follow-up scans (28). The prescription of multiple scans means greater exposure to radiation, particularly for dual-energy X-ray absorptiometry, yielding 10 μSv per scan including total hip and lumbar spine. For any of the modalities examined: pQCT (1 $\mu\text{Sv}/\text{site}$), hr-pQCT (3 μSv per site), or pMRI (none), effective dose would not be a major concern. However, for pMRI, time would be a major challenge as the entire procedure can take up to 15 min with repositioning, factoring in the potential for more motion during scans. To circumvent this limitation, a smaller number of slices could be obtained.

Same-day or 1-wk LSC values were previously reported for hr-pQCT by Cheung et al (31) and Burghardt et al (32), respectively, the values of which were twice as large in Burghardt's cohort of older women as in the younger adults in Cheung's study, but the bone LSC values were around the same order of magnitude. Repeat scans performed within 2 mo of one another were used to quantify LSC in one study by Rinaldi et al (33), yielding values for pQCT-derived cortical vBMD that were 3 times as large as same-day hr-pQCT LSC reported by Cheung et al (31), almost twice as large as 1-wk hr-pQCT LSC reported by Burghardt et al (32), and a tenth the size of 1-year pQCT LSC reported in the present study at the radius. This same pattern of increased LSC with increasing time to repeated scans was also displayed with Ct.Th and integral vBMD across these studies. Apparent microstructural outcomes were not reported in this study of 2-mo LSC for pQCT. No previous study has reported 1-yr LSC values for any of the hr-pQCT, MRI, or pQCT modalities.

Limitations

Because of the amount of travel (70 km) required for completing hr-pQCT procedures, only participants sufficiently capable of traveling longer distances agreed to participate. Syddall et al (34) showed that women with no car access had a higher risk for fractures and lower bone strength as measured by pQCT in the Hertfordshire Cohort Study. Hence, it is plausible that women with bones that are more likely to change over time may be missed. This study has not investigated 1-yr changes in men. Sode et al (35) showed significant differences in bone structure between the sexes at the inner anterior aspect of the ultradistal radius and tibia, as quantified by hr-pQCT. Using pQCT, MacIntyre et al (36) also showed that loss of trabecular bone connectivity and increases in mean hole area was significantly more rapid in women than in men. Although MR images were analyzed by the OsteoQ image foresting algorithm to generate bone structural measurements, MR technology is currently not equipped to generate direct measurements of vBMD. The fact that the cohort size decreased from 36 to 14 participants, by excluding those on antiresorptive therapy and those who have had a fragility fracture, could account for the higher sensitivity of the LSC measure to outlying change values.

Recommendations

Although 1-T pMRI may be appropriate for quantifying bone structure in cross-sectional studies, caution must be exercised when deciding on the duration of follow-up for longitudinal studies owing to the larger LSC compared with pQCT and hr-pQCT. In addition, the lack of densitometric information obtained by pMRI remains a major disadvantage. The pMRI was investigated in the present study, bearing a smaller gantry thus

enabling superior radiofrequency focusing and correspondingly higher SNR than a full body system. However, it is anticipated that similar conclusions can be extended to full body MRI scanners. By virtue of the higher isotropic resolution of 82 μm , combined with the large number of image slices acquired, hr-pQCT was powered to yield bone outcomes that demonstrated small detection limits. In addition, the ability to reproducibly match the same region of interest over follow-up periods is less problematic compared with single-slice pQCT. For studies requiring shorter follow-up periods and those desiring the ability to detect smaller amounts of change, hr-pQCT would be an ideal candidate for quantifying bone outcomes. The pQCT was able to demonstrate equally as precise Tb.Sp measurements as hr-pQCT over 1 yr. With an in-plane resolution of 200 μm , the apparent microstructural measurements yielded RMSCV, LSC, and SEE values larger than hr-pQCT but still smaller than pMRI. In addition, the advantage over pMRI of enabling densitometric measurement makes pQCT a feasible alternative to hr-pQCT.

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Table 1

Participant Characteristics at Baseline for All Procedures Completed

Variable	Fx or current antiresorptive user		No Fx and no antiresorptive therapy		p Value for comparison
	Mean ^a /median ^b	SD ^a /Q1–Q3 ^b	Mean ^a /median ^b	SD ^a /Q1–Q3 ^b	
Age (yr) ^a	76	9	71	6	0.053
BMI (kg/m ²) ^a	27.02	5.43	26.41	2.82	0.655
Weight (kg) ^a	69.0	12.7	68.8	8.5	0.963
Height (m) ^a	1.60	0.07	1.61	0.07	0.531
Calcium (yr) ^b	5.0	0.0–14.0	10.0	0.0–12.0	0.290
Vitamin D ₃ (yr) ^b	5.0	1.0–12.0	5.0	0.1–12.0	0.411

Note: Anthropometrics and medication use descriptive statistics for study participants completing at least baseline and Fx scans for any of the imaging modalities are displayed here.

Abbr: BMI, body mass index; Fx, fragility fracture; SD, standard deviation.

^aParametric variable described using mean and SDs.

^bNonparametric variable characterized by median and first (Q1) and third (Q3) quartiles.

Table 2

The pQCT Distal Radius and Tibia 1-yr Follow-Up Statistics for Participants With and Without Fractures or on Antiresorptive Therapy

Bone variable	All study participants				No Fx and no antiresorptive therapy			
	N	RMSCV	RMSSD	LSC	N	RMSCV	RMSSD	LSC
Distal radius								
BV/TV (fraction)	35	0.075	0.030	0.090	13	0.046	0.020	0.050
Tb.Sp (mm)	35	0.064	0.040	0.100	13	0.046	0.020	0.060
Tb.Sp MI (mm)	35	0.063	0.040	0.100	13	0.045	0.020	0.060
Tb.Th (mm)	35	0.092	0.040	0.110	13	0.050	0.020	0.050
Tb.Th MI (mm)	35	0.092	0.040	0.110	13	0.050	0.020	0.050
Tb.N (#/mm)	35	0.041	0.0	0.1	13	0.025	0.0	0.1
Ct.Th (mm)	35	0.103	0.090	0.260	13	0.108	0.110	0.290
vBMD _i (mg/cm ³)	36	0.112	46.62	129.21	14	0.077	30.03	83.24
vBMD _c (mg/cm ³)	36	0.165	89.21	247.29	14	0.127	61.79	171.27
vBMD _{tr} (mg/cm ³)	36	0.057	18.91	52.42	14	0.027	8.68	24.06
Distal tibia								
BV/TV (fraction)	36	0.020	0.010	0.020	14	0.019	0.010	0.020
Tb.Sp (mm)	36	0.026	0.010	0.030	14	0.023	0.010	0.030
Tb.Sp MI (mm)	36	0.026	0.010	0.030	14	0.023	0.010	0.030
Tb.Th (mm)	36	0.020	0.010	0.020	14	0.021	0.010	0.020
Tb.Th MI (mm)	36	0.020	0.010	0.020	14	0.021	0.010	0.020
Tb.N (#/mm)	36	0.015	0.0	0.1	14	0.013	0.0	0.0
Ct.Th (mm)	36	0.047	0.050	0.150	14	0.052	0.060	0.170
vBMD _i (mg/cm ³)	38	0.0476	21.94	60.80	15	0.019	9.07	25.14
vBMD _c (mg/cm ³)	38	0.072	47.40	131.40	15	0.031	22.50	62.36
vBMD _{tr} (mg/cm ³)	38	0.0368	13.60	37.69	15	0.012	4.70	13.04

Note: The pQCT scans at baseline and 1 yr were analyzed with or without excluding participants who have had a fragility fracture or were on antiresorptive therapy. The RMSCV, RMSSD, and LSC values were reported.

Abbr: BV/TV, bone volume/total volume; Ct.Th, cortical thickness; Fx, fragility fracture; LSC, least significant change; MI, model-independent; pQCT, peripheral quantitative computed tomography; RMSCV, root mean square coefficients of variation; RMSSD, root mean square standard deviation; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; vBMD_i, c, tr, volumetric bone mineral density integral, cortical, and trabecular, respectively.

Table 3

The hr-pQCT Radius and Tibia 1-yr Follow-Up Statistics for Participants With and Without Fractures/on Antiresorptive Therapy

Bone variable	All study participants				No Fx and no antiresorptive therapy			
	N	RMSCV	RMSSD	LSC	N	RMSCV	RMSSD	LSC
Distal radius								
BV/TV (fraction)	40	0.026	0.002	0.007	13	0.017	0.002	0.006
Tb.Sp MI (mm)	40	0.062	0.038	0.106	13	0.068	0.032	0.088
Tb.Th MI (mm)	40	0.047	0.003	0.008	13	0.055	0.003	0.009
Tb.N (#/mm)	40	0.060	0.1	0.3	13	0.067	0.1	0.4
Cl.Th (mm)	40	0.056	0.037	0.102	13	0.055	0.038	0.104
vBMD _i (mg/cm ³)	40	0.024	6.73	18.64	13	0.025	7.34	20.36
vBMD _c (mg/cm ³)	40	0.019	15.23	42.21	13	0.017	13.37	37.06
vBMD _{tr} (mg/cm ³)	40	0.025	2.78	7.70	13	0.018	2.64	7.32
Distal tibia								
BV/TV (fraction)	40	0.020	0.002	0.005	13	0.010	0.001	0.003
Tb.Sp MI (mm)	40	0.077	0.040	0.112	13	0.081	0.041	0.113
Tb.Th MI (mm)	40	0.075	0.006	0.015	13	0.081	0.006	0.015
Tb.N (#/mm)	40	0.077	0.1	0.4	13	0.081	0.2	0.4
Cl.Th (mm)	40	0.032	0.024	0.068	13	0.025	0.024	0.067
vBMD _i (mg/cm ³)	40	0.013	2.75	7.63	13	0.007	1.96	5.44
vBMD _c (mg/cm ³)	40	0.011	8.54	23.68	13	0.007	5.87	16.27
vBMD _{tr} (mg/cm ³)	40	0.019	2.23	6.18	13	0.009	1.31	3.64

Note: The hr-pQCT scans at baseline and 1 yr were analyzed with or without excluding participants who have had a Fx or were on anti-resorptive therapy. The RMSCV, RMSSD, and LSC were reported.

Abb: BV/TV, bone volume/total volume; Cl.Th, cortical thickness; Fx, fragility fracture; hr-pQCT, high-resolution peripheral quantitative computed tomography; LSC, least significant change; MI, model-independent; RMSCV, root mean square coefficients of variation; RMSSD, root mean square standard deviation; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; vBMD_i, c, tr, volumetric bone mineral density integral, cortical, and trabecular, respectively.

The pMRI 1-yr Follow-Up Statistics for Full Image Set in Participants With and Without Fractures/on Antiresorptive Therapy, and With or Without Co-Registration

Table 4

Bone variable	All study participants				No Fx and no antiresorptive therapy			
	N	RMSCV	RMSSD	LSC	N	RMSCV	RMSSD	LSC
Un-co-registered baseline follow-up precision errors								
BV/TV (fraction)	48	0.051	0.023	0.063	17	0.037	0.018	0.049
Tb.Sp (mm)	48	0.172	0.088	0.245	17	0.067	0.042	0.116
Tb.Sp MI (mm)	48	0.169	0.081	0.224	17	0.062	0.038	0.104
Tb.Th (mm)	48	0.185	0.079	0.218	17	0.087	0.051	0.141
Tb.Th MI (mm)	48	0.185	0.078	0.215	17	0.087	0.050	0.138
Tb.N (#/mm)	48	0.170	0.5	1.4	17	0.066	0.1	0.2
Co-registered baseline follow-up precision errors								
BV/TV (fraction)	48	0.048	0.022	0.060	17	0.038	0.018	0.050
Tb.Sp (mm)	48	0.068	0.047	0.130	17	0.059	0.037	0.102
Tb.Sp MI (mm)	48	0.065	0.044	0.122	17	0.058	0.035	0.097
Tb.Th (mm)	48	0.090	0.050	0.140	17	0.071	0.039	0.109
Tb.Th MI (mm)	48	0.090	0.050	0.139	17	0.071	0.039	0.108
Tb.N (#/mm)	48	0.065	0.1	0.2	17	0.055	0.1	0.1

Note: Distal radius scans obtained at baseline and 1 yr later were analyzed with or without excluding participants who have had a Fx or were on antiresorptive therapy. The RMSCV, RMSSD, and LSC were reported.

Abbr: BV/TV, bone volume/total volume; Fx, fragility fracture; LSC, least significant change; MI, model-independent; pMRI, peripheral magnetic resonance imaging; RMSCV, root mean square coefficients of variation; RMSSD, root mean square standard deviation; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness.

Table 5
Comparison of Radius Bone Variables' Standard Errors of the Estimate (SEEs) for All Modalities

Bone variable	pMRI SEE (N = 46)	pMRI SEE (N = 15)	pQCT SEE (N = 34)	pQCT SEE (N = 12)	hr-pQCT SEE (N = 38)	hr-pQCT SEE (N = 11)
BV/TV (fraction)	0.026	0.018	0.028	0.023	0.003	0.003
Tb.Sp (mm)	0.060	0.040	0.166	0.038		
Tb.Sp MI (mm)	0.054	0.038	0.166	0.038	0.050	0.039
Tb.Th (mm)	0.050	0.046	0.038	0.026		
Tb.Th MI (mm)	0.050	0.046	0.038	0.026	0.004	0.004
Tb.N (#/mm)	0.1	0.1	0.1	0.1	0.1	0.2
Ct.Th (mm)			0.142	0.095	0.032	0.028
vBMD _i (mg/cm ³)			66.16	35.25	5.27	5.53
vBMD _c (mg/cm ³)			89.66	59.75	17.00	12.17
vBMD _{tr} (mg/cm ³)			22.81	14.99	4.01	4.00

Note: The SEEs were determined from linear regression models for baseline and follow-up radius volumetric bone variables with [pMRI SEE (N = 46), pQCT SEE (N = 34), hr-pQCT SEE (N = 38)] and without [pMRI SEE (N = 15), pQCT SEE (N = 12), hr-pQCT SEE (N = 11)] including individuals who have had a fragility fracture in the last 15 yrs or who were on antiresorptive therapy.

Abb: BV/TV, bone volume/total volume; Ct.Th, cortical thickness; hr-pQCT, high-resolution peripheral quantitative computed tomography; MI, model-independent; pMRI, peripheral magnetic resonance imaging; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; vBMD_i, c, tr, volumetric bone mineral density integral, cortical, and trabecular, respectively.

Table 6

Comparison of Tibia Bone Variables' Standard Errors of the Estimate (SEEs) for All Modalities

Bone variable	pQCT SEE (N = 34)	pQCT SEE (N = 12)	hr-pQCT SEE (N = 38)	hr-pQCT SEE (N = 11)
BV/TV (fraction)	0.011	0.011	0.003	0.002
Tb.Sp (mm)	0.015	0.013		
Tb.Sp MI (mm)	0.015	0.013	0.057	0.047
Tb.Th (mm)	0.011	0.012		
Tb.Th MI (mm)	0.011	0.012	0.007	0.007
Tb.N (#/mm)	0.02	0.02	0.19	0.19
Ct.Th (mm)	0.070	0.090	0.03	0.03
vBMD _i (mg/cm ³)	26.89	11.37	3.67	2.63
vBMD _c (mg/cm ³)	57.36	30.57	11.75	8.58
vBMD _{tr} (mg/cm ³)	18.04	7.08	2.97	1.56

Note: The SEEs were determined from linear regression models for baseline and follow-up tibia volumetric bone variables with [pQCT SEE (N = 34), hr-pQCT SEE (N = 38)] and without [pQCT SEE (N = 12), hr-pQCT SEE (N = 11)] including individuals who have had a fragility fracture in the last 15 yrs or who were on antiresorptive therapy.

Abbr: BV/TV, bone volume/total volume; Ct.Th, cortical thickness; hr-pQCT, high-resolution peripheral quantitative computed tomography; MI, model-independent; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; vBMD_{i, c, tr}, volumetric bone mineral density integral, cortical, and trabecular, respectively.