

Original Article

Site-Specific Variation of Bone Micro-Architecture in the Distal Radius and Tibia

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Abstract

High-resolution peripheral quantitative computed tomography measures 3-dimensional bone micro-architecture at the distal radius and tibia, and provides new insight issues of bone quality in patients. The typical measurement region of interest (ROI) with an axial dimension of 9.02 mm is positioned at a fixed distance from landmarks at the distal end of the radius or tibia, but little is known about the variation of bone architecture in the vicinity of this region and related sensitivity to measurement location. Variation in ROI position can lead to differences in quantitative outcomes, and this is compounded when reference landmarks are difficult for an operator to discern. Therefore, the purpose of this study was to quantify the site-specific variation in bone micro-architecture at the human distal radius and tibia, and the impact of variation of the ROI position. Using cadavers, a 27.06-mm axial ROI including the typical clinical measurement site was scanned, and the variation of morphological (apparent density, trabecular density, trabecular number, and cortical thickness) and biomechanical (polar moment of inertia, cross-sectional area) indices were assessed along the 27.06 mm length. It was found that the radius has more site-specific variation than the tibia. Furthermore, the shifting of the 9.02 mm clinical ROI position by ± 0.5 mm resulted in approximately a 2% and 6% error in the tibia and radius density, respectively. For longitudinal assessment of bone architecture, site-specific variation is not as critical because comparisons are made within an individual; however, site-specific variation is an important consideration for cross-section studies and assessment of individuals against a normative population database.

Key Words: Architecture; bone; HR-pQCT; radius; tibia; variation.

Introduction

A new high-resolution peripheral quantitative computed tomography (HR-pQCT) has been recently introduced that allows measurement of density and structure at the forearm and tibia with better spatial resolutions (82- μ m voxel size) than previous peripheral quantitative computed tomography systems. On the basis of a standardized distance from anatomical landmarks on the distal radius or distal tibia, a 110 slice

region (9.02 mm) is scanned and evaluated. Morphological quantification is typically done using “semiderived” morphological methods (1–3), although there is evidence that some “direct” methods (4) based on these high-resolution data may also be feasible (5,6). For both approaches, the measurements are based on a relatively small 9.02 mm section of the radius and tibia, yet little is known about how much variation in morphology exists in and adjacent to the measurement region. Using anatomical landmarks at the distal radius and distal tibia, fixed offset distances to the measurement site (9.5 and 22.5 mm, respectively) are applied to provide consistency of measurement site. However, the interpretation of the precise landmark at the distal ends of the bone may vary for each HR-pQCT operator and laboratory (Fig. 1; scout views) and may introduce variability. Although this variation is not critical for *longitudinal* measurements where intrasubject

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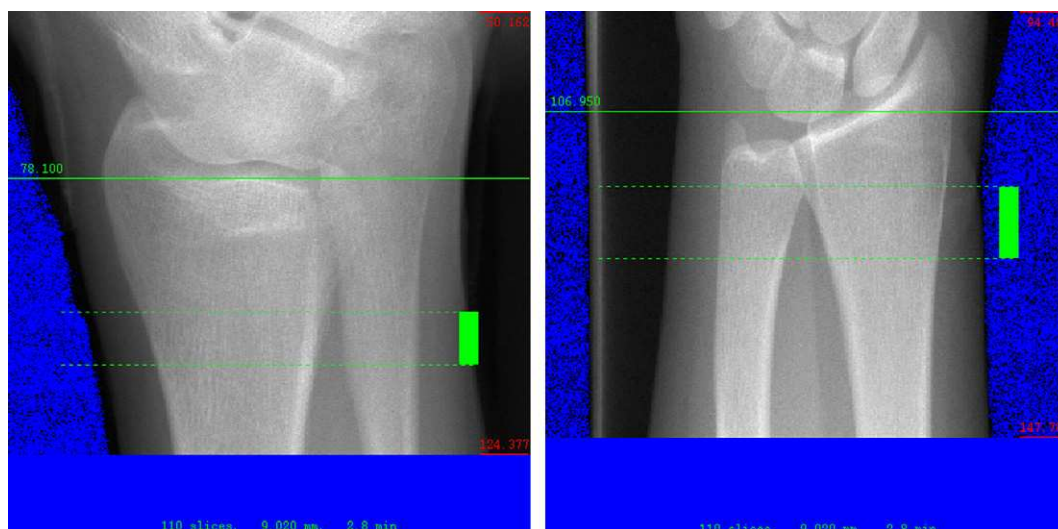


Fig. 1. Typical patient scans of the tibia (left) and radius (right) identifying the scanning region (between the pair of dotted lines). The reference landmark used for the tibia is the plateau of the distal articulating surface (solid line; 22.5 mm offset to scan region). The landmark for the radius is a subtle inflection point on the distal radius (solid line; 9.5 mm offset to scan region).

comparisons are made (assuming the same anatomical landmark can be identified at follow-up scans), the issue of measurement site standardization is particularly important for *cross-sectional* studies of patient populations (e.g., developing baseline normative databases) and for comparison of measurements between HR-pQCT laboratories (7,8). It has previously been shown that the proportion of trabecular bone to cortical bone drops precipitously at about 2–3 cm from the distal radius (9), which corresponds, importantly, to where HR-pQCT measurements are typically performed.

The purpose of this study was to measure the morphological variation in the distal radius and distal tibia. The HR-pQCT system is specifically designed for measurement at these sites, so it is important to understand the degree of variation and hence errors that may be incurred due to positioning of the 9.02-mm scan site.

Methods

Specimens included human radius ($N = 10$) and human tibia ($N = 8$) obtained from the Gross Anatomy Laboratory at the University of Calgary. Fat and soft tissues were absent. The bones varied in size, and the ages and gender and any previous medical history were unavailable. Although it would be ideal to have this information, it has been previously reported that the ratios of cancellous and cortical bone along the length are relatively consistent along genders and age (9). Measurements of the bone lengths and circumference were reported. All procedures were approved by the Office of Medical Bioethics at the University of Calgary.

The specimens were scanned by HR-pQCT (XtremeCT; Scanco Medical, Brüttisellen, Switzerland) in air using a standard scanning protocol (60 kVp, 1 mA, 100 ms integration time). On the basis of selecting a landmark consistent with

our *in vivo* clinical scanning protocol (Fig. 1; scout views), measurements were performed at the standard clinical measurement site (9.02 mm; 110 slices), plus the 9.02-mm adjacent regions located proximally and distally giving a total scanning region of 27.06 mm (330 slices). Because these specimens were dry and scanned in air, a beam hardening correction of 1200 mg HA/cm³ was applied (instead of the standard 200 mg HA/cm³). The 3-dimensional (3D) reconstructed data were preprocessed by setting the minimum attenuation value to the equivalent water (0 mg HA/cm³), subsequently all further analysis was performed as per normal *in vivo* measurements including segmentation of cortical and trabecular regions as described elsewhere (5).

The standard quantitative morphological data for *in vivo* HR-pQCT scans include averaged indices over the 9.02 mm region. The indices reported typically include bone mineral density for the whole bone (D_{100}), and for the separated trabecular region (D_{trab}) and cortical region (D_{cort}). Also, reported are structural data including bone volume ratio (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and cortical thickness (Ct.Th). All of these indices are calculated on a slice-by-slice basis (Image Processing Language, v5.00c, Scanco Medical), and then averaged over the 9.02 mm region (110 slices) to provide a final report. Therefore, to investigate how these indices vary along the axis of the bones, the original slice-by-slice data were extracted and analyzed. Evaluation of the indices was performed over the 27.06-mm region of interest (ROI) corresponding to 330 slices, and focused on primary indices (D_{100} , D_{trab} , Tb.N, and Ct.Th) because these measures are the basis for determining the other reported indices (e.g., BV/TV, Tb.Th, Tb.Sp). The mean and standard deviation was determined for the radius and tibia bones for each of the primary indices on a slice-by-slice basis. Additionally,

Table 1

Physical Characteristics of the Radius and Tibia Bones

	Radius (N = 10)		Tibia (N = 8)	
	Length (mm)	Diameter (mm)	Length (mm)	Diameter (mm)
Mean	230.3	82.7	365.1	98.1
Standard deviation	23.1	13.4	35.7	15.2
Minimum	205.0	60.1	308.0	68.2
Maximum	268.0	96.5	392.0	111.8

The bone length and diameter (at the first slice of the clinical measurement site) are reported as the mean, standard deviation, and range.

the rate of change of these indices was calculated by taking the derivative of the mean data after smoothing was performed to reduce noise. In addition to morphological data, biomechanical indices (which are not part of the standard patient analysis) were evaluated. These included a measure of the polar moment of inertia, cross-sectional area, and proportion of cancellous and cortical area.

In addition to the slice-by-slice analysis, the sensitivity to varying the location of the standard clinical measurement was determined. The variation in position was intended to represent possible differences (error) of landmark selection by different operators or research laboratory, and also the effect of using a relative measurement position (scaled to bone length) instead of a fixed distance from landmarks (e.g., 9.5 and 22.5 mm for radius and tibia, respectively). These results were reported as percent changes of the mean primary indices relative to the baseline clinical measurement position.

Results

The physical bone dimensions are reported (Table 1) to provide an estimate of the variation of bone size within each sample group. A representative 3D scan of the distal tibia and distal radius is shown that illustrates the 27.06 mm ROI scanned and used for subsequent analysis, with red lines demarking the clinical scan region (Fig. 2). On a slice-by-slice basis, the group-wise averaged primary morphological parameters and their standard deviations for the radius (N = 10) and tibia (N = 8) are presented in Fig. 3, as well as the rate of change of those parameters over the entire 330-slice ROI. Similarly, the biomechanical properties are reported in Fig. 4. The rate of change was typically higher in the radius than in the tibia, and in the radius the most distal slices (e.g., slices 0–60) sometimes included the distal articular surface of the joint (example in Fig. 2).

The effect on the morphological results of shifting the scan region proximally or distally from the standard clinical measurement site is presented in Table 2. Representing the possible error due to differences in operator interpretation of landmarks, a 0.5 mm shift resulted in larger percent changes in the radius (~6%) than in the tibia (~2%). The radius was more susceptible to variations in morphological parameters due to its sensitivity to scan position than the tibia. If a relative landmark (adjusted by bone size) was used instead of the standard fixed offsets (i.e., 9.5 and 22.5 mm), the necessary shift was as much as 3.5 mm for the tibia and 1.6 mm for the radius. The size of the bone affects the relative region chosen for analysis.

Discussion

This study quantifies the variation of primary morphological and biomechanical parameters at the distal radius and

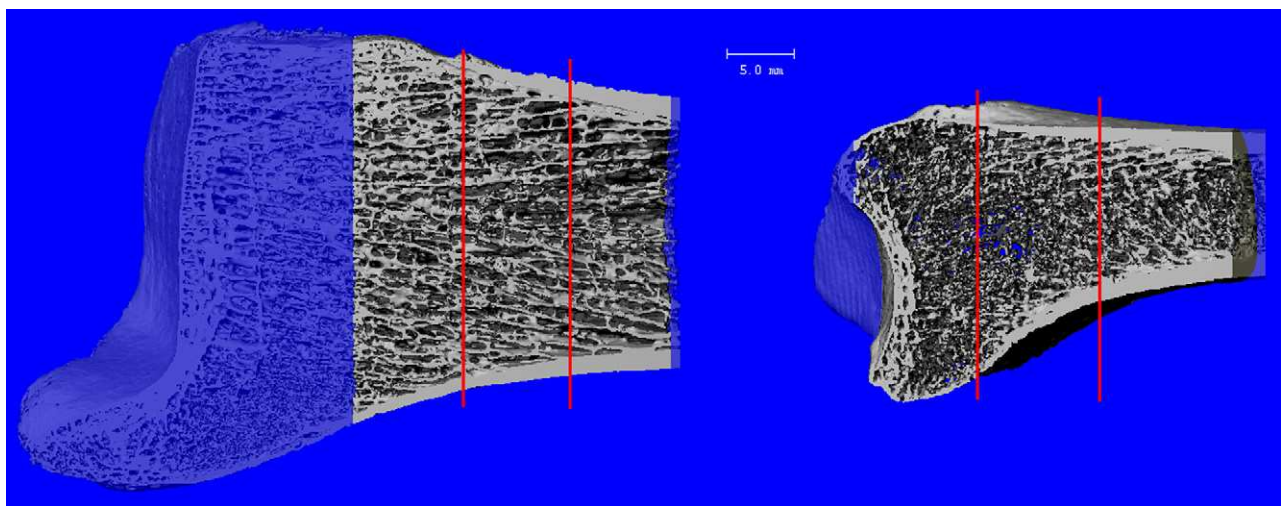


Fig. 2. Cross-section of a representative tibia (left) and radius (right). The 27.06 mm (330 slice) region on which morphological evaluation (solid) was performed is divided into thirds by the red vertical lines. The region between the lines represents the clinical measurement site, and distal and proximal regions are immediately adjacent.

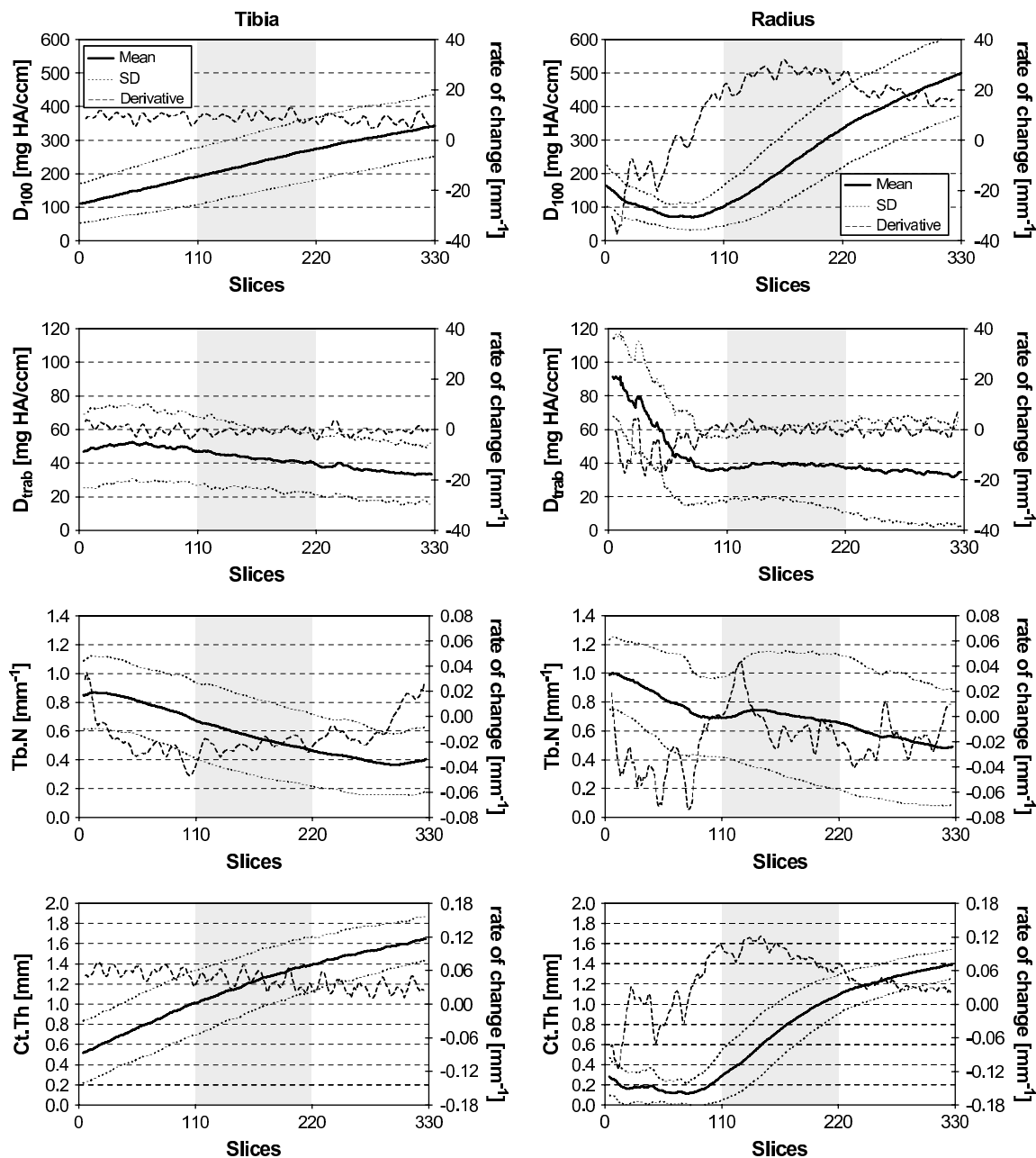


Fig. 3. Primary morphological indices for the tibia and radius including bone mineral density of the entire bone (D_{100}) and cancellous region (D_{trab}), as well as trabecular number (Tb.N) and cortical thickness (Ct.Th). Data between slice 110 and 220 represent the clinical measurement site (gray). On each plot, the left axis represents the morphological indice mean (solid) and $\pm$ standard deviation (dash). The right axis indicates the rate of change (1st derivative) of the indice measured in units per mm (e.g., Ct.Th rate of change is millimeter thickness per millimeter axial distance; mm/mm). Note that absolute density values (D_{100} , D_{trab}) are inaccurate due to the dry bones being scanned in air, but relative changes are representative.

tibia used for clinical assessment of bone architecture by HR-pQCT. The sensitivity of the 9.02 mm scan region to the measurement position is important to quantify because it can impact the interpretation of large cross-sectional studies, and particularly when assessing bone quality on an individual basis relative to population norms. Despite the high precision of HR-pQCT measurements (10), small variations in position

may skew the data and hence complicate clinical interpretation of bone quality.

There are several factors that can lead to differences in the selection of the clinical measurement position, and it appears that the issue is more critical for the radius than the tibia. The standard 9.02-mm measurement volume at the radius coincides with the transitional zone (Fig. 4) as the analysis region

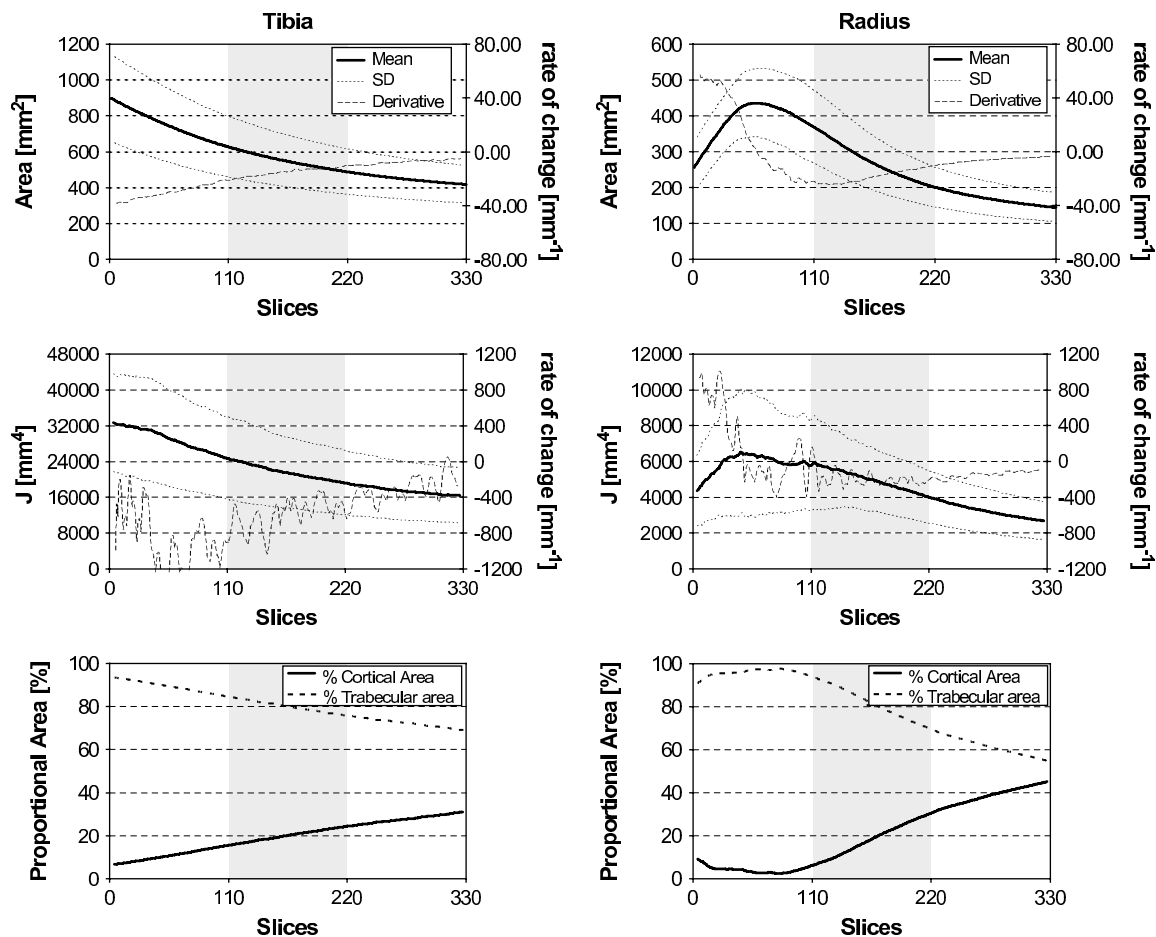


Fig. 4. Biomechanical indices for the tibia and radius including cross-sectional area and polar moment of inertia (J) (top 2 rows). Data between slice 110 and 220 represent the clinical measurement site (gray). On each plot, the left axis represents the morphological indice mean (solid) and $\pm$ standard deviation (dash). The right axis indicates the rate of change (1st derivative) of the indice measured in units per mm. The relative proportion of cortical and trabecular area was also determined along the length scanned (bottom row).

moves from the metaphyseal to the diaphyseal region of the bone. This is reflected by the increase in cortical thickness (Ct.Th) and density (D_{100}), and the magnitude of the derivatives of those values illustrated in Fig. 3. This observation is consistent with the findings in a previous study (6) where it was determined that the load-sharing capacity of the radius was primarily taken by the cancellous region at the most distal slice (metaphyseal) and cortical region in the proximal slice (diaphyseal). The variation in the radius is greater than in the tibia as confirmed both qualitatively (Fig. 2) and quantitatively (Figs. 3 and 4). Compounding the problem, the identification of the landmark in the scout view (Fig. 1) for the radius is more ambiguous than the tibia, and this is reflected in the lower reproducibility of the radius measurements (10). Therefore, the combination of increased natural morphological variation (a precipitous change in cortical bone) at the radius with increased difficulty of identifying a landmark leads to the radius being more susceptible to errors due to position than the tibia.

The morphological variation with measurement position has important clinical implications on the interpretation of HR-pQCT data for cross-sectional study designs and individual assessments on a 1-time basis, but is less critical for longitudinal measurements. Follow-up measurements are usually assessed in the context of the patient's baseline scan, thus the ability to detect changes to bone architecture with disease or treatment is high, and reproducibility has been assessed to be less than 1.0% over a 4-month period (10). The precision is high because the baseline scout view can be used to repeatedly identify the clinical measurement region at follow-up scans (e.g., Fig. 1), and 3D registration can further enhance identification of a common ROI for all measurements within an individual (11). On the other hand, cross-sectional studies (or individual clinical assessments) typically compare morphological results to a normative population database and is subject to positioning errors from landmark interpretation in scout views. On the basis of the data presented here, and the consideration of a 0.5 mm range of possible landmark

Table 2

The Percent Change of Morphological Parameters for the Tibia and Radius When the Position is Adjusted Axially From the Standard Clinical Site (Clinical Site is Defined as the Region Between the Vertical Lines Shown in Fig. 2)

Position (mm)	D ₁₀₀ (mg HA/cm ³)	D _{trab} (mg HA/cm ³)	Tb.N (1/mm ³)	Ct.Th (mm)
Tibia				
Dist: -3.5	-13.9%	7.4%	16.3%	-13.3%
-0.5	-1.9%	0.9%	2.1%	-1.7%
0.0	233.5	43.1	0.56	1.22
+0.5	1.9%	-1.1%	-2.0%	1.7%
Prox: +1.7	6.4%	-3.5%	-6.6%	5.6%
Radius				
Dist: -1.1	-12.5%	-0.6%	0.5%	-13.5%
-0.5	-5.8%	-0.2%	0.2%	-6.1%
0.0	215.4	38.7	0.71	0.72
+0.5	5.9%	0.0%	-0.3%	6.0%
Prox: +1.6	18.8%	0.0%	-1.7%	18.6%

The percent change in morphological results due to a shift in position is relative to the average results reported at the clinical position (italicized). The proximal and distal position shifts ranged from 0.5 mm (representative of possible operator error) up to 3.5 mm (representative of adjustments in position for bone length). The parameters reported are bone mineral density of the whole bone (D₁₀₀) and trabecular region (D_{trab}), and the trabecular number (Tb.N) and cortical thickness (Ct.Th).

positions, the error in tibia measurements is consistently less than 2%, and can be as high as 6% in the radius. The use of a 0.5 mm range is somewhat arbitrary; however, it highlights that in the future, it might be useful in the standard patient analysis to include an estimate of the gradient of morphological parameters within the measurement region. The gradient would provide an estimate of the impact of a positioning error—the greater the gradient within the measurement region, the larger the impact a positioning error would have.

Clearly, standardization of the measurement site is important to reduce the effects of natural morphological variation on HR-pQCT evaluations, but it cannot eliminate the problem. The landmarks for determining the clinical measurement site have been suggested by the manufacturer, and these are used in all cross-sectional studies reported so far (7,8). The development of improved standardization is warranted, but it is not a simple task. Additionally, other factors can play a role in the variation in morphological data including movement artifacts during scanning, and differences in patient size. In the small sample of bones assessed here, the variation in length and diameter was considerable (Table 1). It was explored whether the use of a fixed distance from anatomical landmarks (22.5 mm for the tibia; 9.5 mm for the radius) could be replaced by a relative offset scaled to bone length. Consideration of the most proximal and distal measurement sites (based on scaled offsets from the anatomical landmarks) revealed changes in morphology as high as 19% from baseline (Table 2). However, the difficulty with using relative offsets is the increased complexity of the patient scanning (needing to adjust the offset for each patient on an individual basis). Using fixed distances from landmarks is preferable from a practical standpoint, but perhaps such studies should consider patient size as confounding variable, particularly

for the development of normative databases. Without a size adjustment, the absolute measurement position on adolescents would be located closer to the diaphyseal region than in adults, and the impact would be an underestimation of mineralization and cortical thickness increases that occur during growth over the population. In young children, the limitations of using a fixed distance are even more acute.

A limitation of the current study is that the bones were dry at the time of measurement, and little was known about their origins (e.g., age, gender, medical history). Although the beam hardening calibration and morphological analysis was adjusted to partially account for the fact that the bones were scanned in air (rather than in vivo), the absolute values of the density measurements are underestimated. However, the important outcome of this study was the *relative* change in bone morphology with position and the associated gradients of change, not the absolute measurement values which represent a systematic error compared to in vivo measurements (10). Also, although medical history was not available, all bones were clearly from skeletally mature adults and represented a range of physical sizes. Differences in patterns of morphological and biomechanical variations between specimens was not noted which is consistent with previous reports regarding age and gender distributions (9). Finally, in this study it was decided to conduct the measurements on cadavers because of the need to measure 3 times the normal ROI (which has implications on delivered radiation dosage and the possible confounding effects of movement artifact occurring during in vivo scanning). Nevertheless, the effective radiation dose for a scan is small (3 μ Sv; confirmed by independent measurements); therefore, it may be feasible in the future to conduct these measurements in vivo on patients where age, gender, and medical history are known.

In summary, the natural variation of bone morphology and the errors in identifying landmarks for HR-pQCT are more critical at the radius than the tibia, and while the variation can impact the interpretation of interpopulation data, it is less relevant for longitudinal monitoring of patient health on an individual basis. It is important to standardize the position of the clinical measurement site as clearly as possible to ensure that HR-pQCT data can be shared and compared between centers. Although this study explored the use of a relative rather than fixed offset measurement zone, it would seem wise to maintain the simplest method of defining the scan region (i.e., fixed offset) to avoid adding unnecessary complexity to an otherwise straightforward measurement protocol. These considerations will lead to an improved clinical impact of HR-pQCT by facilitating interlaboratory comparisons of data, and exchange of normative population databases that are currently under development.

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