Quantitative imaging of peripheral trabecular bone microarchitecture using MDCT

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(Received 13 March 2017; revised 10 October 2017; accepted for publication 15 October 2017; published 23 November 2017)

Purpose: Osteoporosis associated with reduced bone mineral density (BMD) and microarchitectural changes puts patients at an elevated risk of fracture. Modern multidetector row CT (MDCT) technology, producing high spatial resolution at increasingly lower dose radiation, is emerging as a viable modality for trabecular bone (Tb) imaging. Wide variation in CT scanners raises concerns of data uniformity in multisite and longitudinal studies. A comprehensive cadaveric study was performed to evaluate MDCT-derived Tb microarchitectural measures. A human pilot study was performed comparing continuity of Tb measures estimated from two MDCT scanners with significantly different image resolution features.

Method: Micro-CT imaging of cadaveric ankle specimens ($n = 25$) was used to examine the validity of MDCT-derived Tb microarchitectural measures. Repeat scan reproducibility of MDCT-based Tb measures and their ability to predict mechanical properties were examined. To assess multiscanner data continuity of Tb measures, the distal tibias of 20 volunteers (age: 26.2 ± 4.5 Y, 10 F) were scanned using the Siemens SOMATOM Definition Flash and the higher resolution Siemens SOMATOM Force scanners with an average 45-day time gap between scans. The correlation of Tb measures derived from the two scanners over 30% and 60% peel regions at the 4% to 8% of distal tibia was analyzed.

Results: MDCT-based Tb measures characterizing bone network area density, plate-rod microarchitecture, and transverse trabeculae showed good correlations ($r \in [0.85, 0.92]$) with the gold standard micro-CT-derived values of matching Tb measures. However, other MDCT-derived Tb measures characterizing trabecular thickness and separation, erosion index, and structure model index produced weak correlation ($r < 0.8$) with their micro-CT-derived values. Most MDCT Tb measures were found repeatable ($\text{ICC} \in [0.94, 0.98]$). The Tb plate-width measure showed a strong correlation ($r = 0.89$) with experimental yield stress, while the transverse trabecular measure produced the highest correlation ($r = 0.81$) with Young's modulus. The data continuity experiment showed that, despite significant differences in image resolution between two scanners (10% MTF along xy-plane and z-direction – Flash: 16.2 and 17.9 lp/cm; Force: 24.8 and 21.0 lp/cm), most Tb measures had high Pearson correlations ($r > 0.95$) between values estimated from the two scanners. Relatively lower correlation coefficients were observed for the bone network area density ($r = 0.91$) and Tb separation ($r = 0.93$) measures.

Conclusion: Most MDCT-derived Tb microarchitectural measures are reproducible and their values derived from two scanners strongly correlate with each other as well as with bone strength. This

study has highlighted those MDCT-derived measures which show the greatest promise for characterization of bone network area density, plate-rod and transverse trabecular distributions with a good correlation ($r \geq 0.85$) compared with their micro-CT-derived values. At the same time, other measures representing trabecular thickness and separation, erosion index, and structure model index produced weak correlations ($r < 0.8$) with their micro-CT-derived values, failing to accurately portray the projected trabecular microarchitectural features. Strong correlations of Tb measures estimated from two scanners suggest that image data from different scanners can be used successfully in multisite and longitudinal studies with linear calibration required for some measures. In summary, modern MDCT scanners are suitable for effective quantitative imaging of peripheral Tb microarchitecture if care is taken to focus on appropriate quantitative metrics. © 2017 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12632]

Key words: bone mechanics, microarchitecture, modulation transfer function, multidetector row CT, trabecular bone

1. INTRODUCTION

Osteoporosis is linked to reduced bone mineral density (BMD) and structural degeneration. This bone disease is associated with increased fracture risk, and the fracture incidence increases progressively with age.¹ The continued increase in life expectancy is predicted to increase fracture incidence, and Cooper et al. estimated that the annual number of hip fractures will increase to 6.3 million by 2050.² Approximately, 40% of women and 13% of men suffer at least one osteoporotic fracture in their lifetime.³ Osteoporotic hip fractures reduce life expectancy by 10–20%, and the annual healthcare cost for the United States alone is 19 billion dollars.⁴ Bone imaging is critically important in identifying fracture risks among individuals for planning therapeutic intervention and monitoring treatment response. Dual-energy X-ray absorptiometry (DXA) is the standard clinical technique to classify BMD measures in postmenopausal women or older men (age ≥ 50 yr) as osteopenic ($-2.5 < T\text{-score} < -1$) or osteoporotic ($T\text{-score} \leq -2.5$). DXA BMD accounts for 60–70% of the variability in bone strength,⁵ and the remaining variability is due to the cumulative and synergistic effects of various factors, including trabecular bone (Tb) microarchitecture.^{6,7} Thus, reliably measuring Tb microarchitecture is of clinical significance; particularly as Tb is more susceptible to hormonal, pharmacologic, and toxic effects.

State-of-the-art volumetric bone imaging modalities, including magnetic resonance imaging (MRI)^{5,8–10} and high-resolution peripheral quantitative computed tomography (HR-pQCT),^{11–13} have been investigated for quantitative assessment of bone microarchitecture at peripheral skeletal sites. Despite considerable effort and success, these techniques suffer from slow-speed scanning that causes motion artifacts,¹¹ smaller field of view (FOV) susceptible to positioning error,¹⁴ need for a specialized scanner, and/or associated hardware; and, in the case of MRI, failure to provide quantitative BMD measures. Recent advances in multidetector row CT (MDCT) technologies have shown promising improvements that overcome the major deficits of MRI and HR-pQCT related to scan speed and FOV. A state-of-the-art

MDCT scanner, e.g., Siemens SOMATOM Force, achieves xy-plane 10% modulation transfer function (MTF) of 24.8 lp/cm $\approx$ 201.6 μ m true in-plane resolution and z-plane 10% MTF of 21.0 lp/cm $\approx$ 238.1 μ m true z-plane resolution using ultra-high resolution (UHR) mode. Such a scanner acquires a 10 cm scan length at a peripheral site using the UHR mode in just 6 s as compared to $\sim$ 2.9 min for 0.9 cm scan length using HR-pQCT.¹⁵ Also, MDCT offers major dose reduction¹⁶ while simultaneously increasing spatial resolution and signal-to-noise-ratio (SNR). If modern MDCT is established as effective for quantitative bone microarchitectural imaging, its wide availability in clinical environments and low radiation dose will immediately put it as a front-runner for large multicenter musculoskeletal studies.

A pertinent challenge with MDCT for bone research emerges due to wide variation in imaging and reconstruction features from different vendors and rapid upgrades in technology. This raises concerns of data uniformity in large-scale multisite or longitudinal studies that typically involve data from multiple scanners. In longitudinal studies, researchers often encounter a situation that a new and more advanced MDCT scanner replaces the older scanner in the middle of the study, which can result in an incomplete process for data acquisition and analysis, or a waste of previous data collected from the older machine. Therefore, differences in data relationships between scanners, and the continuity of scientific analysis results warrant further study. In particular, we were interested in describing the relationship among and consistency of MDCT-based Tb microarchitectural measures, during a scanner switch. One of the goals of this study was to compare Tb microarchitectural measures derived from two MDCT scanners with significantly different image resolution to determine if a multisite cross-sectional or longitudinal study could use data from multiple scanners and still maintain data continuity.

In this paper, we examine the effectiveness of a modern MDCT scanner in terms of accuracy and reproducibility of derived Tb measures. We also assess ability of MDCT scanners to predict actual bone strength. As mentioned earlier, we examine the association of Tb measures derived from two scanners with notably different spatial resolution features.

Through our comparison of two-scanner models, we provide the basis from which other scanner makes and models can similarly be compared.

2. METHODOLOGY

To achieve our aims, the following materials and methods were used — (a) cadaveric ankle specimens, (b) UHR MDCT imaging of cadaveric ankle specimens under *in vivo* conditions, (c) micro-CT imaging of cadaveric distal tibia specimens, (d) mechanical testing on cadaveric distal tibia core specimens to determine their strengths and elastic moduli, (e) UHR MDCT ankle scans of healthy volunteers on two different scanners with a short time gap between, and (f) image processing, computation of Tb microarchitectural measures, and data analysis.

2.A. Cadaveric ankle specimens

Twenty-five fresh-frozen cadaveric ankle specimens were removed at mid-tibia from 17 body donors (mean age at death $\pm$ SD: 79.6 ± 13.2 Y; 9 F). Those bodies were collected under the Deeded Bodies Program at The University of Iowa, Iowa City, IA. Exclusion criteria were evidence of previous fracture or knowledge of bone tumor or bone metastasis. These specimens were placed in a sealed plastic bag and kept frozen until MDCT imaging. Specimens were thawed at room temperature before scanning.

2.B. Healthy volunteers

Multidetector row CT scans of the distal tibia were obtained from 20 healthy volunteers (age: 26.2 ± 4.5 Y; 10 F) using two state-of-the-art scanners. This study was designed around the transition period of the MDCT scanner upgrade at the University of Iowa Comprehensive Lung Imaging Center (ICLIC) research CT facility. First, each volunteer was scanned with the old scanner before upgrade. Then they were recalled after upgrade and rescanned with the new scanner. The range of time intervals between the two scans was 40 to 48 days (mean $\pm$ SD: 44.6 ± 2.7 days). All studies involving human subjects were approved by The University of Iowa Institutional Review Board and all participants provided written informed consent.

2.C. MDCT imaging

Two state-of-the-art MDCT scanners — Scanner 1: Siemens SOMATOM Definition Flash (briefly Flash), Forchheim, Germany; Scanner 2: Siemens SOMATOM Force (briefly Force), Forchheim, Germany — were used. For both scanners, imaging experiments were performed at the ICLIC. The UHR scan mode was used and a scan length of 10 cm beginning at the distal tibia end-plateau was used; an anterior–posterior (A-P) projection scout scan of the entire tibia was acquired to locate the field of view (FOV). A Gammex RMI 467 Tissue Characterization Phantom (Gammex RMI,

Middleton, WI, USA) was scanned to calibrate CT Hounsfield units into BMD (mg/cm^3). *In vivo* ankle scan setup for a Siemens Force MDCT scanner along with the FOV selection on a scout scan and a reconstructed axial image slice are illustrated in Figure 1; a similar setup was used for the Siemens Flash scanner. Scanner-specific CT parameters are detailed in the following.

2.C.1. Flash scanner

Single tube spiral acquisition at 120 kV, 200 effective mAs, 1 sec rotation speed, pitch factor: 1.0, number of detector rows: 16, scan time: 23.2 s, collimation: 16×0.6 mm, total effective dose equivalent: $170 \mu\text{Sv} \approx 20$ days of environmental radiation in the USA. Siemens z-UHR scan mode was applied, which enables Siemens double z sampling technology allowing a dual sampling of the 0.6 mm detectors, splitting the signal so that each detector created a 0.3 mm slice in the z-plane.¹⁷ After scanning in a helical mode with a 400 μm slice thickness, images were reconstructed at 200 μm slice spacing using a normal cone beam method with a special U70u kernel achieving high structural resolution.

2.C.2. Force scanner

Single X-ray source spiral acquisition at 120 kV, 100 effective mAs, 1 s rotation speed, pitch factor: 1.0, number of detector rows: 64, scan time: 5.8 s, collimation: 64×0.6 mm, total effective dose equivalent: $50 \mu\text{Sv} \approx 5$ days of environmental radiation in the USA. Siemens z-UHR scan mode was applied enabling Siemens double z sampling technology. Images were reconstructed at 400 μm slice thickness with 200 μm slice spacing and 150 μm pixel size using Siemens's special kernel Ur77u with Edge Technology to achieve high spatial resolution.

To understand the actual differences in image resolution between the two scanners, we experimentally computed their 10% modulation transfer function (MTF) along the xy-plane and the z-direction. See the Appendix 1 for description of the MTF computation method.

2.D. Micro-CT Imaging

Following repeat MDCT scans, each cadaveric specimen was scanned on a Siemens microCAT II (Preclinical Solutions, Knoxville, TN, USA) cone beam micro-CT scanner after removing soft tissue and dislocating the tibia from the ankle joint to fit the specimen in the scanner. The following micro-CT parameters were used: 100 kV, 200 mAs, 720 projections over 220 degrees, exposure 1 sec per projection, scan time: 12 min, 2 mm Al filter for beam hardening; scan length: 29.5 mm; FOV on the xy-plane: $44.2 \times 44.2 \text{ mm}^2$. Micro-CT scans were reconstructed using filtered back-projection: image size 1536×1536 , 1024 slices at 28.8 μm isotropic voxel size. Three micro-CT scans were acquired for each distal tibia specimen after shifting the scan locations along the tibial axes. These consecutive scans were stitched

FIG. 1. *In vivo* ankle scan setup for a Siemens SOMATOM Force MDCT scanner. Top-row: Positioning of the left ankle. Right leg is bent so as to eliminate from the scanning field and the length of the left foot is resting on the table. Laser beam projections are used to align the tibial long axis with the central z-axis of the scanner by assuring that the two laser beam projections travel along the center of the leg in the coronal and sagittal planes. This alignment step is important to achieve the highest image resolution and to standardize trabecular bone measures. Bottom-left: Positioning of the FOV on an anterior-posterior projection CT scout scan. The distal tibial end-plateau is included in the FOV, which is used to determine different tibial locations for ROI selection. Bottom-right: An axial image slice from the reconstructed MDCT scan data. [Color figure can be viewed at wileyonlinelibrary.com]

to a single micro-CT image using the manufacturer provided software resulting in a total scan length greater than 8.5 cm.

2.E. Mechanical testing of cadaveric Tb specimens

A cylindrical Tb core was harvested from each of the 25 distal tibia specimens, and compressive mechanical tests were performed. Young's modulus (E) of each specimen was determined using an extensometer test, while the Yield stress was determined in a platen test. The platen test was performed because, during the first test, most Tb cores failed near their ends rather than within the extensometer span. Therefore, specimen lengths were shortened to obtain more homogeneous properties across each length. All specimen preparation and mechanical testing was performed at the University of Iowa's Orthopaedic Biomechanics Laboratory. Details of mechanical testing methods are presented in the Appendix 1.

2.F. Image processing and Tb microarchitectural measures

The complete list of Tb measures investigated in this study is shown in Table I. Each MDCT/micro-CT image was

processed through an image-processing cascade in the following sequence — (a) conversion of CT Hounsfield unit (HU) numbers to bone mineral density (BMD) (unit: mg/cm^3) and computation of vBMD, (b) interpolation generating isotropic voxels, (c) selection of volumes of interest (VOIs), (d) fuzzy skeletonization^{23,24} and computation of Tb network area density (Tb.NA), (e) tensor scale analysis^{19,25} for computation of the mean trabecular plate-width (Tb.PW) and plate-to-rod ratio (Tb.PR) and the volumetric BMD contributed by transverse trabeculae (tBMD), (f) digital topological analysis^{26–28} for computation of erosion index (EI),²¹ (g) star-line analysis for computation of trabecular thickness (Tb.Th) and trabecular separation (Tb.Sp) measures,²⁰ and (h) computation of structure model index (SMI).²² Details of the image-processing methods are presented in the Appendix 1.

2.G. Data analysis

To examine the reproducibility of MDCT Tb measures, we computed intraclass correlation coefficients (ICC) from repeat scans. Linear correlation analysis was used to examine relationships between measurement values derived by MDCT

TABLE I. The list of MDCT- and micro-CT-derived Tb measures examined in this paper. The nomenclature of Tb measures used by Bouxsein et al.¹⁸ is followed here wherever possible.

Parameter (unit)	Description
vBMD (mg/cm ³)	Volumetric trabecular bone mineral density
tBMD (mg/cm ³)	Volumetric trabecular bone mineral density contributed by transverse trabeculae characterized by tensor scale analysis ¹⁹
Tb.NA (cm ² /cm ³)	Trabecular bone network area density, i.e., the average area of the medial surface of segmented bone per unit VOI
Tb.PW (μm)	Mean trabecular plate-width computed by tensor scale analysis ¹⁹
Tb.PR (no unit)	Ratio of total plateness and rodness counts over a VOI computed by tensor scale analysis ¹⁹
Tb.Th (μm)	Mean trabecular thickness computed by star-line analysis ²⁰
Tb.Sp (μm)	Mean trabecular separation, i.e., the space between trabecular structures computed by star-line analysis ²⁰
EI (no unit)	Erosion index — A summary measure of digital topological analysis of Tb aimed to represent the extent of bone erosion ²¹
SMI (no unit)	An indicator of the structure of trabeculae; SMI is '0' for parallel plates and '3' for cylindrical rods ²²

VOI, volume of interest; SMI, structure model index.²²

and micro-CT imaging and to assess the ability of MDCT- and micro-CT-derived Tb measures to predict bone strength and stiffness. For these experiments, MDCT images from the Siemens Flash scanner were used.

Scatter-plots for measurements from the two MDCT scanners were examined for possible nonlinearity or heteroskedasticity. Pearson correlation coefficients were calculated and Lin's CCCs (concordance correlation coefficients) were computed as a measure of agreement between scanners and as a criterion of the need for calibration (SAS MCCC macro developed by R. Dierkhising, Mayo Clinic College of Medicine, 2006, was used). Calibration equations for the 6–8% outer region were developed using simple linear regression models.

3. RESULTS

3.A. Validation of Tb measures using an advanced MDCT scanner

Tb plate-rod and orientation characterization using micro-CT and MDCT imaging are presented in Figure 2. Results of quantitative correlation analysis of Tb measures derived from micro-CT and MDCT scanners are presented in Figure 3. For each parameter, the correlation coefficient (*r*) values are plotted as a function of VOI diameter. Seven different values of VOI diameter over the range of 1.05 mm to 7.05 mm were used. For a given VOI size, 10 spherical VOIs were randomly selected in the first MDCT scan of each cadaveric specimen. Thus, a total of 250 VOIs were used for each VOI size. The values of the correlation coefficients for different Tb measures plateaued around the VOI diameter of 5.25 mm. The

values of the correlation coefficients for different Tb measures at the VOI diameter of 5.25 mm are summarized in Table II, along with the observed mean values of the Tb measures derived from the two scanners. The highest correlation coefficient of 0.92 was observed for the network area density measure Tb.NA. Also, the observed correlation coefficients for the volumetric BMD measure vBMD, plate-width measure Tb.PW, plate-rod ratio measure Tb.PR, and tBMD were all ≥ 0.85 . On the other hand, the correlation coefficients for the trabecular thickness measure Tb.Th, trabecular separation measure Tb.Sp, erosion index EI, and structure model index SMI were all < 0.8 , which may be considered as weak correlations. The smallest correlation coefficient of 0.63 was observed for EI.

Results of repeat scan reproducibility of Tb measures derived from the Flash scanner are presented in Figure 4. For each Tb measure, repeat scan ICC values are plotted as a function of the VOI diameter. Twelve different values of VOI diameter over the range of 0.45 to 7.05 mm, i.e., 3 to 47 voxels, were used. In the figure, it can be seen that repeat scan ICC values for all Tb measures except EI and SMI plateau at a VOI diameter around 3 mm. The highest ICC value of 0.98 was observed for both the trabecular network area measure Tb.NA and the transverse BMD measure tBMD. For all other Tb measures except EI and SMI, the ICC values at a VOI diameter of 3 mm were within a tight range of [0.94, 0.98]. The bone mineral density measure vBMD achieved an ICC value of 0.97. The highest ICC values observed for EI and SMI were 0.90 and 0.87, respectively.

Results of linear regression analysis examining the ability of MDCT- and micro-CT-derived Tb measures to predict experimental bone strength are presented in Table III. The highest correlation coefficient for MDCT Tb measures with yield stress was observed for the trabecular plate-width measure Tb.PW ($r = 0.89$). The lowest correlation coefficient with yield stress was observed for both vBMD and EI ($r = 0.78$). Other than vBMD, EI and SMI, the observed correlation coefficients of other Tb measures with yield stress were within a tight range of [0.85, 0.89]. Relatively lower correlation coefficients were observed between Young's modulus and Tb measures. The highest correlation of 0.81 with Young's modulus was observed for the transverse Tb measure tBMD; a moderate correlation of 0.75 was observed for the trabecular plate-width measure Tb.PW ($r = 0.89$). The two measures EI and SMI demonstrated significantly lower correlations with the Young's modulus outcome. Micro-CT-derived Tb measures showed moderately improved performance as compared to MDCT-derived Tb measures in predicting bone's yield stress and Young's modulus.

3.B. Data continuity for Tb measures from two MDCT scanners

Results of MTF or spatial resolution analysis of the two MDCT scanners (coupled with the U70u and Ur77u reconstruction kernels for the Flash and Force, respectively) used in this study are presented in Table IV. (Of note: Other

FIG. 2. Tb plate-rod and orientation characterization using micro-CT (top row) and Siemens Flash MDCT scanners (bottom row). Surface rendition of Tb microstructure (left column) and color-coded display of local plate-width measure (middle column) and orientation characterization (right column) for a Tb region. Although, the effects of resolution difference between the two scanners are apparent, regional agreement of microstructural characterization is notable. Matching plate-like trabeculae in (b, e) are indicated by arrows. As visually observed in (c, f), transverse trabeculae (red) are successfully automatically located. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

FIG. 3. Results of correlation analysis of Tb measures derived from micro-CT and MDCT imaging of cadaveric ankle specimens. Pearson correlation coefficients (r) among Tb measures obtained by micro-CT and MDCT imaging were computed from linear regression models. Values of the correlation coefficients are plotted as a function of VOI size. See Table I for definitions of Tb measures. For this experiment, MDCT images from the Siemens Flash scanner were used. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

TABLE II. Pearson correlation coefficients (r) among the values of Tb measures derived from postregistered micro-CT and MDCT images of cadaveric ankle specimens from matching VOIs ($n = 250$) of diameter 5.25 mm. Mean values of Tb measures observed for the two scanners are shown. See Table I for definitions of Tb measures.

Tb measure	Correlation coefficients (r)	micro-CT (mean value)	MDCT (mean value)
vBMD (mg/cm^3)	0.88	1158	993
tBMD (mg/cm^3)	0.86	194	120
Tb.NA (cm^2/cm^3)	0.92	0.10	0.07
Tb.PW (μm)	0.87	541	861
Tb.PR (no unit)	0.85	2.85	7.02
Tb.Th (μm)	0.71	133	160
Tb.Sp (μm)	0.81	348	468
EI (no unit)	0.63	0.20	0.67
SMI (no unit)	0.78	0.76	2.23

For this experiment, MDCT images from the Siemens Flash scanner were used.

kernels were found to provide increases in the 10% MTF but at the cost of increased reconstruction artifacts.) It may be clarified that different kernels were used for the two different

FIG. 4. Repeat scan reproducibility of Tb measures on a Siemens Flash scanner using cadaveric ankle specimens. For each Tb measure, intraclass correlation coefficients or ICC values are plotted as a function of VOI size. It is of note that EI and SMI have poor reproducibility compared with the very high reproducibility of the other metrics. See Table I for definitions of Tb measures. For this experiment, MDCT images from the Siemens Flash scanner were used. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Correlation of different MDCT- and micro-CT-derived Tb measures with yield stress and Young's modulus of Tb cores from cadaveric ankle specimens determined by mechanical testing. Linear regression analysis was performed to calculate the correlation coefficient (r). See Table I for definitions of Tb measures.

Tb measure	Pearson correlation coefficient (r)			
	MDCT bone measures versus bone strength		Micro-CT bone measures versus bone strength	
	Yield stress	Young's modulus	Yield stress	Young's modulus
vBMD (mg/cm^3)	0.785	0.698	0.763	0.738
tBMD (mg/cm^3)	0.861	0.813	0.872	0.791
Tb.NA (cm^2/cm^3)	0.855	0.712	0.838	0.807
Tb.PW (μm)	0.893	0.757	0.902	0.802
Tb.PR (no unit)	0.838	0.722	0.854	0.820
Tb.Th (μm)	0.849	0.765	0.817	0.685
Tb.Sp (μm)	0.851	0.730	0.848	0.764
EI (no unit)	0.780	0.536	0.781	0.670
SMI (no unit)	0.786	0.541	0.821	0.743

For this experiment, MDCT images from the Siemens Flash scanner were used.

TABLE IV. Results of modulation transfer function (MTF) analysis for the Siemens Flash and Force MDCT scanners.

Scanner	Kernel	CT parameters	10% MTF (lp/cm)	
			xy-plane	z-direction
Siemens flash	U70u	120 kV, 200 mAs, pitch: 1	16.2	17.9
Siemens force	Ur77u	120 kV, 100 mAs, pitch: 1	24.8	21.0

scanners based on their availabilities. For each scanner, we selected the sharpest kernel that did not create any visible reconstruction artifacts as confirmed by an expert on three cadaveric ankle scans. It may be noted that the “sharpness” of bone structure can be affected by the choice of the reconstruction kernel, which may lead to differences in Tb measurements. The Siemens Flash produced an in-plane 10% MTF of 16.2 lp/cm, i.e., 308.6 μm pixel size, while the newer Force scanner produced an in-plane 10% MTF of 24.8 lp/cm or 201.6 μm pixel size. In the z-direction, the Flash and Force scanners produced 10% MTF of 17.9 lp/cm or 279.3 μm pixel size and 21.0 lp/cm or 238.1 μm pixel size, respectively. Results of the data continuity experiment for Tb measures derived from two MDCT scanners are presented in Figures 5 and 6; Table V. Figure 5 presents axial and sagittal slices from CT images of the lower leg of a healthy volunteer scanned in both Flash and Force scanners. The improvement in the spatial resolution using the new Force scanner is visually apparent in both axial and sagittal image slices. Figure 6 presents the values of Pearson correlation coefficients of Tb measures derived from the two scanners. The correlation analyses for different regions are shown. The highest correlation coefficient (0.985) was observed for the trabecular thickness measure Tb.Th in the outer region of the 6–8% tibia; observed r -values for vBMD, Tb.PW, and Tb.PR in the same region were 0.976, 0.980, and 0.979, respectively. Relatively lower correlation coefficients were observed for the network density measure Tb.NA (0.907) and trabecular separation (0.926). Descriptive statistics, Lin's concordance correlation coefficient (CCC), and Pearson correlation coefficients of Tb measures, presented in Table V, were obtained from the two scanners in the outer region of the 6–8% of the distal tibia. High CCC values (>0.95) were observed for several measures, namely vBMD, Tb.PW, and Tb.PR, suggesting that these measures may not need any calibration between the two scanners studied here. Also, Table V includes the best solutions for calibration where needed for the 6–8% outer site: shift (intercept only), percent change (slope only) or linear equation with both intercept and slope included.

4. DISCUSSION AND CONCLUSION

Results presented in Section 3.A demonstrate the potential and validity of modern MDCT scanners for quantitative imaging of Tb microarchitecture at a peripheral site. As observed in Figure 2, thinner trabeculae are partly lost in MDCT imaging due to limited spatial resolution, and also, Tb thickness increases. Thus, disagreements in characterization of Tb microarchitecture at the level of individual voxels or small neighborhoods were expected, and it is noticeable in Figure 2(b,e) and (c,f). However, over a large neighborhood covering several trabeculae, agreements in quantitative assessment of trabecular microarchitecture also are noted. For example, in (b,e) matching plate-like structures, as indicated by arrows, are visually noticeable. This observation was confirmed in the quantitative results of Figure 3 describing

FIG. 5. Axial (left column) and sagittal (right column) slices from CT images of the lower portion of the left leg of a healthy volunteer scanned using the Siemens Flash (low resolution) (upper row) and Force (high resolution) (lower row) scanners. Images were cropped to highlight the distal tibia bone. Image slices from the two scanners were selected from similar locations.

FIG. 6. Results of the data continuity test for the two advanced MDCT scanners using healthy volunteers ($n = 20$). Pearson correlation coefficients for Tb measures obtained from Siemens Flash (lower resolution) and Force (higher resolution) scanners across different regions. Inner and outer regions were defined using 30% and 60% peel at 4–6% and 6–8% of the distal tibia. See Table I for definitions of Tb measures. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE V. Results of the data uniformity study for two MDCT scanners using healthy volunteers ($n = 20$). Descriptive statistics, Lin's concordance correlation coefficient (CCC), and the Pearson correlation coefficient for Tb measures obtained from Siemens Flash (lower resolution) and Force (higher resolution) scanners over the outer region at 6–8% of the distal tibia. See Table I for definitions of Tb measures.

Tb measures outer 6–8%	Flash scanner mean (SD)	Force scanner mean (SD)	CCC	Pearson correlation (r)	Calibration ^a (lower to higher resolution)	
					Intercept	Slope
vBMD (mg/cm^3)	1168.2 (33.49)	1162.8 (34.79)	0.965	0.976	No calibration	
tBMD (mg/cm^3)	286.60 (75.59)	264.40 (69.09)	0.924	0.970	-	0.920
Tb.NA (cm^2/cm^3)	0.081 (0.025)	0.115 (0.030)	0.503	0.907	0.034	-
Tb.PW (μm)	1210.4 (254.88)	1171.1 (215.08)	0.954	0.980	170.66	0.827
Tb.PR (no unit)	2.738 (0.604)	3.556 (0.548)	0.966	0.979	1.176	0.869
Tb.Th (μm)	168.90 (22.72)	139.06 (18.06)	0.467	0.985	-	0.823
Tb.Sp (μm)	505.45 (136.28)	425.44 (129.22)	0.785	0.926	-	0.844
EI (no unit)	0.710 (0.358)	0.470 (0.230)	0.668	0.965	-	0.653
SMI (no unit)	1.081 (1.141)	0.506 (1.155)	0.848	0.953	-0.575	-

^aSimple linear regression analysis was used to derive calibration equations; if the intercept was not statistically significant ($P\text{-value} > 0.1$), a model of regression through the origin was applied; if the slope was not significantly different from 1 ($P\text{-value} > 0.1$), a shift correction was calculated as the difference between the mean values for Force and Flash scanner results.

correlation analysis among Tb measures estimated from micro-CT and MDCT imaging. Tb measures from the two modalities were computed over matching VOIs, and the analysis was performed at different VOI sizes. Over a VOI of diameter 1.05 mm, for all Tb measures, the correlation of their values computed from micro-CT and MDCT imaging were very low ($r < 0.60$). However, over matching VOIs of diameter greater than 5.25 mm, several Tb measures were found to produce good correlation between their values derived from micro-CT and MDCT imaging. High correlation ($r = 0.92$) of the Tb network area measure Tb.NA derived from the two imaging modalities suggests that the image resolution of MDCT is suitable for Tb microstructural imaging. The trabecular plate-rod measure Tb.PW, plate-rod-ratio measure Tb.PR, and transverse trabecular measure tBMD showed good correlations ($r \geq 0.85$) comparable to that of the basic bone density measure vBMD ($r = 0.88$), which was expected to be less dependent on image resolution. These observations are novel and encouraging, and they reconfirm the correctness of the computational algorithms for Tb.PW, Tb.PR, and tBMD.¹⁹ Other Tb measures, namely Tb.Th, Tb.Sp, EI, and SMI, produced weak correlation between the two imaging modalities ($r < 0.8$). Reduced r -values for Tb.Th and Tb.Sp could have been caused partially by resolution-related artifacts of MDCT imaging, e.g., thickening of trabeculae and loss of thinner trabeculae. However, low r -values for the two plate-rod characterization measures EI and SMI are possibly due to limitations of their computational algorithms at relatively low resolution of MDCT, especially in a situation where the other plate-rod measure Tb.PW shows a higher correlation ($r = 0.87$) between values from micro-CT and MDCT scanners.

Results of the comparison between mean values of different Tb measures estimated from micro-CT and MDCT imaging (Table II) suggest that, while there is good correlation between the values of Tb measures from two modalities, the actual values are significantly different. The mean value of vBMD

derived from MDCT is lower than that from micro-CT scans. This observation could be explained by the loss of thin trabeculae at MDCT image resolution. This difference is larger for the tBMD, suggesting that transverse trabeculae are relative thinner and narrower as compared to the longitudinal structures, leading to larger fractional loss of transverse structures at MDCT resolution. Similar arguments can be used to explain the observed differences in the mean values of the network area density measure and the trabecular separation measure Tb.Sp. The increase in the trabecular plate-width measure Tb.PW or the plate-to-rod ratio measure Tb.PR could be explained by filling of narrow marrow holes at MDCT resolution. Although some thinner trabeculae are lost, as suggested by observed results, its effects in Tb.PW or Tb.PR measures are superseded by marrow-hole filling. The increase in the mean value of the trabecular thickness measure obtained from MDCT as compared with the mean value from micro-CT can be explained by trabecular thickening due to larger MTF or lower spatial resolution of MDCT imaging. The observed differences in the mean values of the two measures EI and SMI are somewhat counterintuitive as they wrongly suggest that a trabecular network appears more rod-like at MDCT resolution as compared to its representation from micro-CT imaging.

Results of the reducibility analysis, presented in Figure 4, suggest that most of the MDCT-based Tb measures except EI and SMI are repeatable ($\text{ICC} \in [0.94, 0.98]$) over a VOI of diameter greater than 3 mm, although the measures are not repeatable at the level of individual voxels. It is noticeable that even the pure intensity-based measure vBMD showed low reproducibility for smaller VOI. This suggests that the low reproducibility of Tb microarchitectural measures at smaller VOI is mostly caused by factors related to image quality, such as noise, partial volume, registration, and other artifacts, and the contribution is less from computational errors for Tb measures.

Results of the mechanical test experiment, presented in Table III, suggest that all Tb microarchitectural measures

except EI and SMI outperform the BMD measure vBMD in predicting both yield stress and Young's modulus or stiffness. The two measures EI and SMI showed similar linear correlation as vBMD in predicting yield stress, while their performance to predict modulus was markedly lower. In general, the observed abilities of different measures to predict modulus are lower as compared to their abilities of predicting yield stress. Noticeably, the transverse trabecular parameter tBMD showed the highest ability to predict bone's stiffness, which supports the hypothesis that transverse trabeculae improve bone strength by arresting the buckling of longitudinal trabeculae.²⁹ Among all measures, the Tb plate-rod microarchitectural measure Tb.PW showed the highest ability to predict yield stress, which is consistent with histologic observations in the literature^{7,30,31} confirming the relationship between gradual conversion of trabecular plates to rods and elevated fracture risk. Also, Tb.PW showed a moderate correlation with Young's modulus. It may be clarified that all cadaveric experiments were performed on the Siemens Flash MDCT scanner, only. However, following the fact that the new Siemens Force scanner produces higher resolution images and allows faster scans as compared to the Flash scanner, the Force scanner likely matches or exceeds the performance observed for the old scanner in terms of trabecular characterizations.

Results of MTF analysis and data continuity experiments for two MDCT scanners are presented in Section 3.B. Scatter-plots for measures obtained from two scanners showed that the relationship between them was linear and there appeared to be no heteroskedasticity over the whole range of possible values (inner and outer regions for the 4–6% and 6–8%). Results in Figure 6 and Table V show that, despite significant differences in image resolution between the two scanners (see Table IV), Tb microarchitectural measures estimated from the two scanners are strongly correlated ($r > 0.9$). In general, higher correlations of Tb measures from the two scanners were observed for the outer region at both the 4–6% and 6–8% distal tibia. Although there is no clear difference in data continuity results between the 4–6% and 6–8% sites for the outer region, the 6–8% site offers better data continuity between the two scanners at the inner region. Improved data continuity in the outer region could be explained by the fact that outer regions include relatively thicker trabeculae as compared to inner regions, limiting losses of thinner trabeculae in images using the scanner with lower resolution features. In the outer region, most Tb measures from the two scanners showed high linear correlation ($r > 0.95$). A relatively lower correlation was observed for the Tb network area density measure Tb.NA ($r = 0.91$) and the trabecular separation measure Tb.Sp ($r = 0.93$). While the reduced correlation for Tb.Sp could be attributed to the filling of small marrow holes at lower resolution, the reason for the reduced correlation for Tb.NA could be more complex. Although the values of Tb.Th from the two scanners showed high linear correlation ($r = 0.985$), Lin's concordance correlation coefficient was markedly lower (CCC = 0.47). In other words, trabecular structures in scans

from the two machines had different thickness. Specifically, the scans from the low-resolution scanner show thicker trabeculae (see Figure 5). Thus, a skeletonization algorithm needs a greater extent of thinning or erosion for images from the low-resolution scanner to convert a volume structure to a surface skeleton reducing its area. Although this factor is addressed in the plate-width computation (see Figure 3 in Saha et al.³²), it has not been successfully addressed in the computation of Tb.NA. In summary, although there are opportunities for further improvements in algorithms for Tb measure computation, *in vivo* measures of Tb microarchitecture from two scanners can be used in a cross-sectional or longitudinal study after adjustments using calibration equations, if needed. The calibration equations in Table V will be useful in multicenter studies to distinguish whether an observed difference in a parameter is associated with scanner differences or “real” difference between measured bones. A nonsignificant interaction effect for distal tibial location of Tb measures and slope showed that, for a Tb measure, similar calibration is required independently of the location used for measurement. All measures with much lower CCCs as compared to Pearson's correlation coefficients would require some kind of calibration.

In the two-scanner experiment, different reconstruction kernels were used for the two scanners depending upon their availabilities. It is clarified that different reconstruction kernels may variably affect the “sharpness” of the bone structure, which can lead to differences in morphological measurements due to the redistribution of the intensity values across voxels as a function of the reconstruction kernel. Thus, the kernel selection is an important factor in the assessment of trabecular measures and studies should take care to harmonize these selections across sites.

Although the true image resolutions of current MDCT scanners are larger or comparable to trabecular thicknesses, derived Tb microarchitectural measures characterizing plate-rod and transverse trabecular distributions using advanced tensor scale analysis algorithms show promising correlation with corresponding measurement values estimated from micro-CT imaging. However, other Tb microarchitectural measures including trabecular thickness, trabecular separation, erosion index, and structure model index were observed to produce weak correlation ($r < 0.8$) among their values derived from micro-CT and MDCT scanners. MDCT-derived Tb measures are reproducible and show strong correlation with bone mechanical strength and stiffness. Strong correlation of Tb measures estimated from two scanners with distinctly different resolution features creates the opportunity to use data from different scanners in large multisite cross-sectional and longitudinal studies. The comparisons between scanners demonstrated here provide a basis for similar comparisons across other scanner makes and models. In summary, it has been demonstrated that state-of-the-art MDCT scanners are suitable for effective quantitative imaging of Tb microarchitecture at peripheral sites with appropriate selection of the scanning protocol and quantitative metrics.

ACKNOWLEDGMENTS

This study was funded by NIH grants: R01-AR054439, R01-DE012101, R56-DE012101, UL1-RR024979, and S10-OD018526. The authors thank Ms. Shelby Francis for her efforts with the human subject recruitment for the two-scanner calibration study, and Dr. Matthew Fuld for the scanning of Catphan600 phantom on the Flash scanner.

APPENDIX 1

MODULATION TRANSFER FUNCTION

To evaluate the MTF difference between the Siemens Flash and Force scanners, the Catphan600 Module CTP528 (High-Resolution Module) phantom was scanned on both scanners under clinical mode. Then for each scanner separately, an image was reconstructed by centering in at the bead of 0.28 mm in diameter located in the CTP528 module, using 50 mm DFOV and extended CT scale. Next, a 3D MTF image was produced by employing a 3D FFT process on the reconstructed image followed by a correction step for the bead size. The 1D profile on the z-axis is the MTF profile for z-direction, and the 1D profile on the x- and y-axes were averaged together to produce the MTF profile for the xy-plane. At the end, on each of the 1D MTF profiles, the critical frequency at a certain modulation (e.g., at 10% modulation) was calculated.

Other scanner settings were used as follows. For the Flash scanner, the scan was acquired at 120 kV, 200 mA, 1 s rotation speed, pitch 1.0, convolution kernel U70u, slice thickness 0.4 mm, slice spacing 0.2 mm. For the Force scanner, the scan was acquired at 120 KV, 100 mA, with 1 s rotation time, pitch 1.0, and the scan was reconstructed on the ReconCT workstation with convolution kernel Ur77u, Admire (1), 0.4 mm slice thickness and 0.1 mm slice spacing.

MECHANICAL TESTING OF TB SPECIMENS

Specimen preparation

As explained in more detail elsewhere,³² cylindrical Tb specimens of 8 mm in diameter were cored from the distal tibia *in situ* along the proximal–distal direction. A-P and M-L radiographs were used to determine the central axis of the bone and thus the core location and to ensure elimination of the growth plate from a test specimen. Specimens were cored with saline immersion using an 8.25 mm inner diameter diamond coring bit (Starlite Industries, Rosemont, PA, USA). The core was released from the distal radius by cutting it with a razor saw, and the specimen ends were sanded smooth, flat, and parallel. Specimen length and diameter were measured three times and averaged, and the middle 6 mm of the specimen length was marked for extensometer attachment position. Each core was wrapped in saline-soaked gauze, and

frozen until thawed for testing. For the non-extensometer testing, the specimen ends were again sanded to remove damaged bone from the specimen ends. For extensometer testing, a minimum specimen length of 18 mm was desired, to achieve both the minimum aspect ratio of 2:1 recommended for Tb compression specimens³³ and a 3:1 ratio of specimen length to extensometer gage length used in an earlier study.³³ For the subsequent platen testing, specimen length was dependent on how much bone needed to be removed from the damaged ends; the resulting aspect ratios were all greater than 1:1.

Mechanical testing

As explained in more detail elsewhere,³² the Tb cores were mechanically tested in compression using an electromechanical materials testing machine (MTS Insight, MTS Systems Corp., Eden Prairie, MN, USA). Each specimen was placed between unlubricated, polished, plano-parallel steel platens. For the extensometer test, to minimize specimen end effects, strain was measured with a 6 mm gage length extensometer (model 632.29F-30, MTS Systems Corp., Eden Prairie, MN, USA) attached directly to the mid-section of the bone. For the second test, strain was measured with the testing machine at the compressing platens. A compressive preload of 10 N was applied and strains then set to zero. At a strain rate of 0.005 s^{-1} , each specimen was preconditioned to a low strain with at least 10 cycles and then loaded to failure. Young's modulus was determined for each specimen as the highest 20% section slope of the stress–strain curve. Yield stress was determined as the intersection of the stress–strain curve and a 0.2% strain offset of the modulus.

IMAGE PROCESSING METHODS

BMD computation and isotropic voxel interpolation

An MDCT scan of a Gammex RMI 467 Tissue Characterization Phantom (Gammex RMI, Middleton, WI, USA) was performed after scanning a cadaveric specimen or a human subject with the matching CT protocol and reconstruction kernel. The calibration phantom contains sixteen cylinders with known physical densities. A fully automated algorithm was developed in our laboratory to locate and segment those cylinders using their known dimensions and relative locations. Each segmented cylinder was eroded by five voxels to eliminate partial voluming effects and the average CT number over the eroded region was computed. A conversion function was computed using the correspondence between computed average CT numbers and the known physical density of individual cylinders. After converting an MDCT image into a BMD image, it was interpolated at $150 \mu\text{m}$ isotropic voxels using a windowed sinc interpolation method.³⁴ All subsequent image-processing operations were applied on BMD images at $150 \mu\text{m}$ isotropic voxels.

VOI selection

VOI selection for the bone strength experiment

As explained in more detail elsewhere,²⁰ the 25 cadaveric ankle specimens from Specimen_A were used for this experiment. The size and location of VOIs for image analysis of the cadaveric bone strength study were chosen as per the information recorded during specimen preparation for mechanical testing. First, the tibial bone region was filled using distance transform^{35,36} and connectivity analysis³⁷ and the bone axis was aligned with the coordinate z-axis.³⁸ After reorienting the bone image, a VOI cylinder of 8 mm diameter along the coordinate z-axis was generated and its proximal end was manually positioned at the center of the cortical rim using in-plane translation through a graphical user interface. The location of the distal end of the VOI cylinder in the slice direction and its length were determined as per the core location and length recorded during specimen preparation; the growth plate was visually located in the CT data of each specimen. Finally, the central 6 mm region from the cylinder was used as the VOI for the extensometer test; for the non-extensometer study, the length of the VOI was determined as per data collected during specimen preparation for the second mechanical test.

VOI selection for the repeat scan reproducibility experiment

The 25 cadaveric ankle specimens from Specimen_A were used for this experiment. The purpose of this experiment was to examine the reproducibility performance index as a function of VOI size to assess the localization scale yielding a reliable Tb microarchitectural measure. For a given VOI size, 10 spherical VOIs were randomly selected in the first MDCT scan of each cadaveric specimen (a total of 250 VOIs). Each VOI was randomly located within 30% peeled region covering 1.5 to 4.3 cm proximal sites of distal tibia, or equivalently, 4% to 12% of an average distal tibia. A postregistration algorithm was used to locate the matching VOIs in the second and third repeat scans.

VOI selection for the between-scanner human study

UHR MDCT scans of the distal tibia of 20 human volunteers on two scanners were used for this study. The correlation between measures using images from two MDCT scanners was analyzed at a regional scale using smaller VOIs. Also, the correlation of summary measures from two scanners was analyzed using larger VOIs adjusting for variations among individual-specific tibial length and width values. For the correlation study of regional measures, 50 spherical VOIs each of diameter 4.65 mm, i.e., 31 voxels were randomly selected within the 30% peeled region covering 4% to 12% proximal sites of an individual participant's distal tibia. VOIs near 12% proximal sites containing no Tb structures were excluded from analysis. A total of 989 VOIs data were used for analysis.

These VOIs were first selected in the image from the old scanner, and a postregistration algorithm was used to locate the matching VOIs in the image from the new scanner. For the correlation study of a global measure, regions covering 4% to 6% and 6% to 8% proximal sites of an individual participant's distal tibia were used for VOIs. Inner VOIs were determined using the 60% peel, while outer VOIs were determined in the region between 30% and 60% peels. Global VOIs were independently determined in the images from the two scanners.

FUZZY SKELETONIZATION

Computation of Tb microarchitectural measures is dependent on the quality of the surface skeleton³⁹ that is generated from an input volumetric Tb representation, and is used to microstructural analysis. Binary skeletonization⁴⁰ is always associated with thresholding-related data loss adding skeletal inaccuracies such as disruption of trabecular rods, perforation of plates, and filling of small marrow holes. Fuzzy skeletonization reduces thresholding-related data loss, which improves the preservation of trabecular network connectivity, especially at regions containing relatively thin trabeculae. The fuzzy skeletonization algorithm,^{23,24} adopted in this paper, uses fuzzy distance transform³⁶ to simulate a fuzzy grassfire propagation converting fuzzy volume object to its surface skeleton. A post-skeletal-pruning step^{41,42} is applied to prune noisy branches.

DIGITAL TOPOLOGICAL ANALYSIS

As described in more detail elsewhere,^{21,43,44} digital topological analysis or DTA²⁷ is a three-dimensional method that accurately determines the topological class (e.g., surfaces, curves, junctions) of each individual voxel in a digitized structure. DTA involves inspecting local topological numbers, i.e., numbers of bone components, tunnel, and cavities in the $3 \times 3 \times 3$ excluded (i.e., the central voxel is excluded) neighborhood of each bone voxel.²⁷ The algorithm uses a three-step approach to achieve a unique topological classification at every bone voxel using lookup tables and topological analysis in the extended neighborhood solving for local topological ambiguities in digital manifolds and their junctions. These topological classes are then used to compute several topological parameters for trabecular bone networks. The specific parameter, namely erosion index (EI) was found to be highly sensitive in most studies using DTA, and this DTA parameter is used in our experiments.⁵ The EI is defined as the ratio of all topological parameters expected to increase during the erosion process (specifically, curve, curve-edge, surface-edge, profile-edge, and curve-curve-junction types) compared with those that are expected to decrease (surface and surface-surface junction types).²¹

TENSOR SCALE

As explained in more detail elsewhere,¹⁹ tensor scale analysis was used to characterize Tb plate-rod microarchitecture

and to locate transverse trabeculae. Superiority of tensor scale analysis over volumetric topological analysis or VTA³² was previously established.¹⁹ The tensor scale algorithm¹⁹ is directly applied on a volumetric fuzzy digital object to obtain an ellipsoidal representation of the local structure at a curve-skeletal voxel. This ellipsoidal representation is used to compute local plate-width, platelikeness, rodlikeliness, orientation, etc. These local measures are then propagated tBMD from the curve-skeleton to the surface skeleton and then from the surface skeleton to the object volume. The average trabecular plate-width measure is computed as the BMD-weighted average of local plate-width over a region. At each location, a normalized measure of “platelikeness” is obtained using the eccentricity between the average Tb thickness and the local plate-width, while “rodlikeliness” is computed as the complement of “platelikeliness.” Finally, the trabecular plate-to-rod-ratio (Tb.PR) is defined as the ratio of total counts of “platelikeliness” and “rodlikeliness” over a region. The orientation information of tensor scale ellipsoid is used to distinguish between longitudinal and transverse trabeculae. Finally, the measure tBMD is computed as the volumetric BMD in Tb regions contributed by transverse trabecular structures.

STRUCTURE MODEL INDEX

As described in more detail by Hildebrand and Rüegsegger,²² the structure model index or SMI is an indirect global estimation of the plate-rod characteristic of a three-dimensional structure. SMI is calculated by a differential analysis of a triangulated surface of a structure, which is defined using the surface area derivative with respect to the half-thickness or the radius assumed constant over the entire structure. This derivative is estimated by a simulated thickening of the structure by translating the triangulated surface by a small extent Δ_r in its outward normal direction and dividing the associated change of surface area with Δ_r . For an ideal plate and rod structure the SMI value is 0 and 3, respectively. For a structure with both plates and rods of equal thickness, the value is between 0 and 3, depending on the volume ratio of rods to plates.

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