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CT-Based Characterization of Transverse and Longitudinal Trabeculae and Its Applications

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Abstract

Osteoporosis is a common age-related disease characterized by reduced bone mineral density (BMD), micro-structural deterioration, and enhanced fracture-risk. Although, BMD is clinically used to define osteoporosis, there are compelling evidences that bone micro-structural properties are strong determinants of bone strength and fracture-risk. Reliable measures of effective trabecular bone (Tb) micro-structural features are of paramount clinical significance. Tb consists of transverse and longitudinal micro-structures, and there is a hypothesis that transverse trabeculae improve bone strength by arresting buckling of longitudinal trabeculae. In this paper, we present an emerging clinical CT-based new method for characterizing transverse and longitudinal trabeculae, validate the method, and examine its application in human studies. Specifically, we examine repeat CT scan reproducibility, and evaluate the relationships of these measures with gender and body size using human CT data from the Iowa Bone Development Study (IBDS) ($n = 99$; 49 female). Based on a cadaveric ankle study ($n = 12$), both transverse and longitudinal Tb measures are found reproducible ($ICC > 0.94$). It was observed in the IBDS human data that males have significantly higher trabecular bone measures than females for both inner ($p < 0.05$) and outer ($p < 0.01$) regions of interest (ROIs). For weight, Spearman correlations ranged 0.43-0.48 for inner ROI measures and 0.50-0.52 for outer ROI measures for females versus 0.30-0.34 and 0.23-0.25 for males. Correlation with height was lower (0.36-0.39), but still mostly significant for females. No association of trabecular measures with height was found for males.

Keywords

Osteoporosis; trabecular bone; micro-structure; CT imaging; topology; orientation; transverse trabeculae; longitudinal trabeculae

1. INTRODUCTION

Osteoporosis is a common age-related disease characterized by reduced bone mineral density (BMD), micro-structural deterioration, and enhanced fracture-risk. Approximately, 40% of women and 13% of men suffer osteoporotic fractures in their lifetime.¹ Osteoporotic hip fractures reduce life expectancy by 10-20%,² and increased life expectancy will increase

fracture incidence to 6.3 million by 2050.³ Dual-energy X-ray absorptiometry (DXA) measured areal BMD is the clinical standard for diagnosis of osteoporosis. However, it is generally agreed that around 60% of bone's mechanical competence is explained by variation in BMD.⁴ The remaining variability is due to the cumulative and synergistic effects of various factors, including trabecular bone (Tb) micro-architecture.⁵⁻⁷ A large number of histologic studies^{6,7} have confirmed the relationship between Tb micro-structural features and fracture-risk. Thus, a reliably method measuring Tb micro-structural features from *in vivo* imaging is of significance to osteoporosis-related research and clinical studies.

State-of-the-art volumetric bone imaging modalities, including magnetic resonance imaging (MRI)^{4,8-10} and high resolution peripheral quantitative computed tomography (HR-pQCT),¹¹⁻¹³ have been investigated for quantitative assessment of bone micro-architecture 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 clinical CT technologies have shown promising improvements in terms of spatial resolution, scan-speed, and noise performance that enable Tb micro-structural measurements at peripheral sites at low radiation dose, overcoming the major deficits of MRI and HR-pQCT related to motion artifacts¹¹ and positioning error¹⁴ due to slow scan speed and smaller field of view (FOV). Chen et al. presented emerging clinical CT-based methods for characterization of cortical and trabecular bone micro-structural measures and evaluated their performance.¹⁵

Various topologic and geometric methods are available in literature to measure Tb micro-structure.¹⁶⁻¹⁹ Vesterby *et al.*¹⁶ conceived a stereologic parameter, called star volume, which is the average volume of an object region that can be seen from a point inside that region unobscured in all directions. Hahn *et al.*¹⁷ introduced the "trabecular bone pattern factor" which captures Tb connectivity in terms of the convexity property of the Tb surface defined as the ratio of the differences in perimeter and area under dilation. Hildebrand *et al.*¹⁸ developed a 3-D structure model index, a function of global plate-to-rod ratio, based on the observation that the rate of volume change with respect to half thickness (or the radius) for plate-like elements is different from that for rod-like elements. Feldkamp *et al.*¹⁹ showed that the makeup of TB networks can be expressed in terms of topological entities such as the 3-D Euler number. Saha and his colleagues have pioneered unique algorithms²⁰⁻²⁷ characterizing individual trabecular plates and rods, which have been adopted in a large number of studies.^{10,25,27-44}

There is evidence in literature suggesting that reductions in the number of transverse trabeculae are associated with marked reduction in bone strength leading to failure due to buckling of longitudinal trabeculae.⁴⁵ In this paper, we present a new *in vivo* CT-based method for characterizing transverse and longitudinal trabeculae, validate the method, and examine their applications in human studies. This method will facilitate research and clinical studies to understand the relationships between bone loss and alterations in transverse and longitudinal trabecular micro-structures under different pathophysiologic conditions and their impacts on fracture-risk.

2. METHODS AND ALGORITHMS

A fully automated method has been developed for computing individual trabecular orientation and characterizing longitudinal and transverse trabecular micro-structures in a three-dimensional (3-D) Tb network. The overall approach of this method is to automatically and accurately locate and segment individual trabeculae in a curve skeleton of a 3-D volumetric image, compute orientation of individual trabecular curve segments, propagate the orientation to volumetric trabecular segments, and characterize transverse and longitudinal trabeculae by comparing their orientation with the reference tibial bone axis. The method consists of the following steps—(1) bone volume fraction (BVF) computation and cavity filling, (2) curve skeletonization and pruning, (3) junction detection, (4) ungluing curve segments at junctions, (5) splitting curves into relatively linear segments, (6) orientation computation of individual segments, (7) orientation feature propagation from trabecular curve segments to volumetric trabecular segments, and (8) characterization of transverse and longitudinal trabeculae. These steps are described in the rest of this section. Although, in this paper, the method has been presented and validated on high-resolution clinical CT imaging of distal tibia, it is immediately generalizable to other imaging modalities and anatomic sites capturing Tb micro-structures. Essentially, the first step of BVF computation needs to be tailored based on the target imaging modality. All subsequent steps are modality-independent.

2.1 BVF Computation and Cavity Filling

BVF images were generated from CT scans in two steps—(1) conversion of CT intensity values in the Hounsfield Unit (HU) into bone mineral density (BMD) in mg/cc and (2) mapping of BMD values into a normalized BVF scale between ‘0’ and ‘1’. A Gammex RMI 467 Tissue Characterization Phantom (Gammex RMI, Middleton, WI) with multiple cylindrical inserts with known material density was scanned to calibrate CT HU values into BMD (mg/cc). A BVF image was computed by interpolating the BMD image to 150 micron isotropic voxel size and then mapping BMD values to a normalized scale using the following equation:

$$BVF(p) = \begin{cases} 0, & \text{if } BMD(p) < 940 \text{ mg/cc,} \\ \frac{BMD(p) - 940}{2184 - 940} & \text{if } BMD(p) \geq 940 \text{ mg/cc and } < 2184 \text{ mg/cc,} \\ 1 & \text{otherwise.} \end{cases}$$

In the above equation, 940 mg/cc was used as the bone marrow density, while 2184 mg/cc was used as the density of fully mineralized bone as determined following the results observed by Hernandez *et al.*⁴⁶ Finally, the BVF computation step was completed after applying connectivity analysis to remove small noisy components (less than 30 voxels) and filling cavities artificially generated due to noise and imaging artifacts. See Figure 1(a) for a 3-D representation of Tb network after BVF computation and cavity filling.

2.2 Curve Skeletonization and Pruning

In our method curve skeletonization⁴⁷ was applied on the fuzzy BVF image to identify individual trabeculae in a Tb network. The curve skeleton of a 3-D Tb network was

computed from a BVF representation using a two-step skeletonization approach—(1) computation of a medial surface from a BVF volume representation²² and (2) computation of a medial curve from a medial surface.⁴⁸ Noisy branches in a curve skeleton were pruned using a novel shape-length measure of individual branches computed using collision impact-weighted distance analysis.⁴⁹

2.3 Junction Detection

Junctions are located on a curve skeleton of a Tb network after removing noisy branches to identify and separate individual trabeculae. Effectiveness of individual trabecular orientation computation largely depends on the accuracy of location and segmentation of individual trabeculae in a curve skeleton, which is defined by the performance of junction detection. Although junction detection in a curve network in a Euclidean space is trivial, the same may not be true in a digital space. In a digital curve skeleton, different examples of junction may be found that involve hidden branches and a junction may extend to multiple voxels. Therefore, a simple topological definition of junctions fails to account for different types of junctions in digital curve skeletons. Novel theory and rule-based methods have been developed to successfully characterize different types of junctions and a comprehensive definition of curve junctions in a cubic digital grid is presented. Specifically, we identified three different types of junctions as follows.

1. Conventional topological junction: A curve skeletal voxel p is a conventional junction voxel if other curve skeletal voxels in its $3 \times 3 \times 3$ neighborhood form more than two 26-connected components or a tunnel or cavity.
2. Hidden junction: A curve skeleton voxel p is a hidden junction voxel if it is not in the $3 \times 3 \times 3$ neighborhood of a conventional junction and contains two or more hidden branches. A curve skeletal voxel q in the $3 \times 3 \times 3$ neighborhood of p forms a hidden branch, if it is adjacent to another neighbor of p , does not contribute to forming a tunnel or cavity in the $3 \times 3 \times 3$ neighborhood of p and leads to distinct curve skeletal branches in its own $3 \times 3 \times 3$ neighborhood; see Figure 2.
3. Extended junction: A curve skeletal voxel p is an extended junction voxel if it is not in the $3 \times 3 \times 3$ neighborhood of a conventional topological or hidden junction but forms three or more branches in its $5 \times 5 \times 5$ neighborhood. Such junction voxels appear clusters of multiple connected voxels; see Figure 2.

2.4 Ungluing Curve Segments at Junctions

After locating junction voxels, different trabeculae connected through a junction are separated using an ungluing process. This step is accomplished using the ungluing approach originally described by Saha and Chaudhuri.²¹ During this step, junction voxels and their $3 \times 3 \times 3$ neighbors are removed from a curve skeleton, and a connected component analysis is performed to label all curve segments as individual trabeculae. Finally, the individual trabecular curve segments are augmented in two steps. First, a given trabecular curve segment is augmented to add adjacent voxels in the neighborhood of junction voxels and then further augmented in the next step to add the junction voxels adjacent to the extended segment.

2.5 Splitting Curves into Relatively Linear Segments

Although Sections 2.3 and 2.4 successfully locate and unglue at junctions, long and curved trabecular segments are often present in a Tb network and left undivided after the above two steps. Direct orientation computation for such long curve segments may compromise with accuracy. Therefore, it is necessary to separate such long and curved segments into smaller and relatively linear segments, which is accomplished as follows. Let C be a curve segment, which is a sequence of 26-adjacent voxels and let l_C denote the line joining its two end voxels. First, a second order B-spline is fitted to the curve segment C , and then the farthest point p_C on the B-spline to the line l_C is located. The curve segment C is splitted at the voxel nearest to p_C if the distance between p_C and l_C exceeds a predefined threshold. This process is continued recursively until no curve segment is further splitted. Results of identifying trabecular segments in a curve skeleton after splitting curves are shown in Figure 1(b), while volumetric segmentation of individual trabeculae is presented in Figure 1(c).

2.6 Trabecular Orientation Computation

The orientation of individual trabecular curve segment is determined using principle component analysis of the B-spline fitted to the voxels on a curve segment. Second order B-spline is enough to capture the variation of individual segments. Meanwhile, it reduces the time complexity for computation and, also, it reduces over-fitting artifacts. Finally, computed orientation is propagated from curve skeleton voxels to all Tb voxels in the volume representation, which is accomplished using a nearest skeletal voxel feature propagation algorithm previously developed in our laboratory.²⁶

2.7 Characterization of Transverse and Longitudinal Trabeculae

Individual trabecular segments are characterized as transverse or longitudinal trabeculae using their absolute orientation and the reference orientation of whole bone axis. In this paper, we investigate transverse and longitudinal trabeculae at distal tibia. Thus, the orientation of the tibial bone axis was used as reference, which was determined using a fill-bone algorithm⁵⁰ and principal component analysis. The angle between an individual trabecula and the reference axis line is used to characterize its longitudinality, while its angle with the plane transverse to the reference axis is used to determine its transversity. Color-coded results of transverse (red) and longitudinal (green) trabecular characterization is presented in Figure 1(d).

3. EXPERIMENTS AND RESULTS

Our experiments were designed to evaluate the reproducibility of the new CT-based method characterizing transverse and longitudinal trabeculae. Repeat CT scans of cadaveric ankle specimens were used for evaluating the reproducibility of our algorithm for transverse and longitudinal trabecular classification. Human CT data from a retrospective study was used to evaluate the normative distributions of the new Tb measures and examine their relationships with gender, height, and weight. Our experiments involved the following materials and methods—(1) Cadaveric ankle specimens, (2) CT imaging, (3) human subjects, and (4) image processing and statistical data analysis.

3.1 Cadaveric Ankle Specimens

Twelve fresh-frozen cadaveric ankle specimens, separated at mid tibia, from body donors were collected under the Deeded Bodies Program at The University of Iowa, Iowa City, IA. These specimens were placed in a sealed plastic bag and kept frozen until high-resolution CT imaging. Specimens were thawed at room temperature before scanning. Repeat CT scans were performed on these specimens with repositioning the specimens on the scanner table before each repeat scan.

3.2 CT Imaging

Human distal tibia was scanned on a Siemens SOMATOM Definition Flash (Forchheim, Germany) at the University of Iowa Comprehensive Lung Imaging Center (ICLIC). 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 seconds, collimation: 16×0.6 mm, total effective dose equivalent: $170 \mu\text{Sv} \approx 20$ days of environmental radiation in the U.S. 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.⁵¹ 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.

3.3 Human Subjects

Ankle CT images of 50 healthy males and 49 healthy females (age: range 19 to 20 years; mean $\pm$ SD 19.4 $\pm$ 0.4 years), collected under the ongoing Iowa Bone Development Study (IBDS),^{52,53} were used for our experiments. In general, observed heights and weights for male participants (height 180.4 $\pm$ 8.0 cm, weight 83.6 $\pm$ 14.8 kg) were greater than female participants (mean $\pm$ SD height 165.2 $\pm$ 6.8 cm, weight 67.9 $\pm$ 21.0 kg). CT scans were obtained on the left lower leg using the CT protocol described in Section 3.2. Gender differences and associations with body size for trabecular bone characteristics were tested by fitting a multivariable linear regression model that included sex, height, and weight. The study protocol involving human subjects were approved by the University of Iowa Institutional Review Board and all participants provided written informed consent.

3.4 Image Processing and Statistical Analysis

The complete list of Tb measures investigated in this study is shown in Table 1. Each CT image was processed through an image-processing cascade described in Section 2. For reproducibility analysis, we selected 15 spherical VOIs of diameter 7.05 mm (equivalent to 47 voxels) from each specimen. These VOIs were selected randomly from each specimen over 4 to 8% of tibia with 30% peel from the outer cortical surface. Thus, a total of 180 VOIs from 12 cadaveric ankle specimen data were used for reproducibility analysis. Intra-class correlation coefficient (ICC) values of individual Tb measures from three repeat CT scans were computed to examine repeat scan reproducibility of the method.

For human data from the IBDS study, summary value for each measurement was derived from inner (60 % peeled region) and outer (the annular region between 30 and 60 % peeling) ROIs at 4-6% tibial section. A representative sample of longitudinal IBDS (50 males and 49

females) were randomly selected from the total sample of 325 available scans from “age 19” wave of the study. Distribution characteristics of Tb measures were calculated. Correlation analysis was used to investigate associations between CT measures and their relationship with body size (height, weight, and BMI). Group comparison for sex differences in Tb measures were performed first using t-tests and then repeated with adjustment for weight as the most important covariate using multiple regression models.

3.5 Results

Results of repeat scans reproducibility analysis are presented in Table 2. The experimental results show that both transverse and longitudinal trabecular measures are found highly reproducible under repeat CT scanning – ICC = 0.983 for the transverse measure Tb.tBMD and 0.947 for the longitudinal measure Tb.lBMD. Volumetric trabecular BMD (Tb.vBMD) produced higher repeat scan reproducibility of 0.999.

IBDS participants were on average 19.8 years old and included 49 females (height mean $\pm$ SD=167.2 $\pm$ 6.7 cm, weight 69.3 $\pm$ 18.6 kg) and 50 males (height 179.4 $\pm$ 8.2 cm, weight 85.4 $\pm$ 16.6 kg). Females had more mature bone – 8 years post peak height velocity age comparing with 6 years for males. Description of Tb measures by sex presented in Table 3. Tb measures were highly correlated with values in 0.92-0.99 range for measures in the same ROI and 0.90 and above for corresponding measures in inner and outer ROI. Males showed significantly higher Tb measures than females for both inner (t-tests p-value<0.05) and outer (t-tests p-value<0.01) ROI (Table 3). Associations between body size and Tb measures were stronger for females (Table 4). For weight, Spearman correlations ranged 0.43-0.48 for inner ROI and 0.50-0.52 for outer ROI measures for females versus 0.30-0.34 and 0.23-0.25 for males. Correlation with height was lower (0.36-0.39), but still mostly significant for females, but in multiple regression models for females, height appeared to be not significant predictor in presence of weight. No association of Tb measures with height was found for males. Weight-adjusted sex comparisons demonstrated still significantly higher Tb measures in outer ROI for males while for inner ROI the differences became not statistically significant (data not showed).

4. CONCLUSIONS

A new *in vivo* CT-based method for characterizing transverse and longitudinal trabeculae and computing respective measures has been presented. Transverse trabecular bone micro-structures are important determinants of bone strength as these cross micro-structures resist the buckling of longitudinal trabeculae. A human cadaveric ankle study has been conducted to evaluate the performance of the new method in terms of repeat scan reproducibility. The new transverse and longitudinal bone measures have been found to be highly reproducible under repeat CT scanning. The method has been presented on human ankle CT scans from the IBDS study and the normative distribution of the new transverse and longitudinal trabecular bone measures are investigated. Experimental results have shown that the correlation between body weight and trabecular bone measures is stronger than that between height and trabecular bone measures. Trabecular bone measures in females show stronger correlation with body size than males.

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Figure 1.

Computation of transverse and longitudinal trabeculae in high resolution CT imaging. (a) Three-dimensional reconstruction of the Tb network using CT scan of a cadaveric distal tibia specimen. (b) Results of individual trabecular segmentation on the curve skeleton of (a). Each trabecular segment is shown using a unique color. (c) Volumetric representation of individual trabecular segmentation. (d) A color-coded display of longitudinal (green) and transverse (red) trabecular characterization.

Figure 2.

Illustration of different digital junctions in a curve skeletal. Top row: Examples of conventional topological junctions forming more than two components, or a tunnel or cavity in the neighborhood. Middle row: Examples of junctions involving hidden branches (marked by '*'), which do not contribute separate components in the neighborhood. Bottom row: Examples of extended junctions, where multiple voxels together form a junction.

Table 1.

The list of Tb measures examined in this paper.

Parameter (unit)	Description
Tb.vBMD (mg/cc)	Volumetric trabecular bone mineral density
Tb.tBMD (mg/cc)	Volumetric trabecular bone mineral density contributed by transverse trabeculae
Tb.lBMD (mg/cc)	Volumetric trabecular bone mineral density contributed by longitudinal trabeculae

ROI: region of interest

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Table 2.

Results of reproducibility analysis of Tb measures.

Variables	Reproducibility (ICC)
Tb.vBMD	0.999
Tb.tBMD	0.983
Tb.lBMD	0.947

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Table 3.

Descriptive statistics for trabecular bone measures by Sex.

	Males (N=50)		Females (N=49)		Mean sex diff (SE) (Male = ref)
Variables	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	
Inner ROI					
Tb.vBMD	1146 (33)	1148 (1079, 1212)	1132 (31)	1132 (1043, 1179)	−14.3 (6.5) *
Tb.tBMD	452 (105)	465 (217, 652)	402 (116)	407 (143, 580)	−50.2 (22.2) *
Tb.lBMD	349 (59)	349 (193, 510)	320 (65)	330 (164, 431)	−29.5 (12.5) *
Outer ROI					
Tb.vBMD	1204 (31)	1203 (1148, 1280)	1176 (32)	1174 (1104, 1236)	−28.3 (6.3) **
Tb.tBMD	496 (111)	497 (217, 767)	385 (121)	384 (93, 615)	−110.9 (23.2) **
Tb.lBMD	373 (68)	375 (190, 558)	303 (73)	305 (103, 450)	−69.1 (14.2) **

*
-p-values<0.05**
-p-values<0.01

Table 4.

Spearman Correlations for body size measures with CT-based trabecular bone measures by Sex.

\	Inner ROI			Outer ROI		
	Tb.vBMD	Tb.tBMD	Tb.IBMD	Tb.vBMD	Tb.tBMD	Tb.IBMD
Females (N=49)						
Height (cm)	0.36	0.36	0.39	0.36	0.36	0.37
Weight (kg)	0.48	0.46	0.43	0.52	0.52	0.50
BMI	0.41	0.39	0.34	0.48	0.47	0.45
Males (N=50)						
Height (cm)	−0.01	−0.01	0.05	−0.02	0.01	0.01
Weight (kg)	0.34	0.31	0.30	0.25	0.25	0.23
BMI	0.37	0.33	0.30	0.29	0.27	0.25