

Load distribution and the predictive power of morphological indices in the distal radius and tibia by high resolution peripheral quantitative computed tomography

Joshua A. MacNeil, Steven K. Boyd *

Department of Mechanical and Manufacturing Engineering, Schulich School of Engineering, University of Calgary, 2500 University Drive, N.W., Calgary, Alberta, Canada T2N 1N4

Received 26 July 2006; revised 12 January 2007; accepted 28 February 2007
Available online 12 March 2007

Abstract

A 3D high resolution peripheral quantitative computed tomography scanner (HR-pQCT) (XtremeCT, Scanco Medical, voxel size 82 μm) has been recently developed that can perform in vivo human measurements on peripheral sites, including the wrist and tibia. The goals of this study were to use HR-pQCT measurements to determine the ability of morphological and density measurements to predict bone apparent stiffness and apparent Young's modulus in the distal radius and tibia, to determine the relative importance of cortical and trabecular bone in carrying load in the human distal radius and tibia. Furthermore, the ability of a sub-volume of trabecular bone apparent Young's modulus to predict the Young's modulus of a whole radius and tibia section was determined.

A total of 25 measurements of the radius and 12 measurements of the tibia were used for morphological and finite element analyses of sections, and sub-volume cubes of trabecular bone from the distal radius and tibia. The subjects were chosen to obtain a large variation in age ranges and bone architecture and density.

By combining multiple measurements, a strong ability to predict bone apparent stiffness and apparent Young's modulus was found for morphological and density measurements in the radius and tibia ($R^2 > 0.80$). The relative importance of the trabecular and cortical bone in carrying load was also found to vary consistently with location in the sample for both the radius and the tibia. This indicates that measurements of the cortical and trabecular bone are required for assessing fracture risk. A cubic section of trabecular bone was found to be insufficient to accurately represent the apparent bone Young's modulus of a radius or tibia section.

Morphological and density measurements of the distal radius and tibia have been shown in this study to predict bone apparent Young's modulus and apparent stiffness, and may indicate when a more time consuming finite element analysis is warranted. It should be noted that these results may be an overestimation of the predictive ability of structural parameters, as the influence of bone density is removed from the finite element analyses, and the results were only influenced by bone structure. A measurement of bone apparent Young's modulus is independent of subject size (as opposed to reaction force), and may provide the ability to distinguish between two patients that have similar mean morphological and density measurements; but different overall structures, and therefore, different fracture risk.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Osteoporosis; Bone quality; Finite element analyses; Load distribution; Peripheral quantitative computed tomography

Introduction

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, manifesting clinically as a concurrent increase in fragility and fracture risk

[1,2]. Although it is clear that fracture risk is increased with decreasing bone mineral density (BMD) [3], the decision to treat is a difficult and uncertain decision [4]. A 3D high resolution peripheral quantitative computed tomography (HR-pQCT) scanner (XtremeCT, Scanco Medical, voxel size 82 μm) has been recently developed that can perform in vivo human measurements on peripheral sites such as the wrist and tibia. A previous study has validated HR-pQCT for measuring three key

* Corresponding author. Fax: +1 403 282 8406.

E-mail address: skboyd@ucalgary.ca (S.K. Boyd).



Fig. 1. Standard xCT measurement location for the distal radius (left) and tibia (right).

measurements of bone quality: volumetric BMD, bone micro-architecture, and bone apparent stiffness through a comparison with gold standard measurements [5]. This may allow for improved assessment of fracture risk compared to traditional dual energy X-ray absorptiometry (DXA) areal BMD measurements. Wrist fractures have been shown to be a good predictor of low bone mass, as 75% of all wrist fractures are associated with low bone mass [6], and wrist fractures are the most common symptomatic fractures [7]. Wrist fractures have also been shown to indicate an increased risk to subsequent life threatening fractures in locations such as the hip or spine [8,9].

The traditional method for assessing fracture risk is through areal BMD measurement using DXA and has been shown to have moderate to good correlations to bone strength in the distal radius [10,11]. Volumetric HR-pQCT BMD measurements allow for separate measurements of trabecular and cortical bone density, which are not possible using areal BMD measurements. The ability of volumetric BMD measurements to predict bone apparent Young's modulus and apparent stiffness in the distal radius and tibia is unknown, and may allow density measurements to be used as initial indicators of low bone quality.

Morphological measurements provide a quantification of trabecular and cortical bone micro-architecture and may be valuable measurements for monitoring bone changes. The standard HR-pQCT morphological measurement protocol includes a direct measure of trabecular number (Tb.N), and derived measures of bone volume ratio (BV/TV), trabecular

thickness (Tb.Th), trabecular separation (Tb.Sp) and cortical thickness (Ct.Th) [12,13]. From a previous study, it was found that direct measurements of BV/TV, Ct.Th, and connectivity density (Conn.D), as well as the degree of anisotropy (DA) can be determined using HR-pQCT [5]. Furthermore, it has been shown that Ct.Th, BV/TV and Tb.N have good correlations to bone apparent Young's modulus and strength in the distal radius [10,11]. The ability of morphological measurements to predict bone apparent stiffness and apparent Young's modulus has not been determined for in vivo HR-pQCT measurements of the radius and tibia, and may allow morphological assessment to be an appropriate initial indicator of increased fracture risk. The load sharing relationship between cortical and trabecular bone in carrying mechanical load, may also add insight into the relative importance of morphological changes to the cortical and trabecular bone in assessing fracture risk. In other skeletal sites such as the vertebrae it was found that load sharing varies with location [14].

Traditionally, bone apparent stiffness and apparent Young's modulus measurements using micro-computed tomography data and HR-pQCT have been performed using finite element analyses of cubic or cylindrical sections of trabecular and cortical bone due to computational restrictions [5,15–17]. However, measurements on a sample of trabecular bone, may not accurately predict the behavior of a tibia or radius section as a whole. Finite element modeling of human radii has been investigated using 165 μ m pQCT data and has been shown to

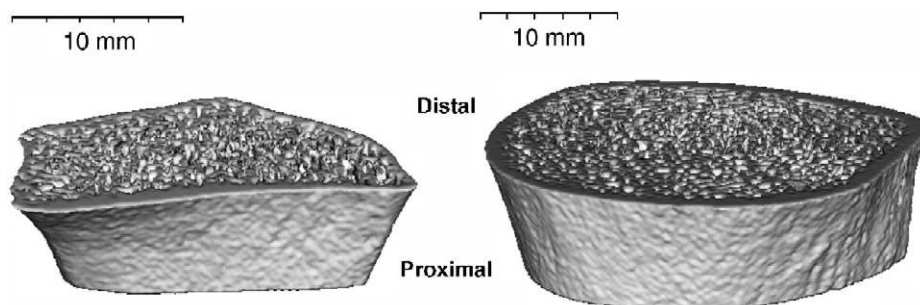


Fig. 2. Representative xCT distal radius (left) and tibia (right) cross sections. Stiffness and morphological measurements were performed on all samples.

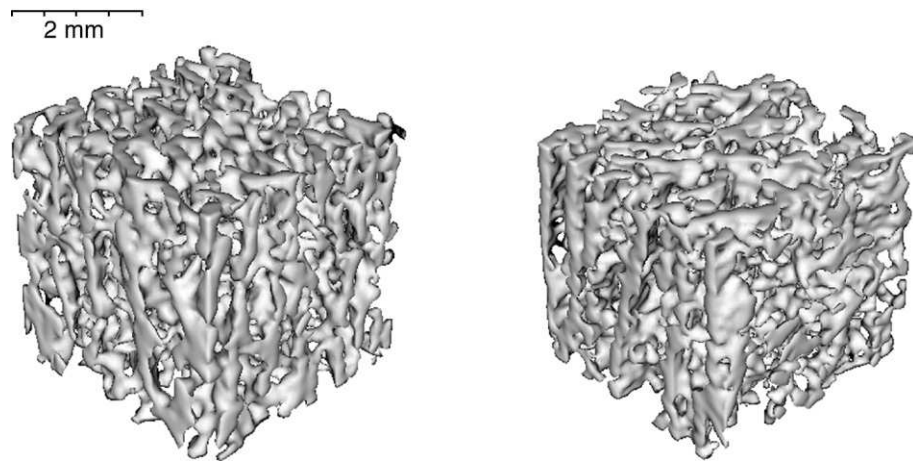


Fig. 3. A $75 \times 75 \times 75$ voxel cube was extracted from each radius (left) and tibia (right) to determine the trabecular bone apparent stiffness matrix for each sample in the best orthotropic coordinate system.

be effective at predicting Colles-type fractures using full wrist joint models as well as using only a section of the radius [11,18]. The apparent Young's modulus of trabecular bone has also been shown to be a good predictor of its apparent yield stress in the bovine tibia [19]. Therefore, measurements of bone apparent Young's modulus and apparent stiffness using finite element modeling of HR-pQCT data, may be good predictors of apparent strength in the distal radius and tibia.

Therefore, the goals of this study are (i) to determine the ability of morphological and density measurements to predict bone apparent stiffness and apparent Young's modulus; (ii) to determine the relative importance of cortical and trabecular bone in carrying load in the human distal radius and tibia; and (iii) to assess whether trabecular bone apparent Young's

modulus of a sub-volume predicts the apparent Young's modulus of a whole radius and tibia section.

Methods

Subjects

Measurements were performed on 11 human subjects ranging in age from 20 to 57 years with HR-pQCT. Some subjects were scanned at both their left and right radius and tibia, while others were scanned at either their left or right radius or tibia due to subject availability. A total of 15 in vivo measurements of the radius and 12 in vivo measurements of the tibia were completed. Measurements performed in a previous study [5] on 10 fresh cadaver forearms (5 male and 5 female) with ages ranging from 55 to 93 were also added to obtain a larger variation in age range of the radius measurements. The cadaver forearms were obtained from the Gross Anatomy Lab at the University of Calgary. All

Table 1

Means and standard deviations for density, morphological, apparent bone stiffness, and Young's moduli measurements of the distal radius and tibia

Measurements	Units	Radius		Tibia	
		Mean	S.D.	Mean	S.D.
Stiffness	N/mm	33,700	13,600	117,000	21,000
E	[MPa]	937	358	1200	170
RF	[N]	2870	1160	9960	1820
Tb. E	[MPa]	584	380	720	297
Tb. Force Proximal	[N]	729	380	3500	890
Tb. Force Distal	[N]	2100	810	6990	1380
Ct. Force Proximal	[N]	2140	940	6460	1190
Ct. Force Distal	[N]	774	548	2970	1020
BV/TV	[%]	12.6	4.3	16.3	1.7
Tb.N	[mm ⁻¹]	1.67	0.49	1.91	0.27
Tb.Th	[mm]	0.0747	0.0146	0.0865	0.0107
Tb.Sp	[mm]	0.592	0.259	0.448	0.070
Ct.Th	[mm]	0.683	0.301	1.26	0.29
BMD	[g/cm ³]	289	100	315	45
Tb. BMD	[g/cm ³]	151	52	195	20
Ct. BMD	[g/cm ³]	804	132	881	37
Cross sectional area	[mm ²]	326	111	887	167
BV/TV*	[%]	24.5	6.8	29.9	2.5
Ct.Th*	[mm]	0.658	0.193	0.714	0.116
Conn.D	[mm ⁻³]	3.56	1.33	3.88	0.88
DA		1.65	0.16	1.67	0.12

Table 2

Radius correlations between apparent bone stiffness measurements, Young's moduli measurements, and density and morphological measurements

Radius	BV/TV	Tb.N	Tb.Th	Tb.Sp	Ct.Th	BMD	Tb. BMD	Ct. BMD	Area	BV/TV*	Ct.Th*	Conn.D	DA
<i>E</i>	0.601	0.391	0.361	0.520	0.736	0.760	0.602	0.696	0.227	0.483	0.666	0.199	0.379
Stiffness	0.673	0.550	0.231	0.562	0.572	0.500	0.672	0.415	0.106	0.468	0.300	0.360	0.179
Tb. <i>E</i>	0.664	0.411	0.314	0.473	0.738	0.750	0.666	0.540	0.008	0.292	0.423	0.132	0.336
Tb. Force Proximal	0.160	0.246	0.004	0.160	0.007	0.158	0.004	0.006	0.013	0.186	0.000	0.352	0.003
Tb. Force Distal	0.465	0.465	0.112	0.407	0.212	0.183	0.464	0.128	0.510	0.381	0.072	0.433	0.060
Ct. Force Proximal	0.717	0.506	0.320	0.576	0.801	0.696	0.719	0.667	0.012	0.445	0.444	0.249	0.296
Ct. Force Distal	0.526	0.312	0.272	0.410	0.845	0.731	0.527	0.694	0.289	0.283	0.579	0.087	0.285

The strongest correlations ($R^2 > 0.60$) are given in bold.

procedures were approved by the Office of Medical Bioethics at the University of Calgary.

HR-pQCT

Each radius and tibia was scanned at one location with HR-pQCT at the standard location for human in vivo measurements (Fig. 1). The default human peripheral in vivo scanning protocol (60 kVp, 1000 μ A, 100 ms integration time, frame averaging of 1), was used for each scan. The total time for each measurement was approximately 3 min and resulted in 110 slices or a 9.02 mm thick section (Fig. 2) of the forearm or tibia. The effective dose from a single scan was $< 3 \mu$ Sv, which is well below the recommended annual dose limit for the general public (International Commission on Radiological Protection).

HR-pQCT morphological evaluation

Morphological measurements were performed on the HR-pQCT images using two methods. The first method used the default patient evaluation protocol available on the system. The radius was segmented from the image data using a semi-automated contouring method. The evaluation software automatically extracted both the cortical and trabecular bone using a Laplace Hamming filter and segmented the cortical and trabecular bone based on a default threshold value. The standard evaluation protocol resulted in measures of total BMD, cortical (Ct.) BMD, trabecular (Tb.) BMD, BV/TV, Tb.N, Tb. Sp, Tb.Th, and Ct.Th. The second method, a so-called extended method used the segmented data from the standard evaluation protocol and performed direct measurement of BV/TV, Ct.Th, Conn.D, and a non-parametric measurement of DA [5].

Finite element analyses

Two finite element analyses were performed on each radius and tibia. The first analysis determined the bone apparent stiffness and apparent Young's modulus of a whole radius and tibia section using custom software. The second analysis determined the full stiffness matrix of a sub-volume cube of trabecular bone selected from the center of the sample (Scanco Finite Element Software, v1.05, Scanco Medical). For both finite element analyses, the segmented images

were automatically converted to finite element meshes using the voxel conversion approach [20], and all elements were assigned a Young's modulus of 10 GPa and a Poisson's ratio of 0.3. This approach did not take into account the variation in tissue modulus that likely occurs with bone density. The boundary condition applied to the whole radius and tibia sections was uniaxial displacement to 1% strain, and the result from each model was the reaction force required to induce 1% strain. The relative components of the force carried by the cortical and trabecular bone at the distal and proximal faces of the section were distinguished based on the automatically segmented cortical and trabecular regions described above in the morphological methods.

The bone apparent stiffness of the sections was calculated by dividing the total resulting reaction force by the applied displacement. The bone apparent Young's modulus (*E*) of each section was calculated by dividing the average stress in the section by the applied strain. The average stress was calculated by dividing the total resulting reaction force by the average slice area, while the strain was determined by dividing the applied displacement by the original section height in the proximal/distal direction. The radius models typically contained 2.5 million elements and 4 million nodes and were solved using a serial supercomputing system (Western Canada Research Grid, 3 GHz 32 bit processor, 4 GB memory). The tibia models typically contained 6.5 million elements and 9.5 million nodes and were solved using a PC with 8 GB memory, and a 64 bit 2.6 GHz processor. The portion of the total load carried by the cortical and trabecular bone on the distal (Ct. Force Distal, Tb. Force Distal) and proximal (Ct. Force Proximal, Tb. Force Proximal) faces of the radii and tibia were determined based on the stress in the voxels labeled as cortical and trabecular bone during the automatic segmentation. The stress in the proximal/distal direction was summed for the cortical and trabecular bone surface voxels and multiplied by the voxel area to obtain force.

A $75 \times 75 \times 75$ voxel sub-volume cube of trabecular bone (Fig. 3) was extracted from each radii and tibia to determine the trabecular bone apparent Young's modulus. Each cube of bone was converted to a finite element mesh using the voxel conversion approach. The trabecular bone sub-volume stiffness matrix was determined (Scanco Finite Element Software, v1.05, Scanco Medical) by performing three uniaxial strain compression and three uniaxial strain shear tests. The stiffness matrix was then optimized to the best orthotropic coordinate system, [21] and the apparent Young's modulus (Tb. *E*) in the primary direction was obtained. This method was used because it removes any error in the model associated with misalignment of the loading directions and the

Table 3

Tibia correlations between apparent bone stiffness measurements, Young's moduli measurements, and density and morphological measurements

Tibia	BV/TV	Tb.N	Tb.Th	Tb.Sp	Ct.Th	BMD	Tb. BMD	Ct. BMD	Area	BV/TV*	Ct.Th*	Conn.D	DA
<i>E</i>	0.011	0.045	0.126	0.022	0.000	0.063	0.010	0.210	0.254	0.071	0.473	0.131	0.706
Stiffness	0.001	0.270	0.307	0.253	0.017	0.008	0.001	0.133	0.714	0.194	0.088	0.052	0.009
Tb. <i>E</i>	0.080	0.291	0.116	0.283	0.000	0.013	0.076	0.105	0.056	0.648	0.523	0.096	0.100
Tb. Force Proximal	0.000	0.051	0.086	0.063	0.005	0.029	0.000	0.013	0.706	0.010	0.008	0.019	0.040
Tb. Force Distal	0.031	0.033	0.147	0.035	0.000	0.091	0.029	0.000	0.726	0.000	0.027	0.007	0.057
Ct. Force Proximal	0.003	0.404	0.401	0.349	0.022	0.000	0.003	0.225	0.437	0.370	0.277	0.066	0.000
Ct. Force Distal	0.091	0.483	0.230	0.433	0.063	0.066	0.089	0.394	0.129	0.629	0.575	0.093	0.023

The strongest correlations ($R^2 > 0.60$) are given in bold.

Table 4
Results from the stepwise multiple regression analysis of the distal radius

Stiffness measurement	Measurements	Constant	Coefficients	S.E.	<i>t</i> value	<i>p</i> value	Adj. <i>R</i> ²
Stiffness	BV/TV	5051.888	356351.4	51392.811	6.934	0.000	0.659
	Area		26.075	8.236	3.166	0.005	0.762
	Ct.Th		85641.295	11372.196	7.531	0.000	0.831
	BMD		−287.824	48.429	−5.943	0.000	0.936
Tb. <i>E</i>	BMD	−814.854	3.598	0.329	10.953	0.000	0.738
	Area		1.095	0.294	3.731	0.001	0.832
<i>E</i>	Area	−9E8	−801768	209003.4	−3.836	0.001	0.651
	BV/TV*		2 E9	4 E8	5.703	0.000	0.786
	Ct.Th*		8E8	1 E8	6.011	0.000	0.858
	DA		6E8	2 E8	4.229	0.000	0.914
Ct. Force Proximal	Ct.Th	−342.950	−6206.192	610.133	−10.172	0.000	0.793
	Area		−0.821	0.442	−1.859	0.078	0.886
	BMD		16.904	2.606	6.488	0.000	0.902
	Tb. BMD		−14.460	2.310	−6.260	0.0000	0.962
Tb. Force Proximal	Area	487.744	−2.185	0.366	−5.964	0.000	0.489
	Conn.D		−141.905	30.622	−4.634	0.000	0.729
Ct. Force Distal	Ct.Th	368.236	−1671.247	149.667	−11.166	0.000	0.837
Tb. Force Distal	BV/TV	819.703	−12947.7	1983.301	−6.528	0.000	0.442
	Area		−3.948	0.766	−5.157	0.000	0.736

The ability of morphological and density measurements to predict apparent bone stiffness and Young's moduli measurements was determined.

primary axes of the trabecular bone. This will improve reproducibility and is the method of choice for Tb. *E* measurements.

Statistical analysis

Correlations between the bone apparent stiffness measurements, Young's moduli measurements, and the morphological and density measurements were performed (SPSS 14.0, Chicago, IL, USA). The correlation between the trabecular bone apparent Young's modulus and the section apparent Young's modulus was also determined. A stepwise multiple regression analysis was also performed to determine the correlation between multiple morphological and density measurements and the bone apparent stiffness and apparent Young's modulus measurements. A second stepwise multiple regression analysis was performed in which total BMD was held constant as the first independent variable so the addition of other morphological and density measurements to the predictive ability of total BMD could be determined.

Results

The mean values for the radius and tibia density, morphological, apparent Young's modulus, and apparent stiffness measurements are provided (Table 1). The ability of the individual morphological measurements to predict bone apparent stiffness and apparent Young's modulus measurements are given as correlations (Tables 2 and 3) with the strongest correlations ($R^2 > 0.60$) given in bold. In the radius, strong correlations were found between bone apparent Young's Modulus and BMD, as well as between bone apparent stiffness and BV/TV. In the tibia, strong correlations were found between bone apparent Young's modulus and DA, as well as between bone apparent stiffness and average slice area.

The results from the multiple regression analysis for the radius and tibia are provided (Tables 4 and 5). For the radius, multiple morphological and density measurements, increased the ability to predict bone apparent Young's modulus to a R^2 of 0.914 from 0.760. The ability to predict bone apparent stiffness

Table 5
Results from the stepwise multiple regression analysis of the distal tibia

Stiffness measurement	Measurements	Constant	Coefficients	S.E.	<i>t</i> value	<i>p</i> value	Adj. <i>R</i> ²
Stiffness	Area	−25,892.4	105.654	13.822	7.644	0.000	0.687
	Ct.Th*		74,909.407	21,550.881	3.476	0.007	0.851
Tb. <i>E</i>	BV/TV*	−2172.019	9677.736	2254.533	4.293	0.002	0.613
	DA	−1401.191	1365.735	187.747	7.274	0.000	0.675
Ct. Force Proximal	Ct.Th		248.333	81.577	3.044	0.014	0.822
	Area	−2148.877	4.852	0.968	5.013	0.001	0.381
	Ct.Th*		6318.336	1509.358	4.186	0.002	0.767
Tb. Force Proximal	Area	13.877	4.129	0.843	4.898	0.001	0.676
Ct. Force Distal	BV/TV*	−6775.623	32,597.445	7928.058	4.112	0.002	0.591
Tb. Force Distal	Area	4140.229	8.268	1.185	6.979	0.000	0.698
	Tb.N		−2168.241	798.148	−2.717	0.024	0.816

The ability of morphological and density measurements to predict apparent bone stiffness and Young's moduli measurements was determined.

Table 6

Results from the stepwise multiple regression analysis of the distal radius, in which total BMD was held constant as the first independent variable

Stiffness measurement	Measurements	Constant	Coefficients	S.E.	<i>t</i> value	<i>p</i> value	Adj. <i>R</i> ²
Stiffness	BMD	5051.888	−287.824	48.429	−5.943	0.000	0.474
	Area		26.075	8.236	3.166	0.005	0.736
	Ct.Th		85,641.295	11,372.196	7.531	0.000	0.792
	BV/TV		356,351.4	51,392.811	6.934	0.000	0.936
Tb. <i>E</i>	BMD	−814.854	3.598	0.329	10.953	0.000	0.738
	Area		1.095	0.294	3.731	0.001	0.832
<i>E</i>	BMD	−7 E8	495,107.3	539,746.6	0.917	0.370	0.749
	Area		−807,465	209,928.8	−3.846	0.001	0.819
	BV/TV*		2 E9	4 E8	4.186	0.001	0.859
	Ct.Th*		7 E8	2 E8	3.630	0.002	0.889
Ct. Force Proximal	DA		5 E8	2 E8	2.555	0.019	0.913
	BMD	−707.935	19.623	2.279	8.610	0.000	0.682
	Ct.Th		−6638.480	596.127	−11.136	0.000	0.810
	Tb. BMD		−17.065	1.940	−8.795	0.000	0.957
Tb. Force Proximal	BMD	190.179	3.424	1.123	3.049	0.006	−0.037
	BV/TV		−10721.9	2521.248	−4.253	0.000	0.564
	Area		−1.711	0.429	−3.992	0.001	0.741
Ct. Force Distal	BMD	111.396	3.658	1.793	2.041	0.053	0.720
	Ct.Th		−2845.402	592.204	−4.805	0.000	0.857
Tb. Force Distal	BMD	−698.636	21.676	3.806	5.694	0.000	0.148
	BV/TV		−31,161.4	4039.386	−7.714	0.000	0.629
	Ct.Th		−4594.274	893.835	−5.140	0.000	0.851
	Area		−1.860	0.647	−2.874	0.009	0.889

The ability of morphological and density measurements to predict apparent bone stiffness and Young's moduli measurements was determined.

was also increased to a R^2 of 0.936 from 0.673. For the tibia, multiple morphological and density measurements, increased the ability to predict bone apparent Young's modulus to a R^2 of 0.822 from 0.706, and the ability to predict bone apparent stiffness was increased to a R^2 of 0.815 from 0.714.

The results from the second multiple regression analysis are provided (Tables 6 and 7) and revealed how other morphological parameters improved the predictive ability when added to total BMD. For the radius, the ability to predict bone apparent Young's modulus was increased to a R^2 of 0.913 from 0.760, and the ability to predict bone apparent stiffness was increased

to a R^2 of 0.936 from 0.496. For the tibia the ability to predict bone apparent Young's modulus was increased to a R^2 of 0.801 from 0.063 and the ability to predict bone apparent stiffness was increased to a R^2 of 0.889 from 0.007.

In order to determine the relative importance of the cortical and trabecular bone in carrying load in the distal radius and tibia, the percent load carried by the cortical and trabecular bone at the distal and proximal faces of the cross section are presented (Fig. 4). At the radius distal face of the cross section the mean load carried by the trabecular bone was found to be 76% of the total, which reversed to 27% at the proximal face of the cross

Table 7

Results from the stepwise multiple regression analysis of the distal tibia, in which total BMD was held constant as the first independent variable

Stiffness measurement	Measurements	Constant	Coefficients	S.E.	<i>t</i> value	<i>p</i> value	Adj. <i>R</i> ²
Stiffness	BMD	−271637	−295.892	87.884	−3.367	0.010	−0.092
	Area		79.798	12.968	6.153	0.000	0.657
	Ct. BMD		470.466	105.685	4.452	0.002	0.889
Tb. <i>E</i>	BMD	−2036.711	−0.840	1.342	−0.626	0.547	−0.086
	BV/TV*		10,111.057	2427.243	4.166	0.002	0.588
<i>E</i>	BMD	−1221.782	1.364	0.506	2.696	0.025	−0.031
	DA		1187.773	181.846	6.532	0.000	0.801
Ct. Force Proximal	BMD	−29471.2	−42.583	4.852	−8.776	0.000	−0.100
	Ct. BMD		52.242	5.353	9.760	0.000	0.561
	Conn.D		861.453	151.007	5.705	0.000	0.903
Tb. Force Proximal	BMD	188.162	−0.496	3.638	−0.136	0.895	−0.068
	Area		4.107	0.901	4.557	0.001	0.641
Ct. Force Distal	BMD	−22081.9	−14.742	4.416	−3.338	0.010	−0.027
	BV/TV*		25561.456	5159.619	4.954	0.001	0.547
	Ct. BMD		25.043	5.606	4.467	0.002	0.854
Tb. Force Distal	BMD	3229.292	−4.847	5.192	−0.934	0.375	0.000
	Area		6.264	1.286	4.870	0.001	0.694

The ability of morphological and density measurements to predict apparent bone stiffness and Young's moduli measurements was determined.

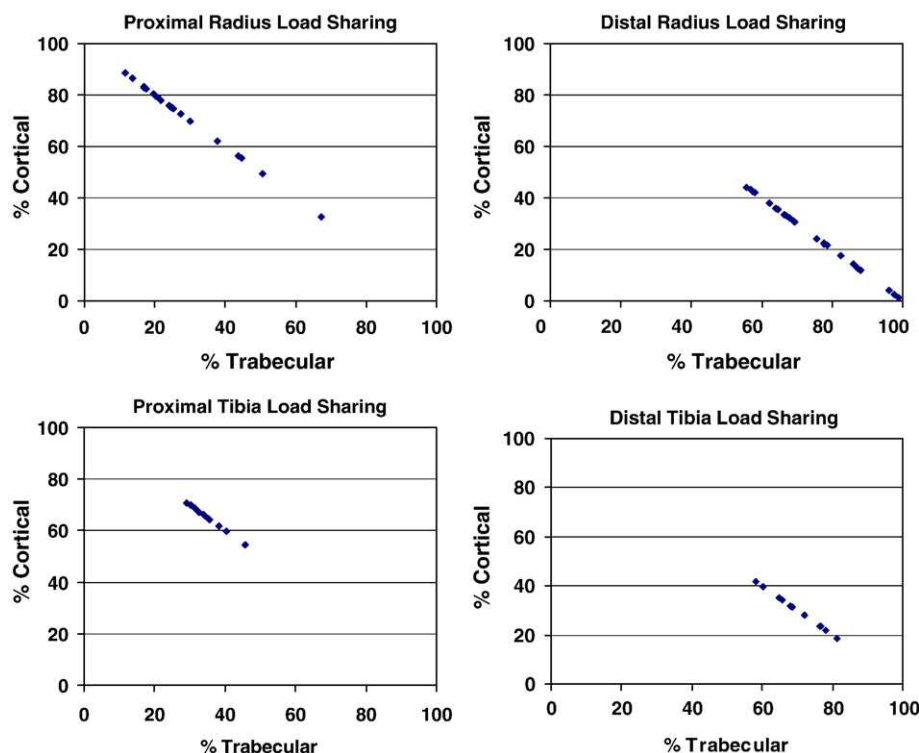


Fig. 4. Proximal (left) and distal (right) load sharing of the radius (above) and tibia (below). The percentage of the load carried by the trabecular load is given on the abscissa and the percentage of the load carried by the cortical bone is given on the ordinate axis.

section. The tibia was found to have less variation in load distributions, as the mean load carried by the trabecular bone at the distal face of the cross section was found to be 71% of the total, which reversed to 35% at the proximal face of the cross section.

A sub-volume cube of trabecular bone was extracted from each radius and tibia sample and the full stiffness matrix in the best orthotropic coordinate system was determined. It was found that the trabecular bone apparent Young's modulus had a moderate correlation ($R^2=0.431$) to apparent Young's modulus

in the radius and a poor correlation ($R^2=0.134$) to apparent Young's modulus in the tibia (Table 4).

Discussion

This study investigated morphological, density, apparent stiffness, and apparent Young's modulus bone measurements, performed on HR-pQCT image data using standard clinical protocols of the distal radius and tibia. The ability of bone apparent stiffness and apparent Young's modulus measurements to be predicted using morphological and density measurements was determined. This study also explored the relative importance of cortical and trabecular bone in carrying loads in the human distal radius and tibia, and the ability of trabecular bone apparent Young's modulus to predict the apparent Young's modulus of radius and tibia sections.

A limitation of this study was that a homogenous Young's modulus was used for all voxels in the finite element analyses and did not take into account the variation in tissue modulus that likely occurs with density. This may increase the error of bone apparent stiffness and apparent Young's modulus measurements in subjects with thin trabeculae, which are likely influenced by partial volume effects. This method also likely leads to an overestimation of the contribution of structural parameters to apparent stiffness and apparent Young's modulus. The influence of bone density is removed from the finite element analyses, and therefore, the results are only influenced by bone structure. This was confirmed by the importance of structural parameters in the multiple regression analysis. The results of this study cannot be

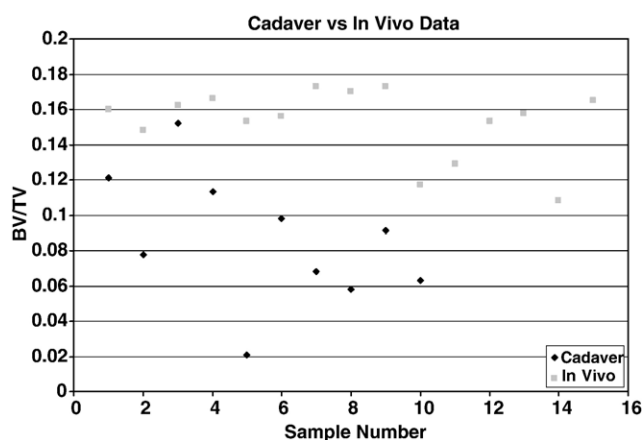


Fig. 5. Comparison of bone volume ratio cadaver and in vivo data. The cadaver data was found to be generally lower due to subject age, however, overlap of the data was observed.

verified with mechanical testing as the majority of the measurements were performed *in vivo* on human subjects; however, finite element modeling has been previously shown to correlate well with experimental results [11,18]. The boundary conditions used in this study were uniaxial compression in the primary loading direction. The predictive ability of the morphological and density measurements can not be assumed to be the same for loading in other directions, or for complex loading conditions. However, it is likely that bone apparent stiffness and apparent Young's modulus, in other loading directions and under complex loading, will also be strongly correlated to the same morphological and density parameters shown to be good predictors in this study. The boundary condition used to find the Young's modulus of the trabecular bone was uniaxial strain, compared to uniaxial displacement for the full radius and tibia models. The measurements of Tb. *E* will represent the upper limit and maybe slightly overestimated [21], however, this should not significantly affect the correlations. *In vivo* and cadaver data were pooled in this study. However, as can be seen in Fig. 5, the cadaver data was generally lower, likely due to subject age, but overlap with the *in vivo* data was observed. The cadaver scans were completed with all of the soft tissue intact and used the same protocol as the *in vivo* scans.

Overall, morphological and density measurements in the radius were shown to be better predictors of radius bone apparent stiffness and apparent Young's modulus, than in the tibia. However, by combining multiple measurements, a strong predictive ability was shown for morphological and density measurements in the radius and tibia, which may allow them to function as initial indicators of fracture risk. Volumetric BMD was found to have the highest correlation to bone apparent Young's modulus and to correlate better to bone apparent Young's modulus in this study than BMD measured using DXA in previous studies [10,11]. However, it was found that BV/TV was the best predictor of bone apparent stiffness in the distal radius, and this agrees well with previous studies investigating distal radius failure load [11,18]. The addition of other measurements to volumetric total BMD was found to significantly improve the ability to predict both bone apparent stiffness and apparent Young's modulus. Therefore, morphological and compartmental measurements of Tb. BMD and cortical BMD may be crucial to predicting fracture in the distal radius and tibia. Cross sectional area, BV/TV, and Ct.Th were shown to be significant measurements for predicting both bone apparent Young's modulus and apparent stiffness and further indicate the importance of 3D measurements. Measurements of morphology and density are clearly less time consuming to perform than a finite element analysis, and therefore may be used to determine whether a finite element analysis is warranted.

It was found that trabecular and cortical bone play equally important roles in carrying load in the distal radius and tibia. The standard areas measured with HR-pQCT were found to be transition regions in which the load is carried primarily by the trabecular bone at the distal face of the cross section, while the load is carried primarily by the cortical bone at the proximal face of the cross section. This may provide support to justify the

selected region of interest (9 mm section) as an ideal region to measure, as transition regions in mechanical structures are often areas of stress concentrations [22]. However, the type of fall and location of impact can significantly impact the loading environment, and will also likely have an important effect on the area of the wrist that fractures.

The ability to perform bone apparent stiffness and apparent Young's modulus measurements on a full distal radius and tibia section may have significant importance, as the apparent Young's modulus of a cube of trabecular bone, was found to only have a moderate correlation to apparent Young's modulus of the full section. It should be noted that these results may be an overestimation of the predictive ability of structural parameters, as the influence of bone density is removed from the finite element analyses, and the results were only influenced by bone structure. A direct measure of bone apparent Young's modulus may provide the ability to distinguish between two patients that have similar mean morphological and density measurements; but different overall structures, and therefore different fracture risk. Bone apparent Young's modulus is a measurement independent of subject size, whereas bone apparent stiffness is subject size dependent. The results of this study may improve the ability to predict fracture in a clinical setting using HR-pQCT, and therefore, may improve diagnosis and treatment of diseases such as osteoporosis.

References

- [1] Kleerekoper M, Villanueva AR, Stanciu J, Rao DS, Parfitt AM. The role of three-dimensional trabecular microstructure in the pathogenesis of vertebral compression fractures. *Calcif Tissue Int* 1985;37:594–7.
- [2] Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. *Endocr Rev* 2002;23:303–26.
- [3] Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332:767–73.
- [4] Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Meta-analyses of therapies for postmenopausal osteoporosis: IX. Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev* 2002;23:570–8.
- [5] Macneil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measured of bone quality. *Med Eng Phys* 2007 Jan 15 [Epub ahead of print].
- [6] Eamshaw SA, Cawte SA, Worley A, Hosking DJ. Colles' fracture of the wrist as an indicator of underlying osteoporosis in postmenopausal women: a prospective study of bone mineral density and bone turnover rate. *Osteoporos Int* 1998;8:53–60.
- [7] Andrade SE, Majumdar SR, Chan KA, Buist DS, Go AS, Goodman M, et al. Low frequency of treatment of osteoporosis among postmenopausal women following a fracture. *Arch Intern Med* 2003; 163:2052–7.
- [8] Cuddihy MT, Gabriel SE, Crowson CS, O'Fallon WM, Melton III LJ. Forearm fractures as predictors of subsequent osteoporotic fractures. *Osteoporos Int* 1999;9:469–75.
- [9] Mallmin H, Ljunghall S, Persson I, Naessen T, Krusemo UB, Bergstrom R. Fracture of the distal forearm as a forecaster of subsequent hip fracture: a population-based cohort study with 24 years of follow-up. *Calcif Tissue Int* 1993;52:269–72.
- [10] Newitt DC, Majumdar S, van Rietbergen B, von Ingersleben G, Harris ST, Genant HK, et al. *In vivo* assessment of architecture and micro-finite element analysis derived indices of mechanical properties of trabecular bone in the radius. *Osteoporos Int* 2002;13:6–17.

- [11] Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Rueggsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone* 2002;30:842–8.
- [12] Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 2005;90: 6508–15.
- [13] Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M, et al. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *J Bone Miner Res* 2006;21:124–31.
- [14] Eswaran SK, Gupta A, Adams MF, Keaveny TM. Cortical and trabecular load sharing in the human vertebral body. *J Bone Miner Res* 2006;21: 307–14.
- [15] Van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micro-mechanical finite-element models. *J Biomech* 1995;28:69–81.
- [16] Van Rietbergen B, Majumdar S, Pistoia W, Newitt DC, Kothari M, Laib A, et al. Assessment of cancellous bone mechanical properties from micro-FE models based on micro-CT, pQCT and MR images. *Technol Health Care* 1998;6:413–20.
- [17] Pistoia W, van Rietbergen B, Laib A, Rueggsegger P. High-resolution three-dimensional-pQCT images can be an adequate basis for in-vivo microFE analysis of bone. *J Biomech Eng* 2001;123:176–83.
- [18] Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Rueggsegger P. Image-based micro-finite-element modeling for improved distal radius strength diagnosis: moving from bench to bedside. *J Clin Densitom* 2004;7:153–60.
- [19] Keaveny TM, Wachtel EF, Ford CM, Hayes WC. Differences between the tensile and compressive strengths of bovine tibial trabecular bone depend on modulus. *J Biomech* 1994;27:1137–46.
- [20] Muller R, Rueggsegger P. Three-dimensional finite element modelling of non-invasively assessed trabecular bone structures. *Med Eng Phys* 1995;17:126–33.
- [21] Van Rietbergen B, Odgaard A, Kabel J, Huiskes R. Direct mechanics assessment of elastic symmetries and properties of trabecular bone architecture. *J Biomech* 1996;29:1653–7.
- [22] Beer FP, Johnston ER, DeWolf JT. *Mechanics of materials*. 4th ed. Boston: McGraw-Hill Higher Education; 2006.