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Variations in morphological and biomechanical indices at the distal radius in subjects with identical BMD

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Abstract

Determination of osteoporotic status is based primarily on areal bone mineral density (aBMD) obtained through dual x-ray absorptiometry (DXA). However, many fractures occur in patients with T-scores above the WHO threshold of osteoporosis, in part because DXA measures are insensitive to biomechanically important alterations in bone quality. The goal of this study was to determine – within groups of subjects with identical radius aBMD values – the extant variation in densitometric, geometric, microstructural, and biomechanical parameters. High resolution peripheral quantitative computed tomography (HR-pQCT) and DXA radius data from males and females spanning large ranges in age, osteoporotic status, and anthropometrics were compiled. 262 distal radius data sets were processed for this study. HR-pQCT scans were analyzed according to the manufacturer's standard clinical protocol to quantify densitometric, geometric, and microstructural indices. Micro finite element analysis was performed to calculate biomechanical indices. Factor of risk of wrist fracture was calculated. Simulated aBMD calculated from HR-pQCT data was used to group scans for evaluation of variation in quantified indices. Indices reflecting the greatest variation within aBMD level were BMD in the central portion of the trabecular compartment (max CV 142), trabecular heterogeneity (max CV 90), and intra-cortical porosity (max CV 151). Of the biomechanical indices, cortical load fraction had the greatest variation (max CV 38). Substantial variations in indices reflecting density, structure, and biomechanical competence exist among subjects with identical aBMD levels. Overlap of these indices among osteoporotic status groups reflects the reported incidence of osteoporotic fracture in subjects classified as osteopenic or normal.

Keywords

HR-pQCT; DXA; BMD; bone structure; biomechanics

Introduction

Osteoporosis is a condition characterized by loss of bone mass and deterioration of micro-architecture, and manifests clinically as an increased incidence of fracture (Consensus

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Development Conference, 1991). Determination of osteoporotic status is based primarily on areal bone mineral density (aBMD) and the related T-score values obtained through dual x-ray absorptiometry (DXA). While aBMD has been shown to be clinically useful in predicting fracture in prospective studies (Cummings et al., 1993; Schott et al., 1998), it does not entirely determine fracture risk (Stone et al., 2003; Sornay-Rendu et al., 2005) or fully capture the impact of therapeutic interventions (Black et al., 1996; Delmas and Seeman, 2004). Over half of osteoporotic fractures occur in patients with aBMD above the WHO threshold of osteoporosis (Schuit et al., 2004; Siris et al., 2004; Sornay-Rendu et al., 2005), in part because DXA measures are insensitive to biomechanically important alterations in bone quality. Therefore the clinical and research communities now agree that fracture prediction based exclusively on DXA measurement is limited.

Recent technological advances have made possible non-invasive high-resolution assessment of bone quality. High-resolution peripheral quantitative computed tomography (HR-pQCT) provides the ability to quantitatively assess volumetric bone mineral density (vBMD) as well as geometric and microstructural features of human cortical and trabecular bone in a compartmental fashion in the appendicular skeleton (Boutroy et al., 2005; Khosla et al., 2006; MacNeil and Boyd, 2007). Micro-finite element (μ FE) analysis based on models derived from HR-pQCT image data provide estimates of biomechanical indices of structural competence (MacNeil and Boyd, 2007; Boutroy et al., 2008; Mueller et al., 2009).

Evaluation of these structural and biomechanical parameters is critical in understanding bone mechanics, assessing fracture risk, and evaluating responses to disease, age, and therapy. Bone structure assessed by HR-pQCT has been shown to discriminate fracture cases from controls independent of aBMD (Sornay-Rendu et al., 2007). Trabecular bone structure is also critical in the evaluation of therapeutic intervention (Chesnut and Rosen, 2001; Riggs and Melton, 2002). Improved predictions of biomechanical properties have been found as a result of including measures of bone structure in addition to densitometric data in statistical regressions (Gordon et al., 1998; Link et al., 2003; Muller et al., 2003). Furthermore, biomechanical indices assessed by μ FE analyses provide information about skeletal fragility not captured by BMD or microstructure measures alone (Boutroy et al., 2008; Vilayphiou et al., 2010).

Despite these advances in bone quality assessment, DXA remains the clinical standard for reasons of cost, ease of use, and standardization. DXA-based aBMD and T-score values are used to rank patients in terms of fracture risk, often without consideration of important structural and biomechanical factors. The goal of this study was to determine – within groups of subjects with identical distal radius aBMD values – the extant variation in densitometric, geometric, microstructural, and biomechanical parameters. We performed this analysis in a pool of subjects that included both males and females and presented large variations in age, osteoporotic status, and anthropometrics. This work is novel in quantifying the ranges in structure and mechanical competence across subjects having an identical aBMD and reinforces the importance of high-resolution volumetric imaging in bone quality assessment.

Materials and Methods

Subjects

HR-pQCT and DXA radius data were drawn from a database compiled from two imaging studies. The first patient cohort is part of a longitudinal investigation into the effects of alendronate on bone microarchitecture and has been described in detail in previous publications (Kazakia et al., 2008). In this cohort, post-menopausal women (n=53) defined as osteopenic were recruited and imaged at 3 time-points. The women were included if they

were between the ages of 45 and 65 at the baseline time-point, had been post-menopausal for at least 1 year, and exhibited low BMD (T-score range -1.1 to -2.5) by DXA at one of the central scan regions. The second cohort, also described in detail elsewhere (Sode et al., 2010), consisted of male and female volunteers between the ages of 20 and 78 years (female: $n=87$, male: $n=55$) for a normative cross-sectional study. For both imaging studies, history of or evidence for metabolic bone disease other than postmenopausal bone loss was an exclusion criterion, as was treatment within the previous year with any compound known to influence bone turnover. The UCSF Committee of Human Research approved the study protocols and all subjects gave written, informed consent prior to participation. A total of 262 radius data sets were processed for this study.

DXA measurements

Bone densitometry data were acquired using DXA in a subset of the subjects. Only those DXA data sets obtained from post-menopausal women and men age 50 or older ($n=173$) were used in this study, in order to adhere to the osteoporotic status definition of the International Society for Clinical Densitometry. Scans were obtained with either the QDR 4500 (Hologic Inc.) or the Lunar Prodigy (GE Healthcare). The standard 1/3 radius region of interest (ROI) used for clinical assessment of osteoporosis status and the ultra-distal ROI were identified automatically by the scanner software, and used to determine T-scores based on the standard NHANES III database. Previous studies have found differences in absolute aBMD measurements but no significant differences in T-scores between devices from these manufacturers (Faulkner et al., 1996; Shepherd et al., 2002; Prevrhal et al., 2005).

HR-pQCT imaging

All subjects were imaged on an HR-pQCT system (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) using the manufacturer's standard protocol described in previous patient studies (Melton et al., 2007; Sornay-Rendu et al., 2007; Kazakia et al., 2008). The scan region spanned 9.02 mm in length beginning 9.5 mm proximal to the mid-jointline, extending proximally. Following the standard protocol, scans were performed using a 60 kVp X-ray source potential and 900 μ A X-ray tube current. A 3072×256 element CCD detector acquired 750 projections at 100 ms integration time per rotation. The 12.6 cm field of view (FOV) was reconstructed across a 1536×1536 matrix yielding 82 μ m voxels. The reconstructed linear attenuation values were converted to hydroxyapatite (HA) mineral densities using a calibration equation determined by scanning a phantom (Scanco Medical AG) containing rods of HA-resin mixtures (0, 100, 200, 400, and 800 mg HA/cm³). Beam hardening effects were further reduced in calibration and patient scans by applying a software beam hardening correction (Burghardt et al., 2008). Representative cross-sectional images are shown in Figure 1.

HR-pQCT analysis

HR-pQCT data were evaluated using the standard patient-style evaluation routines provided by the manufacturer. In this technique, the periosteal perimeter is identified using an edge-finding algorithm which produces a periosteal contour. The total volumetric bone mineral density (vBMD) is calculated from the volume contained within this contour. The cortical compartment is isolated by a two-step segmentation that applies a Gaussian blur followed by thresholding using a fixed pixel intensity criterion. Cortical volumetric BMD (Ct.vBMD) is calculated as the mean density of voxels in the segmented cortical compartment. Cortical thickness (Ct.Th) is calculated as cortical area (Ct.Ar) divided by periosteal contour perimeter (Ct.Pm). Trabecular cross sectional area (Tb.Ar) is calculated from the trabecular compartment identification. The trabecular volume fraction (BV/TV) calculation is based on volumetric BMD in the trabecular compartment (Tb.vBMD) and an assumed tissue density value of 1200 mg HA/cm³. To extract trabecular structure a Laplace-Hamming filter is

applied to the original grayscale data and a fixed global threshold is applied to binarize the bone and background phases (Laib and Ruegsegger, 1999). Tb.N is measured using direct 3D methods as the inverse of the distance between trabecular mid-axes (Hildebrand and Ruegsegger, 1997; Laib et al., 1997). Based on the densitometric BV/TV and direct Tb.N, Tb.Th and Tb.Sp are derived using plate model assumptions (Parfitt, 1987). Trabecular heterogeneity is defined as the standard deviation of trabecular spacing as defined by the distance between trabecular mid-axes (Tb.1/N SD). An extended cortical compartment segmentation technique, described in detail previously (Buie et al., 2007; Burghardt et al., 2010), was applied for the evaluation of cortical microstructure. Based on this segmentation intra-cortical porosity (Ct.Po) was defined as the ratio of pore volume to total cortical volume.

To group by aBMD level, an aBMD value was needed for each image data set. Simulated aBMD was calculated for each radius from the HR-pQCT data using a technique introduced and validated previously (Burghardt et al., 2009). This technique was developed to simulate clinical measurements of aBMD at the distal radius using an automated algorithm that aligns and segments the distal forearm in a way that mimics the subject positioning, soft tissue correction, and ROI analysis used in clinical DXA examinations of the distal radius. HR-pQCT-based aBMD correlates strongly with aBMD of both manufacturers (Hologic: $R^2=0.82$, Lunar: $R^2=0.87$), but underestimates aBMD for both DXA devices ($p < 0.0001$) (Burghardt et al., 2009).

μFE Analysis

Linear μFE analysis was applied to calculate apparent biomechanical properties under uniaxial compression. The details of the technique are described in detail elsewhere (Müller and Ruegsegger, 1995; Burghardt et al., 2010). Briefly, the binary image data set was converted to a mesh of isotropic brick elements and each element was assigned an elastic modulus of 10 GPa (Van Rietbergen et al., 1995) and a Poisson's ratio of 0.3 (Van Rietbergen et al., 1996). Uniaxial compression in the superior-inferior direction was applied to a strain of 1%. An iterative solver (Scanco FE Software v1.12, Scanco Medical) was used to compute reaction forces at the proximal and distal ends of the scan region for the prescribed displacements. For each model, stiffness (K), apparent modulus (E), and load fraction for the cortical compartment (Ct.LF) at the distal face were calculated. Failure load (F) was estimated according to the method described previously (Pistoia et al., 2002).

Factor of risk calculation

Factor of risk for wrist fracture (Φ) was calculated using anthropometric and biomechanical data. The factor of risk is defined as the applied load divided by the estimated failure load, providing a measure of an individual's likelihood of sustaining a wrist fracture during a fall onto an outstretched hand from standing height (Chiu and Robinovitch, 1998; Muller et al., 2003). The applied load was calculated as the product of a damping constant (670 Ns/m) and the impact velocity (Chiu and Robinovitch, 1998; Muller et al., 2003). Failure load (F) was estimated by μFE analysis.

Data analysis

Densitometric, geometric, microstructural, and biomechanical data were compiled for each data set and grouped by simulated aBMD level. Data were also grouped by osteoporotic status as determined by 1/3 and ultra-distal radius T-score. Outliers were reviewed to ensure adequate HR-pQCT image quality; based on this review none of the outliers were excluded (image data were reviewed and necessary exclusions made during the establishment of the two original databases). Coefficient of variation (CV) and percent variation of each parameter were calculated within each aBMD level and osteoporotic status group.

Variability gauge charts were created for visualization. Linear regression models were constructed to evaluate correlations between aBMD and HR-pQCT indices, with coefficients of determination calculated from Pearson correlations. Analysis of variance (ANOVA) and Tukey-Kramer tests were used to compare parameter means between osteoporotic status groups.

Results

The variations in densitometric, geometric, microstructural, and biomechanical indices within each aBMD group are reported (Table 1). aBMD values were normally distributed about a mean of 0.33 g/cm^2 . Maximum and mean CV within aBMD levels are reported as summary statistics. Indices reflecting the greatest variations within aBMD levels were vBMD in the central portion of the trabecular compartment ($\text{Tb.vBMD}_{\text{inn}}$; max CV 142), Tb.1/N SD (max CV 90), and Ct.Po (max CV 151). Of the biomechanical indices, Ct.LF had the greatest variation (max CV 38). CV analysis performed on a subset of data grouped by DXA-based Tscore rather than simulated aBMD also found $\text{Tb.vBMD}_{\text{inn}}$ (max CV 141), Tb.1/N SD (max CV 63), and Ct.Po (max CV 118) to display the greatest variations within groups.

Representative images of aBMD pairs (Fig. 1) illustrate visually dramatic distinctions in geometry as well as trabecular and cortical microstructure. Variations between pairs in Tb.N , Tb.1/N SD , and Ct.Po are particularly appreciable in these images. These structural variations are accompanied by differences in density and load distribution.

Variability gauge charts for densitometric, geometric, microstructural, and biomechanical indices are presented individually (Fig. 2–5). Considerable overlap is seen between each adjacent pair of aBMD levels. As expected, densitometric indices were positively correlated with aBMD values ($R^2 = 0.73$ to 0.37 , $p < 0.0001$). Cortical geometric indices Ct.Ar and Ct.Th were also positively correlated with aBMD ($R^2 = 0.80$ and 0.70 , respectively, $p < 0.0001$) while Tb.Ar had no detectable correlation with aBMD. Microstructural indices showed weak but significant correlations with aBMD. In the trabecular compartment, Tb.N and Tb.Th were positively associated with aBMD ($R^2 = 0.25$ and 0.48 , respectively, $p < 0.0001$) while Tb.Sp and Tb.1/N SD were negatively associated with aBMD ($R^2 = 0.27$, and 0.17 respectively, $p < 0.0001$). In the cortex, Ct.Po was negatively associated with aBMD ($R^2 = 0.11$, $p < 0.0001$). Biomechanical indices showed strong correlations with aBMD with the exception of Ct.LF , which had a subtle but significant negative correlation with aBMD ($R^2 = 0.14$, $p < 0.0001$). Finite element analysis parameters K , E , and F were positively associated with aBMD ($R^2 = 0.77$, 0.61 and 0.83 , respectively, $p < 0.0001$) while factor of risk was negatively associated with aBMD ($R^2 = 0.80$, $p < 0.0001$).

Distributions of biomechanical indices for data sets grouped by osteoporotic status based on the 1/3 radius ROI demonstrate considerable overlap among normal, osteopenic, and osteoporotic subjects (Fig. 6). Statistically significant differences in means were found for K (normals greater than osteopenic or osteoporotic, $p < 0.01$), F (normals greater than osteopenic or osteoporotic, $p < 0.02$), and Φ (osteoporotic greater than normals, $p < 0.01$). Using osteoporotic status classification based on the ultra-distal ROI (more closely matched to the HR-pQCT analysis volume), significant differences were found among all normal, osteopenic, and osteoporotic groups for every biomechanical index ($p < 0.0001$) with the exception of Ct.LF .

Discussion

This study quantifies the variation of densitometric, geometric, microstructural, and biomechanical parameters at the distal radius in subjects with identical aBMD values. These variations are important to quantify because they can influence fracture risk as well as the interpretation of therapeutic response. Despite the utility of DXA measurements in the clinical management of patients, variations in architecture and biomechanical indices are not appreciable through aBMD or T-score assessment. Therefore an understanding of the possible variations may aid in the interpretation of DXA results.

Microstructural parameters demonstrating the greatest variations within aBMD level included trabecular heterogeneity and cortical porosity. Trabecular heterogeneity has been documented to have a strong association with fracture risk, and is greater in subjects with a history of osteoporotic fracture than in controls (Laib et al., 2002; Boutroy et al., 2005; Sornay-Rendu et al., 2007). In two studies by Boutroy *et al*, one including a wide range of ages and BMD values and the second including only postmenopausal women, differences of 25.6% (Boutroy et al., 2005) and 73% (Boutroy et al., 2008) in trabecular heterogeneity were the largest differences between fracture and control groups of the densitometric and architectural measures quantified by DXA and HR-pQCT. Additionally, Sornay-Rendu *et al* reported a 31% difference and Melton *et al* a 28% difference (Sornay-Rendu et al., 2007; Melton et al., 2009) between fracture and control groups. Again, of the measures evaluated, these were the greatest percent differences between groups. In our study, intra-group Tb.1/N SD variations were greater than these reported differences (variations exceeding 73% were found in 9 of the aBMD groups), suggesting that patients sharing a common T-score value may have dichotomous fracture history and fracture risk. Cortical porosity has also been reported to play an important role in biomechanics at the radius (Burghardt et al., 2008) and other sites (Bell et al., 1999; Bell et al., 2000) and, accordingly, is the focus of much attention in recent work evaluating cortical microstructure and therapeutic efficacy (Burr; Macdonald et al., 2010; Nishiyama et al., 2010; Zebaze et al., 2010). Large variations in Ct.Po within aBMD groups indicate that important microstructural and biomechanical differences exist in the cortical compartment of subjects sharing a single aBMD level and osteoporotic status.

The biomechanical measure demonstrating the greatest variation within aBMD groups was Ct.LF. This parameter had a weak correlation with aBMD and was the only biomechanical measure to have no demonstrable association with osteoporotic status. The negative correlation between Ct.LF and aBMD may indicate a compensatory mechanism wherein the cortical compartment assumes a greater load carrying capacity in response to osteoporotic structural changes in the trabecular compartment. However, our results show that much variation exists in the compartmental localization of structural deficits associated with changes in BMD. From this we infer that structural deficits associated with decreased BMD may be manifested by change in either the cortical or trabecular compartment.

A limitation of this work is that equivalent DXA data were not available for all subjects. A subset of the subjects had been scanned using one of two DXA devices known to produce significantly different aBMD values (Shepherd et al., 2002; Prevrhal et al., 2005). Another group of subjects had not undergone DXA scanning. To overcome this limitation, simulated aBMD was calculated from HR-pQCT data in place of DXA-based aBMD for all data sets examined. This produced comparable aBMD values for grouping and variation analysis.

The determination of osteoporotic status based on 1/3 radius or ultra-distal radius T-scores is not established for clinical diagnosis. According to the official position of the International Society for Clinical Densitometry, osteoporotic status is preferably determined based on T-

score of the lumbar spine, total hip or femoral neck. In circumstances where central BMD is not available, the 1/3 radius T-score may be used. Peripheral BMD can be used to assess fracture risk, but device- and site-specific cut points must be used for highest fracture risk accuracy (Miller et al., 2002). Distal radius aBMD is significantly correlated with aBMD measured at both lumbar spine and total hip ($r=0.54$ and 0.60 respectively, $p<0.001$) (Liu et al., 2010). Regardless, the use of radius T-score for the determination of osteoporotic status in this work is for comparison of ranked T-score groups rather than for discussion of results in the context of clinically diagnosed osteoporotic status. Further, our study does not include a fracture incidence cohort. No direct conclusion can be drawn from this work regarding correlations of predictive measures with fracture. Analysis of metric variability in aBMD-matched cohorts with and without fracture would be valuable.

Substantial variations in microstructural indices associated with biomechanical competence and fracture risk exist among subjects with identical aBMD levels. Overlap of these indices among aBMD groups reflects the reported high incidence of osteoporotic fracture in subjects classified in osteopenic or normal according to DXA-based T-score. These observations highlight the importance of volumetric, spatially-resolved imaging techniques in the evaluation of bone quality.

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Figure 1. Representative images of subjects with identical aBMD and T-score at the ultra-distal radius and large variations in select architectural and biomechanical indices. A single, mid-stack slice from each HR-pQCT image data set is shown. Image pairs are scaled appropriately to maintain relative size and image intensity values.

Figure 2.

Densitometric indices for the distal radius calculated from HR-pQCT image data: volumetric bone mineral density of the entire radius (vBMD), the cortical compartment (Ct.vBMD), the trabecular compartment (Tb.vBMD), and a central portion of the trabecular compartment (Tb.vBMD_{inn}). Scans are grouped by aBMD, calculated by HR-pQCT-based simulation.

Figure 3.

Geometric indices for the distal radius calculated from HR-pQCT image data: area of the cortical compartment (Ct.Ar) and of the trabecular compartment (Tb.Ar), cortical perimeter (Ct.Pm), and cortical thickness (Ct.Th). Scans are grouped by aBMD, calculated by HR-pQCT-based simulation.

Figure 4.

Microstructural indices for the distal radius calculated from HR-pQCT image data: trabecular number (Tb.N), thickness (Tb.Th), separation (Tb.Sp), and heterogeneity (Tb.I/N SD), and intra-cortical porosity (Ct.Po). Scans are grouped by aBMD, calculated by HR-pQCT-based simulation.

Figure 5.

Biomechanical indices for the distal radius calculated by μ FE analysis of HR-pQCT image data: stiffness (K), apparent modulus (E), cortical load fraction at the distal face (Ct.Lf), and factor of risk for wrist fracture (Φ). Scans are grouped by aBMD, calculated by HR-pQCT-based simulation.

Figure 6. Biomechanical indices for the distal radius grouped by osteoporotic status as determined by 1/3 radius T-score. (osteoporotic n=13, osteopenic n=50, normal n=110)

Table 1

Densitometric, geometric, microstructural, and biomechanical indices were compiled and grouped by areal BMD (aBMD) level. Coefficient of variation (CV) within each aBMD level was calculated. Maximum and mean CV values are presented in this table; volumetric BMD in the central portion of the trabecular compartment (Tb.vBMD_{inn}), trabecular heterogeneity (Tb.1/N SD), and cortical porosity (Ct.Po) show the greatest variation within aBMD groups. A total of 262 data sets were processed for this study.

	vBMD	Ct.vBMD	Tb.vBMD	Tb.vBMD _{inn}
CV max	26	19	61	142
CV mean	10	6	16	28

	Ct.Ar	Tb.Ar	Ct.Pm	Ct.Th
CV max	43	44	22	49
CV mean	14	19	9	15

	Tb.N	Tb.Th	Tb.Sp	Tb.1/N SD	Ct.Po
CV max	64	26	68	90	151
CV mean	15	12	17	31	66

	K	E	Ct.LF	F	Φ
CV max	24	37	38	25	22
CV mean	11	14	16	10	9