Radiographic Morphometry and Densitometry Predict Strength of Cadaveric Proximal Humeri More Reliably Than Age and DXA Scan Density

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ABSTRACT: Methods are needed for identifying poorer quality cadaver proximal humeri to ensure that they are not disproportionately segregated into experimental groups for fracture studies. We hypothesized that measurements made from radiographs of cadaveric proximal humeri are stronger predictors of fracture strength than chronological age or bone density values derived from dual-energy x-ray absorptiometry (DXA) scans. Thirty-three proximal humeri (range: 39–78 years) were analyzed for: (1) bone mineral density (BMD, g/cm^2) using DXA, (2) bulk density (g/cm^3) using DXA and volume displacement, (3) regional bone density in millimeters of aluminum (mmAl) using radiographs, and (4) regional mean (medial+lateral) cortical thickness and cortical index (CI) using radiographs. The bones were then fractured simulating a fall. Strongest correlations with ultimate fracture load (UFL) were: mean cortical thickness at two diaphyseal locations ($r = 0.71$; $p < 0.001$), and mean mmAl in the humeral head ($r = 0.70$; $p < 0.001$). Weaker correlations were found between UFL and DXA-BMD ($r = 0.60$), bulk density ($r = 0.43$), CI ($r = 0.61$), and age ($r = -0.65$) (p values <0.01). Analyses between UFL and the product of any two characteristics showed six combinations with r-values >0.80, but none included DXA-derived density, CI, or age. Radiographic morphometric and densitometric measurements from radiographs are therefore stronger predictors of UFL than age, CI, or DXA-derived density measurements. © 2015 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 34:331–341, 2016.

Keywords: proximal humerus; fracture; morphometry; densitometry; DXA

There is increased interest in developing methods for determining which among many surgical methods should be employed for fixation or hemi-arthroplasty reconstruction of proximal humerus fractures. This is especially important in elderly patients because they are more likely to have poor quality bone (e.g., obviously osteopenic/osteoporotic with thin cortices in the proximal metaphysis/diaphysis).[1–6] In fact, more than 70% of proximal humeral fractures occur in patients older than 60 years.[7,8] In this context, age-related decreased bone quality of the proximal humerus can result in complications of: (1) shoulder prosthetic arthroplasty (e.g., intraoperative periprosthetic fracture),[9] and (2) fracture fixation such as poor screw purchase, postoperative loosening of the implant, and impaired healing.[10–15] Consequently, there is increased demand for cadaveric humeri because of their increased use in biomechanical studies that test these devices.[16] In these studies, the bones are usually randomly assigned to experimental groups, which could inadvertently result in some disproportionally stronger bones in some groups even though they do not significantly differ in chronological age. In these perspectives we used a cadaveric biomechanical model to determine the strengths of relationships between fracture load data (i.e., ultimate fracture load (UFL) and energy absorption) versus various bone radiographic morphologic and densitometric characteristics of the proximal humerus. More specifically, we sought to develop methods for estimating UFL and energy absorption capacity of cadaveric proximal humeri that, when compared to chronological age, can more reliably identify variations in bone quality for fracture studies.

To address this main goal, this study tested two hypotheses that were based on preliminary observations made in our prior biomechanical study that obtained UFL data from a relatively small sample of cadaveric proximal humeri.[16] Unpublished results of that study suggested that UFL might correlate more strongly with simple morphological measurements made on standard radiographs (e.g., cortical index and mean combined cortical thickness) of the proximal humerus when compared to BMD of the proximal humerus measured using dual-energy x-ray absorptiometry (DXA) scans. We speculated that this observation might reflect the well known limitations of DXA in determining fracture risk: (1) DXA does not measure true volumetric BMD (bone mineral density; units are "areal" (g/cm^2)), (2) DXA cannot distinguish between cortical and trabecular bone compartments, and (3) DXA does not have adequate resolution to measure cortical and trabecular architecture or histomorphology.[17–19] Age itself is also a major factor in determining fracture risk, independent of areal BMD. This is because there is a deterioration in bone "quality" with aging that is not captured by areal BMD.[20] The idea that simple measurements of proximal humerus morphology might more strongly predict UFL is also indirectly supported by: (1) epidemiological

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and laboratory studies that have considered simple measurements from radiographs of the humeral diaphysis in terms of correlating with aging, osteoporosis and/or humerus fracture risk,[5,21–25] and (2) observations that age-related changes in the tapered contour and reductions in the proportion (as a percentage of cross-sectional area) of the cortical bone of fracture prone metaphyseal regions (which is not captured by DXA scans) can strongly influence the risk of fracture in these regions from a ground-level fall.[26–28] In these additional perspectives, we hypothesized that simple measurements of bone density and morphology made using standard radiographs of cadaveric proximal humeri will correlate with UFL more strongly than age. We also hypothesized that the correlation of these simple measures of bone density/morphology with UFL would be stronger than the correlation of UFL with BMD data obtained from DXA scans.

METHODS

Specimens and Regional Density Analysis in Millimeters of Aluminum

With IRB approval (no. 11755, University of Utah) this study used 33 fresh-frozen cadaveric humeri with a mean age of 59 years and range of 39–78 years. The humeri were wrapped in towels soaked with normal saline to keep them moist throughout testing and preparation. This sample included 18 females (mean 61 years, range 42–78) and 15 males (mean 57 years, range 39–77). Twenty-four of these specimens were obtained from a previous study that tested repairs of simulated supraspinatus tendon tears at a slow rate of loading, which did not significantly reduce ultimate fracture load (UFL) and energy absorption (i.e., area under the load-deformation curve).[16] Prior to fracture testing, anterior-posterior (A–P) radiographs were taken of each humerus in neutral rotation next to an aluminum (Al) step wedge (one mm/step; two mm to 12.0 mm of Al). The rationale for using an Al step wedge is that: (1) it is a relatively simple and inexpensive way to standardize the graylevels of the radiographs, and (2) it allows regional density to be expressed in mmAl equivalents, which can be accomplished using linear regressions based on the gray-level values of each successive step of the step wedge.[29,30] Numerical values for mmAl were determined in four clinically relevant 1.0×1.0 cm regions of interest (ROIs) from the digitized radiographs: proximal (H1), middle (H2), and distal (H3) portions of the humeral head ("H"), and at the surgical neck (D1) and at D2 and D3 (Fig. 1).[31]

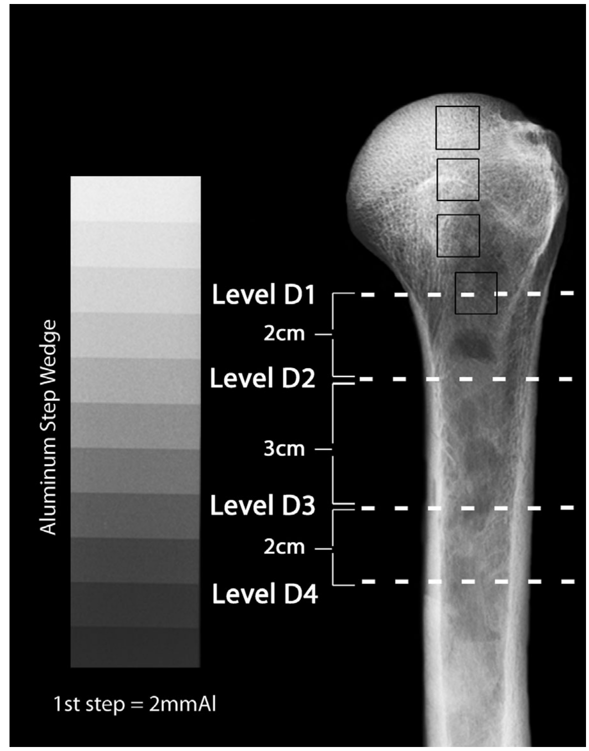

Figure 1. Anterior-posterior (A–P) view of a left cadaveric humerus showing the four locations (dashed white lines) of the metaphysis/diaphysis, where D1 is the surgical neck. From top to bottom, the dark squares indicate H1, H2, H3, (H = head) and D1 locations where mmAl measurements were made.

Proximal Humerus BMD/DXA and Volume Analysis

Dual-energy x-ray absorptiometry (DXA) scans (QDR-2000 Plus; Hologic Inc., Waltham, Massachusetts, USA) were used to determine the bone mineral density (areal BMD, g/cm^2) of the proximal humerus (actually the 'ultra-proximal' humerus = entire head and upper two cm of the metaphysis/diaphysis, D2 in Fig. 1).[32] During DXA scanning the bones were submerged in a water-bath as was done by Tingart et al.[32] The volume of each proximal humerus was then determined by submergence in water (precision error $\pm$ 0.5 cm^3). Whole-bone (bulk) density was calculated as the total grams of the area scanned using DXA divided by the submerged volume. The BMD (g/cm^2), proximal humerus volume (cm^3), and bulk density (g/cm^3, BMD/submerged volume) data were evaluated to determine their effects on fracture load.[33]

Proximal Humerus Radiographic Morphometry

Radiographs of the humeri were taken in air; they were not submerged in water. Cortical thickness, cortical index, and other simple linear measurements were made from the radiographs using a digital caliper with precision of $\pm$ 0.01 mm. Cortical index is defined as the summed thicknesses of the medial and lateral cortices divided by the outer bone diameter.[22,34] Thicknesses of the medial and lateral cortices and the diameters of the radiographed bones were measured at the surgical neck (D1), and at three diaphyseal ("D") locations at the following distances below D1: 2 cm (D2), 5 cm (D3), and 7 cm (D4) (Fig. 1). The A–P humeral head diameter was the only linear measurement that was made on the actual bones. Radiographic measurements were corrected for magnification error using an object of known diameter that was placed adjacent to the bone at one-half of the A–P diameter at D2. Supporting our use of radiographic measurements, a very high correlation has been reported between cortical thickness based on radiographs and that determined from direct anatomical measurements of the proximal humeral diaphysis ($r = 0.98$, $p < 0.01$).[32]

Calculation of Mean Data Values, and Analysis of Observer Reproducibility

For calculating mean data values and for assessing intra- and inter-observer measurement variability, three investigators performed each measurement twice. Additional measurements were made to determine what effect humerus internal and external rotation would have on measurement error. For this analysis, five bones were measured for cortical thicknesses and cortical indices at the same locations described above. These bones were measured in neutral rotation (i.e., the orientation used in the present study) and with 5° and 10° internal, and 5° and 10° external rotation. These rotation magnitudes would be expected to exceed inadvertent rotation error (i.e., estimated to be less than ±5°).[35]

Fracture Testing

Each humerus was loaded in a manner that simulated a backwards fall,[16,36] which included applying a force at 2 mm/sec with a dish-shaped steel device (frustrum) that contacted the superior-posterior aspect of the humeral head with the diaphysis in 30° of extension (Fig. 2) (Bionix 858; MTS Inc, Minneapolis, Minnesota, USA).[37] Test data, recorded on load-deformation curves, included: (1) UFL (N, newtons), and (2) area under the load-deformation curve (i.e., total energy absorbed, N-m).[38]

Each bone was examined to determine the fracture pattern (the numerical designations are in parentheses): two-part surgical neck (1), two-part anatomical neck (1), two-part other (1), greater tuberosity (2), three-part (3), four-part (4), head split (5), or some combination of the preceding patterns without (6) or with (7) greater tuberosity fracture. Rationale for these numerical designations are derived from clinical observations suggesting that they represent, in

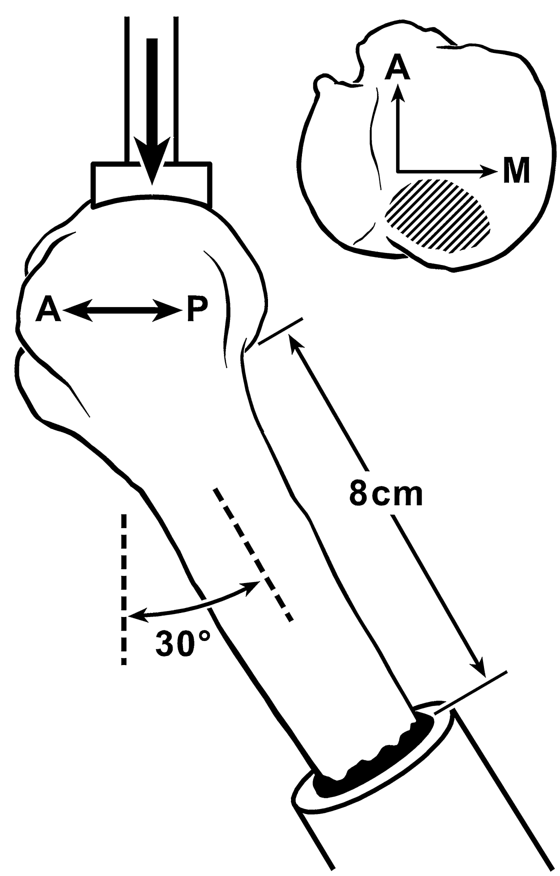

Figure 2. (A) Diagram of a loaded left humerus in lateral view; A = anterior; P = posterior. (B) View of the superior humeral head showing the area (oblique lines) where the force was applied to the humeral head; A = anterior; M = medial.

ascending order, lower to higher skeletal fragility and/or energy absorption.[1,39]

The data were analyzed using commercially available software (NCSS 10.0 and PASS 13, Number Cruncher Statistical System™, Kaysville, Utah, USA). Using data from the smaller sample of cadaver humeri from our prior study,[16] power analyses were conducted to determine the sample sizes needed to ensure adequate age-related variations in UFL and in the simple-to-measure radiographic parameters. The rationale for using age was that a sufficiently broad age range would likely provide a sufficiently broad range of bone strength. This was accomplished by segregating the prior data set into younger and older bones based on a 60-year cutoff (unpublished results; $n = 11$ younger bones; $n = 12$ older bones). An a priori distinction was not made for male versus female sex. The parameters evaluated included: (1) UFL, (2) mean combined cortical thickness at D3-D4, and (3) mmAl at H2. In order to provide 90% power ($\beta = 0.1$) to detect a significant difference ($\alpha < 0.05$) between younger and older age groups,[40] the number of bones required in each age group is at least: (1) $n = 13$ for UFL, (2) $n = 10$ for mean combined cortical thickness, and (3) $n = 12$ for mmAl at H2. Consequently, for the present study the sample was increased to a minimum of 15 in each age group. When using DXA-BMD data from this prior data set, detecting a difference at $\alpha < 0.05$ in this parameter between the two age groups when using $n = 15$/group could be achieved only at 75% power ($\beta = 0.25$).

Differences between fracture loads and other parameters were evaluated using Fisher's PLSD test (ANOVA). Results are expressed as means and standard deviations. Fracture data were also analyzed in terms of relationships with the combination (products or quotients) of two characteristics (i.e. "combined characteristics"), which were evaluated with Pearson product-moment or Spearman coefficients (r values). The rationale for examining products and quotients was to determine if these simple expressions could provide stronger correlations with the fracture data when compared to the individual characteristics. Differences in correlation coefficients between different comparisons were assessed for statistical significance ($p < 0.05$) using Fisher's z test for comparing two correlation coefficients.[40,41] These comparisons between two correlation coefficients (e.g., correlation coefficient of UFL and age vs. correlation coefficient of UFL and cortical index at D1) were made in these contexts: (1) males versus females, and (2) male and female data combined.

RESULTS

Table 1 summarizes comparisons between the bones from the younger and (<60, $n = 18$; 9 male and 9 female) and older (>60, $n = 15$; 6 male and 9 female) groups. Notably, among the six bones from cadavers that were older than seventy years there were two bones (both 77 year olds) that fractured at loads that were greater or similar to nine bones from 42 to 57 year olds (respectively, 4589.1 N and 5694.0 N vs. 2891.5–4670.8 N).

Intra- and inter-observer measurement differences were 2–5%, where the maximum error represented the single occurrence of a two millimeter inter-observer difference with respect to diameter meas-

Table 1. Descriptive Data and Paired Comparisons of Humeri From the Younger Group (<60, $n = 18$) [9 Male and 9 Female] versus the Older Group (>60, $n = 15$) [6 Male and 9 Female]

Characteristics*	Younger <60 yrs.	Older >60 yrs.	*p* value
Ultimate fracture load	5165.5 (1498.7)	3012.4 (1135.0)	**<0.001**
Energy absorption	16.0 (8.0)	6.4 (3.2)	**<0.001**
Morphometric			
P.H. Volume	78.5 (17.3)	71.8 (19.5)	0.3
H.H. AP Breadth	44.2 (3.4)	41.6 (4.2)	0.06
H.H. ML Breadth	51.8 (4.2)	49.2 (3.8)	0.08
Mean CT, D1	4.5 (0.6)	3.7 (1.1)	**0.01**
Mean CT, D2	6.1 (0.9)	4.5 (0.9)	**<0.001**
Mean CT, D3	7.9 (2.1)	5.3 (1.7)	**<0.001**
Mean CT, D4	9.2 (1.2)	6.2 (2.0)	**<0.001**
Avg. Mean CT (D1-D3)	6.2 (0.9)	4.5 (1.0)	**<0.001**
Avg. Mean CT (D1-D4)	6.9 (0.9)	4.9 (1.3)	**<0.001**
Avg. Mean CT (D3-D4)	8.6 (1.4)	5.7 (1.8)	**<0.001**
Cortical Index D1	0.15 (0.03)	0.14 (0.04)	0.3
Cortical Index D2	0.25 (0.05)	0.21 (0.04)	**0.01**
Cortical Index D3	0.34 (0.09)	0.26 (0.08)	**0.01**
Densitometric			
P.H. DEXA-BMD (g/cm^2)	0.38 (0.10)	0.25 (0.09)	**<0.001**
P.H. Bulk Density (g/cm^3)	0.13 (0.03)	0.10 (0.03)	**0.002**
H1 mmAl	7.2 (1.9)	5.9 (0.9)	**0.01**
H2 mmAl	7.8 (1.8)	5.9 (0.7)	**<0.001**
H3 mmAl	5.9 (1.4)	4.5 (0.9)	**0.002**
Avg. Head [H1-H3] mmAl	7.0 (1.6)	5.4 (0.8)	**0.002**
D1 mmAl	5.3 (1.1)	4.2 (0.8)	**0.003**
Avg. H1-D3 mmAl	6.5 (1.5)	5.0 (0.8)	**0.001**

*( ), standard deviation; P.H., proximal humerus; H.H., humeral head; AP, anterior-posterior; ML, medial-lateral; CT, cortical thickness; Avg., averaged; D, diaphysis; H, head. Statistically significant values are bolded and grayed.

urements in one bone. By contrast, all intra-observer analyses showed less than 1.5% differences in measurements made with neutral orientation and with $\pm 5^\circ$ rotations.

Gross examination of the area where the frustrum (i.e., the dish-shaped device) contacted the proximal humeri showed that: (1) none of the bones had evidence of impaction of the frustrum into the bone surface, and (2) 27 of the 33 bones (82%) had fracture surfaces that extended close to (i.e., within one centimeter) or within the contact area of the frustrum. The fractures with this proximity typically involved the greater tuberosity fracture portion of the overall fracture pattern. However, because high-speed videography was not done during testing, it was not possible to determine the locations where the fracture surfaces initiated. Gross inspection also revealed that in 25 of the 33 (76%) bones the fractures traversed the locations where radiographic mmAl density measurements were made at H1–H3 and D1.

Data from males and females were combined for all analyses described below after it was shown that correlation coefficients of comparisons of fracture data and all morphometric and densitometric characteristics (including individual and combined characteristics) did not exhibit any significant differences between males and females (all p values >0.12, with 95% of all p values >0.22).

Correlations of Individual Characteristics With UFL and Energy Absorption

Analysis of *individual* morphometric or densitometric characteristics versus UFL showed 17 of 22 (77%) comparisons with absolute r-values >0.50 (Table 2A). Notably, age, DXA values, and CI correlated less strongly than some of the measures of combined mean cortical thickness and humeral head density (mmAl). Figure 3 shows results of regression analyses of some of the comparisons, including regressions showing all data (Fig. 3 A1, B1, C1, D1) and separate regressions of male and female data (Fig. 3 A2, B2, C2, D2).

The highest correlations of energy absorption with each of the individual characteristics are shown in Table 2B. Notably, the medial-lateral breadth of the humeral head was the strongest correlate in this context.

There were no significant correlations between fracture pattern and any of the individual characteristics, including age. In contrast, fracture pattern versus the paired product or quotient combinations, significant correlations ($p < 0.05$) were found between fracture pattern and three product and 34 quotient

Table 2. (A) Comparisons of UFL Versus Various Morphometric and Densitometric Characteristics Considered Individually (all *r*-values are Shown). (B) Comparisons of Energy Absorption Versus Various Morphometric and Densitometric Characteristics Considered Individually (all *r*-values are Shown).

A: Characteristics*	*r* value	*p* value
Age	**−0.65**	**<0.001**
Morphometric		
P.H. Volume	**0.46**	**0.007**
H.H. AP Breadth	**0.58**	**<0.001**
H.H. ML Breadth	**0.64**	**<0.001**
Mean CT, D1	**0.40**	**0.02**
Mean CT, D2	**0.54**	**<0.001**
Mean CT, D3	**0.68**	**<0.001**
Mean CT, D4	**0.67**	**<0.001**
Avg. Mean CT (D1-D3)	**0.68**	**<0.001**
Avg. Mean CT (D1-D4)	**0.69**	**<0.001**
Avg. Mean CT (D3-D4)	**0.71**	**<0.001**
Cortical Index D1	0.30	0.09
Cortical Index D2	**0.40**	**0.02**
Cortical Index D3	**0.61**	**<0.01**
Densitometric		
P.H. DEXA-BMD (g/cm^2)	**0.60**	**<0.001**
P.H. Bulk Density (g/cm^3)	**0.43**	**0.01**
H1 mmAl	**0.70**	**<0.001**
H2 mmAl	**0.70**	**<0.001**
H3 mmAl	**0.61**	**<0.001**
Avg. Head [H1-H3] mmAl	**0.70**	**<0.001**
D1 mmAl	**0.58**	**<0.001**
Avg. H1-D3 mmAl	**0.70**	**<0.001**
B		
Age	**−0.62**	**<0.001**
Morphometric		
P.H. Volume	**0.53**	**0.002**
H.H. AP Breadth	**0.59**	**<0.001**
H.H. ML Breadth	**0.69**	**<0.001**
Mean CT, D1	0.21	0.2
Mean CT, D2	**0.45**	**0.01**
Mean CT, D3	**0.57**	**<0.001**
Mean CT, D4	**0.51**	**0.002**
Avg. Mean CT (D1-D3)	**0.53**	**0.001**
Avg. Mean CT (D1-D4)	**0.54**	**0.001**
Avg. Mean CT (D3-D4)	**0.57**	**<0.001**
Cortical Index D1	0.04	0.8
Cortical Index D2	0.23	0.2
Cortical Index D3	**0.44**	**0.01**
Densitometric		
P.H. DEXA-BMD (g/cm^2)	**0.57**	**<0.001**
P.H. Bulk Density (g/cm^3)	**0.35**	**0.05**
H1 mmAl	**0.65**	**<0.001**
H2 mmAl	**0.65**	**<0.001**
H3 mmAl	**0.51**	**<0.001**
Avg. Head [H1-H3] mmAl	**0.64**	**<0.001**
D1 mmAl	**0.47**	**0.01**
Avg. H1-D3 mmAl	**0.60**	**<0.001**

*P.H., proximal humerus; H.H., humeral head; AP, anterior-posterior; ML, medial-lateral; CT, cortical thickness; Avg., averaged; D, diaphysis; H, head. Statistically significant values are bolded and grayed.

combinations (results not shown). However, none of these correlations exceeded the absolute *r*-value of 0.46.

Correlations of Combined Characteristics With UFL and Energy Absorption

When analyzing UFL versus each of the paired product or quotient combinations, only six had absolute *r*-values >0.800, and all of these characteristics were *products* of morphometric *and* densitometric characteristics (Table 3). The *quotient* of any two morphometric and/or densitometric characteristics revealed no correlations with UFL that exceeded the absolute r-value of 0.561. Results using energy absorption data showed that: (1) in only one instance did the product of two characteristics have an r-value that exceeded the absolute value of 0.8 [(volume proximal humerus)•(mmAl at H2); $r = 0.808$], and (2) there were only two instances when the quotient of two characteristics exceeded the absolute *r*-value of 0.7 (but neither of these were greater than 0.8).

Correlations Between Mean Cortical Thickness or Cortical Index (CI) With BMD & UFL

When analyzing relationships between BMD and varying magnitudes of combined (medial+lateral) cortical thickness, BMD was not significantly different ($p \sim 0.6$) when using the 4 mm cutoff at the surgical neck (D1) (Table 4A). In contrast, BMD was significantly increased in the specimens with >4 mm at all other diaphyseal locations ($p < 0.02$). (A 4 mm threshold was evaluated because at this cut-off value Tingart et al. (2003) reported significant differences in BMD.) When the threshold was raised to 5 mm, BMD was also not significantly different ($p = 0.3$) at the surgical neck (D1). However, BMD was significantly greater in the specimens with >5 or 6 mm at all other diaphyseal locations ($p < 0.02$). Assessment of these additional mean cortical thickness thresholds was important because a statistically significant difference in the UFL or energy absorption was *not* found between the bones >4 mm at D3 and D4 versus those <4 mm ($p > 0.07$). By contrast, when using the 5 mm threshold, UFL was significantly greater ($p < 0.02$) and energy absorption trended towards being greater ($p = 0.06$) at D3 and D4. UFL and energy absorption were significantly greater in bones >6 mm at D3, D4, and D1-D4 ($p < 0.01$).

When analyzing the relationship between BMD and the 0.4 cortical index (CI) cutoff, BMD was significantly greater in the bones above the 0.4 CI threshold at the D3 and D4 ($p < 0.01$) (Table 4B). Ultimate fracture load was also significantly greater in the bones above the 0.4 CI threshold at the D3 and D4 ($p < 0.05$). By contrast, energy absorption was not significantly different between bones separated by the 0.4 CI cutoff at D3 and D4 (p values >0.07).

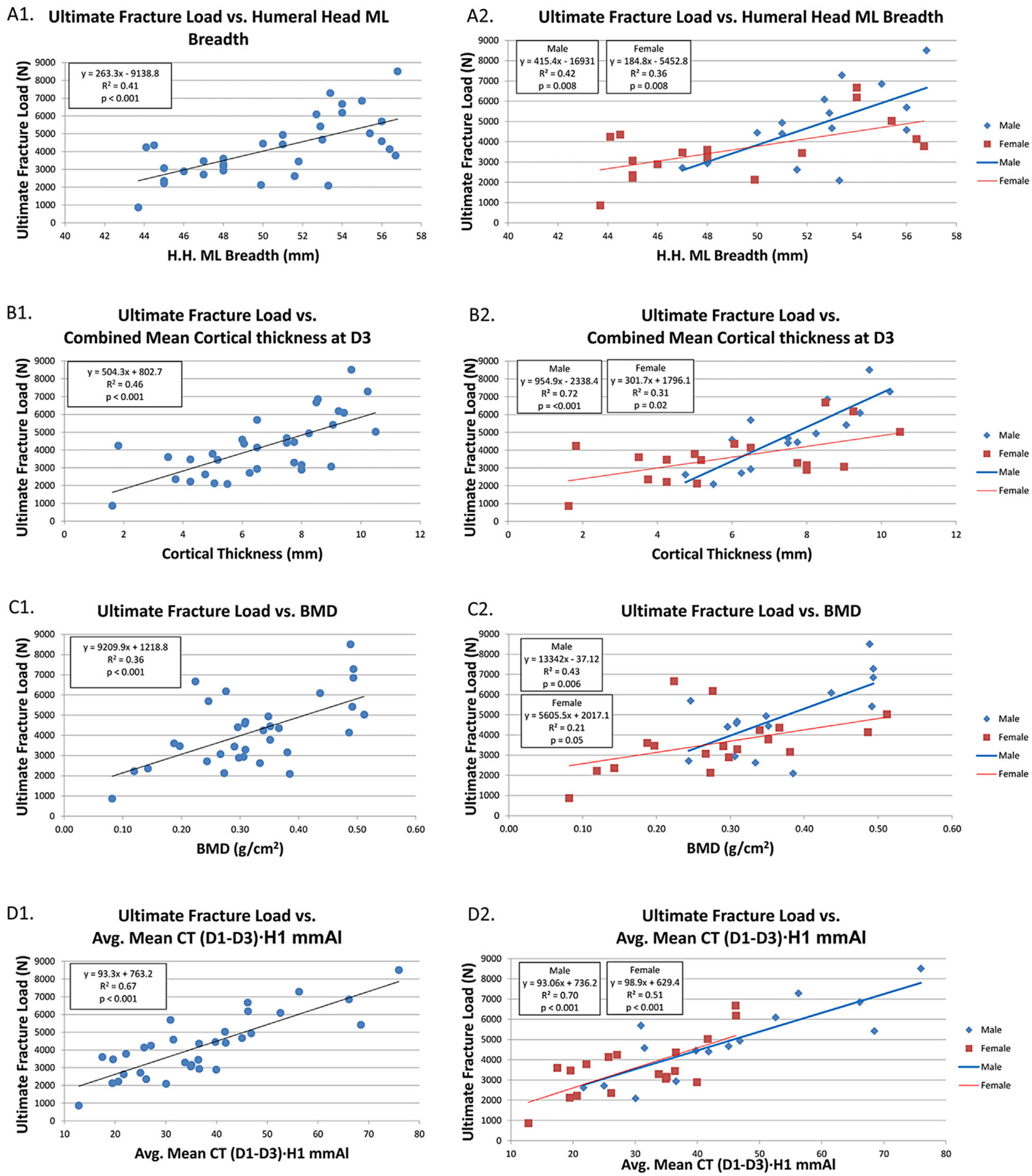

Figure 3. Linear regressions of UFL versus: (A) humeral head medial-lateral (ML) breadth, (B) combined mean cortical thickness at D3, (C) BMD derived from DXA measurements, and (D) averaged mean CT (D1-D3)•H1 mmAl. A1, B1, C1, and D1 indicate regressions with all data (i.e., males and females combined). A2, B2, C2, and D2 indicate regressions showing males and females in separate regressions. In each case (including those shown and not shown) of male versus female regressions there were no significant differences in the correlation coefficients.

Comparisons Between Two Correlation Coefficients

The strength of correlation coefficients between two regressions showed no differences that were clearly statistically significant when evaluating the comparisons that are most important in specifically testing the hypotheses of this study (Table 5). However, in this context the three strongest correlations shown in Table 3 (products of two characteristics) did show statistical trends (p values ~0.07) when compared to all other correlations of individual or "combined" (product or quotient) characteristics that are shown in Table 5 (see values with superscripted "**T**" in Table 5).

Table 3. Comparisons of UFL Versus the Product of two Characteristics (Shown are the Comparisons With Absolute r-values >0.800) (MULTIPLIED OR DIVIDED†) (Shown are Absolute r values Greater than $|0.800|$)

Characteristics*	r value	p value
Avg. Mean CT (D1-D3)•H1 mmAl	0.821	<0.001
Avg. Mean CT (D3-D4)•H1 mmAl	0.820	<0.001
Avg. Mean CT (D1-D4)•H1 mmAl	0.820	<0.001
P.H. Volume•Mean H1-D1 mmAl	0.814	<0.001
Mean CT (D3)•H1 mmAl	0.809	<0.001
Avg. Mean CT (D3-D4)•Mean H1-H3 mmAl	0.804	<0.001

†Note that all attempts at dividing any two characteristics revealed no correlations that exceeded the absolute value of $r = 0.561$. Avg., averaged for the "D" regions shown; CT, cortical thickness; D, diaphysis; H, head; P.H., proximal humerus.

Table 4. Comparisons of age, BMD, UFL (N), and Energy Absorption (N-m) at: (A) the Three Combined Mean Cortical Thickness Cutoffs, and (B) the 0.4 Cortical Index (CI) Cutoff

A. Cortical Thickness

	Mean Age		n		*P* values			
4 mm	<4 mm	>4 mm	<4 mm	>4 mm	Age	BMD	N	N-m
D1	63.1	56.8	12	21	0.1	0.6	0.2	0.9
D2	68.0	56.7	7	26	**0.01**	**0.006**	**0.04**	**0.05**
D3	68.5	57.8	4	29	0.07	**0.008**	0.08	0.1
D4	75.0	58.0	2	31	**0.03**	**0.01**	0.1	0.3
D1-3	73.4	56.5	5	28	**<0.001**	**<0.001**	**0.01**	**0.04**
D3-4	75.0	58.0	2	31	**0.03**	**0.01**	0.1	0.3
D1-4	73.0	57.7	3	30	**0.02**	**0.001**	**0.04**	0.2
	Mean Age		n					
5 mm	<5 mm	>5 mm	<5 mm	>5 mm	Age	BMD	N	N-m
D1	59.9	46.5	31	2	0.1	0.4	0.5	0.4
D2	67.5	54.2	12	21	**<0.001**	**0.02**	0.1	0.2
D3	66.4	56.7	8	25	**0.03**	**0.002**	**0.01**	0.06
D4	72.0	57.3	4	29	**0.01**	**<0.001**	**0.01**	0.07
D1-3	66.5	55.4	11	22	**0.005**	**0.004**	**<0.001**	**0.005**
D3-4	70.2	56.6	6	27	**0.005**	**<0.001**	**0.007**	**0.03**
D1-4	71.0	55.8	7	26	**<0.001**	**<0.001**	**0.002**	**0.009**
	Mean Age		n					
6 mm	<6 mm	>6 mm	<6 mm	>6 mm	Age	BMD	N	N-m
D1	All D1 data <6 mm				All D1 data <6 mm			
D2	65.4	49.4	20	13	**<0.001**	**0.006**	**<0.001**	**0.006**
D3	67.3	54.3	12	21	**<0.001**	**0.004**	**0.001**	**0.009**
D4	71.0	55.8	7	26	**<0.001**	**<0.001**	**0.002**	**0.009**
D1-3	64.9	48.9	21	12	**<0.001**	**0.006**	**<0.001**	**0.003**
D3-4	69.0	55.8	8	25	**0.002**	**<0.001**	**0.003**	**0.008**
D1-4	65.1	53.4	16	17	**0.001**	**0.003**	**<0.001**	**0.005**

B. Cortical Index (CI)

	Mean Age		n					
0.4 CI	<0.4 CI	>0.4 CI	<0.4 CI	>0.4 CI	Age	BMD	N	N-m
D1	All D1 data <0.4 CI				All D1 data <0.4 CI			
D2	All D2 data <0.4 CI				All D2 data <0.4 CI			
D3	60.0	50.0	30	3	0.1	**0.008**	**0.04**	0.07
D4	62.4	54.0	20	13	**0.03**	**0.003**	**0.05**	0.6

n, number of bones.

Table 5. *p* Values for Comparisons Between Two Correlation Coefficients

	UFL versus Age	UFL versus DXA	UFL versus D3-4 Ct. Th	UFL versus D1-4 Ct. Th	UFL versus H1mmAl	UFL versus H1-3 mmAl	UFL versus D1-3CtTh •H1mmAl	UFL versus D3-4Ct. Th •H1mmAl	UFL versus D1-4Ct. Th •H1mmAl
UFL versus Age									
UFL versus DXA	0.80								
UFL versus D3-4 Ct. Th	0.61	0.44							
UFL versus D1-4 Ct. Th	0.71	0.53	0.89						
UFL versus H1mmAl	0.68	0.51	0.91	0.98					
UFL versus H1-3 mmAl	0.66	0.49	0.94	0.95	0.98				
UFL versus D1-3CtTh•H1mmAl	0.12*	0.07T*	0.30	0.24	0.25	0.27			
UFL versus D3-4Ct. Th•H1mmAl	0.12*	0.07T*	0.31	0.25	0.26	0.28	0.99		
UFL versus D1-4Ct. Th•H1mmAl	0.12*	0.07T*	0.31	0.25	0.26	0.28	0.99	0.99	

T, statistical trend.*A retrospective power analysis conducted with Fisher's z-transformation test showed that the *p* values of 0.07 become statistically significant ($p = 0.05$) when increasing the sample size to approximately 37. The *p* values of 0.12 become statistically significant when the sample size is increased to approximately 48.The comparisons shown include correlations involving age, areal BMD of the proximal humerus, and some of the strongest correlations that used individual and "combined" characteristics. **T** = trend

DISCUSSION

Results of this study suggest that morphometric and densitometric characteristics made using A-P radiographs of cadaveric proximal humeri are stronger predictors of UFL and energy absorbed to fracture when compared to chronological age, CI, and bone density values derived from DXA scans. It is likely that the correlations are weaker when using DXA data because, by providing areal BMD, DXA does not capture age-related changes in the proportion and distribution of cortical bone mass of the proximal humerus. In turn, we speculate that this outcome is strongly influenced by an important role that the amount and distribution of cortical bone of the proximal humerus metaphyseal/diaphyseal region has in resisting mechanical stress (and more so than the trabecular bone) from a ground-level fall that is sufficient to fracture the proximal humerus.[27,28,42] As mentioned above in the Introduction section, these findings are consistent with studies showing that DXA scans do not correlate strongly with fracture risk in a substantial percentage of patients.[43,44] In these contexts, the use of DXA scans to estimate proximal humerus quality/strength must be questioned, especially in view of the fact that DXA measurements are becoming more common in biomechanical studies.[4,45–47] Our results also showed that "combined" characteristics (i.e., products of two characteristics) are even stronger predictors of UFL (but not fracture energy absorption) when compared to the individual characteristics. However, data from clinical trials that show poor predictive power of DXA measurements may not be directly relevant to laboratory studies where the loading is much better controlled.

Only the three strongest correlations found between the products of two characteristics and UFL showed a statistical trend ($p \sim 0.07$) in being different from the other correlations that most directly tested our two hypotheses (Table 5). Statistically significant differences ($p < 0.05$) in the six comparisons with *p* values between 0.05 and 0.15 shown in Table 5 would likely to emerge with a modest increase in sample size. This possibility is supported by our retrospective power analysis using Fisher's z-test and the results from the correlation analyses that we obtained in this study. For example, increasing the current sample size from 33 to 37 bones would likely reduce *p* values of 0.07 to <0.05, and approximately 48 bones would be needed to show statistically significant differences when considering the fourth, fifth, and sixth strongest of the two-correlation comparisons (see lower left of Table 5 where the current p values for six comparisons are listed as either 0.07 or 0.12). Consequently, the data reported herein pave the way for future studies of larger samples of bones that are needed to more clearly establish which of the individual or "combined" morphometric and/or densitometric characteristics are: (1) the strongest predictors of UFL and energy absorbed to fracture, and (2) the most useful for identifying poorer quality proximal humeri for fracture studies. Similar methods for segregating bones into 'quality categories' based on simple measurements from standard radiographs, though not based on fracture data, have been described for the proximal femur[48] and humerus.[25,32]

Similar to Tingart et al.[32], our combined mean (medial + lateral) cortical thickness threshold of 4 mm was found to significantly correlate with proximal humerus BMD obtained from DXA scans. However, in our study the 4 mm threshold was *not* associated with a significant difference in UFL (fracture data were not obtained by Tingart et al.). In fact, when using our data, a significant difference in UFL did not occur between the two groups until the threshold was set at 6 mm. Nevertheless, the 4 mm threshold is now integral in a treatment algorithm for proximal humerus fractures.[49,50] In this algorithm the <4 mm threshold is a branch point where hemi-arthroplasty reconstruction is recommended and not open reduction and internal fixation. This algorithm may need revision in view of our data showing that the 6 mm threshold is more strongly correlated with UFL. Further support for this revision is provided by the results of the study of Mather et al. [24] that identified a mean combined cortical thickness value of 6 mm in the proximal humeral metaphysis as a potential threshold for identifying systemic osteoporosis. Results of that study showed that measurements of cortical bone thickness made on standard clinical A–P shoulder radiographs moderately correlated with DXA measurements made of the proximal femur ($r = 0.64$, $p < 0.00001$) and lumbar spine ($r = 0.49$, $p < 0.00001$) (the humeri were not DXA scanned and no mechanical testing was done).

Additional potentially clinically relevant findings of our study are the results showing that the bones above and below a cortical index (CI) of 0.4 are significantly different in terms of UFL. In a study examining 113 patients (mean 66 years, range: 18–100 years) treated surgically for proximal humerus fractures, Hepp et al.[5] reported that all but three bones had a CI value of less than 0.40 (calculated in terms of cortical areas). Osterhoff et al.[51] also found a similar relationship in their study of 20 proximal humerus fractures (mean 73 years, range: 52–96 years). However, the prospects for the continuing use of a 0.4 or even lower CI thresholds[22] for identifying poorer quality bones for biomechanical studies is diminished by these findings of the present study: (1) CI at D3 does not correlate as strongly with UFL ($r = 0.61$) when compared to mean combined cortical thickness at D3-D4 ($r = 0.71$) and mmAl at H2 ($r = 0.70$) (Table 2A), and (2) CI was not found to be important when paired products and quotients where evaluated in correlation analyses with respect to UFL or energy absorbed to fracture (Table 3).

In addition to constraints of the sample size, another limitation of our study is the lack of soft tissues, which can attenuate force applied to the humerus, as has been shown in proximal femur fractures.[52] Also, only two-dimensional measurement techniques were used in this study. Three-dimensional measurements might increase predictive power for determining bone quality because they can more accurately differentiate trabecular and cortical bone.[3,6,31] Future studies could also consider correlating three-dimensional measurements with other loading rates and configurations that simulate various types of falls.[36]

The fractures that were produced in our study, including those in the bones that had fracture surfaces in the vicinity of the frustrum, grossly resemble fractures that occur clinically.[1] However, another limitation of the present study is that we could not determine spatial-temporal details of fracture initiation and propagation because high speed videography or other motion detection technologies were not utilized. Future studies using these technologies are needed in order to more completely understand the mechanics of the fracture produced by the simulated fall configuration used in this study.

In conclusion, several simple-to-measure individual characteristics and, in seven instances, the product of two characteristics of bone density and/or morphology that can all be measured from A-P radiographs of cadaveric proximal humeri can be stronger predictors of UFL and energy absorption when compared to chronological age, BMD, and bulk density. These characteristics can also be used to help more reliably segregate bones into 'quality categories' prior to destructive testing. Studies are now needed to assess these relationships on larger samples of bones using advanced imaging technologies and varying load rates and fall configurations in dissected proximal humeri and in shoulders with retained soft tissues.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the final submitted manuscript. All authors participated in the acquisition of radiographic data and writing of the manuscript. DXA data and mechanical testing data were primarily obtained by JGS and PJO.

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