

Regional variation in vertebral bone morphology and its contribution to vertebral fracture strength

P.A. Hulme^{a,*}, S.K. Boyd^b, S.J. Ferguson^a

^a MEM Research Center, University of Bern, Stauffacherstrasse 78, CH 3014, Bern, Switzerland

^b Schulich School of Engineering, University of Calgary, Calgary, Alberta, Canada

Received 12 April 2007; revised 6 August 2007; accepted 7 August 2007

Available online 17 August 2007

Abstract

Vertebral fractures may result in pain, loss of height, spinal instability, kyphotic deformity and ultimately increased morbidity. Fracture risk can be estimated by vertebral bone mineral density (BMD). However, vertebral fractures may be better defined by more selective methods that account for micro-architecture.

Our aim was to quantify regional variations in bone architecture parameters (BAPs) and to assess the degree with which regional variations in BAPs affect vertebral fracture strength. The influence of disc health and endplate thickness on fracture strength was also determined.

The soft tissue and posterior elements of 20 human functional spine units (FSU) were removed (T9 to L5, mean 74.45±4.25 years). After micro-CT scanning of the entire FSU, the strength of the specimens was determined using a materials testing system. Specimens were loaded in compression to failure. BAPs were assessed for 10 regions of the vertebral cancellous bone. Disc health (glycosaminoglycan content of the nucleus pulposus) was determined using the degree of binding with Alcian Blue.

Vertebrae were not morphologically homogeneous. Posterior regions of the vertebrae had greater bone volume, more connections, reduced trabecular separation and more plate-like isotropic structures than their corresponding anterior regions. Significant heterogeneity also exists between posterior superior and inferior regions (BV/TV: posterior superior 12.6±2.8%, inferior 14.6±3%; anterior superior 10.5±2.2%, inferior 10.7±2.4%). Of the two endplates that abutted a common disc, the cranial inferior endplate was thicker (0.44±0.15 mm) than the caudal superior endplate (0.37±0.13 mm). Our study found good correlations between BV/TV, connective density and yield strength. Fracture risk prediction, using BV/TV multiplied by the cross sectional area of the endplate, can be improved through regional analysis of the underlying cancellous bone of the endplate of interest (R^2 0.78) rather than analysis of the entire vertebra (R^2 0.65) or BMD (R^2 0.47). Degenerated discs lack a defined nucleus. A negative linear relationship between disc health and vertebral strength (R^2 0.70) was observed, likely due to a shift in loading from the weaker anterior vertebral region to the stronger posterior region and cortical shell.

Our results show the importance of considering regional variations in cancellous BAPs and disc health when assessing fracture risk.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Micro-CT; Vertebral body; Trabecular bone; Microstructural properties; Regional variation

Introduction

Osteoporosis is estimated to afflict 200 million women worldwide [1]. In the US alone, osteoporotic fractures are estimated to affect 24 million individuals. 1.5 million new fractures, nearly half of which are vertebral (700,000), are reported each year, outnumbering fractures of the hip and ankle combined [2–5]. Vertebral fracture may result in pain at the fracture site, loss of

height due to vertebral collapse, spinal instability and in many cases a kyphotic deformity [6]. Chronic pain and kyphotic deformity may lead to depression, decreased appetite (leading to poor nutrition), decreased pulmonary function, impaired mobility and a reduction in the quality of life, the ultimate result being a significant increase in morbidity [7–10]. The World Health Organization defines osteoporosis as a bone mineral density (BMD) of more than 2.5 standard deviations below the mean of a young healthy reference population of the same gender. However, BMD only partially determines fracture risk [11]. Various investigators have found that bone quality, and hence fracture

* Corresponding author. Fax: +41 31 631 5960.

E-mail address: Paul.Hulme@MEMcenter.unibe.ch (P.A. Hulme).

risk, is independent of BMD, as determined through dual energy X-ray absorptiometry (DEXA), and have suggested a role for micro-architecture, turnover, damage accumulation and mineralization [12–17]. DEXA itself does not account for regional variability in bone quality or vertebral geometry and may include structures that do not add to the mechanical strength of the vertebra, including posterior elements and osteophytes [18]. Furthermore, osteoporosis drug treatment strategies have shown poor correlations between BMD and the risk of vertebral fracture [19–24]. Hence, vertebral fracture risk may be better defined by more selective methods.

Regional vertebral morphology has been examined using histological methods [11] or using micro-CT measurement of bone cores [25,26], but few studies consider the analysis of the vertebral body as a whole [27]. Bone volume for vertebrae has been determined to be between 6.5% and 16% [11,15,25,28]. Observed age-related architectural changes to the cancellous bone include: a decrease in bone volume compared with the total vertebra volume (BV/TV), a shift from plate-like trabeculae to more rod-like structures (SMI), a decrease in connectivity density (Conn.D), an increase in orientation of trabeculae along the axis of principle loading (DA), an increase in trabecular separation (Tb.Sp) and a corresponding decrease in trabeculae number (Tb.N) [11,29–31]. Trabecular thickness (Tb.Th) has been reported to increase or decrease with age [11,31]. An increase in trabecular thickness has been explained as either adaptive remodeling of the remaining vertical trabeculae or removal of the thinner struts resulting in an increase in mean trabecular thickness [15,26,32]. The etiology of these structural changes remains unclear, whether it is excessive osteoclastic resorption or incomplete osteoblast activity resulting in perforation and thinning of trabecular elements [31,33,34]. However, the net result is a reduction in vertebral fracture strength.

The aim of this study was to describe the regional morphology of the elderly human thoracolumbar vertebra using micro-CT and to relate its derived bone architecture parameters (BAP) to vertebral failure. The micro-CT gantry allows for entire functional spine units (FSU) to be scanned non-destructively, allowing subsequent material tests to be performed using physiologically relevant loading configurations. We hypothesize that the bone architecture parameters (BAP) of the less dense anterior and central vertebral body regions will be a better predictor of failure than those of the whole vertebra or DEXA measurements [25,28]. We extended our regional analysis to determine if BAPs can help explain the reported preferential failure of the superior endplate [35]. Additionally, we considered the role of disc health on endplate thickness, the underlying trabecular bone and vertebral failure.

Methods

Sample preparation

The surrounding soft tissue and posterior elements of 22 osteoporotic cadaveric human functional spine units (FSU) were removed (average 74.45 ± 4.25 years). Vertebrae were grouped as follows: one T9–T10, three T11–T12, five T12–L1, five L1–L2, four L2–L3, two L3–L4 and two L4–L5. Previous investigators have found little difference between male and female bone mor-

phology and no major difference in BV/TV between T9 and L5 (1% T9 to L5, 0.5% T11 to L5). Since morphologic changes due to the aforementioned confounding factors are minimal, we pooled all the vertebrae together for analysis [15,26,36]. Our study population consisted of vertebrae that were used in a preceding experiment that involved submaximal uniaxial compressive loading of the FSU. Six of 22 specimens had polymethylmethacrylate (PMMA, Vertecem, Synthes, Switzerland) present in the caudal vertebra. Morphology was assessed prior to cement injection. Bone mineral density (BMD) was assessed using dual energy x-ray absorptiometry (DEXA) (Discovery C, Hologic, Bedford, MA).

Impressions were made of the cranial and caudal endplates in semi-cured bone cement (Sulfix, Sulzer Orthopaedics Ltd). A jig ensured that the two end caps were parallel to each other. The molded end caps only extended to the cortical rim, thereby not adding any structural strength to the FSU. Specimens were stored in air evacuated polyethylene bags at -20°C until testing.

Micro-CT scanning and determination of morphology

All measurements were performed on a microcomputed tomography system (XtremeCT, Scanco Medical AG, Bassersdorf, Switzerland). Scans ranged from 770 to 990 slices with a nominal isotropic resolution of $82\ \mu\text{m}$ (field of view $125\ \text{mm}$, 1536×1536 pixels, integration time 200 ms). Scans were performed in air, before mechanical testing. Total scan time per specimen approached 30 minutes. Regions of interest (ROI) were identified for trabecular bone and endplate thickness analysis. The region for trabecular bone analysis included the cancellous bone from just below the cranial endplate to just above the caudal endplate, separated into 10 regions (Fig. 1). ROI were filtered using a Laplace–Hamming filter and segmented using a global threshold. Bone architecture parameters (BAP) analyzed included (Image Processing Language, v4.29d, Scanco Medical AG, Bassersdorf, Switzerland): bone volume ratio (BV/TV), connectivity density (Conn.D), structure model index (SMI), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and degree of anisotropy (DA) (Table 1). Trabecular thickness, number and separation were based on direct measures using a distance transformation and not using trabecular model assumptions [37].

Endplate thickness was determined using a region of interest (ROI) that encompassed only the endplate. A Gaussian filter (sigma 0.8, support 1) was used to reduce noise. The segmentation threshold was chosen to preserve as much of

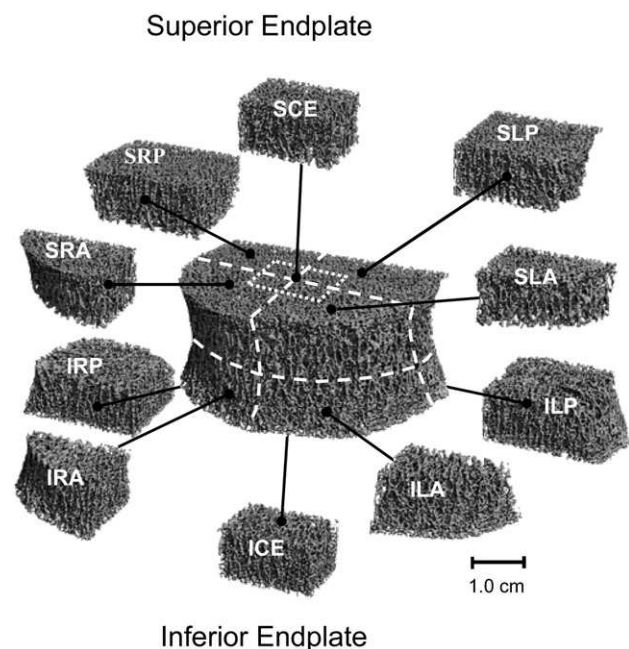


Fig. 1. Regions of the vertebra for which bone architecture parameters were determined. Regions were composed of superior (S), inferior (I), anterior (A), posterior (P), left (L), right (R) and central (CE) regions.

Table 1
Explanation of bone architecture parameters

Term	Units	Explanation
BV/TV	Ratio or %	Proportion or percentage of the volume of interest that is bone
Conn.D	1/mm ³	Connectivity density: Indicates the number of connections normalized by the volume of interest
SMI	0–3	Structural model index: a quantification of the prevalent type of trabecular element. 0 for parallel plate, 3 for cylindrical rods.
Tb.N	1/mm	Trabecular number: the number of trabeculae encountered per unit length
Tb.Th	mm	Trabecular thickness
Tb.Sp	mm	Trabecular separation: the average separation between trabeculae (marrow space)
DA	1	Degree of anisotropy: a measure of preferential alignment of the trabeculae along a directional axis. (1=isotropic, >1 anisotropic)

the interconnecting trabeculae as possible without artificially thickening the endplate or any of the trabeculae. Endplate thickness was determined by identification of the upper and lower surface of the endplate (custom programs written in C; Visual Studio 6.0, Microsoft; and Matlab, MathWorks Inc., Natick, MA). Exploiting the difference in area between trabeculae and trabecular separation, a 2D median filter was used to remove trabeculae that may have been included in the determination of the lower endplate surface. Endplate thickness was calculated as the distance between the upper and lower endplate surface. The endplate was separated into the ring apophysis and the central endplate region. The central endplate region was determined by visual inspection of the endplate height map (the central endplate region is lower than the ring apophysis). User selected points defined the transition between the ring apophysis and the central endplate region, which were connected using a cubic spline (Matlab, MathWorks Inc., Natick, MA). The ring apophysis and central endplate region were further separated into anterior and posterior regions.

Mechanical testing

Prior to mechanical testing, samples were defrosted overnight in a 0.15-M NaCl bath at 5 °C. Three hours prior to mechanical testing, the samples were removed from the refrigerator and allowed to reach room temperature. Testing was performed on an MTS 858 Mini Bionix II servohydraulic testing machine (MTS, Eden Prairie, MN, USA). The samples were kept moist with saline soaked gauze throughout the test. Loading was performed in a similar manner to our previous FSU mechanical testing procedure [38]. The FSUs were loaded to 50 N and cycled for 600 cycles between 50 and 450 N at 1 Hz for pre-conditioning. Immediately following cyclic loading, the sample was compressed under displacement control at 0.5 mm/s to a total compression of 10 mm. During compression, load and displacement data were recorded at 100 Hz. Anteroposterior and lateral single section scans using micro-CT were performed after mechanical testing of the failed FSU to determine the location of the fracture. It should be noted that 9 of 22 analyzed specimens failed during the loading step of the preceding experimental series in which specimens were also tested under axial compression but at a slower loading rate, 0.004 ± 0.003 mm/s. The reduced loading rate is not thought to have altered the experimental outcome. Ochiva et al. [39] found no difference in endplate fracture load between low (10 mm/s) and high loading rates (2500 mm/s), thus differences between the loading rate of 0.5 mm/s and the lower loading rate used in the previous experimental series should be negligible.

Disc health assessment

A decrease in the proteoglycan content of the nucleus pulposus has been associated with disc degeneration [40–43]. To determine proteoglycan content of the nucleus pulposus (NP), samples were removed from the specimen, weighed (wet weight) and lyophilized (dry weight). Samples were then digested

with papain (Sigma) in a cysteine buffer (L-cysteine hydrochloride, Fluka) [44]. Proteoglycan content was determined using the degree of binding with Alcian Blue (Alcian Blue 8 GX, Fluka) and reported as the ratio of the weight of the glycosaminoglycan (GAG) side chains divided by the weight of the dry tissue sample [45]. GAG content was normalized by dry tissue weight since the effect of mechanical testing, scanning and NP sample removal on disc hydration may not have been consistent between samples.

Statistics

Regional variations in bone architecture parameters and endplate thickness were explored using a one-way ANOVA (Statistica, StatSoft, Tulsa). Newman–Keuls post hoc analysis was used to identify differences between trabecular regions. A significance value of $p=0.05$ was defined. Relationships between bone quality, endplate thickness, disc health (GAG content) and mechanical strength; endplate thickness, disc health and bone quality; and disc health and endplate thickness were assessed using linear regression. The quality of the fit is reported as the correlation coefficient R^2 .

Results

Two specimens were removed from the analysis due to an imaging error on one and the presence of extensive vertebral sclerosis on the other. The remaining specimens had an average age of 74.2 ± 4.3 years and were grouped as follows: one T9–T10, three T11–T12, five T12–L1, four L1–L2, four L2–L3, one L3–L4 and two L4–L5. The average BAPs for the sample population ($n=20$) are given in Table 2. The mean water content of the nucleus pulposus of the discs was $70 \pm 3\%$ and the mean GAG content was 0.17 ± 0.06 (mg GAG/mg dry tissue, $n=20$).

Regional morphological variations—trabecular bone

The posterior regions of the vertebrae had greater bone volume, more connections, more trabeculae, reduced trabecular separation and more plate-like isotropic structures than their corresponding anterior regions (Fig. 2). Vertical inhomogeneity was observed only in the posterior regions. The posterior inferior region had higher bone volume ratio, greater connectivity density and a greater number of trabeculae, which were more plate-like in structure and isotropic than its corresponding superior region. It should be noted that there was no statistical differences noted between any regions using a direct 3D measure of trabecular thickness [37]. Semi-derived trabecular thickness assessment [31] resulted in lower thickness measurements

Table 2
Bone architectural parameters for whole vertebrae

	Number of vertebrae	Mean	Minimum	Maximum	SD
Age (years)	40	74.2	63.0	80.0	4.2
Failure load (N)	40	2918	1250	5407	1227
BMD (g/cm ²)	40	0.494	0.380	0.624	0.066
BV/TV (%)	40	12.5	7.4	16.9	2.4
Conn.D (1/mm ³)	40	1.322	0.612	2.234	0.372
SMI	40	2.422	1.967	3.022	0.311
Tb.N (1/mm)	40	0.896	0.718	1.073	0.084
Tb.Th (mm)	40	0.215	0.183	0.250	0.018
Tb.Sp (mm)	40	1.110	0.917	1.391	0.111
DA	40	1.359	1.172	1.525	0.077

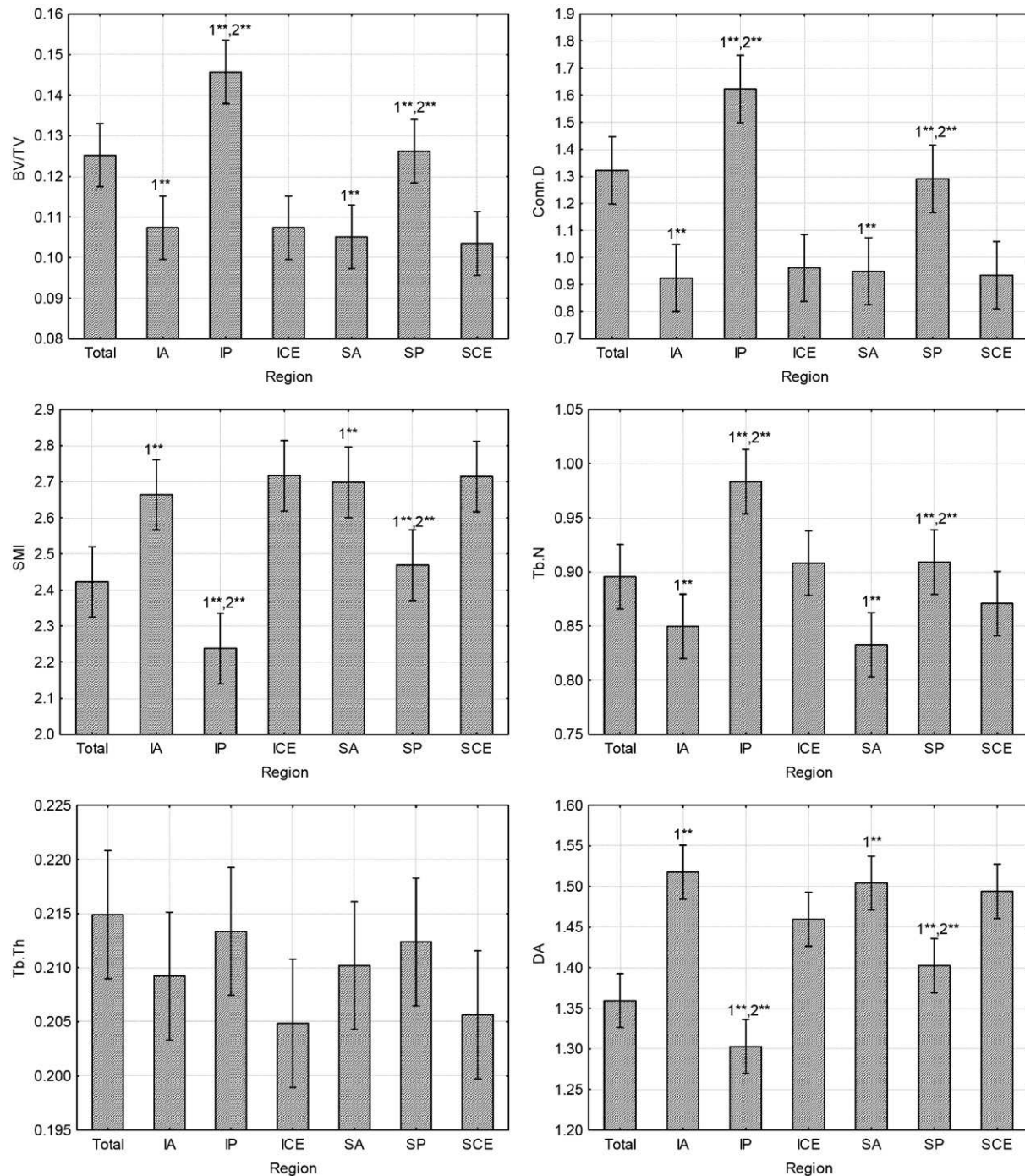


Fig. 2. Regional variation in bone architecture parameters. Data are displayed as the mean bone architecture parameter $\pm$ 95% C.I. (1) Significant difference between transverse regions (i.e. anterior and posterior) of the same vertical region (i.e. superior or inferior); (2) significant difference between vertical regions of same transverse region (* $p < 0.05$, ** $p < 0.005$).

(total: 0.139 ± 0.022 mm), less variability but no change in overall regional distribution. Regions of low trabecular thickness include anterior and central regions.

Regional morphological variations—endplate

The endplate was thinnest in the center and the anterior of the central endplate region and greatest in the posterior ring apophysis (Fig. 3). Differences in endplate thickness were noted

between endplates abutting a common disc. The mean thickness of the cranial inferior endplate within the central region was 0.44 ± 0.15 mm (max 0.87 mm, min 0.27 mm, $n = 19$) while the caudal superior endplate thickness was 0.37 ± 0.13 mm (max 0.70 mm, min 0.19 mm, $n = 19$). The inferior cranial endplate was thicker than the superior caudal endplate for all regions except the anterior ring apophysis. However, differences were only statistically significant for the posterior central endplate region (Fig. 3).

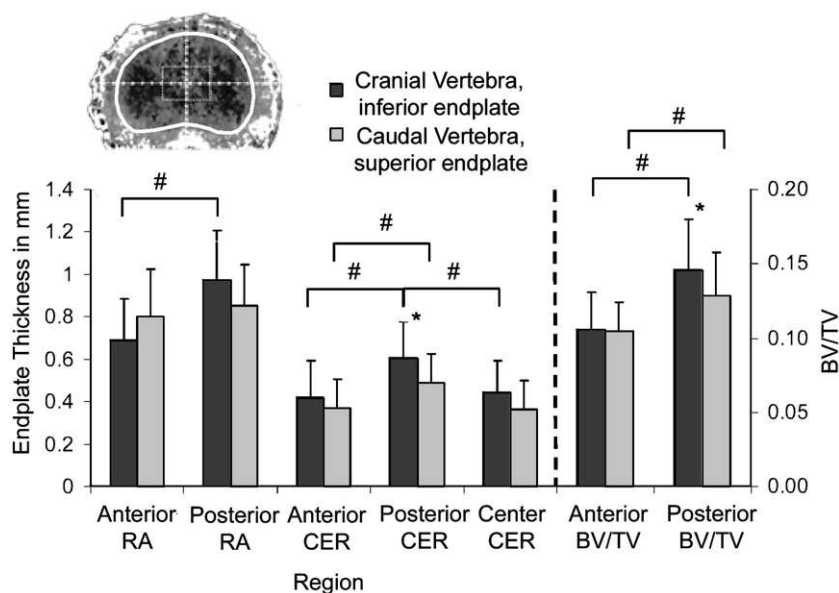


Fig. 3. Regional thickness of the caudal and cranial endplate. Insert illustrates a typical endplate thickness map, the white boundary indicates the central endplate region. Dark regions are thinner than lighter regions ($n=19$ inferior, 19 superior endplates; RA: ring apophysis; CER: central endplate region; * $p<0.05$ between cranial inferior and caudal superior endplates; # $p<0.05$ between regions on either the cranial or caudal endplate). Data are displayed as the mean $\pm$ 1 SD.

There were large variations in endplate thickness between specimens, dependent upon the presence of sclerotic bone formation. The molded endcaps, created to facilitate mechanics testing, were present during the micro-CT scans. Unfortunately, the contrast between the molds and the endplate was not sufficient to resolve the two components; thus, analysis of the superior cranial and inferior caudal endplate was not possible.

A positive correlation was noted between the central region's endplate thickness and the BV/TV of the underlying trabecular bone (R^2 0.44, $p<0.001$).

Bone morphology parameters that best predict vertebral failure

Pearson's correlation coefficients between regional BAPs and vertebral fracture strength are given in Table 3 and Figs. 4–6. Correlations were improved through consideration of vertebral geometry (BAP $\times$ CSA). Cross-sectional area (CSA) of the endplates was determined from the micro-CT scans, after digital removal of the osteophytes. While the BAPs derived from the analysis of an entire vertebra had good correlations with failure strength, it was not until regional variations were taken into consideration that significant improvements were noted over traditional BMD measurements (Figs. 5, 6). Regional measures of connectivity density and BV/TV best predicted vertebral failure load (BV/TV $R^2=0.78$ Fig. 7, Conn.D $R^2=0.70$ Table 3). The best correlations between BAPs and fracture strength were obtained when the trabecular zone below the fractured endplate was analyzed (Fig. 5), confirming the role of regional BAPs in fracture prediction. There was also significant transverse variability in the ability of BAPs to predict vertebral strength. With few exceptions the posterior region correlated best with fracture load (Fig. 6), possibly due to the loading protocol and the effects of disc health [46,47].

Preferential failure of the superior endplate may be explained through morphological analysis of the vertebrae which about a common disc [35,48,49]. During our experimental series, 13 of 14 FSUs (without cement present in the caudal vertebra) experienced caudal superior endplate fractures. Cranial inferior endplate fractures occurred in those FSUs whose caudal vertebrae were augmented with PMMA. The superior endplate caudal to a disc was found to be thinner than the inferior cranial endplate, but only the posterior region's differences reached statistical significance (Fig. 3). However, since only a moderate correlation was determined between endplate thickness and vertebral yield strength (R^2 0.38, $p=0.003$), it is unlikely that endplate thickness is the sole cause for preferential superior endplate failure. The endplate derives its strength from the underlying trabecular bone. While no difference could be detected between the underlying anterior trabecular bone region of the cranial inferior and caudal superior endplate, the cranial posterior trabecular region does have superior bone quality: higher bone volume and connectivity density, more plate like elements and increased trabecular number ($p=0.04$, 0.01, 0.05, 0.01, respectively, $n=20$).

Disc health (GAG content of the NP) and morphology

There was a weak negative correlation noted between BV/TV beneath the endplate and disc health (R^2 0.19, $p=0.006$). A negative correlation was found between disc health and the central endplate thickness (R^2 0.33, $p<0.001$). Disc health was assessed by determining the ratio of mg GAG to mg dry tissue.

The effect of disc degeneration on vertebral fracture strength

Disc health had a significant effect on vertebral failure load (Fig. 8). Disc health had a negative linear relationship with vertebral failure strength (R^2 0.70, $p<0.001$).

Discussion

Vertebrae are not morphologically homogeneous. While vertical homogeneity was observed for the anterior trabecular regions, there is considerable posterior vertical and transverse inhomogeneity, confirming previous reports. The presented methodology differs from previous investigations in that it is not limited to histological analysis of specific regions or the

analysis of regional bone plugs, thus allowing non-invasive morphology assessment of the entire vertebral body, followed by mechanical analysis [11,17,25,26,28,36,50]. This methodology allows the direct assessment of the relation between structure and function. Banse et al. [28] reported a 25% and 20% difference in bone volume between the superior and inferior posterior regions for thoracolumbar and lumbar vertebrae, respectively. Our results are similar, with a combined

Table 3

Pearson's correlation coefficients relating bone architecture parameters and vertebral failure strength

Bone architecture parameter	Region closest to fracture			Region furthest from Fx	Superior region	Inferior region
	BAP–Load	BAP–Stress	BAP×CSA–Load	BAP×CSA–Load	BAP×CSA–Load (Z 1,2)	BAP×CSA–Load (Z 3,4)
BMD	0.34	0.35	0.49	0.49	0.49	0.49
<i>BV/TV</i>						
Total	0.32	0.46	0.65	0.65	0.65	0.65
Center	0.16	0.33	0.52	0.26	0.50	0.29
Average anterior	0.37	0.50	0.63	0.40	0.58	0.43
Average posterior	0.46	0.62	0.75	0.33	0.64	0.57
Average anterior and posterior	0.48	0.64	0.78	0.40	0.67	0.55
<i>Conn.D</i>						
Total	0.22	0.29	0.41	0.41	0.41	0.41
Center	0.28	0.38	0.48	0.16	0.32	0.02
Average anterior	0.22	0.22	0.33	0.17	0.29	0.22
Average posterior	0.40	0.59	0.70	0.13	0.48	0.39
Average anterior and posterior	0.37	0.48	0.57	0.17	0.40	0.32
<i>SMI</i>						
Total	0.23	0.35	0.47	0.47	0.47	0.47
Center	0.13	0.22	0.36	0.34	0.45	0.24
Average anterior	0.23	0.26	0.34	0.34	0.38	0.31
Average posterior	0.44	0.58	0.67	0.24	0.49	0.44
Average anterior and posterior	0.39	0.48	0.54	0.32	0.47	0.40
<i>Tb.N</i>						
Total	0.09	0.14	0.32	0.32	0.32	0.32
Center	0.24	0.34	0.44	0.14	0.19	0.37
Average anterior	0.17	0.22	0.38	0.15	0.24	0.28
Average posterior	0.11	0.20	0.37	0.21	0.31	0.35
Average anterior and posterior	0.15	0.23	0.39	0.19	0.28	0.33
<i>Tb.Th</i>						
Total	0.06	0.09	0.26	0.26	0.26	0.26
Center	0.00	0.02	0.18	0.22	0.25	0.14
Average anterior	0.00	0.02	0.15	0.25	0.25	0.15
Average posterior	0.11	0.09	0.26	0.28	0.35	0.19
Average anterior and posterior	0.04	0.05	0.22	0.29	0.32	0.19
<i>Tb.Sp</i>						
Total	0.09	0.14	0.27	0.27	0.27	0.27
Center	0.19	0.30	0.36	0.08	0.14	0.27
Average anterior	0.16	0.23	0.33	0.13	0.20	0.21
Average posterior	0.10	0.19	0.33	0.17	0.26	0.32
Average anterior and posterior	0.14	0.23	0.35	0.15	0.24	0.27
<i>DA</i>						
Total	0.01	0.12	0.32	0.32	0.32	0.32
Center	0.32	0.16	0.00	0.19	0.01	0.18
Average anterior	0.01	0.08	0.26	0.45	0.29	0.41
Average posterior	0.06	0.01	0.07	0.47	0.21	0.30
Average anterior and posterior	0.01	0.01	0.18	0.53	0.28	0.40

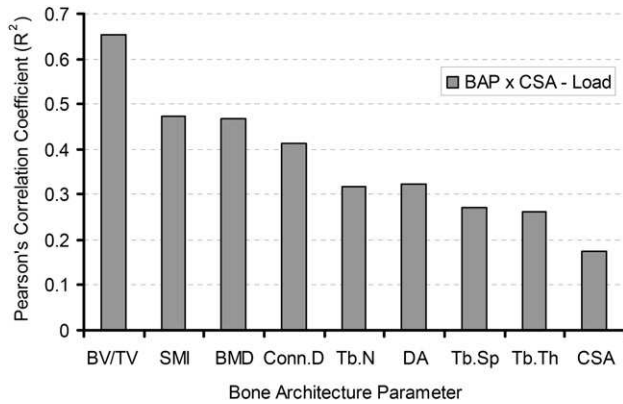


Fig. 4. Correlation of bone architecture parameters evaluated for the vertebra as a whole with measured failure strength ($n=20$, SMI is divided by CSA, all correlations $p<0.05$).

thoracolumbar and lumbar difference of 16%. The ratio of the average anterior and posterior ash density (1.24), reported by Nepper-Rasmussen and Mosekilde [50], agrees with the transverse variation of BV/TV found in the current study (1.28, ratio of mean posterior BV/TV to mean anterior BV/TV). The regional re-enforcement of trabecular bone is reflected in observed vertebral fracture location. Low energy compression fractures can occur in the anterior or posterior superior regions of the vertebra, but rarely the inferior posterior region [28,51,52]. One rationale for the regional inhomogeneity of BV/TV, higher in the inferior posterior region, is that the cortical shell of the superior posterior region is re-enforced by the posterior elements, relying less on the trabeculae for strength (Fig. 9). However, the inferior posterior region of the cortical shell does not have re-enforcement, lacking any posterior elements and thus must rely on the trabecular core for strength [28].

The increased BV/TV of the posterior inferior vertebral region, and to a lesser extent a thickening of the posterior endplate, likely strengthens the inferior endplate resulting in a preferential failure of the superior endplate. Our results show how vertebral morphology can influence function. In the study by Grant et al. [48], only the posterior inferior endplate was found to be significantly stronger than the superior endplate. Similarly, in the present study the greatest increase in bone quality and endplate thickness was noted in the inferior posterior region (Fig. 3).

The relationship between vertebral strength and structure is complex, involving contributions from the endplate, cortical shell, trabeculae and intervertebral disc health [11]. The present study found good correlations between BV/TV and Conn.D and yield strength (Fig. 5). There was greater variability in Conn.D and to a lesser extent BV/TV between specimens, compared with the other BAP parameters. A high standard deviation could indicate BAPs that are sensitive to remodeling changes (hence useful for fracture prediction), or a reflection of measurement inaccuracies. However, both BV/TV and Conn.D correlated strongly with fracture strength; thus, the first hypothesis is more probable. It should be noted that a small variability in BAP does not necessarily reflect poor ability to predict fracture strength, only that appropriate equipment is required to resolve the differences between samples.

The strength of bone is significantly more sensitive to a loss of trabeculae compared with a similar overall reduction in bone mass [31,53,54]. The high correlation of Conn.D with failure highlights its importance in the maintenance of bone strength (Table 3). As bone volume decreases, there is a corresponding decrease in connectivity density (Fig. 10), possibly due to the loss of small interconnecting trabeculae with small initial diameter [36]. The ratio of vertical trabeculae to horizontal, while almost 2:1 for

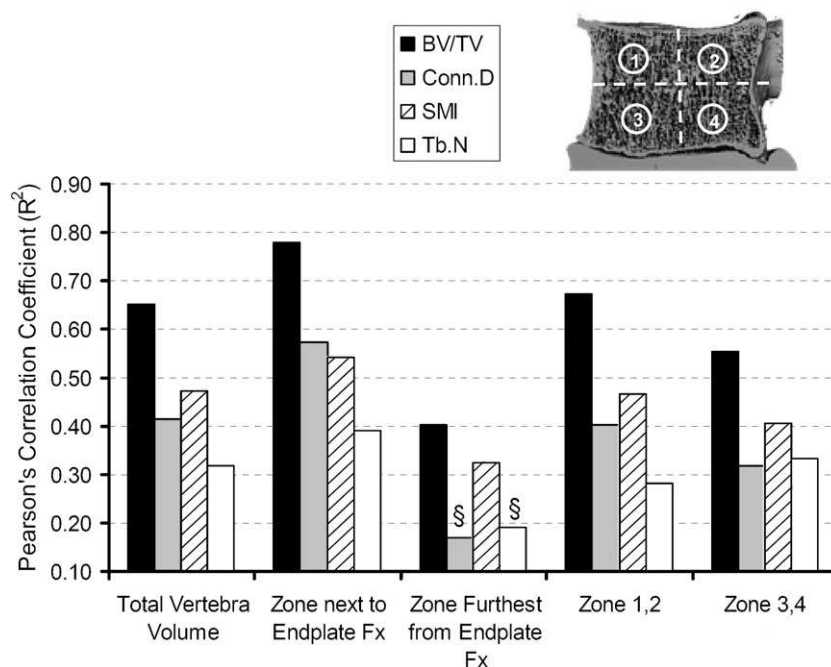


Fig. 5. Correlation between regional BAP×CSA and failure load for various vertebral regions (SMI is divided by CSA, § $p>0.05$).

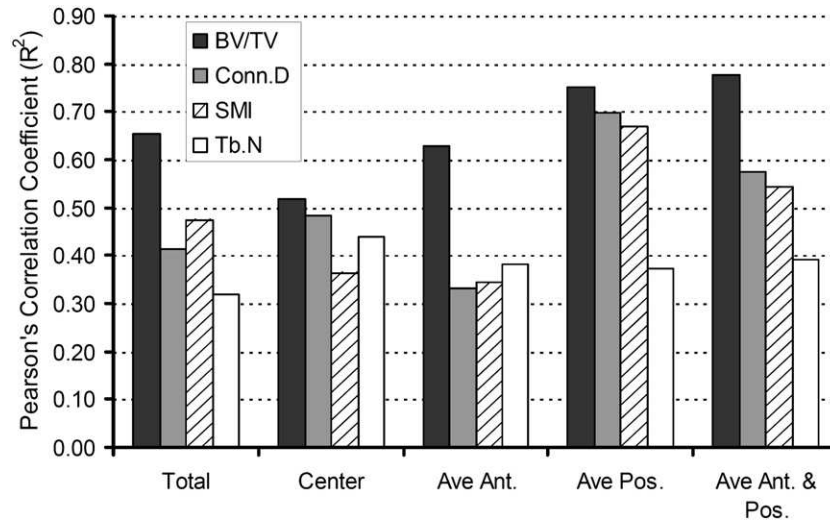


Fig. 6. Correlation of BAP×CSA and vertebral failure load for various transverse regions (SMI is divided by CSA, all correlations $p < 0.05$).

young individuals, increases with age [32,55]. Thus, trabecular perforation and subsequent removal occurs preferentially for horizontal struts [18,56]. The loss of horizontal trabeculae leads to an increased susceptibility to buckling, a recognized primary mode of failure for cancellous bone [53,55–57].

A linear regression model was used to determine the correlation between bone architecture and failure load and stress. Although the use of a power model is more biologically correct, Cody et al. [58] and Ebbesen et al. [59] found minimal improvement using the power relationship. The inclusion of extrema into the data would probably necessitate the use of a power model, but for examination of a specific age cohort with minimal variation in bone volume, a linear model is valid [59]. Correlation between failure and bone architecture parameters (BAP) can be improved if, as other authors have suggested, load is correlated to BAP×CSA [60–62]. In addition to multiplying BAP by CSA, we tried other fracture prediction schemes [58]. There was no improvement in correlation coefficient noted using

the standard deviation of regional BAP or the relative density index (ratio of the maximum and minimum regional BAP), two schemes postulated to reflect bone remodeling changes [58].

The correlation of BAPs with failure stress or load differed according to the region analyzed. We did not find improved correlations between BAPs and yield for the anterior or central region as was hypothesized (Table 3, Fig. 6), possibly due to the loading protocol which preferentially loads the posterior regions [46]. For both the normal and degenerated FSU, the majority of the load is carried by the posterior vertebral body during upright postures [46]. Cody et al. [58] found that bone mineral density had the highest correlation with failure load in the inferior region. This region had moderate correlation between BV/TV and fracture load in the present study but correlation was higher when analyzing the superior region or the entire vertebra [58]. One would expect that the weakest zone (superior half of the vertebra) would dictate at what load the vertebra would fail. While good correlations were found between the BAPs of the

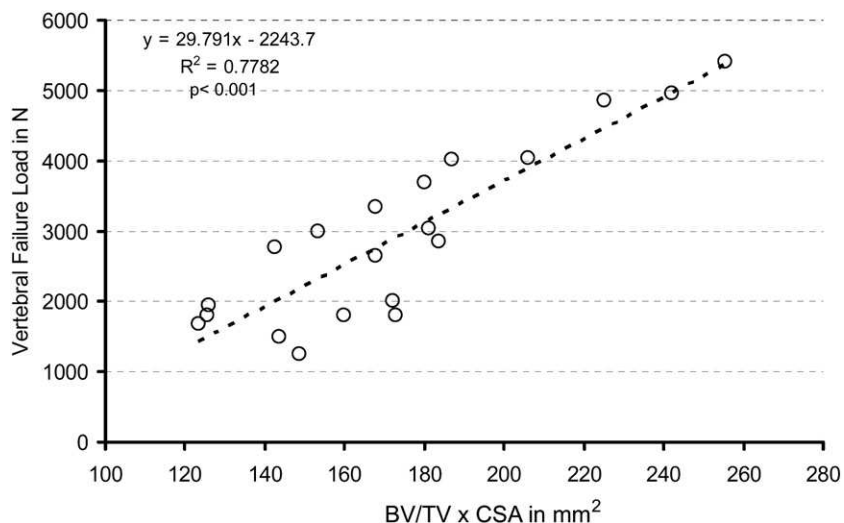


Fig. 7. A linear relationship exists between BV/TV×CSA and vertebral fracture strength. The subchondral bone below the fractured endplate was analyzed (mean of the anterior and posterior region).

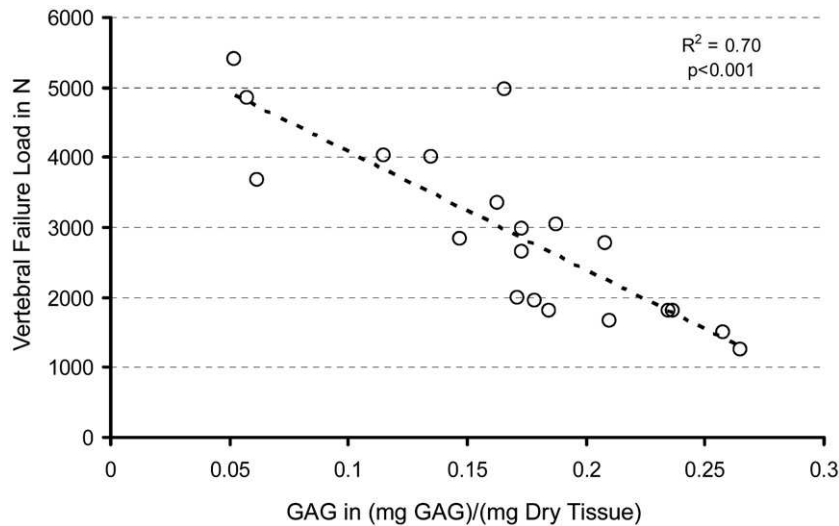


Fig. 8. Correlation of disc health (GAG content of the nucleus pulposus) with vertebral failure strength.

superior region and vertebral strength, there was no improvement over using analysis of the entire vertebra, likely due to the two fracture modalities that were created (caudal superior endplate fracture vs. cranial mixed fracture mode). Vertebral fracture strength could not be explained through analysis of one specific region, instead BAPs from the region in which the fracture occurred (Fig. 5) correlated best with vertebral fracture strength. This result highlights the importance of regional assessments for fracture risk.

The loading protocol of this study was limited to uniaxial compression, resulting in ostensibly endplate fractures with some cortical involvement. However, most elderly fractures that occur are wedge fractures, the result of applied compression and bending moment to induce flexion [63,64]. One would expect in this situation that the importance of BAPs of the anterior vertebral body region might predict fracture strength more effectively. Due to the bore size of the micro-CT, posterior elements were removed from the specimens; therefore, the contribution of the neural arch to load bearing was not considered. The neural arch only carries a minor fraction of the load for an FSU

with a normal disc under axial compression. However, the presence of a degenerative disc shifts a considerable portion of the load to the neural arch [46,65]. Thus, our experimental construct represents a worst case scenario, when the entire load fraction is carried by the vertebral body. The lack of posterior elements may also explain the low failure loads recorded. Changes in loading pattern from the *in vivo* situation (i.e., elimination of the neural arch) may shift regional trabecular loading anteriorly resulting in early failure of the vertebra.

Previous quantitative computed tomography (QCT) and DEXA studies have found correlations between vertebral strength and the product of QCT bone mineral density (or DEXA) and cross-sectional area between $R^2=0.45$ to 0.88 for multiple vertebral segment constructs [58,60,66–68] and 0.26 to 0.82 for single vertebra tests [61,62,69–71]. Given our study population and the relatively unrestrictive inclusion criteria, the correlation between micro-CT derived BAP $\times$ CSA and failure load was good ($R^2=0.78$). We hypothesize that strict inclusion criteria will yield significantly improved correlations. Our results have shown only moderate correlation between BMD $\times$ CSA and

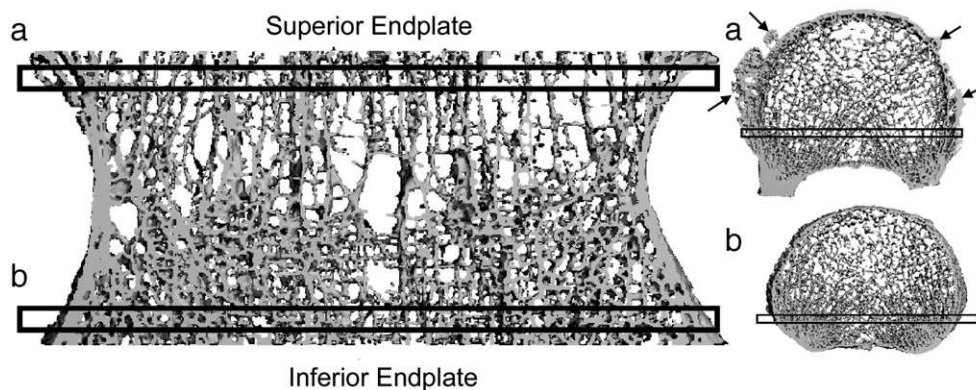


Fig. 9. Vertical morphological heterogeneity is evident in this sagittal slice through a vertebral specimen. Bone volume ratio and connectivity density are higher in the posterior inferior region. Sections (a) and (b) illustrate a transverse slice near the superior and inferior endplates, note both the presence of transverse heterogeneity within the slices and vertical heterogeneity between the posterior regions of the slices. Boxes highlight the regions from which the slices were constructed (sagittal slice is 1.64 mm thick, transverse slices are 2.46 mm thick). Arrows indicate osteophytes.

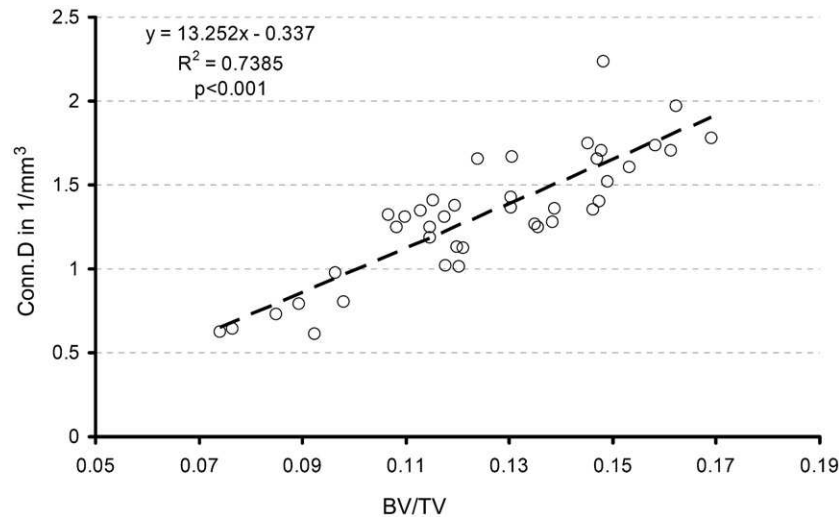


Fig. 10. A linear relationship exists between bone volume ratio and the connectivity density—as the bone volume ratio decreases, connections are lost between trabeculae.

load ($R^2=0.47$). AP DEXA is a general measurement of bone quality, including contributions from the cancellous bone, cortical shell and posterior elements, and is influenced by sclerotic growth and osteophytes. The experimental protocol required that the posterior elements be removed to facilitate mechanical testing and micro-CT scanning. However, remnants still remained to a varying degree on the FSU, which would affect the BMD, increasing values for those with greater remnants without a corresponding increase in mechanical strength. Some specimens also had considerable osteophytes (evident on Fig. 9a), which do not add to the mechanical strength of the vertebrae, but increase their BMD. The determination of BAP by micro-CT has the advantage of allowing the volume of analysis to be specified, allowing the user to remove any anomalous regions.

We did not consider the contribution of the cortical shell to vertebral fracture strength. The percentage of the load carried by the cancellous bone and cortical shell varies dependent upon the distance from the endplates [27,47,72–74]. Near the endplates, the majority of the load is carried by the cancellous bone, which changes to about equal sharing between the cortical shell and cancellous bone at the midtransverse plane [27,47,72–74]. All of the specimens in this experimental series had endplate fractures, a region in which most of the load is carried by the cancellous core [27,47,72–75]. Thus, only BAPs for the cancellous core were correlated to fracture strength. However, this is not to say that the cortical shell has no role in fracture prediction. An improvement in fracture prediction was noted by Andresen et al. [76] after considering the contribution of both the BMD of the cancellous bone and cortical shell. The importance of the cortical shell for structural strength, especially for osteoporotic vertebrae, has been highlighted by various other investigators [27,74,76,77]. Future studies should consider the combined role of cortical shell and cancellous bone in fracture prediction.

We found a strong negative correlation between disc health (GAG content) and endplate failure load (Fig. 8). A negative correlation also exists between disc health and endplate thick-

ness and BV/TV. While specimens with poor disc health typically had increased BV/TV and endplate thickness, the effect of disc health on bone quality alone cannot explain the correlation between disc health and fracture strength. A shift in load transfer between vertebral bodies also occurs for degenerative discs. Degenerative discs lack a defined nucleus and under axial compressive loads typically have lower stresses in the anterior half of the disc [46]. Load shift towards the periphery of the vertebral body and the posterior elements decreases the amount of bone at risk of fracture. A shift in loading from the weaker anterior vertebral region to the stronger posterior region results in higher vertebral fracture strength [46,47].

A limitation to the micro-CT analysis is that the measurements were performed using a nominal resolution of 82 μm , which is close to the mean thickness of human trabeculae, thus partial volume effects may result in a measurement bias. However, to reasonably determine bone architecture, resolutions below 100 μm have been shown to be acceptable [78,79]. The performance of the micro-CT scanner used in this study (XtremeCT) has been assessed versus the gold standard of a high-resolution micro-CT scanner (19 μm) [79]. It was found that bone architecture parameters BV/TV, Conn.D, Tb.N, Tb.Sp and DA performed well. Although BV/TV was over estimated by 28%, it was a significant improvement over the 60% reported by Banse et al. [28] using different equipment. The resolution of the scanner can result in measurement inaccuracies for the parameters, Tb.Th and SMI [79]; however, it should be noted that in the present study, we were not constrained to *in vivo* scanning protocols, thus integration time could be increased. This yields improved image contrast and likely improved determination of bone architecture parameters over the previously reported *in vivo* protocol-based accuracy and precision assessments [79,80].

Our research has demonstrated the relation between whole vertebra micro-architectural parameters and fracture strength using micro-CT and identified regional variation in trabecular morphology. In addition we have identified disc health as an

important contributor to vertebral fracture prediction. Micro-CT currently cannot be used clinically to directly assess bone quality of vertebral bodies and to date the relation between peripheral X-ray-based analysis and vertebral failure strength lacks adequate correlation [66,70]. *In vivo* assessment using lower resolution clinical CT scanners permit reasonable estimates of BV/TV but may not have the resolution required to estimate Conn.D, the two parameters that this study identifies as best correlating with fracture strength [68]. However, an understanding of regional morphology may be used to focus DEXA or clinical CT analysis to specific trabecular zones to further improve fracture prediction for specific fracture modalities.

Acknowledgments

Funding for this research was provided by AOSpine (Grant # SRN 02/105). The authors wish to thank Josh MacNeil for his assistance with micro-CT data acquisition and analysis, Jennifer Vuong for lyophilizing the NP samples and Ladina Ettinger for her assistance with the GAG analysis.

References

- [1] Iqbal MM. Osteoporosis: epidemiology, diagnosis, and treatment. *South Med J* 2000;93:2–18.
- [2] Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton III LJ. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993;137:1001–5.
- [3] Truumees E, Hilibrand A, Vaccaro AR. Percutaneous vertebral augmentation. *Spine J* 2004;4:218–29.
- [4] Zoarski GH, Snow P, Olan WJ, Stallmeyer MJ, Dick BW, Hebel JR, et al. Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. *J Vasc Interv Radiol* 2002;13:139–48.
- [5] Riggs BL, Melton III LJ. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995;17:505S–11S.
- [6] Silverman SL. The clinical consequences of vertebral compression fracture. *Bone* 1992;13(Suppl 2):S27–31.
- [7] Cooper C, Atkinson EJ, O'Fallon WM, Melton III LJ. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. *J Bone Miner Res* 1992;7:221–7.
- [8] Coumans JV, Reinhardt MK, Lieberman IH. Kyphoplasty for vertebral compression fractures: 1-year clinical outcomes from a prospective study. *J Neurosurg* 2003;99:44–50.
- [9] Lyles KW, Gold DT, Shipp KM, Pieper CF, Martinez S, Mulhausen PL. Association of osteoporotic vertebral compression fractures with impaired functional status. *Am J Med* 1993;94:595–601.
- [10] Evans AJ, Jensen ME, Kip KE, DeNardo AJ, Lawler GJ, Negin GA, et al. Vertebral compression fractures: pain reduction and improvement in functional mobility after percutaneous polymethylmethacrylate vertebroplasty retrospective report of 245 cases. *Radiology* 2003;226:366–72.
- [11] Hordon LD, Raisi M, Aaron JE, Paxton SK, Beneton M, Kanis JA. Trabecular architecture in women and men of similar bone mass with and without vertebral fracture: I. Two-dimensional histology. *Bone* 2000;27:271–6.
- [12] Hui SL, Slemenda CW, Johnston Jr CC. Age and bone mass as predictors of fracture in a prospective study. *J Clin Invest* 1988;81:1804–9.
- [13] Burr DB, Forwood MR, Fyhr DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. *J Bone Miner Res* 1997;12:6–15.
- [14] Ciarelli TE, Fyhr DP, Schaffler MB, Goldstein SA. Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. *J Bone Miner Res* 2000;15:32–40.
- [15] Stauber M, Müller R. Age-related changes in trabecular bone microstructures: global and local morphometry. *Osteoporos Int* 2006;17:616–26.
- [16] Homminga J, McCreadie BR, Ciarelli TE, Weinans H, Goldstein SA, Huiskes R. Cancellous bone mechanical properties from normals and patients with hip fractures differ on the structure level, not on the bone hard tissue level. *Bone* 2002;30:759–64.
- [17] Legrand E, Chappard D, Pascaretti C, Duquenne M, Krebs S, Rohmer V, et al. Trabecular bone microarchitecture, bone mineral density, and vertebral fractures in male osteoporosis. *J Bone Miner Res* 2000;15:13–9.
- [18] Mosekilde L. Age-related changes in bone mass, structure, and strength-effects of loading. *Z Rheumatol* 2000;59(Suppl 1):1–9.
- [19] Eastell R, Barton I, Hannon RA, Chines A, Gamero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 2003;18:1051–6.
- [20] Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002;112:281–9.
- [21] Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 2002;17:1–10.
- [22] Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom* 2004;7:255–61.
- [23] Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res* 2005;20:2097–104.
- [24] Sarkar S, Reginster JY, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Miner Res* 2004;19:394–401.
- [25] Gong H, Zhang M, Qin L, Lee KK, Guo X, Shi SQ. Regional variations in microstructural properties of vertebral trabeculae with structural groups. *Spine* 2006;31:24–32.
- [26] Stauber M, Muller R. Age-related changes in trabecular bone microstructures: global and local morphometry. *Osteoporos Int* 2006;17:616–26.
- [27] 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.
- [28] Banse X, Devogelaer JP, Munting E, Delloye C, Cornu O, Grynepas M. Inhomogeneity of human vertebral cancellous bone: systematic density and structure patterns inside the vertebral body. *Bone* 2001;28:563–71.
- [29] Hildebrand T, Rueggsegger P. Quantification of bone microarchitecture with the Structure Model Index. *Comput Methods Biomech Biomed Engin* 1997;1:15–23.
- [30] Gong H, Zhang M, Yeung HY, Qin L. Regional variations in microstructural properties of vertebral trabeculae with aging. *J Bone Miner Metab* 2005;23:174–80.
- [31] Parfitt AM, Mathews CH, Villanueva AR, Kleerekoper M, Frame B, Rao DS. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the micro-anatomic and cellular mechanisms of bone loss. *J Clin Invest* 1983;72:1396–409.
- [32] Thomsen JS, Ebbesen EN, Mosekilde LI. Age-related differences between thinning of horizontal and vertical trabeculae in human lumbar bone as assessed by a new computerized method. *Bone* 2002;31:136–42.
- [33] 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.
- [34] Mosekilde L. Sex differences in age-related loss of vertebral trabecular bone mass and structure-biomechanical consequences. *Bone* 1989;10:425–32.
- [35] Roberts S, McCall IW, Menage J, Haddaway MJ, Eisenstein SM. Does the thickness of the vertebral subchondral bone reflect the composition of the intervertebral disc? *Eur Spine J* 1997;6:385–9.

- [36] Grote HJ, Amling M, Vogel M, Hahn M, Post M, Delling G. Intervertebral variation in trabecular microarchitecture throughout the normal spine in relation to age. *Bone* 1995;16:301–8.
- [37] Hildebrand T, Rüeggsegger P. A new method for the model-independent assessment of thickness in three-dimensional images. *J Microsc* 1997;185: 67–75.
- [38] Berlemann U, Ferguson SJ, Nolte LP, Heini PE. Adjacent vertebral failure after vertebroplasty. A biomechanical investigation. *J Bone Joint Surg Br* 2002;84:748–52.
- [39] Ochia RS, Tencer AF, Ching RP. Effect of loading rate on endplate and vertebral body strength in human lumbar vertebrae. *J Biomech* 2003;36: 1875–81.
- [40] Pearce RH, Grimmer BJ, Adams ME. Degeneration and the chemical composition of the human lumbar intervertebral disc. *J Orthop Res* 1987;5: 198–205.
- [41] Guio BH, Fessler RG. Molecular biology of degenerative disc disease. *Neurosurgery* 2000;47:1034–40.
- [42] Johannessen W, Auerbach JD, Wheaton AJ, Kurji A, Borthakur A, Reddy R, et al. Assessment of human disc degeneration and proteoglycan content using T1rho-weighted magnetic resonance imaging. *Spine* 2006;31:1253–7.
- [43] Cs-Szabo G, Ragasa-San Juan D, Turumella V, Masuda K, Thonar EJ, An HS. Changes in mRNA and protein levels of proteoglycans of the annulus fibrosus and nucleus pulposus during intervertebral disc degeneration. *Spine* 2002;27:2212–9.
- [44] Proteoglycans. In: Chaplin MF, Kennedy JF, editors. *Carbohydrate Analysis A Practical Approach*. Washington, D.C.: Oxford University Press; 1994.
- [45] Björnsson S. Simultaneous preparation and quantitation of proteoglycans by precipitation with Alcian blue. *Anal Biochem* 1993;210:282–91.
- [46] Pollintine P, Dolan P, Tobias JH, Adams MA. Intervertebral disc degeneration can lead to “stress-shielding” of the anterior vertebral body: a cause of osteoporotic vertebral fracture? *Spine* 2004;29:774–82.
- [47] Homminga J, Weinans H, Gowin W, Felsenberg D, Huiskes R. Osteoporosis changes the amount of vertebral trabecular bone at risk of fracture but not the vertebral load distribution. *Spine* 2001;26:1555–61.
- [48] Grant JP, Oxland TR, Dvorak MF. Mapping the structural properties of the lumbosacral vertebral endplates. *Spine* 2001;26:889–96.
- [49] Zhao F, Pollintine P, Hole B, Adams M, Dolan P. Why do vertebral fractures usually affect the cranial endplate? *Proceedings of the Annual Congress of the International Society for the Study of the Lumbar Spine*, (June 13–17, 2006: Bergen, Norway); 2006.
- [50] Nepper-Rasmussen J, Mosekilde L. Local differences in mineral content in vertebral trabecular bone measured by dual-energy computed tomography. *Acta Radiol* 1989;30:369–71.
- [51] Silva MJ, Keaveny TM, Hayes WC. Computed tomography-based finite element analysis predicts failure loads and fracture patterns for vertebral sections. *J Orthop Res* 1998;16:300–8.
- [52] Magerl F, Aebi M, Gertzbein SD, Harms J, Nazarian S. A comprehensive classification of thoracic and lumbar injuries. *Eur Spine J* 1994;3:184–201.
- [53] Silva MJ, Gibson LJ. Modeling the mechanical behavior of vertebral trabecular bone: effects of age-related changes in microstructure. *Bone* 1997;21:191–9.
- [54] Guo XE, Kim CH. Mechanical consequence of trabecular bone loss and its treatment: a three-dimensional model simulation. *Bone* 2002;30:404–11.
- [55] McDonnell P, McHugh PE, O’Mahoney D. Vertebral osteoporosis and trabecular bone quality. *Ann Biomed Eng* 2007;35:170–89.
- [56] Rubin CD. Emerging concepts in osteoporosis and bone strength. *Curr Med Res Opin* 2005;21:1049–56.
- [57] Davison KS, Siminoski K, Adachi JD, Hanley DA, Goltzman D, Hodsman AB, et al. Bone strength: the whole is greater than the sum of its parts. *Semin Arthritis Rheum* 2006;36:22–31.
- [58] Cody DD, Goldstein SA, Flynn MJ, Brown EB. Correlations between vertebral regional bone mineral density (rBMD) and whole bone fracture load. *Spine* 1991;16:146–54.
- [59] Ebbesen EN, Thomsen JS, Beck-Nielsen H, Nepper-Rasmussen HJ, Mosekilde L. Lumbar vertebral body compressive strength evaluated by dual-energy X-ray absorptiometry, quantitative computed tomography, and ashing. *Bone* 1999;25:713–24.
- [60] Biggemann M, Hilweg D, Brinckmann P. Prediction of the compressive strength of vertebral bodies of the lumbar spine by quantitative computed tomography. *Skeletal Radiol* 1988;17:264–9.
- [61] Cheng XG, Nicholson PH, Boonen S, Lowet G, Brys P, Aerssens J, et al. Prediction of vertebral strength in vitro by spinal bone densitometry and calcaneal ultrasound. *J Bone Miner Res* 1997;12:1721–8.
- [62] Singer K, Edmondston S, Day R, Bredahl P, Price R. Prediction of thoracic and lumbar vertebral body compressive strength: correlations with bone mineral density and vertebral region. *Bone* 1995;17:167–74.
- [63] Wasnich RD. Vertebral fracture epidemiology. *Bone* 1996;18:179S–83S.
- [64] Melton III LJ, Kan SH, Frye MA, Wahner HW, O’Fallon WM, Riggs BL. Epidemiology of vertebral fractures in women. *Am J Epidemiol* 1989;129: 1000–11.
- [65] Pollintine P, Przybyla AS, Dolan P, Adams MA. Neural arch load-bearing in old and degenerated spines. *J Biomech* 2004;37:197–204.
- [66] Lochmuller EM, Burklein D, Kuhn V, Glaser C, Müller R, Gluer CC, et al. Mechanical strength of the thoracolumbar spine in the elderly: prediction from in situ dual-energy X-ray absorptiometry, quantitative computed tomography (QCT), upper and lower limb peripheral QCT, and quantitative ultrasound. *Bone* 2002;31:77–84.
- [67] Moro M, Hecker AT, Bouxsein ML, Myers ER. Failure load of thoracic vertebrae correlates with lumbar bone mineral density measured by DXA. *Calcif Tissue Int* 1995;56:206–9.
- [68] Ito M, Ikeda K, Nishiguchi M, Shindo H, Uetani M, Hosoi T, et al. Multi-detector row CT imaging of vertebral microstructure for evaluation of fracture risk. *J Bone Miner Res* 2005;20:1828–36.
- [69] Edmondston SJ, Singer KP, Day RE, Price RI, Bredahl PD. Ex vivo estimation of thoracolumbar vertebral body compressive strength: the relative contributions of bone densitometry and vertebral morphometry. *Osteoporos Int* 1997;7:142–8.
- [70] Bjarnason K, Hassager C, Svendsen OL, Stang H, Christiansen C. Anteroposterior and lateral spinal DXA for the assessment of vertebral body strength: comparison with hip and forearm measurement. *Osteoporos Int* 1996;6:37–42.
- [71] Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33:744–50.
- [72] Homminga J, Van Rietbergen B, Lochmuller EM, Weinans H, Eckstein F, Huiskes R. The osteoporotic vertebral structure is well adapted to the loads of daily life, but not to infrequent “error” loads. *Bone* 2004;34:510–6.
- [73] Silva MJ, Keaveny TM, Hayes WC. Load sharing between the shell and centrum in the lumbar vertebral body. *Spine* 1997;22:140–50.
- [74] Cao KD, Grimm MJ, Yang KH. Load sharing within a human lumbar vertebral body using the finite element method. *Spine* 2001;26:E253–60.
- [75] Alonso CA, Bermejo AL, Yuste Pena AS, Garcia DL. Epidural anesthesia for percutaneous vertebroplasty. *Rev Esp Anestesiol Reanim* 2003;50: 429–30.
- [76] Andresen R, Werner HJ, Schober HC. Contribution of the cortical shell of vertebrae to mechanical behaviour of the lumbar vertebrae with implications for predicting fracture risk. *Br J Radiol* 1998;71:759–65.
- [77] Ritzel H, Amling M, Post M, Hahn M, Delling G. The thickness of human vertebral cortical bone and its changes in aging and osteoporosis: a histomorphometric analysis of the complete spinal column from thirty-seven autopsy specimens. *J Bone Miner Res* 1997;12:89–95.
- [78] Müller R, Rüeggsegger P. Micro-tomographic imaging for the nondestructive evaluation of trabecular bone architecture. In: Lowet G, editor. *Bone Research in Biomechanics*. Amsterdam, The Netherlands: IOS Press; 1997.
- [79] MacNeil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 2007; [doi:10.1016/j.medengphys.2006.11.002](https://doi.org/10.1016/j.medengphys.2006.11.002).
- [80] 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.