

# The Effect of Regional Variations of the Trabecular Bone Properties on the Compressive Strength of Human Vertebral Bodies

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**Abstract**—Cancellous centrum is a major component of the vertebral body and significantly contributes to its structural strength and fracture risk. We hypothesized that the variability of cancellous bone properties in the centrum is associated with vertebral strength. Microcomputed tomography (micro-CT)-based gray level density (GLD), bone volume fraction (BV/TV), and finite element modulus ( $E$ ) were examined for different regions of the trabecular centrum and correlated with vertebral body strength determined experimentally. Two sets of images in the cancellous centrum were digitally prepared from micro-CT images of eight human vertebral bodies (T10–L5). One set included a cubic volume (1 per vertebral centrum,  $n = 8$ ) in which the largest amount of cancellous material from the centrum was included but all the shell materials were excluded. The other set included cylindrical volumes (6 per vertebral centrum,  $n = 48$ ) from the anterior (4 regions: front, center, left, and right of the midline of vertebra) and the posterior (2 regions: left and right) regions of the centrum. Significant positive correlations of vertebral strength with GLD ( $r^2 = 0.57$ ,  $p = 0.03$ ) and  $E$  ( $r^2 = 0.63$ ,  $p = 0.02$ ) of the whole centrum and with GLD ( $r^2 = 0.65$ ,  $p = 0.02$ ), BV/TV ( $r^2 = 0.72$ ,  $p = 0.01$ ) and  $E$  ( $r^2 = 0.85$ ,  $p = 0.001$ ) of the central region of the vertebral centrum were found. Vertebral strength decreased with increasing coefficient of variation of GLD, BV/TV, and  $E$  calculated from subregions of the vertebral centrum. The values of GLD, BV/TV, and  $E$  in centrum were significantly smaller for the anterior region than for the posterior region. Overall, these findings supported the significant role of regional variability of centrum properties in determining the whole vertebral strength.

**Keywords**—Vertebral centrum, Anatomic site differences, Micro-CT, Large-scale finite element modeling, BV/TV.

## INTRODUCTION

Inhomogeneity of cancellous bone architecture and density within vertebral centrum has been consistently

observed in human vertebrae.<sup>1,9,29</sup> This intra-centrum variation of cancellous bone properties is considered to play an important role in determining the fracture of a whole vertebral body.<sup>8,20,28</sup> Consistent with these considerations, it has been shown that regression models taking into account the regional variations of bone mineral density (rBMD) in the vertebral centrum are more predictive of vertebral strength compared to single point measurements.<sup>6,21</sup> Other studies also demonstrated that trabecular thickness can vary without changing bone quantity within a cancellous bone specimen<sup>17</sup> and that increases in the intraspecimen variations of trabecular architecture can affect cancellous bone modulus independent of bone volume fraction.<sup>32</sup> However, a direct relationship between variability in the regional properties of cancellous tissue and whole vertebral body strength has not been established.

Finite element (FE) analysis has been accepted as a useful tool to compute the modulus of cancellous bone. With the use of a quantitative computed tomography (QCT)-based FE model of vertebral centrum, Kopperdahl *et al.*<sup>16</sup> found that increase in regional strain energy density of the centrum had a strong correlation with structural stiffness reduction of sagittal constructs of vertebrae. Due to the low scanning resolution, however, QCT-based models could not examine the micro-architectural variations in the cancellous centrum. High-resolution microcomputed tomography (micro-CT) allows for the utilization of the finer details of the microstructure in large-scale finite element (LS-FE) analyses, thus help making more mechanistic approaches for understanding modulus and strength of cancellous bone.<sup>12,19,25,30,33</sup>

Using the LS-FE analysis, it has been demonstrated that cancellous tissue strength decreases with increasing scatter of trabecular shear stresses in human vertebral cancellous bone tissue.<sup>10</sup> This result was attributed to the notion that structures with highly scattered tissue

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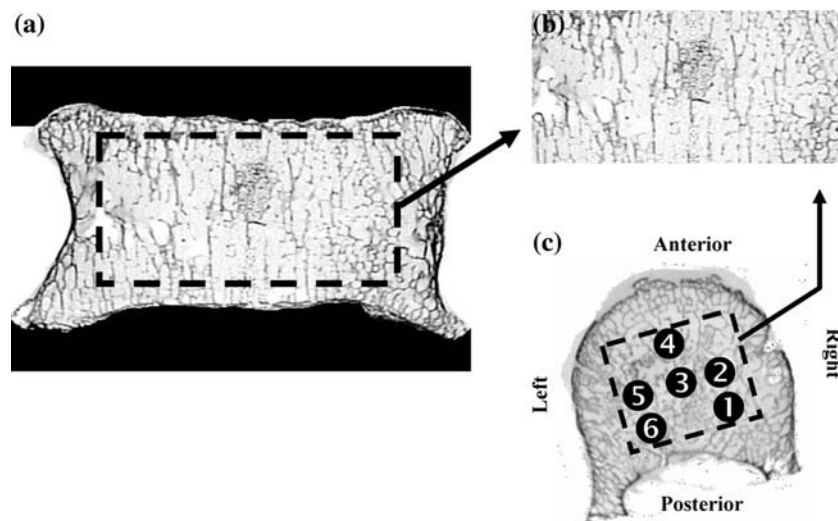
properties would fail earlier, i.e., have lower structural strength in association with weak points in a structure. In this study, we expanded this notion to organ level hypothesizing that the regional variation of properties of cancellous bone cores in vertebral centrum correlates with strength of whole vertebral body. This hypothesis was tested by measuring the properties (micro-CT gray level density (GLD), bone volume fraction (BV/TV), and FE-calculated apparent modulus ( $E$ )) of multiple regions within the human vertebral centrum and correlating the within-vertebra variability of these properties with the experimentally determined strength of whole vertebral bodies.

## METHODS

Eight vertebrae (T10–L5) were obtained from two human cadavers (78 and 89 years, male). All of the vertebral specimens were micro-CT-scanned and reconstructed at  $119\ \mu\text{m}$  voxel size. The micro-CT system has been described in detail<sup>24</sup> and has been utilized in previous work from our laboratory.<sup>10,11,35</sup> A  $119\ \mu\text{m}$  was the smallest available voxel size in this scanning system for the size of whole vertebral bodies used in this study (average width  $\pm$  SD =  $55.80 \pm 2.131\ \text{mm}$ ). Bone and marrow were segmented using a local threshold field based on a heuristic threshold method as introduced in previous studies.<sup>13,33,37</sup> Gray levels in bone voxels were maintained during segmentation. Three-dimensional models were prepared from each vertebra by digitally cutting volumes out of the vertebral body images using Image J (NIH, USA) software (Fig. 1). Two sets of models were prepared

from the cancellous centrum of each vertebral body. In one set of these models, a cubic volume of each cancellous centrum was digitally trimmed out (referred to as the “prism model” hereafter; Fig. 1b). This cubic volume included the largest amount of cancellous material from the centrum (as described in Fig. 1a and c) while excluding all the shell material. In the other set of models, cylindrical regions (6 per vertebral centrum) were digitally cored from the micro-CT images of each cancellous centrum using Image J (NIH, USA) software. The cylindrical volumes were from four regions in the anterior (front (C4), center (C3), left (C5), and right (C2) of a midline of vertebra) and from two regions in the posterior (left (C1) and right (C6)) portion of the centrum (Fig. 1c). These regions corresponded to those examined by Cody *et al.*<sup>6</sup> Length of the cylindrical specimens was 10 mm (84 voxels), starting 5 mm (42 voxels) below the superior end-plate of the vertebral body and ranging across almost all the distance between the end plates ( $117 \pm 20$  voxels). The diameter of cylinders was 8 mm (67 voxels) consistent with that of specimens used in the previous studies.<sup>10,11,33</sup>

After segmentation, GLD (gray-level/ $\text{mm}^3$ ) was calculated by dividing the sum of gray levels of bone voxels by an apparent total volume (TV) of each prism and cylindrical model. BV/TV was measured by counting bone voxels within the model volume. Finite element models were constructed from the same images. The number of cubic elements was  $17,322 \pm 4021$  for prism and  $1261 \pm 343$  for cylindrical models. An isotropic tissue modulus of 5 GPa and a Poisson’s ratio of 0.3 were assigned as material properties, which provides good agreement between FE-calculated and experimentally measured apparent mechanical properties



**FIGURE 1.** Specimens for experiments and FE simulations. (a) Schematic drawing for the compressive mechanical test of human whole vertebral body. (b) “Prism model”; a cube of the cancellous centrum that was digitally trimmed out. (c) “Cylindrical model”; the cylindrical regions that were digitally cored out. The dashed line indicates the area of centrum covered by the prism model.

of cancellous bone.<sup>11,35</sup> The upper and lower faces of the models were fixed except that an axial displacement was allowed to produce 0.005 compressive strain on one of the ends. A special-purpose solver based on element-by-element preconditioned conjugate gradient iterative algorithm was utilized.<sup>11,25</sup> A total of 56 simulations (8 prism models and 48 cylindrical models (6 regions  $\times$  8 specimens)) were operated. FE apparent stress was calculated as the total reaction force per apparent area. Based on that, FE apparent modulus ( $E$ ) was computed by dividing the FE apparent stress by 0.005 strain.<sup>33</sup>

All vertebral bodies were uniaxially compressed to fracture using a servo-hydraulic testing machine (Instron 8501, MA). The applied strain rate (0.01/s) was calculated based on the length of each vertebra that was measured from micro-CT images. To ensure uniform load distribution, low-temperature melting point Wood's metal was used to constrain the irregularly shaped end plates of vertebrae during compression.<sup>14,15,34</sup> The strength of vertebrae was determined as the maximum load sustained during fracture.

Coefficient of variation ( $COV_w$ ) of tissue properties within a vertebral body was calculated for GLD, BV/TV, and  $E$  ( $COV_w = SD_w/Avg_w$  where  $Avg_w$  and  $SD_w$  are the average and standard deviation of properties from six regions within a vertebral body—subscript  $w$  indicates that the parameters represent the within-vertebra average and variability).  $COV$  from each set of six regions was considered as a property of that vertebra. Thus it was possible to calculate the between-vertebra variability of within-vertebra variability ( $COV_b(COV_w)$ )—this will become clearer in discussion). Primary tests included simple regressions of whole vertebral body strength ( $F_{max}$ ) with the  $COV_w$  of GLD, BV/TV, and  $E$ .

Secondary analyses were performed in order to gain further insight into the nature of the relationships found between the variability of tissue properties and vertebral strength. First,  $F_{max}$  was regressed over average ( $Avg_w$ ) GLD, BV/TV, and  $E$  from the cylindrical regions. Second, the relationship of  $F_{max}$  with GLD, BV/TV, and  $E$  was examined for the prism centrum and each of the six cylindrical regions using linear regression. Third, the variation of GLD, BV/TV, and  $E$  between specific regions of the centrum was investigated. Repeated measures ANOVA (SigmaStat, SPSS Inc.) with each vertebral specimen as a subject and the region within the centrum as the repeated factor was performed to identify differences between the cylindrical regions. *Post hoc* analyses were performed using Fisher's LSD test. The  $p$ -values were adjusted according to the number of tests performed within an aim taking into account the correlation between multiple factors.<sup>27</sup>

## RESULTS

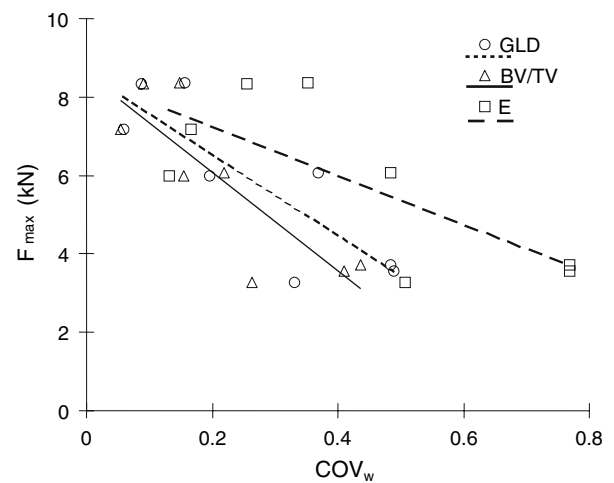
Within-vertebra  $COV_w$  of GLD, BV/TV, and  $E$  from the six cores had significant negative correlations with vertebral strength (Table 1 and Fig. 2) indicating that an increase in the variability of cancellous bone structure in the centrum could result in reduced vertebral strength. Correlations between the strength of vertebral body and any averaged ( $Avg_w$ ) value of GLD, BV/TV, and  $E$  over the core regions were not statistically demonstrable ( $p > 0.11$ ). The between-vertebra variability of the within-vertebra variability of parameters ( $COV_b(COV_w) = 0.63$  for GLD, 0.63 for BV/TV and 0.54 for  $E$ ) was higher than that of the within-vertebra average ( $COV_b(Avg_w) = 0.17$  for GLD, 0.14 for BV/TV and 0.22 for  $E$ ) of the same parameters.

Significant positive correlations of vertebral strength with FE modulus ( $E$ ) of the whole centrum (prism) model and with properties of C2 and C3 cancellous bone regions were found (Table 2).

**TABLE 1. Linear regressions between vertebral strength ( $F_{max}$ ) and average ( $Avg_w$ ) and coefficient of variation ( $COV_w$ ) of GLD (gray level density), BV/TV, and  $E$  within each vertebral body ( $n = 8$ ).**

Y	X	$r^2$	$p$
$F_{max}$ (kN)	GLD	$Avg_w$	0.28
		$COV_w$	<b>0.72</b>
	BV/TV	$Avg_w$	0.36
		$COV_w$	<b>0.71</b>
	$E$ (MPa)	$Avg_w$	0.37
		$COV_w$	<b>0.51</b>

Unit of gray level density is gray-level/mm<sup>3</sup>. Significant correlations ( $p < 0.046$  for  $\alpha = 0.05$  after adjustment for multiple tests) were highlighted by bold style.



**FIGURE 2. Vertebral body strength decreases with increase in  $COV_w$  of GLD, BV/TV and  $COV_w$  of  $E$  (Table 1). The regression equations are  $y = -10.43x + 8.64$  for GLD,  $y = -12.59x + 8.60$  for BV/TV,  $y = -6.78x + 8.57$  for  $E$ .**

**TABLE 2. Correlations of vertebral strength with GLD (gray level density), BV/TV, and *E* of each regional model.**

Y	X	Region	$r^2$	$p$	
$F_{\max}$ (kN)	GLD	Prism	0.57	0.03	
		C1	0.00001	0.98	
		C2	0.53	0.04	
		<b>C3</b>	<b>0.65</b>	<b>0.02</b>	
		C4	0.443	0.07	
		C5	0.203	0.26	
		C6	0.007	0.84	
		BV/TV	Prism	0.39	0.10
			C1	0.03	0.67
			<b>C2</b>	<b>0.70</b>	<b>0.01</b>
			<b>C3</b>	<b>0.72</b>	<b>0.01</b>
			C4	0.41	0.09
	C5		0.24	0.22	
	E (MPa)	C6	0.004	0.88	
		<b>Prism</b>	<b>0.63</b>	<b>0.02</b>	
		C1	0.11	0.42	
		<b>C2</b>	<b>0.72</b>	<b>0.01</b>	
		<b>C3</b>	<b>0.85</b>	<b>0.001</b>	
		C4	0.34	0.13	
			C5	0.09	0.46
			C6	0.0001	0.95

Regions that have significant correlation ( $p < 0.025$  for  $\alpha = 0.05$ , after adjustment for multiple tests) were highlighted by bold style.

**TABLE 3. Between-vertebra average (Avg), SD, and COV of regional GLD (gray level density), BV/TV, and *E* calculated from eight vertebrae for each region.**

X	Region	Avg <sub>b</sub>	SD <sub>b</sub>	COV <sub>b</sub>
GLD	C1	43487.61	12931.39	0.30
	C2***	30863.55	11389.46	0.37
	C3***	28767.89	11274.86	0.39
	C4***	30035.31	9673.97	0.32
	C5***	29637.46	9577.99	0.32
	C6	44606.40	8426.55	0.19
BV/TV	C1	0.36	0.08	0.22
	C2***	0.26	0.09	0.32
	C3***	0.26	0.09	0.36
	C4***	0.26	0.08	0.31
	C5***	0.27	0.08	0.30
	C6	0.36	0.06	0.17
E (MPa)	C1	736.45	328.44	0.45
	C2	518.83	279.17	0.54
	C3***	409.21	243.87	0.60
	C4***	476.71	229.04	0.48
	C5*	416.35	238.36	0.57
	C6	659.00	258.27	0.39

Subscript b is used to indicate between-vertebra average and variability, which are different from the within-vertebra average and variability used in regression analyses.

\*Different from C1, \*\*Different from C6 ( $p < 0.009$  for all).

There was a significant effect of the location of cancellous cores on GLD, BV/TV, and *E* ( $p < 0.001$ ; RMANOVA) (Table 3). Adjustment for multiple tests revealed that the level of significance corresponding to an  $\alpha$  of 0.05 in these tests was  $p = 0.012$ . *Post hoc*

analysis indicated that GLD and BV/TV values from cores within the anterior region (C2, C3, C4, and C5) were significantly smaller than those within the posterior region (C1 and C6) ( $p < 0.001$  for all). In addition, *E* values from C3, C4, and C5 were smaller than that from C1 and *E* values from C3 and C5 were smaller than that from C6 ( $p < 0.009$  for all). A minimum  $p$  value of 0.019 was obtained for all other differences, which is considered nonsignificant after adjusting for multiple tests.

## DISCUSSION

The primary goal of this study was to examine whether the variability of vertebral centrum properties has effects on the strength of whole vertebral body. Our results indicate, as hypothesized, that increased variability of cancellous tissue properties within a vertebra is associated with decreased strength in that vertebra. We used within-vertebra COV as a property of the vertebral body that represents the nonuniformity of cancellous bone properties in that vertebra. Theoretically, the mean and the standard deviation of a distribution are independent of each other, however, this is often not the case for bone properties.<sup>7,10,36</sup> The use of COV rather than the standard deviation allowed us to examine the effect of property variability independent of the mean. The between-vertebra variability of the within-vertebra variability ( $COV_b(COV_w)$ ) of parameters was higher than that of the within-vertebra average ( $COV_b(Avg_w)$ ) of the same parameters. These findings suggest the variability of centrum properties is sensitive to differences between vertebrae and may be a good correlate of fracture risk in equal bone-mass groups of individuals.

Experimental evaluation of both cancellous core moduli and vertebral strength would not be possible due to the destructive nature of the procedures. This study utilized a nondestructive digital coring technique combined with finite element modeling to calculate regional cancellous bone properties. Cancellous bone modulus calculated using micro-CT imaging and LS-FE modeling is a strong predictor of cancellous bone experimental modulus and strength.<sup>11,19,35</sup> Therefore, FE modulus of cancellous bone was used as a surrogate for experimental modulus.

The number of specimens used in this study was relatively small ( $n = 8$ ). Consequently, we used adjusted  $p$ -values and concentrated on significant results. While demonstration of statistically nonsignificant results as no-difference or no-relationship would require a higher power, the statistically significant results demonstrated in the current study would be sufficient for proof of concept related to main hypotheses. In



addition, vertebrae from a large range of anatomical sites (T10 to L5) were included so as to create variability in the set. From the sampled vertebrae significant results were obtained that could be generalized to thoraco-lumbar vertebrae.

Another limitation of the current study is that our findings are limited to the variability in the axial plane of vertebrae. Because our digital cancellous bone specimens spanned much of the centrum in the supero-inferior direction, a potential effect of tissue-variability in this direction<sup>1,6</sup> was not investigated.

The values of BV/TV in this study (0.26–0.36) were generally higher than those observed in histological analyses (0.14–0.16 for human lumbar)<sup>18</sup> but well within the range of values obtained from high-resolution micro-CT scans (0.09–0.39),<sup>10</sup> though it is expected that these values are higher than their true value due to the large voxel size used in the current study.<sup>13,18</sup> Consequently, FE-calculated modulus values were higher than those in previous studies (536.09 ± 279.24 MPa vs. 283.4 ± 136.0 MPa)<sup>33</sup> that utilized the same modeling approach as in the present study but with better resolution. Increasing the scanning resolution could minimize the artifact, however, this was not possible due to the large specimen size. Ruegsegger *et al.*<sup>26</sup> indicated that the architectural parameters of bone measured using micro-CT images could be corrected when scanned up to 200 μm voxel size. Other studies reported that scanning vertebral bone at 150 μm resulted in trabecular architectural parameters that were substantially different in numbers than those measured by histomorphometry but that the low-resolution scans were highly correlated with the “gold standard.”<sup>5,22</sup> Therefore, we anticipated that accuracy of the measured parameters would be affected by the 119 μm voxel size but this would not affect conclusions that are based on the relative variations of these parameters.

The main goal of the alloy-filler used in the compression experiment was to provide a uniform boundary between the loader and vertebral end-plates so as to avoid stress concentrations that could cause premature failure of the specimen. Though this is different from loading *in vivo*, testing of vertebral strength using fillers is customary and allows for a standardized evaluation of vertebral bone.<sup>3,8,14,20</sup> The range of values of vertebral strength measured in the current study (3238.95–8371.09 N) was comparable with that in previous studies (2000–8000 N)<sup>20</sup> in which a polymer-filler material was used to constrain the end-plates of vertebrae during mechanical testing. According to a recent study, variations in load distributions over the vertebral end-plate do not appreciably affect the ability of finite element models to predict the uniaxial, quasi-static compressive strength of vertebral

bodies.<sup>2</sup> This indicates that experimental measurement of vertebral strength without precisely mimicking the *in vivo* load distribution as was done in the current study provides accurate information on the strength of vertebral bodies relative to each other and is acceptable for the purpose of this study.

FE modulus of the cancellous centrum (prism) correlated with vertebral body strength whereas the relationships of centrum GLD and BV/TV with vertebral body strength were not significant after considering multiple tests performed. The small sample size used in this study is not sufficient for supporting a negative conclusion (that the latter two have no relationship with vertebral strength). Rather, the significant relationship found between centrum modulus and vertebral strength supports the notion that mechanical properties of centrum play an important role in determining vertebral strength.<sup>4,6,28</sup> On the other hand, regional variability of cancellous bone modulus is especially relevant given that cancellous bone modulus can be changed due to variations in the trabecular architecture without changing bone volume.<sup>17,32</sup>

Despite of the significant correlation between vertebral strength and modulus from the prism model (Table 2), modulus averaged over cancellous cylinders did not correlate to bone strength (Table 1). It can be argued for the modulus that modeling cancellous bone *in-situ* vs. *ex-situ* may cause such differences in results. Un *et al.*<sup>31</sup> found, using micro-CT-based FE simulation of cored vertebral cancellous bones, that interruption of trabecular connectivity around the excised bone had the tissue-level stress decreased at the outermost region of the model. This side-artifact led to errors in computation of FE modulus. Consistent with the results of Un *et al.*,<sup>31</sup> the differences between the prism model and averaged cylinder models may be attributed to constraint differences between models.

The relationships between regional properties and vertebral strength appear to be different between supposedly similar regions such as C2 and C5 in the vertebral body (Table 2). This is not necessarily a discrepancy as similar results were found by others as well.<sup>6</sup> Adaptive response of bone to changes in loading due to spine tissues other than bone (such as partial degeneration of intervertebral discs) may explain these differences. Nonsymmetric use of body weight, for instance due to abnormal posture and gait pattern of an individual, could also result in a nonsymmetric distribution of tissue properties. However, it is beyond the scope of this work to elucidate these mechanisms.

All of the measured parameters, i.e., GLD, BV/TV, and FE modulus (*E*) were significantly different between anterior and posterior centrum consistent with the previous findings for rBMD<sup>6</sup> and trabecular architecture.<sup>1,29</sup> Cody *et al.*<sup>6</sup> showed rBMD correlated

with vertebral strength differently depending on local variations in density within centrum. Agreed with their observation, we found the correlations between the measured parameters and vertebral strength varied between regions, even within the regions of the anterior portion. Previous studies indicated the anterior part of the vertebral body is more susceptible to bone loss and responsible for increased fracture risk.<sup>23,29</sup> Consistent with this assertion, the regional properties of C3 were characterized by low average values and highest between-vertebra variability (COV<sub>b</sub>) in the current study (Table 3). Our finding that all examined parameters had the strongest correlation with vertebral strength for C3 (center) region of the anterior centrum is also consistent with this assertion.

In conclusion, we found that vertebral strength is lower when the within-vertebra variability of bone properties is higher. This variability is such that the properties of the central-anterior regions dictate the compressive strength of the vertebra. Future studies could include extension of the current study to estimation of fracture risk in vertebral bone. Furthermore, biological mechanisms that determine tissue modulus variability, especially with reduced bone mass should be investigated.

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