Increased Microstructural Variability is Associated With Decreased Structural Strength But With Increased Measures of Structural Ductility in Human Vertebrae

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The lack of accuracy in the prediction of vertebral fracture risk from average density measurements, all external factors being equal, may not just be because bone mineral density (BMD) is less than a perfect surrogate for bone strength but also because strength alone may not be sufficient to fully characterize the structural failure of a vertebra. Apart from bone quantity, the regional variation of cancellous architecture would have a role in governing the mechanical properties of vertebrae. In this study, we estimated various microstructural parameters of the vertebral cancellous centrum based on stereological analysis. An earlier study indicated that within-vertebra variability, measured as the coefficient of variation (COV) of bone volume fraction (BV/TV) or as COV of finite element-estimated apparent modulus (E_{FE}) correlated well with vertebral strength. Therefore, as an extension to our earlier study, we investigated (i) whether the relationships of vertebral strength found with COV of BV/TV and COV of E_{FE} could be extended to the COV of other microstructural parameters and microcomputed tomography-estimated BMD and (ii) whether COV of microstructural parameters were associated with structural ductility measures. COV-based measures were more strongly associated with vertebral strength and ductility measures than average microstructural measures. Moreover, our results support a hypothesis that decreased microstructural variability, while associated with increased strength, may result in decreased structural toughness and ductility. The current findings suggest that variability-based measures could provide an improvement, as a supplement to clinical BMD, in screening for fracture risk through an improved prediction of bone strength and ductility. Further understanding of the biological mechanisms underlying microstructural variability may help develop new treatment strategies for improved structural ductility. [DOI: 10.1115/1.3148473]

Keywords: micro-CT, vertebrae, strength, ductility, heterogeneity

1 Introduction

Osteoporosis is associated with bone mineral density (BMD), but it is often accepted apprehensively in predicting fracture risk and bone strength because of its vague differentiation between fractures in osteoporotic and nonosteoporotic groups [1]. Although the amount of bone mass contributes to the strength of bone, it alone cannot account for how the material is distributed in the structure, and bone strength prediction models can often be improved when factors additional to BMD are included [2–4]. Therefore, using information about the organization of trabeculae, in addition to bone density, may increase the success in predicting fractures [5].

Previous studies indicated that the integrity of the trabecular centrum plays an important role in determining the strength of a whole vertebral body [6]. Due to the heterogeneity of trabecular bone density and architecture within the vertebral centrum [4,7], each region may influence the total strength of the vertebra to a different extent. Previous studies on the regional variation of bone density and architectural parameters in human vertebrae [8,9] reported that failure strength cannot be predicted through analysis of one specific anatomic region and that prediction of vertebral strength can be improved over traditional BMD measurements when the regional variation of architectural parameters is considered. We have previously quantified the regional variation of cancellous bone properties as the coefficient of variation of bone volume fraction (BV/TV) and finite element (FE)-estimated apparent modulus of cancellous bone within a vertebra and have shown that increasing values of these parameters are highly associated with decreased vertebral strength [10].

One of the implications of the relationship between within-vertebra variability of cancellous bone FE modulus and vertebral strength is that such a relationship could be useful in predicting vertebral strength. However, it is often density or microstructural parameters, rather than FE-estimated parameters, that are more readily extractable from various images [5,7,10–13]. Although the within-vertebra variability of BV/TV determined from microcomputed tomography (μCT) images was found to correlate with vertebral strength, it is not known whether the variability of cancellous microstructural parameters other than BV/TV would correlate with strength. Therefore, one of the objectives of this study was to extend our earlier study [10] and examine the relationship between within-vertebra variability of cancellous bone microstructure and the structural strength of human vertebral bodies.

The increased strength in vertebrae with a more homogeneous cancellous bone is consistent with a structural design that has the goal of increasing uniaxial stiffness [14] and with the strong correlation between bone stiffness and strength at various hierarchical levels [12,15–19]. However, homogenization of the structure may result in the loss of weak and strong sites, which, when present, would not fail simultaneously under an overload and provide damage-tolerance and ductility to the vertebral structure [20]. Our recent finding that T12-L1 vertebrae, which collapse more often than other vertebrae, have a more homogeneous cancellous bone than other vertebrae [21] supports the idea that mechanical properties other than ultimate strength are important in determining the risk of vertebral fractures. Therefore, a second objective of this study was to examine if there is evidence that decreased within-vertebra variability of cancellous properties is associated with decreased measures of structural ductility by further analysis of the mechanical test data from our original study [10].

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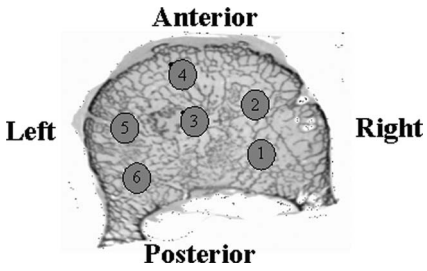

Fig. 1 Regions of digital cores, cylinders of 10 mm length and 8 mm diameter, from which average and variability (COV) measures were estimated for a vertebral body

2 Materials and Methods

The specimen preparation, μCT scanning, image processing, and mechanical test procedures were described in our previous study [10]. Briefly, eight vertebrae (T10~L5) obtained from two human cadavers (78 years and 89 years, male) were scanned using μCT, and six cylindrical biopsy regions ($\varnothing 8$ mm $\times$ 10 mm) were digitally cored from each vertebral centrum (Fig. 1). Thus, a total 48 cylindrical images of cancellous bone were used. A solid radiographic reference was also included in each scan. Bone volume fraction (BV/TV), bone surface area fraction (BS/BV), trabecular number (Tb.N), trabecular spacing (Tb.Sp), trabecular thickness (Tb.Th), connectivity by Euler number (Eu.N), mean intercept length along primary, secondary and tertiary directions (MIL1, MIL2, and MIL3), and degree of anisotropy (DA=MIL1/MIL3) were measured for each digital core using 3D stereology [12]. Then, in order to simulate BMD that can be measured in vivo, the images scanned at 119 μm voxel size were reconstructed at 1 mm voxel size [22,23]. The solid radiographic reference was used to convert μCT gray levels to density-based estimates. After this, μCT equivalent of clinical BMD (μCT-BMD) was calculated for each core. Within-vertebra average (Avg) and standard deviation (SD) of the architectural and μCT-BMD parameters were calculated for each vertebral body from six digitally cored regions. The within-vertebra coefficient of variation (COV=SD/Avg) was calculated for each parameter as an indication of the variability of these parameters within a vertebral body.

The whole vertebra specimens were uniaxially compressed to fracture with a nominal strain rate of 0.01/s using a servohydraulic testing machine (Instron 8501, Canton, MA). The height of each vertebra was measured from μCT images. To ensure uniform load distribution, low-temperature melting point Wood's metal was used to constrain the end plates of vertebrae [24]. Stiffness (K) was estimated as the maximum of the slopes calculated along the load displacement curve before failure. The strength of vertebrae was determined as the maximum load ($F_{\max}$) sustained. In addition, ultimate displacement (Δ_u), the maximum displacement traveled by the cross-head before specimen's failure, and work to fracture (W), the total amount of work done for fracture, were obtained as measures of structural ductility. Also, postyield energy (W_{py}) was estimated as a ductility measure, where yield point was found using 5% secant stiffness method [25]. In order to assess the variation of structural ductility measures relative to strength, W_{py}, W and Δ_u were normalized with strength to produce postyield energy to strength ratio ($W_{\text{py}}/F_{\max}$), work to fracture to strength ratio ($W/F_{\max}$), and ultimate displacement to strength ratio ($\Delta_u/F_{\max}$).

Pearson's correlation analysis was performed to examine the relationship of vertebral body compressive strength and ductility with average and variability of microstructural and BMD parameters.

3 Results

Strength correlated positively ($P=0.039$, $P=0.047$, and $P=0.015$) with the average values of Tb.N, MIL1, and DA and negatively ($P=0.047$) with average Tb.Sp, while the relationships between stiffness and average measures were nonsignificant, except for DA ($P=0.031$). Whereas, COV of BV/TV ($P=0.0004$), Tb.N ($P=0.0085$), Tb.Sp ($P=0.0001$), and Eu.N ($P=0.035$) negatively correlated with stiffness and COV of BV/TV ($P=0.0002$), Tb.N ($P=0.0048$), Tb.Sp ($P=0.0007$), Eu.N ($P=0.032$), and MIL2 ($P=0.035$) with strength (Table 1, Figs. 2(a) and 2(b)). For comparison with the average and COV of BV/TV, a significant negative correlation was found between minimum BV/TV and strength ($P=0.036$, $r=0.74$).

Among ductility parameters, work to fracture significantly increased with average measures of BV/TV ($P=0.027$) and MIL1 ($P=0.044$) and significantly decreased with average Tb.Sp ($P=0.031$). Increasing variability of the microstructure was generally associated with increased values of ductility parameters, except for work to fracture, but this when normalized with strength, again positively associated with increasing microstructural variability. Especially interesting was the case of MIL2 where increasing COV of MIL2 was negatively ($P=0.035$) associated with strength but positively associated with ultimate displacement ($P=0.042$), $W_{\text{py}}/F_{\max}$ ($P=0.048$), and $\Delta_u/F_{\max}$ ($P=0.024$) (Table 1 and Fig. 3).

The relationships of within-vertebra average ($P=0.263$) and the variability of μCT-BMD ($P=0.100$, Fig. 2(c)) with the vertebral strength, although potentially demonstrable with a larger sample size, were not significant in the current sample. However, stiffness correlated positively with average ($P=0.047$) and negatively with COV ($P=0.045$) of μCT-BMD.

4 Discussion

The main objective in this study was to investigate the relationships between statistical measures of micro-architectural parameters and the strength and ductile behavior of human vertebrae. Since this investigation is an extension to our earlier work [10], most of the limitations discussed in the previous study apply to the current investigation also. In addition, for BMD measurements, we reconstructed images at a typical 1 mm voxel size consistent with previous studies of vertebral mineral density [22] and finite element models [22,23]. Recognizing that factors other than reconstruction voxel size contribute to resolution [11,26,27], our BMD measurements might not accurately reflect clinical CT resolution, hence the acronym μCT-BMD.

In this study we characterized ductility using work to fracture, ultimate displacement, postyield energy, and their ratios relative to strength. Among these parameters, work to fracture is related to both strength and displacement unlike the other ductility parameters considered in this study. Consequently, when work to fracture was normalized with strength, its relationships with the microstructure were similar to those of other ductility parameters. Although the currently employed parameters were sufficient to make our initial point, this work could be expanded to include more rigorous failure criteria. For example, note that the $W/F_{\max}$ is similar, in principle, to the reciprocal of cushion factor commonly used in evaluating the energy absorption efficiency of cellular materials [28]; however, this study did not include the post-maximum load mechanical behavior of the vertebrae.

Our results indicate that an increase in the variability of cancellous microstructure within a vertebra is strongly associated with a decrease in vertebral strength. The stronger association of the ver-

Table 1 Correlation coefficients (r) of within-vertebra variability of cancellous microstructure with structural strength and ductility parameters

		K	F_{max}	W	W_{py}	Δ_u	W/F_{max}	W_{py}/F_{max}	Δ_u/F_{max}
BV/TV	AVG			+0.76					
	COV	−0.94	−0.96					+0.74	+0.82
BS/BV	AVG								
	COV				+0.71	+0.82	+0.83		+0.73
Tb.N	AVG		+0.73						
	COV	−0.84	−0.87	−0.75					
Tb.Sp	AVG		−0.71	−0.75					
	COV	−0.96	−0.93						
Tb.Th	AVG								
	COV				+0.70	+0.83	+0.85	+0.75	+0.75
Eu.N	AVG								
	COV	−0.74	−0.75	−0.74					
MIL1	AVG		+0.71	+0.72					
	COV								
MIL2	AVG								
	COV		−0.74			+0.73	+0.71		+0.77
MIL3	AVG								
	COV				+0.84	+0.88	+0.93	+0.87	+0.85
DA	AVG	+0.75	+0.81			−0.74	−0.80	−0.80	−0.86
	COV								
μCT-BMD	AVG	+0.71							
	COV	−0.72							

tebral strength with the scatter than with the average of cancellous microstructure suggests that within-vertebra variability of the microstructure may help determine fracture risk in equal bone-mass groups. High variability of the microstructure may indicate presence of relatively weak regions that may be a dominant factor in determining vertebral strength [29]. Minimum BV/TV did negatively correlate with strength but not as strong as COV in the current study.

Our results also indicate that within-vertebra variability of the microstructure (COV of BV/TV and MIL2), while negatively associated with strength, is positively associated with ductility properties (Table 1). This is consistent with the observations that, in engineering and biological materials including bone, increased stiffness and strength of the vertebra come at the cost of reduced toughness and ductility [30]. Our result is also consistent with previous findings that vertebral fatigue life (related to tolerance for progressive damage, toughness, and ductility) and strength are competing properties [4,31]. The issue of characterization of bone integrity is at least twofold: finding a more accurate surrogate for bone strength than average density and finding a mechanical parameter(s) that is more representative of a progressive failure process than strength. One implication of the finding that increased microstructural variability is associated with reduced strength but increased ductility is that variability-based parameters can be developed to improve fracture risk prediction from average density-based predictions alone. A potential advantage of using microstructural parameters is the applicability to images such as those measured using histomorphometry or 2D imaging modalities [32] that are not necessarily amenable to complete computational mechanical analysis.

The current results must be considered in the context of a pilot study as the sample size was small and the hypothesis was general and not parameter-specific. As such, further studies are necessary to determine which specific parameter would be most useful and whether or not the results are expandable to clinical modalities. For example, despite the similarity between BV/TV and BMD, COV of BV/TV was more strongly correlated with vertebral strength or stiffness than COV of μCT-BMD. A sample size analysis suggests that the relationship between strength and COV of μCT-BMD is statistically demonstrable at a power of 0.8 and an α of 0.05 using a sample size of 18. If it turns out that imaging methods that can resolve the details of trabecular microstructure are necessary for noninvasive use of the variability information in a clinical environment, alternative imaging techniques could be considered. For example, an analysis of calcaneal cancellous microstructure from X-ray radiograms was able to distinguish fracture cases from controls in a recent study [33]. With the advances in digital X-ray technology, techniques such as tomosynthesis would be able to provide in vivo images that can be used for the type of analyses presented in the current work [34].

The relationships presented here have other implications on the mechanisms of vertebral fracture risk. It is a well accepted notion that bone structurally adapts to local loads by modifying its architecture. There is good evidence that these adaptations result in the maintenance of bone stiffness (thus, strength, suggested by the strong correlations between the two [12,15–19]) in directions of most habitual loading [35,36]. Homogeneous distribution of microstructural properties could represent an effort to increase stiffness under uniaxial loading. However, overhomogenization of the bone structure could come at a cost of increased brittleness, as suggested by the current data, and result in a clinical fracture even though the bone appears strong on screens. If true, for studies aiming at improving bone mechanical integrity, the outcome mea-

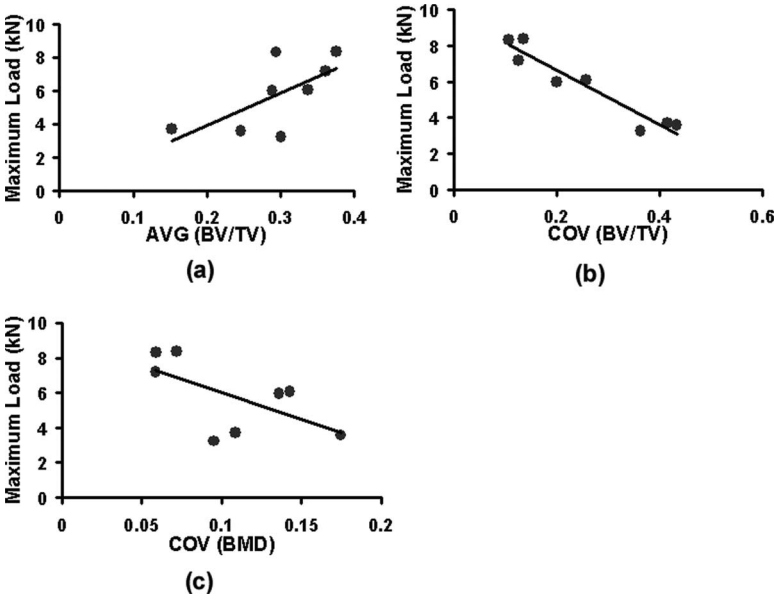

Fig. 2 (*a*) **A positive nonsignificant relationship of vertebral strength with average BV/TV was observed, whereas** (*b*) **a strong and negative relationship was found between strength and the coefficient of variation of BV/TV** (r**=0.95,** P**=0.0002).** (*c*) **In comparison, the relationship between strength and COV of** μ**CT-BMD was negative but nonsignificant.**

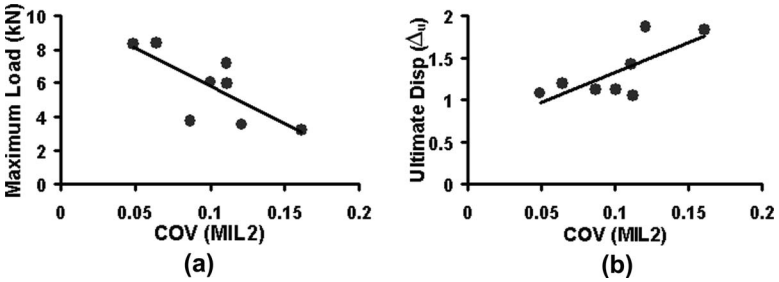

Fig. 3 (*a*) **Vertebral strength decreased with increasing COV of MIL2** (r**= –0.74,** P**=0.035), whereas** (*b*) **ultimate displacement of the vertebra increased with increasing COV of MIL2** (r**=0.75,** P**=0.042**)

sures should include measures of ductility. If the role of microstructural variability in age- and disease-related increase in bone fragility can be further substantiated, cellular and molecular mechanisms underlying heterogeneity of bone microstructure would be of interest.

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