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Heterogeneity and Spatial Distribution of Intravertebral Trabecular Bone Mineral Density in the Lumbar Spine is Associated with Prevalent Vertebral Fracture

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Abstract

The spatial heterogeneity in trabecular bone density within the vertebral centrum is associated with vertebral strength and could explain why volumetric bone mineral density (vBMD) exhibits low sensitivity in identifying fracture risk. This study evaluated whether the heterogeneity and spatial distribution of trabecular vBMD are associated with prevalent vertebral fracture.

We examined the volumetric QCT scans of the L3 vertebra in 148 participants in the Framingham Heart Study Multidetector CT study. Of these individuals, 37 were identified as cases of prevalent fracture, and 111 were controls, matched on sex and age with three controls per case. vBMD was calculated within 5-mm contiguous cubic regions of the centrum. Two measures of heterogeneity were calculated: 1) interquartile range (IQR); and 2) quartile coefficient of variation (QCV).

Spatial distributions of the trabecular vBMD were also calculated: anterior/posterior, central/outer, superior/mid-transverse, and inferior/mid-transverse. Heterogeneity and spatial distributions were compared between cases and controls using Wilcoxon Rank Sum tests and *t*-tests and tested for association with prevalent fractures with conditional logistic regressions independent of integral vBMD.

Prevalent fracture cases had lower mean (SD) integral vBMD (134 (38) vs. 165 (42) mg/cm³, *p*<0.001), higher QCV (0.22 (0.13) vs. 0.17 (0.09), *p*=0.003), and lower anterior/posterior rBMD

(0.65 (0.13) vs 0.78 (0.16), $p < 0.001$) than controls. QCV was positively associated with increased odds of prevalent fracture (OR=1.61; 95% CI: 1.04–2.49, $p=0.034$), but this association was not independent of integral vBMD ($p=0.598$). Increased anterior/posterior trabecular vBMD ratio was associated with decreased odds of prevalent fracture independent of integral vBMD (OR= 0.38; 95% CI: 0.20–0.71, $p=0.003$).

In conclusion, increased trabecular vBMD in the anterior vs. posterior centrum, but not trabecular vBMD heterogeneity, was associated with decreased risk of prevalent fracture independent of integral vBMD. Regional measurements of trabecular vBMD could aid in determining the risk and underlying mechanisms of vertebral fracture.

Keywords

Biomechanics; Fracture risk assessment; Bone QCT/ μ CT; Osteoporosis; General population studies

Introduction

Approximately four million Americans were diagnosed with a prevalent vertebral fracture in 2013 (1). In spite of the high prevalence and burden of vertebral fractures, the structural determinants of fracture risk in the spine are incompletely understood. The most commonly assessed structural determinant, areal bone mineral density (aBMD) measured by DXA, has well known limitations: as a 2-D projection measure of bone density, aBMD is confounded by bone size and overlying calcification, and for anterior-posterior scans, aBMD does not separately evaluate the vertebral body from the posterior elements (2–4). The corresponding 3-D measure, volumetric BMD (vBMD) measured by quantitative computed tomography (QCT), overcomes these limitations but is still only moderately predictive of vertebral strength and vertebral fracture, even after adjusting for cross-sectional area (5–10). Although measurements of vBMD are typically reported as a single, average value for the entire vertebral body (*e.g.*, integral vBMD) or the entire trabecular centrum (*e.g.*, trabecular vBMD), the distribution of bone within the centrum is known to be spatially heterogeneous and age-dependent (11–14). Given that heterogeneity in density is known to affect the biomechanics of failure of trabecular bone (15,16), a study of the association between measures of the intravertebral heterogeneity in density and vertebral fracture may yield a better understanding of fracture risk.

Prior studies have indicated that several measures of the intravertebral heterogeneity in trabecular bone mineral density are associated with the strength of vertebrae tested *ex vivo*. Measurements of vBMD from multiple sub-regions of the centrum, as well as the variances in density within each region, were found to provide better predictions of vertebral strength than were obtained from using integral vBMD (17). These measurements are relatively simple to evaluate from QCT scans of the spine. However, conflicting reports exist as to whether the magnitude of the density variation (such as quantified by the Gaussian coefficient of variation (CV), interquartile range (IQR) or the quartile coefficient of variation (QCV)) among multiple sub-regions of the centrum are positively or negatively associated with vertebral strength (11,18–20). Earlier studies sampled density in only a small number

of isolated sub-regions of the centrum and found negative correlations between CV and strength (19,20). More recent studies showed that when sampling density in a large number of contiguous sub-regions throughout the centrum, and when using non-parametric measures of heterogeneity (IQR and QCV) to accommodate the non-Gaussian distribution of sub-region densities, higher heterogeneity was associated with higher strength (11,18). Though the more comprehensive sampling provides thorough measures of the intravertebral heterogeneity in density, the association of density with vertebral fracture is unclear as the occurrence of vertebral fracture depends on more than simply vertebral strength (21).

The influence of the spatial distribution of trabecular bone density within the centrum on vertebral strength has also been investigated. *Ex vivo* observations have noted regional associations between trabecular bone mineral density and vertebral fracture patterns (15,22); for example, wedge fractures may be associated with low bone mineral density in the superior-anterior region (14,23). Finite element models have provided a more robust examination of the role of spatial heterogeneity in trabecular bone. These models have shown significant, though modest, improvements upon direct measures of trabecular vBMD in predicting *ex vivo* strength (24), delineating prevalent fractures (10,25,26) and predicting incident fractures (27). The creation of subject-specific finite element models, however, can be time-consuming, diminishing their potential translation to use in large-scale clinical trials or clinical care. Thus, it is desirable to establish relationships between the distribution of trabecular vBMD, which can be quickly obtained from available CT images, directly with vertebral strength and fracture risk.

The goal of this work was to determine the association of trabecular bone heterogeneity and spatial distribution with prevalent vertebral fracture, independent of integral vBMD. We evaluated multiple measures of heterogeneity and spatial distributions of trabecular vBMD in a study of prevalent vertebral fracture in 148 subjects, including 37 individuals with prevalent vertebral fracture and 111 age- and sex-matched controls. Based on our prior *ex vivo* results (11,18), we hypothesized that individuals with prevalent vertebral fracture would present with lower intravertebral heterogeneity and decreased anterior/posterior spatial distribution of trabecular vBMD, independent of integral vBMD.

Methods

Participants

Participants were members of the Third Generation Multi-Detector Computed Tomography (MDCT) Study, an ancillary study of the Framingham Heart Study Offspring (FHS) (28). Chest and abdominal computed tomography (CT) scans were acquired in 3,529 participants in the MDCT Study (35 to 90 years) in 2002 to 2005. Women who were pregnant or less than 40 years of age, men less than 35 years of age, or any individual greater than 320 pounds were excluded from the MDCT Study. Individuals with a mild prevalent vertebral fracture (Genant's semi-quantitative (SQ) score of 1) were excluded from the study in order to focus on more severe, unambiguous fractures.

Data from the present study were obtained as a part of a larger study of kyphosis (29,30). Volumetric quantitative computed tomography (QCT) scans were collected based on

landmarks for cardiac assessments, typically limiting the available vertebral levels to the ranges T8-T10 and L3-L5. As the lumbar region has more loss of vBMD with age than the thoracic region (28) and the L3 was present in the largest proportion of study participants (~98%), we chose to analyze the L3 from these images. Individuals with a prevalent fracture of L3 (SQ1+; N=9) were excluded from our analyses due to error in quantifying vBMD in a fractured vertebra. All participants signed written informed consent before enrollment and examination. This study was approved by the Institutional Review Board at Boston University Medical Center and Hebrew SeniorLife.

Selection of Cases and Controls

Prevalent vertebral fracture status was ascertained using the SQ method (31) on CT lateral scout views of all 3,529 participants (32,33). We included as cases all individuals with moderate (SQ2) and severe (SQ3) fractures from T4-L4, excluding L3 (N=37). Of the 37 cases: 23 had only thoracic fractures, 10 had only lumbar fractures, and 4 had both lumbar and thoracic fractures. Participants in the MDCT Study who were not classified as cases were eligible for selection as controls. We selected three controls for each case, using random stratified sampling. We matched on sex and 5-year age group. We used three controls for each case as this was the maximal number of controls per case that met the matching criteria

CT Image Acquisition

All measures of vBMD were performed using QCT. The QCT scans were acquired in the supine position using an eight-slice multidetector CT scanner (GE Lightspeed Ultra/Plus, General Electric Medical Systems, Waukesha, WI, USA). Details of the imaging protocol have been published previously (28,34). Abdominal QCT scans were collected using a nominal in-plane pixel size of 0.68×0.68 mm, a slice thickness of 2.5 mm, tube voltage of 120 kVp, tube current 120/400 mA (for participants 200/>200 lb body weight, respectively), gantry rotation of 500 ms, and a data collection diameter of 500 mm. The scan field of view was defined as 60 contiguous CT slices (150 mm) superior to the L5/S1 junction. A calibration phantom with hydroxyapatite regions (Image Analysis, Columbia, KY, USA), scanned concurrently with patients, was used to linearly translate pixel intensity to equivalent mineral density.

Integral and Trabecular vBMD

All analyses of vBMD were completed by one individual blinded to fracture status (BA). The cortical and trabecular bone of the L3 vertebral body were separately contoured using Canny edge detection on each axial QCT slice (28). Schmorl's nodes and osteophytes were both included in the trabecular and cortical contours, respectively. Osteophyte and sclerotic bone severity, scored nominally from 0 (no osteophyte/sclerosis) to 3 (severe osteophyte/sclerosis), and location were tabulated as potential co-variables for bone density measurements. Osteophytes and reactive bone were each scored on a nominal scale from 0 (no osteophyte/reactive bone present) to 3 (severe osteophyte/reactive bone), though there were no significant differences in the prevalence of either abnormality between prevalent fracture cases and controls (Supplemental Information). The upper and lower thresholds of the edge detection were manually adjusted such that the contour laid upon the low intensity

pixels just interior to the higher intensity regions of the cortical shell. Contoured regions that were isolated within the centrum, and not connected to the cortical shell, were manually erased. Integral vBMD was measured inclusive of endplate and cortical bone, while trabecular vBMD was measured exclusive of both.

Heterogeneity in Trabecular vBMD

We used two statistical measures of intravertebral heterogeneity in trabecular vBMD: QCV and IQR. We calculated QCV and IQR by first dividing the centrum into contiguous cubes of side length equal to 5 mm (Figure 1) and determining vBMD of the first and third quartiles of all cubes (Q_1 and Q_3 , respectively; Figure 2) (11,18). IQR and QCV were computed by

$$IQR = Q_3 - Q_1 \quad QCV = \frac{Q_3 - Q_1}{Q_3 + Q_1} \quad (1)$$

Spatial Distribution in Trabecular vBMD

We used four measures of spatial distribution in trabecular vBMD: anterior/posterior, central/outer, superior/mid-transverse, and inferior/mid-transverse. Regional values of volumetric BMD (rBMD) were calculated for 27 sub-regions of the trabecular centrum (three layers of nine sub-regions), and these sub-divisions were combined to calculate the rBMD for each of the following regions: anterior, posterior, superior, mid-transverse, inferior, central and outer (Figure 1C) (18,35). With the exception of the superior, mid-transverse, and inferior regions, each region was continuous through the full height of the vertebra. The four measures of spatial distribution in trabecular vBMD were then computed as the ratios of rBMD values (anterior/posterior, central/outer, superior/mid-transverse, and inferior/mid-transverse). Use of these ratios, rather than the individual regional values, avoided the problem of a high degree of inter-correlation among regional values, and between regional values and each of integral vBMD and trabecular vBMD. Intra-reader repeatability of all bone measures was calculated from a read-reread analysis with a few days between reads. Intra-class correlations ranged from 0.72 (inferior/mid-transverse rBMD ratio) to 0.96 (anterior/posterior rBMD ratio). Coefficients of variation ranged from 2.7% (integral vBMD) to 6.6% (IQR).

Statistical Analyses

Mean values ($\pm$ SD) for all variables were calculated and compared between prevalent fracture cases and controls—for both sexes combined and for men and women separately. We used t-tests to test for differences in vBMD measures and spatial distributions of trabecular vBMD. We used Wilcoxon Rank Sum to test for differences in heterogeneity of trabecular vBMD (IQR and QCV) as these metrics displayed skewed distributions. Conditional logistic regression was used to calculate odds ratios (95% confidence intervals (CIs)) for associations of heterogeneity (IQR, QCV) and spatial distribution (anterior/posterior, central/outer, superior/mid-transverse, and inferior/mid-transverse) of trabecular vBMD with prevalent vertebral fracture. In these regression analyses, case vs. control status was the dependent variable, and heterogeneity or spatial distribution of trabecular BMD was

the independent variable. We used two different regression models. The base model did not have any covariates, while the full model had height, weight, and integral vBMD as covariates. Height and weight were included as separate covariates, despite their collinearity, due to their established relationship with integral vBMD and fracture risk (36). Integral vBMD was included as a covariate to test the independent association of prevalent fracture with heterogeneity and spatial distributions of trabecular vBMD. The use of rBMD ratios avoided collinearity among independent variables. Independent variables were linear in the logit (Supplemental Table 1). Further, the use of all covariates as continuous variables in the model reduces bias from sparse data (37). The full model used a total of three covariates and follows the general guideline of at least 10 cases per predictor. As an exploratory analysis, we also repeated the conditional logistic regression analyses for men and women separately; however, caution should be made when interpreting the results due to the low statistical power. Significance was set at $p < 0.05$ for all tests.

Results

Characteristics of Prevalent Fracture Cases and Controls

There were no differences between prevalent fracture cases and controls with respect to either sex or age, as would be expected based on our experimental design (Table 1). Male cases (mean (SD): 92.8 (17.0)), however, trended towards weighing more than male controls (84.8 (11.3); $p = 0.050$). Individuals with prevalent vertebral fracture had lower integral vBMD (134 (38) vs. 165 (42) mg/cm^3 , $p < 0.001$) and trabecular vBMD (96 (38) vs 119 (45) mg/cm^3 , $p = 0.009$). Further, cases had similar IQR (32.8 (9.9) vs. 35.7 (14.7) mg/cm^3 , $p = 0.145$), and higher QCV (0.22 (0.13) vs. 0.17 (0.09), $p = 0.003$) than controls (Table 1). The anterior/posterior vBMD ratio was also lower in cases than controls (0.65 (0.13) vs 0.78 (0.16), $p < 0.001$).

Association between Density Measures and Risk of Fracture

Prevalent fracture was associated with measures of average density and some measures of heterogeneity. Decreased integral (OR= 0.26, 95% CI: 0.13–0.52, $p < 0.001$) and trabecular (OR= 0.42, 95% CI: 0.23–0.76, $p = 0.005$) vBMD were associated with increased odds of fracture. Increased QCV was also associated with prevalent fracture in the base model (Table 2; OR= 1.61, 95% CI: 1.04–2.49, $p = 0.034$) but not the full model (OR=1.15 (0.69–1.90), $p = 0.598$). No association was found between IQR and prevalent fracture in the base model ($p = 0.267$), but a trend towards a positive association was found in the full model (OR= 1.57, 95% CI: 0.95–2.61, $p = 0.079$). It is noted here that the coexistence of this association of prevalent fracture with vBMD-adjusted IQR and unadjusted QCV may reflect the underlying mathematical differences in definitions of IQR and QCV (equation (1)). The denominator of QCV, $(Q_1 + Q_3)^{-1}$, is very similar in value to twice the value of the integral BMD, rendering QCV nearly equivalent to a vBMD-adjusted IQR term.

Spatial distributions of trabecular vBMD were also associated with risk of prevalent fractures. Increased anterior/posterior trabecular vBMD was inversely associated with prevalent vertebral fracture both in the full (OR= 0.38, 95% CI: 0.20–0.71, $p = 0.003$) and base (OR= 0.29, 95% CI: 0.15–0.56, $p < 0.001$) models (Table 2). There were also trends

towards positive and negative associations between prevalent fracture and, respectively, center/outer trabecular vBMD (OR=1.60; 95% CI: 0.95–2.67; p=0.075) and inferior/mid-transverse trabecular vBMD (OR=0.58; 95% CI: 0.33–1.03; p=0.065) in the full model. These two associations were more evident in men (center/outer: p=0.091; inferior/mid-transverse: p=0.053) than women (center/outer: p=0.925; inferior/mid-transverse: p=0.600).

Discussion

Previous *ex vivo* studies have highlighted the importance of intravertebral heterogeneity and spatial distributions of trabecular vBMD on mechanical strength. Yet, the relationship between risk of vertebral fracture and either heterogeneity or spatial distributions is not well established *in vivo*. Here, we evaluated multiple measures of heterogeneity and spatial distributions of trabecular vBMD in subjects from the community-based Framingham Heart Study cohort. Using a study of prevalent fracture cases and sex- and age-matched controls, we found that individuals with increased heterogeneity in trabecular vBMD, as measured by QCV, had increased risk of prevalent fracture; however, the association was not independent of integral vBMD, height, and weight. Further, individuals with decreased vBMD in the anterior region of the trabecular centrum, compared to the posterior region, had an increased likelihood of prevalent vertebral fracture independent of integral vBMD. We also found trends towards increased risk of prevalent fracture in association with increased vBMD in the central vs. outer region of the trabecular centrum, and decreased risk of prevalent fracture in association with increased vBMD in the inferior vs. mid-transverse region. These results suggest that spatial heterogeneity of trabecular vBMD within the vertebra may be an important structural determinant of bone fragility in the spine.

Individuals with prevalent fractures generally present with lower integral and trabecular vBMD than controls (9,38), a relationship that is anticipated given the relationship between declining vBMD (35,39,40) and increasing fracture rates with age (41,42). In line with these findings, we observed that individuals with a prevalent fracture presented with approximately 20% lower integral (134 vs. 165 mg/cm³) and trabecular (96 vs 119 mg/cm³) vBMD at the L3 level (Table 1). These decreases are comparable to previous findings of 15% and 23% lower values in integral (43) and trabecular (44) vBMD for prevalent cases vs control. For comparison, areal BMD measured from DXA only presents with less than a 10% difference between case and control subjects (10), suggesting a reduced sensitivity for this measure in predicting fracture.

Yet, average measures of vBMD in the vertebra are not strongly predictive of fracture risk. Fewer than half of patients with a vertebral fracture who are treated have a clinical diagnosis of osteoporosis via DXA (45) or low integral vBMD via QCT (4,7,38). Moreover, average measures of integral vBMD may not be well suited to represent the capacity of the vertebra to withstand the complex strain distributions that can arise in the vertebra during even habitual activities (46). These strain distributions may predispose certain regions of the vertebra to higher risk of failure than others. The distribution of vBMD within the trabecular centrum has therefore been hypothesized to improve predictions of vertebral strength and fracture. Measures of intravertebral heterogeneity in trabecular vBMD, typically measured from QCT or micro-computed tomography scans, have been found to correlate with

vertebral strength; however, the results of these studies do not paint a consistent picture of whether increased heterogeneity is positively or negatively associated with bone strength (18–20,47), stiffness (19,20), and toughness (47). Variations in experimental protocols, including differences in trabecular vBMD sampling, loading mode, spinal level, and use of isolated vertebrae vs spine segments, likely contribute to this discrepancy. Our data suggests that individuals with a prevalent fracture have higher heterogeneity in trabecular vBMD, as quantified with QCV, than controls, lending support to an inverse relationship between heterogeneity and strength, in contrast to our hypothesis. However, we stress that the scenarios under which non-traumatic fractures occur are largely unknown. So, while there is a likely a relationship between vertebral strength and fracture, discrepancies in simplified loading scenarios within the laboratory (from which strength is calculated) and dynamic, complex loading scenarios *in vivo* (from which fracture risk is calculated) make it difficult to directly compare strength and fracture risk. Thus, comparisons between our findings in the role of trabecular vBMD heterogeneity in prevalent fracture risk and previous findings of its role in vertebral strength must be interpreted with this caveat.

An increase in the anterior/posterior trabecular vBMD ratio was associated with decreased odds of prevalent fracture in the full model. *Ex vivo* studies on the association between anterior/posterior trabecular vBMD and strength have not all reached the same conclusion (18, 25). Our data sheds new light onto this debate as laboratory tests inherently simplify loading protocols. For example, both *ex vivo* tests only applied axial compression with the posterior elements removed during specimen preparation. Without the neural arch to bear some of the applied compressive load, the posterior region of the vertebral body may have been exposed to higher forces than it would be otherwise. Moreover, the extent to which prevalent vertebral fracture is associated with axial compression loading vs. another loading scenario, such as forward bending, is unknown. Given the evidence that forward bending increases the amount of load placed on the anterior as compared to posterior region of the vertebral body (48,49), it stands to reason that the negative association we found between anterior/posterior trabecular vBMD ratio and fracture risk might suggest that a high value of this ratio is protective against fracture in forward flexion. Similarly, the trends towards associations between prevalent fracture and the center/outer and inferior/mid-transverse trabecular vBMD ratios may reflect the influence of disc degeneration, and its associated effects on the regional distributions of stress and strain within the vertebral body, on risk of failure within the vertebral bone tissue (50).

The design of this study inherently limited our observations to individuals who presented with a prevalent vertebral fracture, with an unknown time since the fracture occurred. The heterogeneity and/or spatial distributions of trabecular vBMD may have changed in the time since fracture. In addition, the values of the heterogeneity measures at L3 may not be similar to those at other spinal levels, including the level with prevalent fracture in the cases. We did not account for spinal level of the fracture, even though the distance between the fractured level and the assessed level (L3) may be important. Our previous publication (43) describes the spatial distribution of fractures in this population, with all but one case in the mid-thoracic and upper lumbar regions, above the L3. The density distribution at levels near the fractured level may change following fracture, due to bone remodeling in response to changes in vertebral loading and inflammatory responses caused by the fracture.

Unfortunately, we did not have sufficient numbers to study these possibilities in this cohort. Additionally, although measures of areal BMD and trabecular bone score in this population would be beneficial to directly compare its association with prevalent fractures versus our QCT-derived vBMD measures, DXA was not available within one year of the QCT scan for all participants in our study, making this direct comparison not possible for this manuscript. Our sample size was insufficient to adequately power subsequent delineation of the effect of sex, despite the known effects of sex on the age-dependent decline of vBMD (28,35,51) and fracture rates (41,52). Finally, the image processing steps in our approach are currently time consuming, limiting clinical utility at this time. However, with advances in image processing, these issues could be resolved, making the approach a viable clinical tool to predict fracture risk.

In conclusion, our case-control study of 148 subjects from the Framingham Heart Study found that measures of the intravertebral distribution of trabecular vBMD were associated with increased risk of prevalent fracture. Most notably, the anterior/posterior trabecular vBMD ratio was inversely associated with fracture, independently of integral vBMD. Thus, additional measures of the distribution of volumetric bone mineral density within the vertebra may provide important insight into fracture risk beyond the standard measures of integral vBMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A. An example QCT slice of the L3 vertebra, with an overlay of 5 mm cubes used to determine intravertebral heterogeneity of bone mineral density. *B.* The same QCT slice broken into nine equally sized sections, to be combined for regional analyses that enable measurement of the spatial distribution of bone mineral density. The thick black line shows cortical contour, while the red line shows the trabecular contour. *C.* The regional definitions of the vertebral centrum used to determine the spatial distribution of bone mineral density.

Figure 2.

The histograms of BMD sampled within two different vertebrae, one with high IQR and QCV and one with low IQR and QCV.

Table 1.

Comparison of descriptive characteristics and bone QCT measures between prevalent fracture cases and controls. Data (mean (SD)) are presented as unadjusted for age or sex. P values reported for IQR and QCV are from Wilcoxon rank sum tests.

	All		Women		Men	
	Controls	Cases	Controls	Cases	Controls	Cases
N	111	37	48	16	63	21
Age	68.1 (9.0)	68.2 (9.3)	69.7 (9.1)	69.9 (9.5)	66.8 (8.9)	67.0 (9.2)
Weight (kg)	77.8 (14.9)	80.5 (20.5)	68.8 (14.2)	64.5 (11.7)	84.8 (11.3)	92.8 (17.0)
Height (cm)	168 (10)	168 (12)	159 (6)	157 (5)	175 (5.8)	177 (8.3)
Post-menopause (# (%))			41 (91)	14 (93)		
vBMD (mg/cc)						
Integral	165 (42) ^b	134 (38) ^b	150 (40) ^b	110 (30) ^b	180 (40) ^b	150 (40) ^b
Trabecular	119 (45) ^b	96 (38) ^b	107 (55)	77 (34)	128 (34) ^a	110 (35) ^a
Heterogeneity of Trabecular vBMD						
IQR (mg/cc)	35.7 (14.7)	32.8 (9.9)	34.7 (19.2)	31.8 (10.1)	36.4 (10.1)	33.5 (10.0)
QCV	0.17 (0.09) ^b	0.22 (0.13) ^b	0.19 (0.11) ^b	0.28 (0.18) ^b	0.16 (0.07) ^b	0.17 (0.05)
Spatial Distribution of Trabecular vBMD						
Anterior/Posterior	0.78 (0.16) ^b	0.65 (0.13) ^b	0.75 (0.17)	0.61 (0.17)	0.80 (0.15) ^b	0.68 (0.09) ^b
Center/Outer	0.88 (0.10)	0.93 (0.15)	0.91 (0.11)	0.97 (0.19)	0.86 (0.09)	0.90 (0.11)
Superior/Mid-trans.	0.99 (0.15)	1.01 (0.12)	1.00 (0.20)	1.04 (0.14)	0.98 (0.11)	0.99 (0.11)
Inferior/Mid-trans.	1.08 (0.15)	1.04 (0.11)	1.05 (0.14)	1.04 (0.10)	1.10 (0.16)	1.05 (0.11)
Vertebral Bone Abnormalities						
Osteophyte Score	0.80 (0.91)	0.57 (0.84)	0.67 (0.88)	0.31 (0.60)	0.91 (0.93)	0.76 (0.94)
Sclerotic Bone Score	0.12 (0.35)	0.11 (0.32)	0.15 (0.41)	0.13 (0.34)	0.10 (0.30)	0.10 (0.30)

^a: 0.010 < p < 0.050;

^b: p < 0.010

Table 2.

Odds ratios (and 95% confidence intervals) for association between prevalent fracture and vBMD, heterogeneity in trabecular vBMD, and spatial distributions of trabecular vBMD for one SD increase in the independent metric. The base model does not include any covariates. The full model adjusts for height, weight, and integral vBMD.

Base Model	vBMD								
	Integral	0.26 (0.13–0.52)	<0.001	0.09 (0.02–0.49)	0.005	0.41 (0.22–0.78)	0.007		
	Trabecular	0.42 (0.23–0.76)	0.005	0.25 (0.06–0.94)	0.040	0.56 (0.32–1.00)	0.049		
Heterogeneity of Trabecular vBMD									
	IQR	0.75 (0.45–1.25)	0.267	0.82 (0.40–1.67)	0.580	0.70 (0.39–1.26)	0.230		
	QCV	1.61 (1.04–2.49)	0.034	2.10 (1.01–4.35)	0.046	1.18 (0.72–1.95)	0.507		
Spatial Distribution of Trabecular vBMD									
	Anterior/Posterior	0.29 (0.15–0.56)	<0.001	0.26 (0.09–0.78)	0.016	0.32 (0.15–0.71)	0.005		
	Center/Outer	1.70 (1.10–2.63)	0.017	1.65 (0.88–3.06)	0.116	1.76 (0.97–3.17)	0.061		
	Superior/Mid-trans.	1.19 (0.83–1.73)	0.344	1.23 (0.72–2.09)	0.447	1.18 (0.67–2.07)	0.565		
	Inferior/Mid-trans.	0.75 (0.48–1.16)	0.192	0.89 (0.50–1.58)	0.685	0.64 (0.34–1.22)	0.176		
Full Model	vBMD								
	Integral vBMD ¹	0.23 (0.11–0.47)	<0.001	0.01 (0.00–0.28)	0.007	0.35 (0.18–0.70)	0.003		
	Trabecular vBMD ¹	0.38 (0.21–0.69)	0.001	0.25 (0.07–0.97)	0.045	0.46 (0.25–0.86)	0.014		
Heterogeneity of Trabecular vBMD									
	IQR	1.57 (0.95–2.61)	0.079	2.32 (0.49–10.90)	0.287	1.58 (0.72–3.48)	0.253		
	QCV	1.15 (0.69–1.90)	0.598	0.96 (0.29–3.18)	0.946	0.87 (0.43–1.76)	0.703		
Spatial Distribution of Trabecular vBMD									
	Anterior/Posterior	0.38 (0.20–0.71)	0.003	0.56 (0.24–1.33)	0.188	0.25 (0.08–0.75)	0.013		
	Center/Outer	1.60 (0.95–2.67)	0.075	1.04 (0.47–2.29)	0.925	2.11 (0.89–4.99)	0.091		
	Superior/Mid-trans.	1.24 (0.80–1.93)	0.337	1.62 (0.73–3.60)	0.238	1.05 (0.51–2.13)	0.899		
	Inferior/Mid-trans.	0.58 (0.33–1.03)	0.065	0.72 (0.21–2.45)	0.600	0.42 (0.18–1.01)	0.053		

¹Integral and trabecular vBMD in the full model are reported with adjustment only to height and weight, with no adjustment to integral vBMD