The associations between QCT-based vertebral bone measurements and prevalent vertebral fractures depend on the spinal locations of both bone measurement and fracture

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Abstract

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Summary—We examined how spinal location affects the relationships between quantitative computed tomography (QCT)-based bone measurements and prevalent vertebral fractures. Upper spine (T4–T10) fractures appear to be more strongly related to bone measures than lower spine (T11–L4) fractures, while lower spine measurements are at least as strongly related to fractures as upper spine measurements.

Introduction—Vertebral fracture (VF), a common injury in older adults, is most prevalent in the mid-thoracic (T7–T8) and thoracolumbar (T12–L1) areas of the spine. However, measurements of bone mineral density (BMD) are typically made in the lumbar spine. It is not clear how the associations between bone measurements and VFs are affected by the spinal locations of both bone measurements and VF.

Methods—A community-based case–control study includes 40 cases with moderate or severe prevalent VF and 80 age- and sex-matched controls. Measures of vertebral BMD, strength (estimated by finite element analysis), and factor of risk (load:strength ratio) were determined based on QCT scans at the L3 and T10 vertebrae. Associations were determined between bone measures and prevalent VF occurring at any location, in the upper spine (T4–T10), or in the lower spine (T11–L4).

Results—Prevalent VF at any location was significantly associated with bone measures, with odds ratios (ORs) generally higher for measurements made at L3 (ORs=1.9–3.9) than at T10 (ORs=1.5–2.4). Upper spine fracture was associated with these measures at both T10 and L3 (ORs=1.9–8.2), while lower spine fracture was less strongly associated (ORs=1.0–2.4) and only reached significance for volumetric BMD measures at L3.

Conclusions—Closer proximity between the locations of bone measures and prevalent VF does not strengthen associations between bone measures and fracture. Furthermore, VF etiology may vary by region, with VFs in the upper spine more strongly related to skeletal fragility.

Keywords

Introduction

Vertebral fracture (VF) is the most common type of fracture in older adults, accounting for about 27 % of all osteoporotic fractures [1] and with a prevalence of 30–50 % among those over age 50 years [2, 3]. VFs are associated with significant morbidity, including hyperkyphosis [4, 5], reduced pulmonary function [5, 6], back pain [7, 8], functional limitations [8, 9], and reduced quality of life [10], as well as increased mortality rates [7, 11, 12]. In spite of being an underdiagnosed condition [13], the direct financial burden of VFs exceeds $1 billion annually in the USA [1]. Furthermore, due to the aging of the population, annual VFs and associated costs are projected to increase by 50 % by the year 2025 [1].

Established risk factors for VF include advanced age [14–16], female sex [15], low areal bone mineral density (aBMD) [15, 17], and prior fracture [15, 16, 18, 19] among others. However, while aBMD measured by dual-energy X-ray absorptiometry (DXA) is currently the clinical gold standard for determining fracture risk, its limitations are increasingly recognized, as only about half of individuals with fractures have osteoporosis as defined by low aBMD [17, 20, 21]. Most spinal imaging for bone mineral density (BMD) measurement is done in the lumbar spine (i.e., L1 to L4 level), as the overlying ribcage prevents the use of DXA to determine aBMD in the thoracic spine. However, vertebral fractures are not restricted to this area. Furthermore, VF prevalence varies by vertebral level, with peaks in prevalence occurring in the mid-thoracic (T7–T8) and thoracolumbar junction (T12–L1) regions of the spine [14, 15, 22]. The reasons for this bimodal distribution of fractures

regionally along the spine remain largely unknown. It has been suggested that "biomechanical factors," such as thoracic kyphosis and the stiffness of the rib cage predispose these areas to fracture by increasing vertebral loading in these locations [14, 23, 24]. On the other hand, a previous study of older women found that *incident* fractures in the upper spine (T4–T10) were more strongly associated with both lumbar aBMD and the presence of prevalent VFs than were incident fractures in the lower spine (T12–L4) [22]. This suggests that skeletal fragility is a stronger risk factor for upper spine VFs than lower spine VFs. However, further biomechanical or epidemiological analyses investigating whether mid-thoracic and thoracolumbar VFs have similar or different etiologies are lacking. Furthermore, it remains unclear whether the associations of bone measurements with VF depend on the location of bone measurement in addition to the location of VF.

The purpose of this study was to determine whether the associations between prevalent VF and radiographically based bone measures, including BMD, vertebral strength estimated by finite element analysis (FEA), and factor of risk (load to strength ratio) vary with the spinal region of fracture and with the vertebral level of measurement. We hypothesized that bone measures at T10 would be more strongly associated with prevalent VF in the upper spine region (defined as T4–T10) than corresponding measures at L3. We further hypothesized that prevalent VF in the upper spine region would be more strongly associated with bone measures at either T10 or L3 than prevalent VF in the lower spine region (defined as T11–L4).

Materials and methods

Participants

We performed a case–control study using participants selected from 3,479 individuals who underwent a quantitative computed tomography (QCT) scan of the trunk as part of the Framingham Heart Study Offspring and Third Generation Multidetector CT Study [25]. Prevalent VF was diagnosed by radiologists from the QCT scan lateral scout views using the semiquantitative technique of Genant et al. [26]. This method was previously validated [27] and has excellent inter- and intra-reader agreement in evaluating moderate/severe prevalent VF (semiquantitative grade 2). Cases included 40 participants ages 50 and older (22 men, 18 women, mean age 68±9 years) with one or more moderate or severe prevalent VF, excluding individuals with fractures at L3. Prevalent VF in vertebral levels T4–T10 were classified as upper spine fractures, while prevalent VF in levels T11–L4 were classified as lower spine fractures, similar to the regional classification used for incident VF by Nevitt et al. [22]. Eighty age- and sex-matched (2:1 matching) controls were randomly selected from individuals with no prevalent VF. This study was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center, Hebrew SeniorLife, and Boston University.

Bone measurements from QCT

As previously reported [25, 28], volumetric QCT scans were acquired using an eight slice multidetector CT machine (Lightspeed Ultra, General Electric, Milwaukee, WI) at a tube voltage of 120 kVp and tube current of 320 mA (400 mA for subjects with body weight >220 lb). Scans had an in-plane pixel size of 0.68 by 0.68 mm and slice thickness of 2.5 mm. Each subject underwent two scans at the same visit: a chest scan, which included approximately vertebral levels T7–T11 and an abdominal scan, which included approximately vertebral levels L2–L5. An external hydroxyapatite phantom (Image Analysis, Inc., Lexington, KY) was scanned with each subject to allow conversion of CT Hounsfield units to equivalent mineral density.

Integral (IntBMD), trabecular (TbBMD), and peripheral (PeBMD) volumetric BMD and cross-sectional area (CSA) at the midsection of the vertebral bodies, as well as simulated DXA measurements of posterior–anterior vertebral aBMD [29] were determined from QCTscans at vertebral levels T10 and L3. Trabecular BMD was calculated by virtually removing the outer 2 mm of the vertebral body, which includes the cortical shell, and determining the average BMD of the remaining trabecular bone. Similarly, peripheral BMD was the average BMD of the outer 2 mm layer of bone. In subjects where the desired level had a prevalent VF, morphometric abnormality, or was missing from the scan, the measurements (including FEA) were made at T9 (15 subjects) or T11 (two subjects) instead of T10 and L4 (one subject) instead of L3.

QCT-based FEA to estimate vertebral strength

We employed QCT-based FEA to estimate vertebral compressive strength variables. These analyses were performed by ON Diagnostics (Berkeley, CA) using previously published methods [30, 31]. All FEA analysts were blinded to subject fracture status (case or control). Briefly, each CT image was first density calibrated using the external phantom and the vertebra of interest was then segmented from the surrounding tissue using a constant threshold value. The vertebra image was spatially resampled to a voxel size of $1 \times 1 \times 1$ mm^3 voxels, rotated into a standard coordinate system, and cropped to remove the posterior elements from the vertebral body. A voxel-based finite element mesh was created by converting each voxel into a $1 \times 1 \times 1$ mm^3 eight-node cube-shaped element. Element-specific material properties were assigned based on the volumetric BMD within each element [32], and the resulting vertebral models were then virtually loaded to failure via uniform compressive loading applied to the endplates [31]. Compressive strength, defined as the total reaction force generated at an imposed overall deformation equivalent to 1.9 % strain [31], was calculated by nonlinear finite element analysis. Biomechanical testing of 52 elderly cadaveric vertebral bodies found this approach for estimating vertebral strength to be highly correlated (r^2=0.85) with experimentally measured values [31]. Trabecular strength (TbStrength) was the strength estimated with the outer 2 mm layer of the vertebral body removed, and peripheral strength (PeStrength) was the difference between total strength and trabecular strength.

Factor of risk

The factor of risk, Φ, was calculated as the ratio of estimated compressive loading to the FEA-estimated vertebral compressive strength. In theory, a factor of risk greater than one would indicate that the applied force exceeds bone strength, implying a high risk of VF [33]. Vertebral compressive loading at T10 and L3 was estimated using a musculoskeletal model of the thoracolumbar spine [34]. Specifically, loading was estimated for two quasi-static loading conditions: (1) standing with 75° forward flexion while holding 20 kg in the hands (Φ_{bend}) and (2) standing with 30° forward flexion and 30° of axial rotation (twist) while holding 20 kg in the hands (Φ_{twist}).

Data analysis

Standard descriptive statistics were computed and variable distributions checked. Conditional logistic regressions were performed to determine the association between prevalent VF and IntBMD, TbBMD, and PeBMD volumetric bone density and simulated aBMD; vertebral body CSA, total (Strength), trabecular (TbStrength), and peripheral (PeStrength) strength estimated by QCT-FEA; and the factor of risk estimates. Odds ratios (and 95 % confidence intervals) for prevalent VF were calculated for bone measurements at T10 and L3 vertebrae, for all prevalent VF, upper spine (T4–T10) VF, and lower spine

(T11–L4) VF. Statistical analyses were performed in SAS (SAS Institute Inc., Cary, NC, USA) with significance set at α=0.05.

Results

Cases did not differ from controls in terms of height, body mass, or BMI (Table 1). Among the 40 cases, 17 had prevalent VF in the upper spine region, 20 had prevalent VF in the lower spine region, and 3 had prevalent VF in both regions. There were a total of 46 prevalent VF, 23 in the upper spine region, and 23 in the lower spine region, primarily at T12 and L1 (Fig. 1). Furthermore, the pattern of VF prevalence and proportion of fractures in each spinal region was similar in men and women and the sexes were combined in the analyses.

For measurements made at L3, cases had lower volumetric BMD and strength and higher factor of risk than controls (p <0.05, Table 2). Measurements made at T10 showed similar relationships between cases and controls, but the differences were only significant for IntBMD and TbBMD (p <0.05). Estimated aBMD was lower in cases, but did not reach significance at either T10 (p =0.15) or L3 (p =0.07). However, vertebral CSA was larger in cases than controls at T10 (p =0.03) and approached significance at L3 (p =0.07).

When examining the association of any VF with bone measures, odds ratios (OR, per 1 SD decline) for L3 density, strength, and factor of risk measures ranged from 1.9–3.9 and were all significant, while ORs for T10 density, strength, and factor of risk measures ranged from 1.5–2.4 and did not all reach significance (Table 3).When examining only upper spine VFs, density measures at L3 (ORs of 2.8–5.6) were all significant, while density measures at T10 had similar associations (ORs of 2.1–4.3) and all reached significance except for PeBMD. However, associations for strength and factor of risk measures at T10 (ORs of 1.9–2.3) did not reach significance, while associations for strength and factor of risk measures at L3 (ORs of 5.9–8.4) were larger in magnitude and all reached significance. When examining only lower spine VFs, density, strength, and factor of risk measures at T10 showed no significant associations (ORs of 1.0–1.7), and while ORs were of larger magnitude for measures at L3 (ORs of 1.5–2.4), only IntBMD, TbBMD, and PeBMD reached significance. Prevalent VF at any location was associated with larger vertebral CSA at both T10 (OR=0.49) and L3 (OR=0.45). T10 CSA was significantly associated with upper spine fractures (OR=0.16), but not lower spine fractures (OR=0.99). L3 CSA did not reach significance when looking at only upper spine fractures (OR=0.45) or lower spine fractures (OR=0.49). The results and trends were largely the same when ORs were adjusted for height and body mass.

Discussion

In this study, we examined how the associations between prevalent VF and QCT-based bone measures (BMD, CSA, FEA-based vertebral strength, and factor of risk) vary with the vertebral level of measurement and with the spinal region of fracture. Contrary to our hypothesis, prevalent VFs throughout the spine appear to be at least as strongly associated with bone density, strength, and factor of risk measures at L3 as with similar measures at T10. In fact, although density measures at T10 and L3 appear to have similar associations with prevalent upper spine fractures, strength and factor of risk measures at L3 appeared to be more strongly associated with prevalent upper spine fractures than similar measures at T10. In our sample, T10 was on average closer to the levels of fracture than L3 (2.5 levels vs. 4.7 levels away). Thus, an overall closer proximity of the measured level to the fractured level does not equate to a stronger association with prevalent VF. Furthermore, the results indicate that current clinical measures of bone, which are generally acquired in the lumbar

vertebrae, are at least as strongly associated with prevalent VF as measures taken at other spinal levels. Thus, this does not suggest any need to alter current clinical practice in terms of the location used to measure vertebral bone density or strength. However, it is unclear why bone measures at L3 appear to have stronger associations with prevalent VF than measures at T10. One possibility is that the larger, stronger L3 level is more prone to age-related declines in strength and density or such declines are more easily detectable at L3 using current techniques. Further study is needed to explore these possibilities.

Prevalent fractures in the upper spine region appear to be more strongly associated with QCT-based bone measurements than fractures in the lower spine region, similar to previous findings relating lumbar aBMD and *incident* fractures in older women [22]. This regional difference likely indicates that fractures in the two regions have some as yet undetermined differences in their etiology, which could help explain the phenomenon that vertebral fracture prevalence is not uniform across vertebral levels, but highest around T7–T8 and T12–L1. The apparently stronger associations of bone measurements with prevalent and incident fractures in the upper spine suggest that upper spine fractures are more directly related to skeletal fragility than lower spine fractures, while some other factor or factors contribute to the risk of lower spine fractures. For example, impact from a backwards fall could preferentially load the lower spine, accounting for many vertebral fractures that occur in this region. Supporting this possibility, a retrospective analysis of 562 patients with traumatic VF (mean age 43.8 years, range 6–100 years) found that 67.6 % of traumatic VF caused by falls occurred in vertebral levels T11–L2 [35]. Furthermore, low energy falls were the most common cause of traumatic VF in patients older than 60 and 65.8 % of traumatic VF caused by low energy falls occurred in vertebral levels T11–L2 [35]. About four out of five traumatic VF in older adults are due to falls [35, 36], and about two out of five total incident VF in older adults are known to be caused by falls [37, 38], the majority low energy falls from standing height or less. Thus, it seems likely that falls are a significant factor in causing lower spine VF in older adults, but there is a need for further study of how falling affects vertebral loading throughout the spine and whether falls are the primary cause of the T12–L1 peak in fracture prevalence and incidence in older adults.

In a somewhat counterintuitive outcome, smaller vertebral CSA was associated with decreased risk of prevalent vertebral fracture. However, vertebral CSA is positively associated with vertebral strength [39] and previous studies have reported that vertebral size was smaller in those with vertebral fractures than those without, although most were based on 2D methods rather than CT scans [40]. On the other hand, vertebral cross-sectional area is higher in older adults compared to young adults, presumably due to age-related periosteal apposition [41]. However, this increased vertebral size in older adults does not overcome profoundly decreased bone density, as BMD is more strongly correlated with vertebral strength than CSA [39] and older adults have markedly lower vertebral strength than young adults [30]. Perhaps among older adults, those with lower bone strength have greater stimulus for periosteal expansion than those with adequate bone strength, which may result in higher vertebral CSA despite lower bone strength. Another possibility is that vertebral CSA is associated with VF in a way that is distinct from vertebral strength, such as by affecting vertebral loading. Clearly, additional study is needed to clarify the role of vertebral size in the risk of VF.

This study has several limitations, most notably its relatively small sample size and examination of prevalent VFs. While our results suggest a stronger association of bone measurements with upper spine VFs than lower spine VFs and a stronger association of VFs in any location with L3 bone measurements than T10 bone measurements, the confidence intervals of the ORs overlap and we cannot make meaningful statistical comparisons between them because of the small number of cases available. Only prevalent VF data were

available in the study sample, limiting the conclusions that could be drawn with respect to estimating the risk of incident VF. Additionally, assessment of prevalent fracture using morphometric methods is subject to error, which may vary with spinal region. The reliability of fracture assessment is lower in the upper thoracic spine than in the lumbar spine, but is excellent when considering only moderate/severe fractures [27]. Thus, we chose to examine only moderate/severe prevalent fractures, reducing the effects of potential errors in fracture assessment and potentially increasing the relevance of the findings to fracture risk, as moderate/severe prevalent VF tend to be more strongly associated with future VF than mild prevalent VF [42, 43]. The definitions of spinal regions used are somewhat arbitrary, but provide a logical separation between the two widely reported peaks in fracture prevalence and are consistent with the primary groupings used by Nevitt et al. [22]. Similarly, our selection of T10 and L3 as the levels for bone analysis is somewhat arbitrary, but corresponds to a common location for clinical imaging (L3) and a level central to the most common locations of VFs and present in the QCT scans of most subjects in this study (T10). Furthermore, we selected the levels for bone analysis so they would not correspond to the peaks in fracture prevalence reported in the literature (i.e., T7–T8 and T12–L1), as valid analysis of the QCT-based bone measures used here cannot be performed on a vertebral body with a prevalent fracture. Finally, as only two measurement locations were examined, we cannot make any conclusions regarding possible associations between VF and bone measures made elsewhere, such as higher in the thoracic spine.

This study provides a unique examination of the dependence of associations between vertebral bone measures and prevalent VF on the location of both measurement and fracture in a community-based population of men and women. The findings suggest that closer proximity between the level of bone measures and the level of fracture does not strengthen associations with prevalent fracture, and that bone measures in the lumbar spine, used clinically based on convenience of measurement, are as good as or better than measures taken elsewhere. Furthermore, this study supports the concept that VF in the lower spine and upper spine has significantly different etiologies. Altogether, these findings provide significant motivation for further study of how well bone measures predict VF risk in different spinal regions and whether VF etiology varies by spinal region. Better understanding of these issues could lead to improved prediction and prevention of VF in older adults.

Acknowledgments

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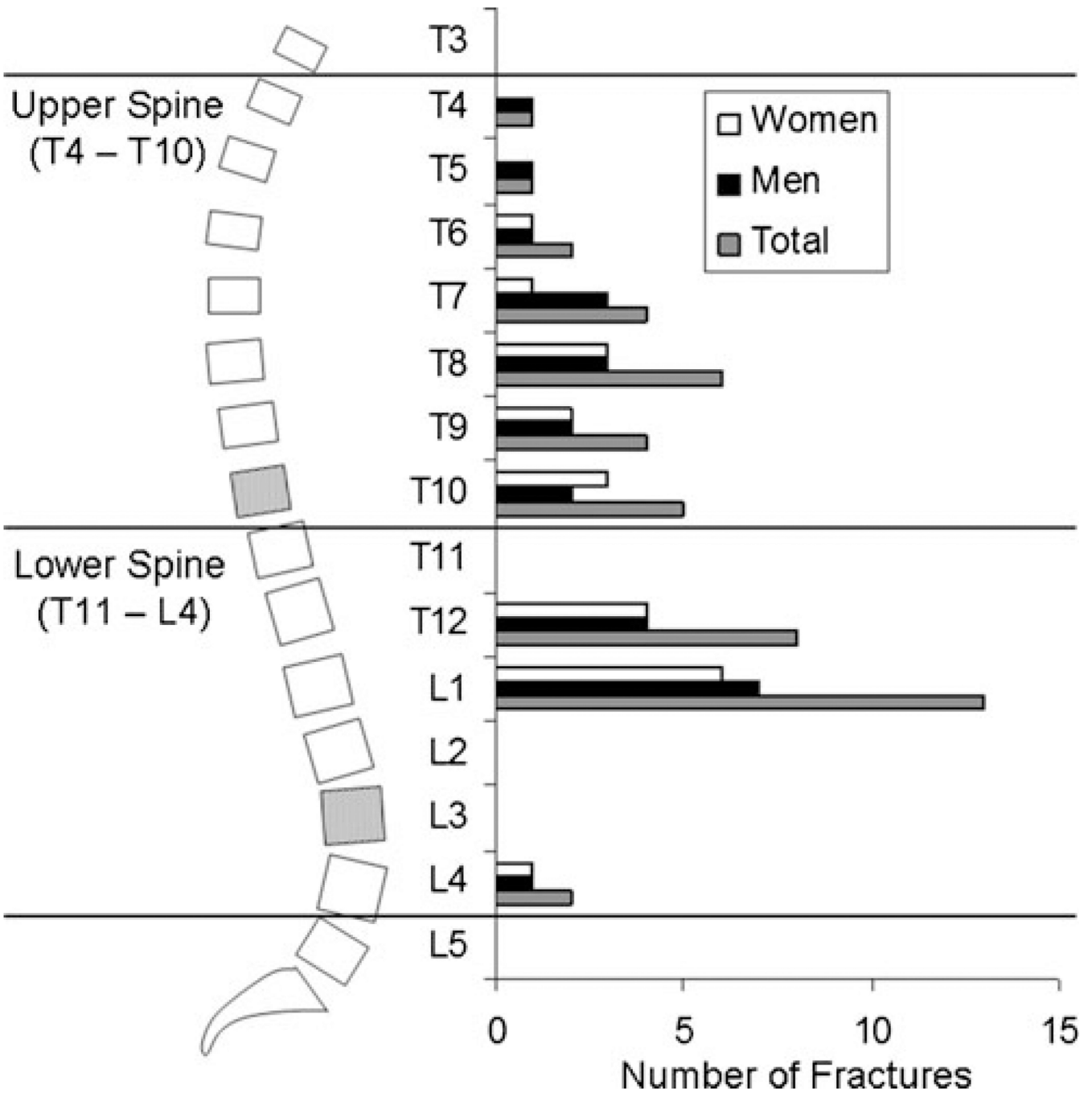
Fig. 1.
In this study, the upper spine region was defined as vertebral levels T4–T10 and the lower spine region as T11–L4. QCT-based bone measures were made at T10 and L3 (*shaded* vertebral levels). Prevalent moderate/severe vertebral fractures were classified based on the region in which they occurred. The distribution of 46 prevalent vertebral fractures in 40 cases in this study (*right*) was consistent with previous reports, with highest prevalence occurring around the mid-thoracic spine (T7–T8) and thoracolumbar junction (T12–L1). Men and women displayed similar prevalence patterns and were combined in the analyses

Table 1

Mean (SD) participant characteristics for cases and controls

	Controls (*N*=80)	Cases (*N*=40)
Sex (men/women)	44/36	22/18
Age (years)	67.8 (9.3)	67.9 (9.4)
Height (cm)	168 (11)	167 (13)
Body mass (kg)	82.4 (18.4)	79.4 (21.3)
BMI (kg/m^2)	29.1 (4.9)	28.0 (5.1)

Table 2

Mean (SD) measures of bone density, CSA, strength, and factor of risk evaluated at levels T10 and L3 for controls (*N*=80) and cases (*N*=40)

Measurement	T10		L3	
	Controls	**Cases**	**Controls**	**Cases**
IntBMD (mg/cm^3)	210 (52)	187 (45)[*]	198 (51)	168 (38)[*]
TbBMD (mg/cm^3)	183 (51)	158 (43)[*]	172 (51)	142 (38)[*]
PeBMD (mg/cm^3)	262 (55)	242 (52)	260 (51	232 (40)[*]
aBMD (g/cm^2)	0.95 (0.25)	0.88 (0.28)	1.16 (0.29)	1.05 (0.27)
CSA (cm^2)	10.5 (1.9)	11.3 (2.1)[*]	13.3 (2.2)	14.3 (2.9)
Strength (kN)	6.95 (3.02)	5.98 (2.63)	8.52 (3.83)	6.93 (2.86)[*]
TbStrength (kN)	3.85 (1.82)	3.32 (1.62)	4.43 (2.24)	3.55 (1.89)[*]
PeStrength (kN)	3.10 (1.27)	2.66 (1.09)	4.09 (1.72)	3.38 (1.08)[*]
Φ_{bend}	0.14 (0.06)	0.15 (0.05)	0.40 (0.13)	0.49 (0.23)[*]
Φ_{twist}	0.16 (0.07)	0.18 (0.07)	0.26 (0.08)	0.32 (0.15)[*]

[*]
p<0.05 (significantly different than controls)

Table 3

Associations of bone measurements at T10 and L3 with prevalent moderate/severe vertebral fractures by fracture location. OR (95 % CI, per 1SD decrease) are shown for combined group (all fracture locations), upper spine fractures (T4–T10) and lower spine fractures (T11–L4). ORs in italics are significant ($p<0.05$)

	All fractures (40 cases, 80 controls)	Upper spine fractures (17 cases, 34 controls)	Lower spine fractures (20 cases, 40 controls)
Measurements at T10			
IntBMD	*2.1 (1.2–3.7)*	*3.4 (1.2–9.7)*	1.4 (0.7–2.9)
TbBMD	*2.4 (1.3–4.3)*	*4.3 (1.3–14.6)*	1.6 (0.7–3.3)
PeBMD	*1.7 (1.0–2.8)*	2.1 (0.9–4.6)	1.3 (0.6–2.5)
aBMD	1.6 (0.9–2.8)	*2.7 (1.0–7.1)*	1.0 (0.5–2.1)
CSA	*0.49 (0.28–0.83)*	*0.16 (0.04–0.58)*	0.99 (0.46 –2.11)
Strength	*1.9 (1.0 –3.3)*	2.0 (0.8–4.9)	1.6 (0.7–3.5)
TbStrength	1.7 (1.0–3.1)	1.9 (0.7–4.6)	1.5 (0.7–3.1)
PeStrength	*1.9 (1.1–3.3)*	2.0 (0.8–4.8)	1.7 (0.8–3.6)
Φ_{bend}[a]	1.5 (1.0–2.5)	2.1 (1.0–4.6)	1.2 (0.7–2.2)
Φ_{twist}[a]	1.6 (1.0–2.6)	2.3 (1.0–5.3)	1.2 (0.7–2.3)
Measurements at L3			
IntBMD	*3.4 (1.7–6.8)*	*5.3 (1.3–21.0)*	*2.3 (1.1–5.1)*
TbBMD	*3.4 (1.7–6.9)*	*5.6 (1.3–23.4)*	*2.4 (1.1–5.2)*
PeBMD	*3.2 (1.6–6.2)*	*3.7 (1.2–12.1)*	*2.4 (1.1–5.3)*
aBMD	*1.9 (1.1–3.3)*	*2.8 (1.0–8.0)*	1.5 (0.7–3.0)
CSA	*0.45 (0.25–0.83)*	0.45 (0.20–1.03)	0.49 (0.20–1.18)
Strength	*3.0 (1.4–6.9)*	*8.2 (1.2–57.8)*	1.9 (0.7–3.5)
TbStrength	*2.5 (1.2–5.3)*	*6.2 (1.2–32.9)*	1.7 (0.7–3.9)
PeStrength	*3.9 (1.6–10.0)*	*8.4 (1.0–67.8)*	2.2 (0.9–5.5)
Φ_{bend}[a]	*2.5 (1.4–4.7)*	*5.9 (1.5–23.3)*	1.7 (0.9–3.5)
Φ_{twist}[a]	*2.5 (1.4–4.8)*	*6.0 (1.5–24.0)*	1.8 (0.9–3.6)

[a]Per 1 SD increase