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The trabecular effect: a population-based longitudinal study on age and sex differences in bone mineral density and vertebral load bearing capacity

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Abstract

Background—Approximately 16–24% of postmenopausal women are affected by vertebral fractures, negatively affecting their quality of life. Trabecular and cortical bones in vertebrae decline differently with age, thus having a distinct impact on vertebral failure loads. The purpose of this study was to investigate the effect of trabecular and cortical volumetric bone mineral density loss over time on estimated failure loads; and to evaluate the effect of sex and age.

Method—Fracture properties from a cohort of 82 patients were evaluated for L₁–L₃ vertebrae at baseline and 6th year using an image-based method that implements axial rigidity analysis. Cortical and trabecular volumetric bone mineral density were obtained, as well as their individual contribution to total failure load. Regression analyses were performed to determine the effect of age and sex on volumetric bone mineral density and failure loads.

Findings—Decline in trabecular and cortical volumetric bone mineral density, and failure load was sex-dependent ($p = 0.0095$). Cortical and trabecular volumetric bone mineral density reduced 2.08 (g/cm³)/year and 2.02 (g/cm³)/year, respectively. A 1012N difference in failure load, ~70% attributed to trabecular bone, was found between men and women of similar age. Over 6 years, this difference increased by 287N. Areal bone mineral density measured by dual X-ray absorptiometry explained ~60% of the vertebral failure load.

Interpretation—Trabecular bone has a significantly greater effect than cortical bone on the structural integrity and load bearing capacity of vertebrae. This might lead to a higher incidence of

fragility fractures in osteoporotic women. Our non-invasive, quantitative computed tomography image-based approach may improve prevention, monitoring, and management of fractures.

Keywords

Osteoporosis; Quantitative Computed Tomography; Trabecular Bone; Fracture Risk; Age; Sex

Introduction

Osteoporosis results in loss of bone mass and micro-architectural disruption, leading to a reduction in bone strength and an increased risk of fracture. Globally, the incidence of fractures due to osteoporosis is estimated to be about 2.3 million per year (Manhard et al., 2016). Approximately 16–24% of postmenopausal women are affected by vertebral fractures, negatively affecting their quality of life (Melton, 1997; Samelson et al., 2006). The gold standard for diagnosis of osteoporosis and fracture risk is the assessment of areal bone mineral density (aBMD), measured by dual X-ray absorptiometry (DXA) (Kanis, 2002). aBMD, as a single unit of merit, is a 2D measurement which does not account for 3D distribution of minerals in cortical and trabecular bone regions, as well as the complex geometry of the bone tissue.

Quantitative computed tomography (QCT) allows for the acquisition of 3D vertebral body geometry as well as quantitative measurements of volumetric bone mineral density (vBMD) of both cortical and trabecular bones (Giambini et al., 2013; Link, 2016; Manhard et al., 2016). Trabecular and cortical bones in vertebrae decline differently with age, thus having a distinct impact on vertebral failure loads. Previous studies have shown trabecular bone to be a key contributor to the load bearing capacity of vertebrae. An increased rate of loss in trabecular bone mass after the age of 50 years has been associated with a higher incidence of fragility fractures in the hip and spine (Chen et al., 2013). However, cortical bone loss also increases dramatically at this age (Riggs et al., 2004; Riggs and Melton, 1995).

In addition to mineral content, structural properties of the tissue affect failure loads (Chavassieux et al., 2007). Image-based axial rigidity analysis has been previously implemented to estimate fracture loads on metastatic cancer and osteoporotic patients, and cadaveric cohorts, showing promising results in predicting failure loads (Giambini et al., 2016; Snyder et al., 2009; Villa-Camacho et al., 2014). Axial rigidity analysis has also been previously used to investigate the effect of sex on fracture properties, suggesting that women had overall lower failure loads and vBMD compared to men of similar age (Bouxsein et al., 2006a). However, these previous studies have not evaluated the individual contribution of trabecular and cortical bone regions to the overall load bearing capacity of vertebrae.

We have previously developed an image-based method that implements axial rigidity analysis to non-invasively estimate the load bearing capacity of trabecular and cortical bone regions, as well as the total failure load, accounting for all contributing factors affecting the structural integrity of the vertebra (Giambini et al., 2016). The purpose of this study was twofold: 1) to investigate the effect of trabecular and cortical vBMD loss over time on estimated failure loads of lumbar vertebrae; and 2) to evaluate the effect of sex and age on regional bone loss and estimated failure loads.

Methods

Patient Population

A sub-cohort of 82 patients was obtained from the Mayo Clinic Bone Health Study. The subject database contained a series of QCT scans of the lumbar vertebrae (L₁, L₂, and L₃) at baseline, 3-year and 6-years follow up visits. Standard clinical CT scanning protocols were used during the visits (120kVp, 220mAs, smooth reconstruction algorithm: B30). Dual X-ray absorptiometry was also obtained as part of the routine clinical examination on all three visits to obtain areal bone mineral density (aBMD). The sub-cohort used in this study included patient data from baseline and the 6th year visit, and was restricted according to the following inclusion criteria: 1) absence of lumbar vertebral fractures at baseline and at the 6th year follow-up visit; 2) patient age over 50 yrs. at baseline.

Data Analysis

A vertebral fracture properties analysis was performed from the Digital Imaging and Communications in Medicine (DICOM) images obtained during the QCT scanning process. Fracture properties were evaluated at the L₁, L₂ and L₃ vertebrae at the two time points, baseline and 6th year, yielding a total sample size of 492 specimens (82 patients × 3 vertebrae × 2 points in time). Outcomes from the QCT fracture analysis at both time points and all vertebral levels included cortical and trabecular vBMD values, as well as the individual contribution of cortical and trabecular bones to the total vertebral failure loads (N), namely cortical and trabecular failure loads.

Failure loads of the vertebrae were estimated using axial rigidity analysis as previously described (Giambini et al., 2016). Briefly, for each patient, the vertebrae of interest were selected and axial rigidity analysis from the CT images was performed to obtain fracture properties. The vertebrae were identified in the CT image and identifiers were placed on the top and bottom vertebral endplates and aligned in the coronal and sagittal planes. This process was repeated for all vertebrae. The calibration phantom used during scanning process at baseline and 6-year follow-up was selected as input for the analysis. An elliptical region of interest (ROI) was placed to cover the entire vertebral body while excluding the posterior bones. Axial rigidity (EA) was calculated from the material modulus (E) ([Pa]), obtained from the conversion of Hounsfield units (HU) from the CT into vBMD, and from the cross sectional area of the vertebra, as described in equation 1 (Giambini et al., 2016):

$$EA = \int E_{vBMD} da \quad (1)$$

where $-da$ corresponds to pixel area. Young's modulus was related to vBMD according to the following equation (Crawford et al., 2003):

$$E_z = -34.7 + 3230(vBMD) \quad (2)$$

Failure load was determined from the vertebral cross-section with the lowest axial rigidity and was calculated by (Crawford et al., 2003) (Fig. 1):

$$F_{max} = 0.0068 \times EA \quad (3)$$

Statistical Analysis

JMP version 10.0.0 (SAS Institute Inc., NC, USA) was used for statistical analysis. Data is presented as mean (SD).

Paired *t*-test Analysis—Percent loss over time of cortical and trabecular vBMD for vertebral levels L₁, L₂, and L₃ was compared. Similarly, percent loss over time of aBMD obtained from DXA was also evaluated. Percent decline of the load bearing capacity of cortical and trabecular regions of the weakest vertebrae were evaluated. Additionally, failure load decline between trabecular and cortical bones was compared.

Linear Regression Analysis—Cross-sectional and longitudinal regression analyses were performed. Cross-sectional multiple linear regression analyses were implemented at baseline to evaluate the effect of sex and age, as explanatory variables, on cortical and trabecular vBMD values or failure loads as outcomes. Longitudinal linear regression analyses were performed with outcome measurements including differences between vBMD values as well differences between estimated failure loads at both time points. Explanatory variables included sex, age at baseline, and outcome values measured at baseline. Finally, linear regression analysis was performed to compare the estimated failure loads with aBMD outcomes from DXA and sex. In all multivariate analyses interactions between sex and age were considered. However, insignificant interactions were removed, and the analyses were repeated. Demographic data is described using summary statistics. Significance was set at $p < 0.05$.

Results

Volumetric Bone Mineral Density (vBMD) Analyses

The QCT subject cohort used in this study consisted of 47 women and 35 men, with a mean (SD) age of 69 (8.4) and 73 (9.6) years at baseline, respectively. Table 1 summarizes the mean (SD) results of cortical and trabecular vBMD values of the L₁, L₂, and L₃ vertebrae from both sexes, at baseline and at the 6th year follow-up. Percent vBMD differences over time are also shown. In women, cortical vBMD of the L₁ and L₂ vertebrae significantly decreased by 5.91% and 3.91% over a period of 6 years, while the decline in cortical vBMD of L₃ was not significant ($p = 0.10$). On the other hand, cortical vBMD for all three vertebral levels in men did not show significant changes after 6 years ($p = 0.32$). There was a significantly higher decline in trabecular vBMD for women, ranging from 23.32% to 26.32% at the three levels ($p < 0.0001$), compared to men. The decline in trabecular vBMD for men, however, was also significant ($p < 0.0001$) over the 6th year period ranging from 15.37% to 17.89% at the three levels.

The distribution of vBMD values with respect to age for both sexes at baseline and 6th year follow-up is shown in Fig. 2. Table 2 shows a summary of the cross-sectional and longitudinal linear regression analyses. Cross-sectional linear regression analysis at baseline showed that sex and age were significant explanatory variables for cortical vBMD outcome measurements ($p = 0.0012$). Women presented 32.41 g/cm³ (11.61% of the mean cortical vBMD for women in our cohort) lower cortical vBMD compared to men, at a similar age. When evaluating trabecular vBMD, however, age was statistically significant ($p < 0.0001$) and there was no significant difference between women and men outcomes ($p = 0.18$). Cortical and trabecular vBMD reduced 2.08 (g/cm³)/year and 2.02 (g/cm³)/year, respectively. Longitudinal linear regression analysis showed that the decline in cortical and trabecular vBMD was dependent on sex ($p = 0.0095$). After 6 years, the decline in cortical vBMD was higher in women than in men by 17.16 g/cm³ (6.15% of the mean cortical vBMD for women in our cohort). Trabecular vBMD loss was also higher in women than in men by 10.26 g/cm³ (8.75% of the mean trabecular vBMD for women in our cohort), irrespective of the age at baseline.

Vertebral Load Bearing Capacity Analyses

Vertebral failure loads were predicted for all three levels (L₁, L₂, and L₃) at both time points. The weakest vertebra from each patient was then used for further statistical analyses. The distribution of estimated failure loads for both sexes at baseline and 6th year follow-up is shown in Fig. 3. At baseline, the number of weakest vertebrae at the L₁, L₂, and L₃ levels were 57, 15, and 10, respectively. At the 6th year follow-up, the respective values were 54, 11, and 17. The L₁ vertebra showed the largest number of estimated fractures in both sexes.

Table 1 describes estimated failure load outcomes for trabecular and cortical regions, percent failure load decline in these bones, as well as the total vertebral failure load. In both, men and women at baseline, 71% of the total failure load was carried by trabecular bone, with only 29% experienced by the cortex. These values were similar at the 6th year follow-up. Although the load bearing capacity of the trabecular and cortical regions decreased over time, the rate of decline was higher for trabecular bone ($p < 0.0001$). Loss of vertebral load bearing capacity in women was attributed to a decline of 31% in trabecular and 17% in cortical failure loads. In men, a reduction in load bearing capacity was only attributed to 22% loss of trabecular failure load, while being insignificant for the cortex.

Cross-sectional linear regression analyses at baseline indicated that sex and age were significant predictors of estimated failure loads ($p < 0.0001$). Women presented weaker vertebrae than men by 1012N (36.6% of the mean failure load at baseline for women in our cohort), at a similar age. This difference is evidenced by the vertical distance between the two regression lines in Fig. 3A. From this 1012N sex-difference in load, about 712N (70%) and 300N (30%) were due to loss in the load bearing capacity of the trabecular and cortical regions, respectively.

Longitudinal linear regression analyses showed that sex and failure load at baseline were significant explanatory variables for the difference in failure load over a 6-year period ($p = 0.0070$). The difference in failure load in 6 years became larger between women and men

by 287N (10.38% of the mean failure load at baseline for women in our cohort), resulting in much weaker vertebrae for women.

Finally, DXA-measured aBMD (kg/m^2) values from both sexes were compared at baseline and at the 6-year visit. Men showed higher aBMD values when compared to women longitudinally. Baseline values for women and men, respectively, were 1.12 (0.16) and 1.24 (0.18), and 6th year outcomes were 1.08 (0.15), and 1.21 (0.17). Both sexes showed a significant decrease ($p = 0.0424$; paired t-test) in aBMD over time. The distribution of estimated failure loads with respect to DXA-measured aBMD for both sexes at baseline and 6th year follow-up is shown in Fig. 4. A cross-sectional analysis, with estimated failure load as the outcome and DXA-measured aBMD and sex as explanatory variables, showed a positive correlation between failure load and aBMD, explaining 52% and 61% of the variability in failure load at baseline and at the 6th year follow-up, respectively. The results at baseline are shown in Table 2.

Discussion

In this study, a population based cohort of 82 patients who underwent CT imaging at two time points was used to evaluate trabecular and cortical bone loss progression, along with estimated fracture properties of the lumbar vertebrae over time. Using axial rigidity analysis, longitudinal loss of cortical and trabecular vBMD, and vertebral failure loads were quantitatively measured; and the effects of age and sex on both vBMD and failure loads in the trabecular and cortical regions were investigated. A 1012N difference in failure load, ~70% attributed to trabecular bone, was observed between men and women of similar age. Additionally, the decline in trabecular bone load bearing capacity was higher than that seen in cortical bone for both sexes. These results suggest that trabecular bone has a greater effect on the structural integrity of the vertebral body over time, also accounting for the majority of observed sex differences in failure load.

Axial rigidity analysis has been previously used to predict failure loads of vertebrae in cadaveric specimens and patient cohorts, showing to be equally sensitive and significantly more specific than current radiographic criteria for predicting fractures (Snyder et al., 2009; Taneichi et al., 1997). Several studies have also implemented this method as an alternative to available fracture risk assessment methods (Anez-Bustillos et al., 2014; Bouxsein et al., 2006b; Buckley et al., 2007; Damron et al., 2016; Giambini et al., 2016; Hong et al., 2004; Rennick et al., 2013; Snyder et al., 2009; Villa-Camacho et al., 2014; Whealan et al., 2000). These studies, however, did not show a correlation of aBMD clinically measured by DXA with the estimated failure loads by this method. In the current study, however, a positive correlation between QCT-derived failure loads and clinical DXA-measured aBMD reiterated the credibility of the axial rigidity method for estimating vertebral failure loads.

Women had consistently weaker vertebrae than men of similar age. A 1012N-difference in failure load at baseline between both sexes of the same age was equivalent to 37% of women's mean failure load. Additionally, a 287N-difference between both sexes was observed over a period of 6 years. Such large differences were mainly due to trabecular bone, which accounted for almost 70% of the total vertebral load bearing capacity, and

which rate of loss was significantly higher in women than in men. This may explain the higher incidence and multiplicity of fragility fractures seen in elderly women than men (Masi, 2008). These results align with the findings from a previous study showing that women's femurs were significantly weaker than men's at the same age by about 1750N, suggesting a more effective contribution of bone mineral, geometry and other factors to the overall strength in men (Rezaei and Dragomir-Daescu, 2015). On the other hand, differences in physiological factors, such as hormone levels, between men and women, may also play a role in bone loss over time; adding to the higher rate of trabecular and cortical vBMD loss in women.

The L₁ vertebrae tended to be the weakest vertebrae in our cohort at both time points. This might be due to differences in geometries, with L₁ vertebrae likely having the smallest size compared to L₂ and L₃. The smaller failure loads observed in the L₁ vertebra could also be attributed to its anatomic location, being situated in the transition point between the thoracic (kyphotic) spine and the lumbar (lordotic) spine. This inflection point between the curvatures has been shown to be the location of the majority of the non-traumatic vertebral fractures due to the unequal distribution of load from T12 to L1 (Ruiz Santiago et al., 2016; Wood et al., 2014).

When compared to cortical bone, trabecular vBMD decreased substantially with age in both sexes. This significant decrease can be related to the pathogenesis of osteoporosis, with trabecular bone being lost at a higher rate than cortical bone due to trabecular fenestration and an increased rate of resorption by the marrow (Chen et al., 2013; Consensus, 2001; Manhard et al., 2016; Masi, 2008; McDonnell et al., 2007; Riggs et al., 2004). Similar to our findings, Riggs et al. demonstrated that women lost more vertebral trabecular vBMD over time compared to men, postulating that trabecular bone loss begins at earlier stages in life than cortical bone loss (Riggs et al., 2004).

This study has several limitations. This image-based approach only considers compressive forces for prediction of vertebral failure loads, and the estimated predictions do not account for varying physiological daily loads, diet, or body mass index (BMI). These variables impact bone quality and quantity thus influencing fracture strength. Therefore, there is a possibility of over/under-estimating the fracture properties. Also, our analysis does not consider the effect of the posterior processes, muscles, ligaments and intervertebral discs, which are important in preventing fractures. However, some of these structures may not have a significant role when evaluating compression fractures. Quantitative computed tomography-based finite element analysis (QCT/FEA) is an additional approach used for prediction of bone fractures. While this computational method can accurately predict vertebral fractures, the process for model development is complicated and time consuming. The method involves segmentation of the bony structures on the CT images, assignment of material properties based on empirical equations, application of boundary conditions to mimic a specific loading type, and finally, performing the simulation and validating the model. This approach requires the involvement of a professional who understands engineering fundamentals to assess and post-process the results. Additionally, computation cost is an important issue in the process. In the current work, we are presenting an alternative approach to FEA that has limitations but also advantages. The axial rigidity

analysis is very simple to apply, with minimal training needed in the process, and takes only a few seconds to obtain the results of interest. These advantages make it very appealing to clinicians who could potentially use this approach in the office computer and get an estimate of fracture properties in minutes.

While our group has previously validated the axial rigidity analysis method on whole cadaveric vertebral bodies containing simulated metastatic defects and augmentation materials (Giambini et al., 2016), the current study investigated both trabecular and cortical failure loads separately using an osteoporotic population cohort. Although the results are in line with previous studies showing the importance of trabecular bone in vertebral load bearing capacity (Chen et al., 2013; McDonnell et al., 2007), the image-based estimated trabecular and cortical failure loads need further validation. Future studies implementing higher image resolutions, such as micro-CT imaging, which can capture micro-architectural structure, could provide a more detailed analysis and evaluation of the contribution of trabecular and cortical bones to vertebral failure loads. Additionally, further validation is needed to include large number of intact specimens from the thoracic and lumbar regions of the spine that include fracture-preventing compensatory mechanisms such as the intervertebral discs and posterior bony processes.

Conclusions

Our non-invasive QCT image-based approach to separately estimate the load bearing capacity of vertebral cortical and trabecular regions in an *in-vivo* osteoporotic cohort showed failure load, and cortical and trabecular vBMD decline over time to be sex dependent. Trabecular bone accounted for approximately 70% of the overall load bearing capacity of vertebrae, with the rate of trabecular bone decline being significantly higher than that of cortical bone. The image-based approach showed good reliability when compared to clinically available DXA measurements, as demonstrated by the positive correlation between aBMD and estimated failure loads. However, compared to the clinically available areal-BMD, the QCT-based method measures volumetric BMD and accounts for geometry and heterogeneous distribution of minerals within the vertebral body. Additionally, our method is able to correlate vBMD loss over time with estimated failure loads to monitor the natural progress of osteoporosis, potentially improving prevention, diagnosis, monitoring, and management of fragility fractures. The tool presented in this study can accommodate clinically standard CT images for analysis and has shown good inter-reliability and promising results when implemented on a large patient cohort. The axial rigidity method could possibly offer physicians a more comprehensive tool for vertebral fracture prevention, rather than supporting its comorbidities.

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Highlights

- Failure load and volumetric bone mineral density decline over time and are sex dependent
- Trabecular bone accounts for 70% of the overall vertebral load bearing capacity
- Trabecular failure load decline is significantly higher than cortical
- Positive correlation between estimated failure loads and dual X-ray absorptiometry
- Non-invasive method may improve prevention and diagnosis of fragility fractures

Fig. 1. An elliptical region covers the vertebral body excluding the posterior bones. The vertebral cross-section with the weakest axial rigidity was used to determine vertebral failure load.

Fig. 2.
The effect of age and sex differences on cortical and trabecular volumetric bone mineral density at **A)** baseline and **B)** after 6 years.

Fig. 3. Cross-sectional effect of age and sex differences on vertebral failure load at **A)** baseline and **B)** after 6 years.

Fig. 4. Estimated failure load vs. aBMD at **A)** baseline and **B)** after 6 years for both sexes.

Table 1

Volumetric Bone Mineral Density (vBMD) and Failure Load Summary Data

	Cortical vBMD (g/cm ³)				Trabecular vBMD (g/cm ³)				Failure Load (N)		
	L1	L2	L3	L1	L2	L3	L1	L2	Trabecular	Cortical	Total
Female											
Baseline	274.57 (51.96)	283.04 (46.52)	279.95 (52.88)	115.02 (26.27)	117.72 (27.22)	119.17 (29.94)	1954.47 (548.17)	811.27 (329.78)	2765.75 (834.01)		
6 th year	258.34 (47.89)	271.96 (47.27)	271.08 (53.04)	84.74 (26.82)	90.27 (33.04)	89.20 (23.51)	1348.56 (493.42)	671.19 (288.33)	2019.76 (737.52)		
%	5.91	3.91	3.17	26.32	23.32	25.15	31.00	17.27	26.97		
<i>p-value</i> *	0.0015	0.0204	0.10	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		
Male											
Baseline	296.15 (59.88)	301.34 (48.15)	318.07 (56.72)	114.73 (30.47)	119.06 (32.40)	119.69 (33.18)	2556.38 (681.01)	1060.86 (390.91)	3617.24 (1023.91)		
6 th year	300.41 (74.43)	310.01 (62.25)	323.0 (63.46)	95.06 (34.94)	97.76 (31.32)	101.29 (33.44)	1991.65 (711.59)	1023.46 (401.06)	3015.11 (1061.06)		
%	-1.40	-2.88	-1.55	17.10	17.89	15.37	22.09	3.53	16.65		
<i>p-value</i> *	0.41	0.32	0.47	<0.0001	<0.0001	<0.0001	<0.0001	0.25	<0.0001		

Data is presented as Mean (SD). % represents percent difference

* Paired t-test

Table 2

Multiple linear regression analyses were performed to determine significant explanatory variables for longitudinal changes observed in cortical and trabecular vBMD, and total failure load.

<i>Summary Statistics</i>			
<i>Cross-Sectional Analysis at Baseline</i>			
<i>Outcomes</i>	Explanatory Variables		
	<i>Sex</i>	<i>Age</i>	<i>aBMD</i>
Cortical vBMD (g/cm ³)	0.0012	0.0002	-
Trabecular vBMD (g/cm ³)	0.18	<0.0001	-
Failure Load (N)	<0.0001	<0.0001	-
Failure Load (N)	0.0123	-	<0.0001
<i>Longitudinal Analysis</i>			
<i>Outcomes</i>	Explanatory Variables		
	<i>Outcomes at Baseline</i>	<i>Sex</i>	<i>Age at Baseline</i>
Cortical vBMD (%)	0.73	0.0095	0.19
Trabecular vBMD (%)	0.0170	0.0001	0.19
Failure Load (N) (%)	0.0070	0.0068	0.39

% represents percent difference between baseline and 6th year follow-up outcomes.