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Assessing forearm fracture risk in postmenopausal women

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Abstract

Purpose—To test the clinical utility of approaches for assessing forearm fracture risk.

Methods—Among 100 postmenopausal women with a distal forearm fracture (cases) and 105 with no osteoporotic fracture (controls), we measured areal bone mineral density (aBMD) and assessed radius volumetric BMD, geometry and microstructure using high-resolution peripheral QCT; ultradistal radius failure load was evaluated in micro-finite element (μ FE) models.

Results—Fracture cases had inferior bone density, geometry, microstructure and strength. The most significant determinant of fracture in five categories were: bone density (femoral neck aBMD: odds ratio [OR] per SD, 2.0; 95% CI, 1.4–2.8), geometry (cortical thickness: OR, 1.5; 95% CI, 1.1–2.1), microstructure (structure model index [SMI]: OR, 0.5; 95% CI, 0.4–0.7), and strength (μ FE failure load: OR, 1.8; 95% CI, 1.3–2.5); the factor-of-risk (applied load in a forward fall $\div$ μ FE failure load) was 15% worse in cases (OR, 1.9; 95% CI, 1.4–2.6). Areas under ROC curves (AUC) ranged from 0.62 to 0.68. The predictors of forearm fracture risk that entered a multivariable model were femoral neck aBMD and SMI (combined AUC, 0.71).

Conclusions—Detailed bone structure and strength measurements provide insight into forearm fracture pathogenesis, but femoral neck aBMD performs adequately for routine clinical risk assessment.

Keywords

Bone density; Bone quality; Colles' fracture; Epidemiology; Risk assessment

Introduction

High-resolution peripheral quantitative computed tomography (HRpQCT) can measure numerous macro- and microstructural variables in the distal radius, along with volumetric

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Conflict of interests None

BMD (vBMD) of cortical and trabecular bone separately [1]. Indeed, Boutroy and colleagues [2] showed that distal radius vBMD and microstructural parameters better discriminated 35 postmenopausal women with mixed fractures from 78 postmenopausal women without fracture than did areal bone mineral density (aBMD) of the hip or spine by dual-energy X-ray absorptiometry (DXA). In a preliminary study, we also found that various bone density, geometry, microstructure and strength parameters discriminated 18 postmenopausal Rochester, MN women with a distal forearm (Colles') fracture from an equal number of age-matched control women with no history of an osteoporotic fracture [3]. Similar results had been reported among 34 postmenopausal women with forearm fractures compared to 34 age-matched controls [4]. One of the more interesting variables in the latter study was trabecular separation distribution (Tb.Sp.SD), a measure of inhomogeneous bone structure, which was 75% greater (worse) among the women with fractures. Likewise, Tb.Sp.SD was 36% greater among the forearm fracture patients in our preliminary study, but the difference was not statistically significant given the limited sample size [3]. Moreover, most of the bone structure and density variables were correlated, and it was not possible in our earlier investigation to identify the best predictors of fracture risk. In the present report, we have evaluated bone microstructure and strength parameters obtained from improved micro-finite element (μ FE) biomechanical models [5], including an assessment of cortical porosity hypothesized to be particularly germane to forearm fracture risk [6], in a much larger study population in order to test the clinical utility of these various approaches to fracture risk assessment.

Materials and methods

Study subjects

Following approval by Mayo Clinic's Institutional Review Board, we identified 100 postmenopausal Olmsted County, MN women newly diagnosed with a Colles' fracture in 2001–08. None of them had been included in our preliminary study [3]. The event that precipitated the fracture was characterized according to the scheme of Palvanen and colleagues [7]. Control subjects were not individually matched to cases but rather were frequency matched based on the expected age-distribution of forearm fractures in this community [8]. The resulting 105 postmenopausal controls were recruited simultaneously from a study cohort [9] that had been randomly sampled from the local population ($n = 66$), augmented by community women who were attended at Mayo Clinic at least once for any reason in 2003–05 ($n = 39$) and were identified in a similar manner. None of the controls had a history of an osteoporotic fracture, i.e., a hip, spine or forearm fracture that occurred after age 35 years. Written informed consent was obtained from all subjects before participation in the study.

Bone densitometry

aBMD (g/cm^2) measurements were made from DXA scans performed at the wrist, femur neck, lumbar spine and total body (Lunar Prodigy System, GE Healthcare, Madison, WI).

Total, cortical and trabecular vBMD (mg/cm^3), as well as bone structure measurements, were obtained from the non-dominant (or unfractured) wrist on all subjects using the XtremeCT (Scanco Medical AG, Brüttisellen, Switzerland). Beginning 9.5 mm from a reference line set manually at the endplate of the radius, data were obtained using a 3-dimensional stack of 110 high-resolution CT slices with an isotropic voxel size of $82\text{ }\mu\text{m}$, using an effective energy of 60 keV, field of view of 125.9 mm and image matrix of 1536×1536 pixels.

Bone structure

As described elsewhere [10], bone volume/total volume (BV/TV, %) of the ultradistal radius was derived from trabecular vBMD, and a trabecular thickness-independent structure extraction was employed to identify three-dimensional ridges (center points of the trabeculae); trabecular number (Tb.N, mm^{-1}) was then taken as the inverse of the mean spacing of the ridges [11]. Analogous with standard histomorphometry [12], trabecular thickness (Tb.Th, μm) was calculated as $\text{BV/TV} \div \text{Tb.N}$, and trabecular spacing (Tb.Sp, μm) as $(1-\text{BV/TV}) \div \text{Tb.N}$. Tb.Sp.SD, the standard deviation of Tb.Sp, is a measure of trabecular variation [13]. Validation studies show excellent correlation ($R \geq 0.96$) for these parameters compared to the gold-standard ex vivo μCT (resolution $\leq 20 \mu\text{m}$) technique [14]. Connectivity density (Conn.D, $1/\text{mm}^3$) is another measure of trabecular architecture disruption, while the structure model index (SMI) assesses whether trabeculae are more plate-like or more rod-like.

As defined by the manufacturer, the cortex was segmented from the gray scale image with a Gaussian filter (sigma = 2 and support = 3 voxels) and subsequent thresholding at 160 permille of the detector's dynamic range, corresponding to a density of approximately 560 mg/cm^3 [11]. Cortical vBMD and area were measured directly, and the periosteal circumference calculated from the contour; cortical thickness (Ct.Th, mm) was then calculated as $\text{area} \div \text{circumference}$. Excellent correlation ($R=0.98$) has also been shown with Ct.Th measurements by μCT [15]. In addition, the automatically generated cortical mask was applied to the whole bone structure to obtain the cortical bone, followed by an inversion resulting in a negative image that included only the "cortical pores"; the cortical porosity index was then defined as the ratio of cortical pore volume to cortical bone volume [10].

Bone strength parameters

Bone strength at the ultradistal radius was calculated directly from μFE models [16], as described elsewhere [10]. Failure loads calculated from such μFE models correlated highly ($R = 0.87$) with compressive loads producing Colles' fractures in 54 cadaveric forearms [17]. Additionally, the relative load supported by cortical versus trabecular bone in the radius was assessed by calculating the strain energy dissipated in the cortex as a fraction of the total strain energy. Strain energy is defined as the potential energy stored in a volume by virtue of an elastic deformation, which equals to the work that must be done to produce this deformation.

Load to strength ratio

We also assessed the ratio of fall load to overall bone strength, as determined by μFE , to estimate the factor-of-risk (ϕ). With fall load in the numerator and bone strength in the denominator, higher values indicate increasing fracture risk [18]. For this analysis, the load applied to the wrist was estimated from predicted impact forces during a fall on the outstretched hand [19]. Individual height data were used to estimate subject-specific applied loads using the formula, $670 \text{ Ns/m} * \sqrt{2 * 9.81 * (\text{height}/2)}$

Statistical analysis

Bone variables were summarized using means and standard deviations. Given similar ages in the two groups, the Student's t-test was used to compare differences in means between fracture cases and controls. Pearson correlation coefficients were used to evaluate relationships between key bone density, structure and strength variables. None of the variables significantly violated test assumptions.

The relative risk of fracture associated with different bone parameters was estimated by odds ratios (OR) obtained from logistic regression models, where case status was the dependent variable and bone density, geometry, microstructure and strength (all per SD decrease) and the load-to-strength ratio (per SD increase) were the potential predictors. The most significant variable from each of the five main variable categories was chosen to represent that category. Stepwise methods with forward selection and backward elimination were then used to choose independent variables from among the five selected parameters for a final model.

As an additional expression of fracture discrimination, the area under a receiver operating characteristic (ROC) curve (AUC) was assessed by the probability of concordance (c-index), also obtained from the logistic regression models [20]. Comparisons of these areas were based on the predictive values from the logistic models [21]. All analyses were performed using SAS (SAS Institute Inc., Cary, NC) and Splus (Insightful Corp., Seattle, WA).

Results

The 100 postmenopausal women with a history of Colles' fracture (median age, 63 years; interquartile range (IQR), 56–71 years) experienced the fracture a median 7 months prior to study (IQR, 3 to 13 months). Fifty-six of the fractures had occurred on the left side and 44 on the right, and the scans were made on the opposite wrists. Eighty-nine fractures resulted from a fall from standing height, while 7 were due to falls from less than standing height and 4 from somewhat greater than standing height (e.g., slipped off a log). As illustrated in Fig. 1, 53 of the falls were forward or to the side, 46 were backwards or to the side, and the orientation of one fall was uncertain.

The fracture cases were frequency matched to 105 comparably aged ($p = 0.484$) control women (median, 62 years; IQR, 59–72 years) without a prior osteoporotic fracture. In this group, the left (non-dominant) wrist was scanned in 96 women and the right in 9. Reflecting the ethnic composition of postmenopausal women in the community (96% white in 2000), only 2% of the subjects were nonwhite. Thirty-three percent of the cases, compared to 29% of controls, were being treated with an antiresorptive agent at the time of the study (mostly bisphosphonates in cases and estrogens in controls), while 18% of cases and 24% of controls were on thyroid replacement. Fracture cases and controls had identical average heights (mean $\pm$ SD, 161.4 ± 6.1 versus 161.4 ± 5.7 cm) and similar weights (73.6 ± 17.1 versus 73.8 ± 14.5 kg), as well as body mass index (28.2 ± 6.1 versus 28.4 ± 5.7 kg/m²). Consequently, the estimated mean traumatic load on the distal radius, given a fall forward onto the outstretched arm, was practically identical in the case and control women (2666 ± 51 versus 2665 ± 47 N; $p = 0.968$). Therefore, only skeletal variables discriminated cases from controls.

The fracture cases had lower aBMD at all DXA measurement sites in the forearm (Table 1). Values were 12% lower at the ultradistal radius, the site of Colles' fractures, and ultradistal radius aBMD discriminated cases from controls better than did 1/3 radius aBMD or total radius aBMD. Despite their similar heights and weights, however, total body bone mineral content was 7% less in cases than controls ($p = 0.001$), and femoral neck and lumbar spine aBMD were lower among the fracture patients as well. Total, trabecular and cortical vBMD in the ultradistal radius were also significantly lower in the cases (Table 1), although the deficit in trabecular bone was relatively greater than that in cortical bone, and ultradistal radius trabecular vBMD discriminated fractures from controls better than the other vBMD measures. The most significant predictor of Colles' fracture risk among all bone density parameters in a multivariable analysis was femoral neck aBMD (OR per SD decrease, 2.0;

95% CI, 1.4–2.8). However, most of the bone density parameters performed comparably in discriminating cases from controls, with AUCs ranging from 0.59–0.67 (Table 1).

With respect to the bone macro- and microstructural variables, cross-sectional area of the radius was similar in the two groups, although endocortical area was slightly larger and Ct.Th significantly narrower in the fracture cases (Table 1). At the same time, cortical porosity was similar in cases and controls, whereas the fracture patients had significantly lower Tb.N and Tb.Th, as well as greater Tb.Sp. and Tb.Sp.SD, all indicating disruption of trabecular architecture. In particular, trabecular variability (Tb.Sp.SD) was 28% greater (worse) among the cases and, conversely, Conn.D was 19% higher among the controls (Table 1). The SMI was 9% greater among the women with a fracture, indicating a shift toward more rod-like trabeculae. The best of the bone macrostructure variables was Ct.Th (OR, 1.5; 95% CI, 1.1–2.1), whereas the most significant microstructure parameter was SMI (OR, 0.5; 95% CI, 0.4–0.7) such that each SD decrease reduced the risk of fracture by half. Again, however, the microstructural variables related to disruption of trabecular architecture all discriminated fracture cases from controls to a comparable degree (Table 1).

The estimated failure load (~ strength) of the distal radius under compression was significantly greater among the control women (Table 1). In cortical bone, the strain energy density, defined as average strain energy dissipated per volume unit of bone, did not differ in cases compared to controls (0.26 ± 0.03 versus 0.26 ± 0.02 J/mm³; $p = 0.142$) but, in trabecular bone, was slightly lower among the cases (0.15 ± 0.03 versus 0.16 ± 0.03 J/mm³; $p = 0.003$), as the proportion of the load borne by cortical bone was somewhat greater in the fracture patients. When the μ FE failure load was related to the estimated traumatic load in a fall for each subject, the ratio of applied loads to failure loads (ϕ) was 15% higher (worse) among the fracture cases (Table 1). The bone strength variable that best predicted forearm fracture risk was overall μ FE bone strength (OR, 1.8; 95% CI, 1.3–2.5), whereas the odds ratio associated with each SD increase in ϕ was 1.9 (95% CI, 1.4–2.6).

Odds ratios relate to the area under an ROC curve and, since the odds ratios were of similar magnitude, the AUC varied only from 0.50 to 0.68, as delineated in Table 1. This is partly due to correlations among these variables. For example, relative to femoral neck aBMD, the correlations with Ct.Th, SMI, μ FE bone strength and ϕ were 0.45, –0.39, 0.57 and –0.50, respectively (all $p < 0.001$). Likewise, bone strength was positively correlated with Ct.Th (0.59; $p < 0.001$) and negatively with SMI (–0.65; $p < 0.001$). When these parameters were considered together in a multivariable analysis, femoral neck aBMD had the most significant association with Colles' fracture risk ($p = 0.002$). The only other variable to enter the model was SMI ($p = 0.002$). However, the final model showed only modest improvement in AUC compared to femoral neck aBMD alone (0.71 versus 0.66; $p = 0.078$). Note further that many variables were interchangeable. In particular, there was no statistically significant difference in predictive power between Ct.Th and SMI ($p = 0.267$), between μ FE bone strength and femoral neck aBMD ($p = 0.766$) or between femoral neck aBMD and ultradistal radius trabecular vBMD ($p = 0.823$). Thus, an assessment using just a wrist HRpQCT variable, e.g., trabecular vBMD, reduced the AUC only to 0.67 from 0.71 for hip aBMD and SMI combined. Neither osteoporosis treatment nor thyroid replacement therapy had any significant effect on these results.

Discussion

Although aBMD by DXA has proven clinically useful for estimating future fracture risk [22], the test has limited sensitivity and specificity [23]. This has stimulated a search for better ways to assess bone fragility in practice [24], especially with respect to those aspects of bone “quality” not encompassed by bone density measurements [25]. In a preliminary

study, we showed that 18 postmenopausal women with a Colles' fracture exhibited an array of deficits in bone macrostructure, microstructure and strength compared to age-matched controls [3], but the limited sample size precluded any assessment of which skeletal parameter might be best for evaluating fracture risk. The present, much larger study found similar results insofar as many aspects of bone density and structure were associated with distal forearm fractures. In multivariable modeling, aBMD measured at the ultradistal radius performed better than other DXA wrist measurements. On the other hand, aBMD at the femoral neck is the preferred skeletal site for routine clinical use [26], and it performed as well and was the most significant predictor of Colles' fractures when potential skeletal risk factors were assessed together in a multivariable analysis. In part, this is because aBMD is confounded by bone size, an independent predictor of forearm fracture risk [9]. Note, however, that femoral neck aBMD is not required for forearm fracture risk assessment since many skeletal parameters in the wrist performed comparably in distinguishing Colles' fractures from controls. Thus, the area under the ROC curve was 0.66 for femoral neck aBMD but 0.65 for ultradistal radius aBMD, 0.67 for ultradistal radius trabecular vBMD and 0.65 for μ FE-modeled radius bone strength.

The only other bone parameter to enter the final multivariable model was SMI, lower values of which were protective in the multivariable model. It has been shown that SMI is dependent on the image resolution in a complex manner, possibly preventing a direct comparison to other studies using different resolutions [15,27]. Nonetheless, SMI was 9% higher among the cases, indicating a shift from plate-like to more rod-like trabeculae. Although correlated with femoral neck aBMD (-0.39 ; $p < 0.001$), the contribution of SMI suggests that Colles' fractures are associated with disruption of trabecular architecture. This is supported by the 12% reduction in trabecular number, 15% increase in Tb.Sp, 19% decrease in connectivity density and 28% increase in Tb.Sp.SD compared to little absolute reduction in Tb.Th, which is assessed somewhat less precisely [2,28]. It is noteworthy in this regard that the age-related reduction in distal radius vBMD in men, whose forearm fracture risk is much lower than that in women [29], is accompanied by trabecular thinning rather than the loss of trabeculae seen in aging women [30,31]. Observations similar to ours were made recently by Boutroy and colleagues [32], who found a 20% reduction in Tb.N, 29% increase in Tb.Sp and 48% greater Tb.Sp.SD in 33 forearm fracture cases compared to an equal number of age-matched postmenopausal controls; all of these differences were statistically significant, as was an 8% reduction in Tb.Th in their study. That group concluded that trabecular architecture contributed just 12% of the total variance in bone strength. However, that value was obtained only after adjusting for other bone density and strength predictors, including vBMD which is correlated with bone microstructure, and others have attributed more biomechanical importance to trabecular components in the non-weightbearing distal radius [28].

The focus on trabecular microstructure is not to deny a role for cortical bone in Colles' fracture pathogenesis. Cortical bone strength makes an important contribution to forearm fracture risk as indicated by ex vivo studies [33,34]. In our analysis, cortical bone carried 68% of the load on the radius among the fractures cases, and Ct.Th was 11% less in that group. These results resemble previous reports [32], but the proportion of load carried by cortical bone in the ultradistal radius was not as strong a predictor of fracture risk in our study. However, it has long been speculated that cortical porosity could also be an important determinant of Colles' fracture risk and, specifically, that it could explain the peak incidence of such fractures in perimenopausal women and adolescents of both sexes [6,35], which has been attributed to transient increases in bone turnover [36]. Unexpectedly, an index of cortical porosity derived from the HRpQCT scans [10] was not associated with Colles' fractures in this analysis. However, our approach may have been limited by the resolution of HRpQCT [37] even though good agreement has been reported between histology and μ CT

[38]. The index of cortical porosity is dependent on the segmentation of the cortex so that results are only comparable as long as the standard segmentation approach is being used. Even then, this procedure is known to be problematic at sites with a very thin cortex [39]. In addition, these women were, on average, a decade beyond the menopause when acute estrogen deficiency leads to increased bone turnover [40].

Bone strength, estimated by μ FE at the wrist, predicted Colles' fractures and was 12% lower among the cases. Additionally, ϕ , the ratio of bone load to bone strength, was also associated with fractures in this study, reflecting the importance of the bone loading component in assessing forearm fracture risk [9,41]. This makes sense because Colles' fractures almost never occur in the absence of trauma (typically described as a fall forward onto the outstretched hand), which was the bone load modeled in this analysis [19]. However, the actual orientations of the falls that precipitated the Colles' fractures in this study were much more diverse: Only about a fourth reflected the classic picture so that some of our traumatic loading estimates may have been inaccurate. Despite this potential problem, the mean value of ϕ in the cases was 1.3, as expected from the theoretical notion that a factor-of-risk exceeding 1.0 signifies an increased likelihood of fracture [18]. Conversely, the mean ϕ among controls was 1.1, suggesting an underestimation of the tissue elastic modulus, for which there is still no consensus value [3,16,30,42]. Also, the criteria used to determine bone strength from linear elastic μ FE simulations includes assumptions that can provoke underestimation [16]. While the estimates of ϕ may be imprecise, it nevertheless appears that most postmenopausal women are at risk of a Colles' fracture given a fall [43], which may help explain why it has been difficult to identify clinical risk factors that clearly differentiate women with a distal forearm fracture from controls [44].

This study had the advantage of state-of-the-art in vivo assessments of bone structure by HRpQCT ("noninvasive bone biopsy") and bone strength by advanced μ FE techniques [5], which were applied to assess forearm fracture risk in a larger group of community women than previously evaluated in this manner. However, the HRpQCT scans were performed at a standard site irrespective of forearm length, and the specific fracture site was not identified. Moreover, the μ FE assessment based on these images may not have simulated the types of loads that some women experienced in the distal radius. In particular, the μ FE analyses simulated an axial compression of the ultradistal radius; this is thought to be an important loading mechanism leading to Colles' fractures [45,46], and assessments made at the most distal region of the radius appear to provide the best measure of radius strength [47]. The effect of bending was not simulated in the μ FE modeling because the large cross-section of the radius compared to the relatively small stack of bone measured with HRpQCT would not lead to meaningful results. In addition, material properties of bone might contribute to the pathogenesis of Colles' fracture [48], but we could not assess them in vivo. Finally, our findings are limited by the retrospective study design and corresponding delay between the fracture and subsequent assessment. Although some skeletal parameters could have changed in the interim, none were significantly correlated with duration of the delay except for a marginal positive association with lumbar spine aBMD ($p = 0.042$).

Despite these limitations, we found, as have others [4,28,32], that forearm fracture risk is significantly associated with a diverse array of bone density, structure and strength parameters. The consideration of potential bone loading also seems important, although additional work is needed to describe the loads actually encountered in the various fall orientations that lead to Colles' fractures [7]. While these observations provide a stronger basis upon which to define the pathogenesis of Colles' fractures, most of the structure and strength variables are correlated with femoral neck aBMD, which appears to provide an adequate measure of bone fragility at the wrist for routine clinical purposes [26].

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Please pick the picture that most closely resembles the way you fell.

CP1344271

Fig. 1.

Representation of the orientation of the fall that precipitated the Colles' fracture (orientation was uncertain in one woman) among 100 postmenopausal Rochester, MN women. Adapted from Palvanen M, et al. *Osteoporos Int* 11:822–31, 2000.

Comparison of 100 postmenopausal Rochester, MN women with a distal forearm fracture (cases) to 105 community women of similar age with no history of an osteoporotic fracture (controls) with respect to five main variable categories

Table 1

Variable (units)	Controls		Cases		Difference		OR	
	$\bar{x} \pm SD$		$\bar{x} \pm SD$		%	(95% CI)	AUC	
<u>Bone density</u>								
Femoral neck aBMD (g/cm ²)	0.88 ± 0.15		0.81 ± 0.11		-8 ^{***}	2.0 (1.4-2.8)	0.66	
Lumbar spine aBMD (g/cm ²)	1.13 ± 0.16		1.02 ± 0.17		-10 ^{***}	1.9 (1.4-2.6)	0.66	
Total radius aBMD (g/cm ²)	0.62 ± 0.09		0.58 ± 0.10		-6 ^{**}	1.6 (1.2-2.1)	0.61	
1/3 radius aBMD (g/cm ²)	0.79 ± 0.11		0.76 ± 0.13		-4 [*]	1.4 (1.1-1.9)	0.59	
Ultradistal radius aBMD (g/cm ²)	0.42 ± 0.08		0.37 ± 0.08		-12 ^{***}	1.9 (1.4-2.6)	0.65	
Total radius vBMD, (mg/cm ³)	333 ± 78		295 ± 72		-11 ^{***}	1.7 (1.3-2.3)	0.65	
Radius trabecular vBMD (mg/cm ³)	138 ± 41		115 ± 37		-17 ^{***}	1.9 (1.4-2.5)	0.67	
Radius cortical vBMD (mg/cm ³)	881 ± 80		855 ± 76		-3 [*]	1.4 (1.1-1.9)	0.62	
<u>Bone geometry</u>								
Cross-sectional area (mm ²)	225 ± 36		224 ± 40		0	1.0 (0.8-1.3)	0.50	
Endocortical area (mm ²)	168 ± 38		172 ± 39		2	0.9 (0.7-1.2)	0.53	
Cortical thickness (mm)	0.84 ± 0.23		0.75 ± 0.20		-11 ^{**}	1.5 (1.1-2.1)	0.62	
Section modulus (mm ³)	309 ± 62		285 ± 66		-8 ^{**}	1.5 (1.1-2.0)	0.62	
<u>Bone microstructure</u>								
Cortical porosity index (%)	1.08 ± 0.56		1.08 ± 0.63		0	1.0 (0.8-1.3)	0.48	
Trabecular number (1/mm)	1.64 ± 0.37		1.44 ± 0.35		-12 ^{***}	1.8 (1.3-2.4)	0.68	
Trabecular thickness (μm)	70 ± 11		66 ± 10		-5 [*]	1.4 (1.1-1.9)	0.60	
Trabecular separation (Tb.Sp, μm)	595 ± 280		682 ± 232		15 [*]	0.7 (0.5-0.9)	0.68	
Tb.Sp.SD (μm)	294 ± 216		376 ± 229		28 [*]	0.7 (0.5-0.9)	0.68	
Connectivity density (1/mm ³)	3.04 ± 1.08		2.47 ± 0.97		-19 ^{***}	1.8 (1.3-2.5)	0.66	
Structure model index	2.33 ± 0.38		2.55 ± 0.33		9 ^{***}	0.5 (0.4-0.7)	0.68	
<u>Bone strength</u>								
Overall failure load (N)	2543 ± 553		2247 ± 534		-12 ^{***}	1.8 (1.3-2.5)	0.65	

Variable (units)	Controls $\bar{x} \pm SD$	Cases $\bar{x} \pm SD$	Difference %	OR (95% CI)	AUC
Cortical strain energy (J)	133 $\pm$ 33	120 $\pm$ 30	-9 **	1.5 (1.1-2.0)	0.59
Trabecular strain energy (J)	72 $\pm$ 28	59 $\pm$ 25	-18 ***	1.7 (1.2-2.3)	0.66
Cortical strain energy density (J/mm ³)	0.26 $\pm$ 0.02	0.26 $\pm$ 0.03	0	1.2 (0.9-1.6)	0.55
Trabecular strain energy density (J/mm ³)	0.16 $\pm$ 0.03	0.15 $\pm$ 0.03	-6 **	1.5 (1.2-2.1)	0.62
Load carried by cortical bone (%)	65 $\pm$ 10	68 $\pm$ 8	4	0.8 (0.6-1.0)	0.58
Factor-of-risk (ϕ)					
Fall load (N)/failure load (N) ratio	1.10 $\pm$ 0.24	1.26 $\pm$ 0.33	15 ****	1.9 (1.4-2.6)	0.65

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$

OR: Odds ratio per SD decrease for all variables except ϕ , which is per SD increase, where the SD is based on all cases and controls; AUC: Area under the receiver operator characteristic (ROC) curve