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PERSONAL VIEW

Cortical and trabecular architecture are altered in postmenopausal women with fractures

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Tribute

On the one-year anniversary of Professor Pierre Delmas' death, we wish to reflect on his impact on us personally and on the field of osteoporosis research. In the past year, we have had time to think of how extremely fortunate we were to have had the opportunity to work for many years with Prof. Delmas. Elisabeth Sornay-Rendu has served as the primary clinical investigator of the OFELY study since its inception, development and implementation 18 years ago; Françoise Munoz has served as the research unit statistician since 2000; Stephanie Boutroy joined the unit in 2004 as an engineer, and completed her PhD on the in vivo assessment of bone microarchitecture in 2008; and Mary Bouxsein joined the unit as a biomechanics consultant and collaborator in 2003.

Pierre's vision to establish the OFELY cohort and more recently the STRAMBO cohort has allowed the investigation of a number of key issues in skeletal health, including the roles of BMD, bone loss and bone turnover in skeletal fragility. He recognized that there was more to bone fragility than BMD, even renaming his research unit "Qualité Osseuse dans L'ostéoporose" or "Bone Quality in Osteoporosis". His keen interest in new technology led us to explore in vivo assessment of bone microarchitecture, as detailed in the accompanying review. The OFELY cohort has contributed more than 50 publications that have advanced our knowledge of the pathophysiology of postmenopausal osteoporosis. Pierre's commitment and energy have allowed us to continue studying and enrolling subjects in the OFELY cohort, and we expect to continue using this cohort to ask pertinent and important questions.

Pierre's dynamism, inquisitive mind and scientific rigor defined how he led his research group. He demanded excellent, rigorous research without compromise. While he is not here to discuss data or inquire, with a twinkle in his eye, about the progress on the next manuscript, he continues to influence our work by inspiring us to conduct our research with passion, purpose and rigor. His spirit endures in our hearts and in the excellent research we aim to achieve.

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microstructural deterioration of bone tissue with a consequent increase in bone fragility [1]. The importance of trabecular and cortical microstructure to bone strength [2, 3] and fracture risk [4–6] has been well documented, and therefore evaluation of both microarchitecture and BMD may improve estimation of the risk of fracture. However, until recently there were no methods to assess this microstructural deterioration non-invasively, and thus the diagnosis of osteoporosis is based on assessment of bone mass and areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry (DXA).

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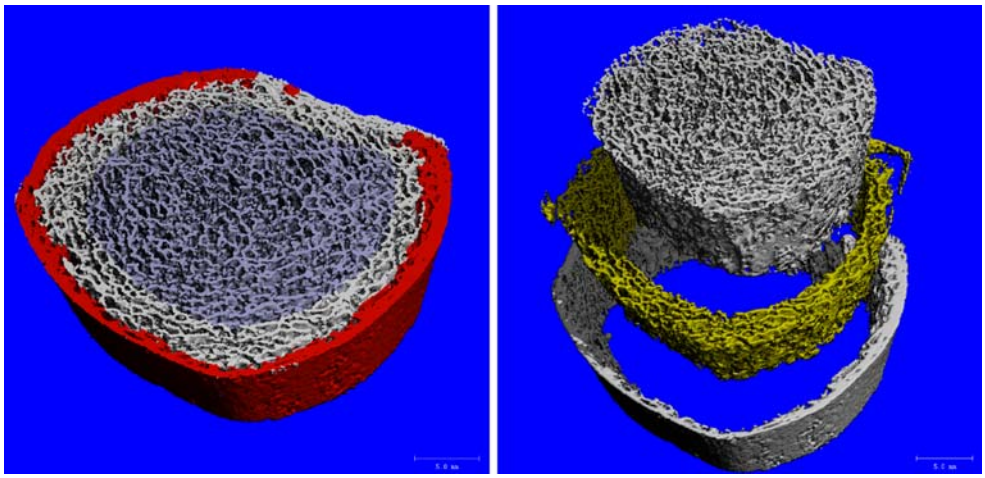

Fig. 1 Representative 3D reconstruction of images from hr-pQCT, showing separation of cortical and trabecular compartments (image courtesy of Scanco Medical AG)

Whereas previously the only way to assess bone microarchitecture was via histomorphometric analysis of iliac crest biopsies, recently non-invasive imaging methods, including high-resolution peripheral quantitative computed tomography (hr-pQCT) and high-resolution magnetic resonance imaging (hr-MRI) have been developed that allow 3D assessment of bone microstructure in vivo. Our laboratory has performed several of the initial studies examining the clinical utility of hr-pQCT (XtremeCT, Scanco Medical AG, Basserdorf, Switzerland), which permits in vivo assessment of cortical and trabecular architecture at the distal radius and tibia with a voxel size of 82 μm^3 (Fig. 1). We have assessed its reproducibility and determined whether in vivo microarchitecture measurements are associated with skeletal fragility [7–9]. We review key findings from these studies below.

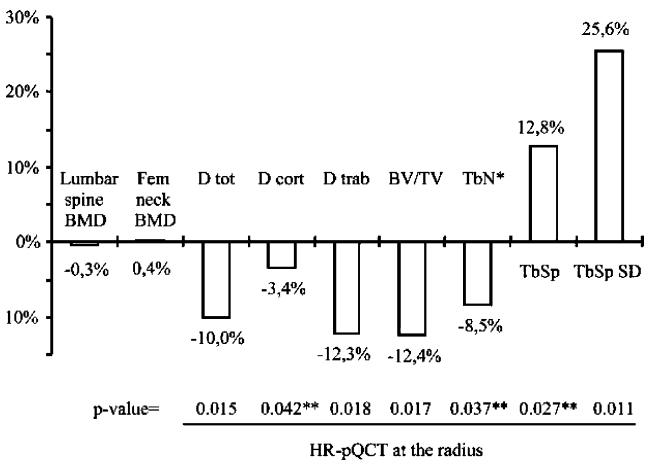

Fig. 2 Percent difference in BMD and hr-pQCT parameters between osteopenic women with previous history of fracture and those who were fracture free. ** Not significant after Bonferroni correction. From Boutroy et al. [7], with permission

Altered microarchitecture in osteopenic postmenopausal women with a history of fragility fracture

In our first study using this device, we compared hr-pQCT measurements in 108 healthy premenopausal, 113 postmenopausal osteopenic and 35 postmenopausal osteoporotic women. We showed that volumetric density as well as trabecular and cortical microarchitecture differed significantly between healthy normal, postmenopausal osteopenic and postmenopausal osteoporotic women. We also compared trabecular and cortical microarchitecture, assessed by hr-pQCT, in 35 osteopenic women with a previous fragility fracture and 78 osteopenic women without prior history of a fragility fracture. At the distal radius, despite having no difference in aBMD at the hip or spine, women with previous fractures had lower total and trabecular densities and a higher intraindividual distribution of separation than women without fracture [7] (Fig. 2), suggesting that assessment of trabecular microarchitecture may improve fracture prediction in women with moderately low BMD values. Trabecular deterioration in a woman diagnosed as osteopenic by BMD measurement is shown in Fig. 3.

Altered microarchitecture in postmenopausal women with a history of fracture

In a second study, we evaluated the independent contribution of aBMD, cortical and trabecular architecture to the risk of fracture in postmenopausal women, including those diagnosed as normal, osteopenic and osteoporotic according to the WHO definition [8]. This study enrolled subjects from the OFELY study, a prospective cohort of women from France that was started by Prof. Delmas, with subjects recruited between February 1992 and December 1993 and continuing with annual follow-up. The general description of this cohort is provided in detail elsewhere [10, 11]. In the

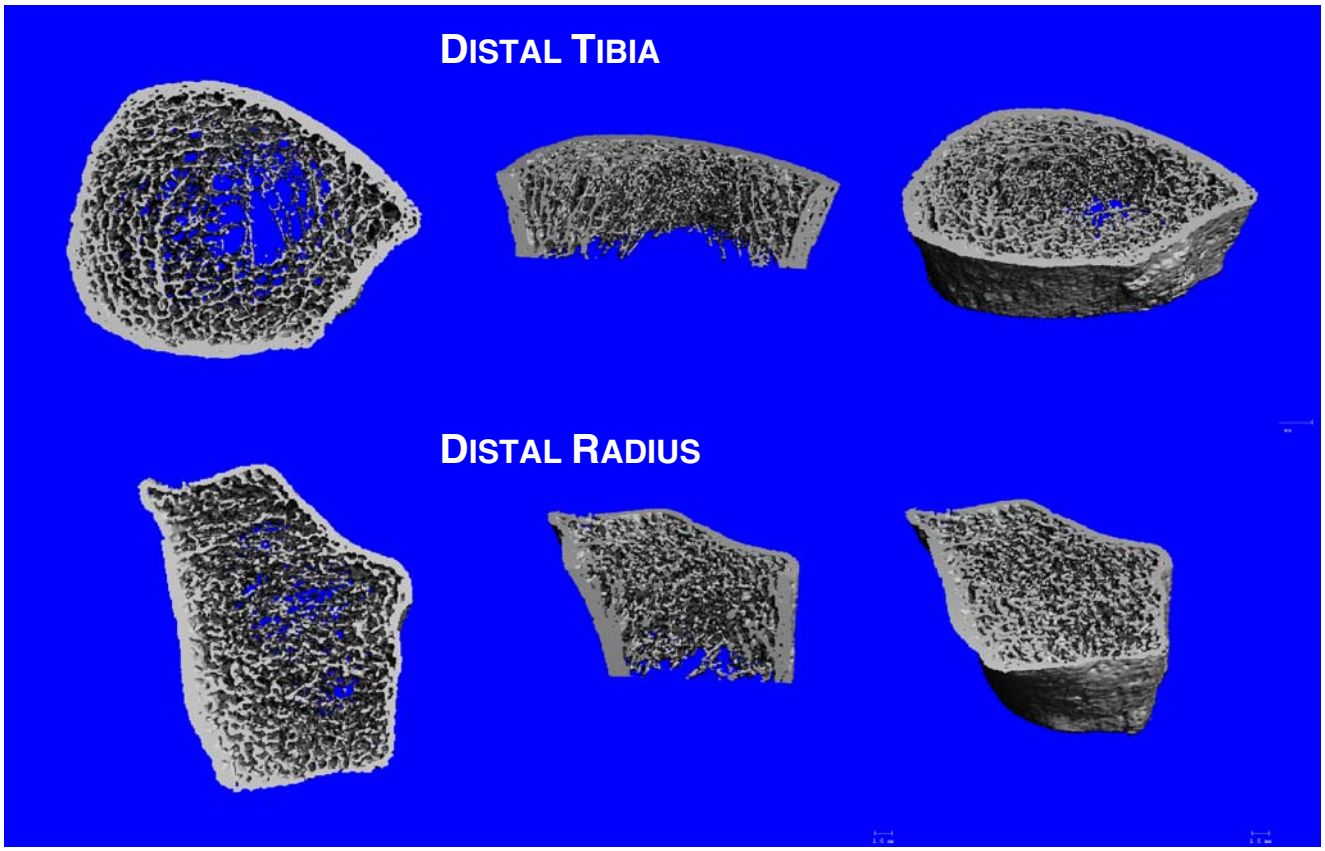

Fig. 3 3D reconstruction of images from hr-pQCT in a woman who was diagnosed as osteopenic by aBMD measurement, showing marked deterioration of the trabecular bone compartment at both distal radius and distal tibia

current case–control study, 101 women (mean age 73.7± 8 years) who sustained a fragility fracture during the 13 years' follow-up of the study were each age-matched with one control from the same cohort who never had a fracture. The non-dominant forearm and distal tibia were scanned using hr-pQCT, and aBMD was measured at the ultradistal radius (including the area analysed with hr-pQCT) and at the total hip by DXA.

We found that at the distal radius, women with fractures had lower volumetric total and trabecular bone densities

Table 1 Comparison of bone microarchitecture at the distal radius and tibia in postmenopausal women with fragility fractures (Fx, $n=101$) and in controls ($n=101$), both before and after adjustment for aBMD. Values are mean±SD

	Distal radius				Distal tibia			
	W with Fx	Controls	p	Adjusted p*	W with Fx	Controls	p	Adjusted p**
D tot[a] (mg/cm^3)	227.8±60.1	265.0±73.2	<0.0001	0.19	214.4±49.4	247.2±57.8	<0.0001	0.007
D trab[b](mg/cm^3)	105.5±38.4	129.5±36.9	<0.0001	0.05	128.7±35.2	148.5±38.7	0.0001	0.029
BV/TV[c] (%)	8.7±3.2	10.8±3.2	<0.0001	0.05	10.7±2.9	12.4±3.2	<0.0001	0.028
Cort Th[d] (mm)	0.533±0.16	0.606±0.21	0.0007	0.70	0.732±0.26	0.872±0.29	<0.0001	0.027
TbN[e] (1/mm)	1.30±0.38	1.51±0.33	<0.0001	0.09	1.39±0.33	1.46±0.34	0.135	0.69
TbTh[f] (mm)	0.067±0.01	0.071±0.11	0.019	0.74	0.077±0.01	0.087±0.02	0.001	0.001
TbSp[g] (mm)	0.798±0.38	0.633±0.21	0.0002	0.06	0.69±0.23	0.67±0.35	0.54	0.55
TbSpSd[h] (mm)	0.481±0.40	0.367±0.32	0.004	0.09	0.40±0.32	0.39±0.45	0.81	0.49

[a] Total volumetric bone density; [b] trabecular volumetric bone density; [c] trabecular bone volume fraction; [d] cortical thickness; [e] trabecular number; [f] trabecular thickness; [g] trabecular separation; [h] distribution of trabecular separation.

*p-value adjusted for ultradistal radius aBMD

**p-value adjusted for total hip aBMD

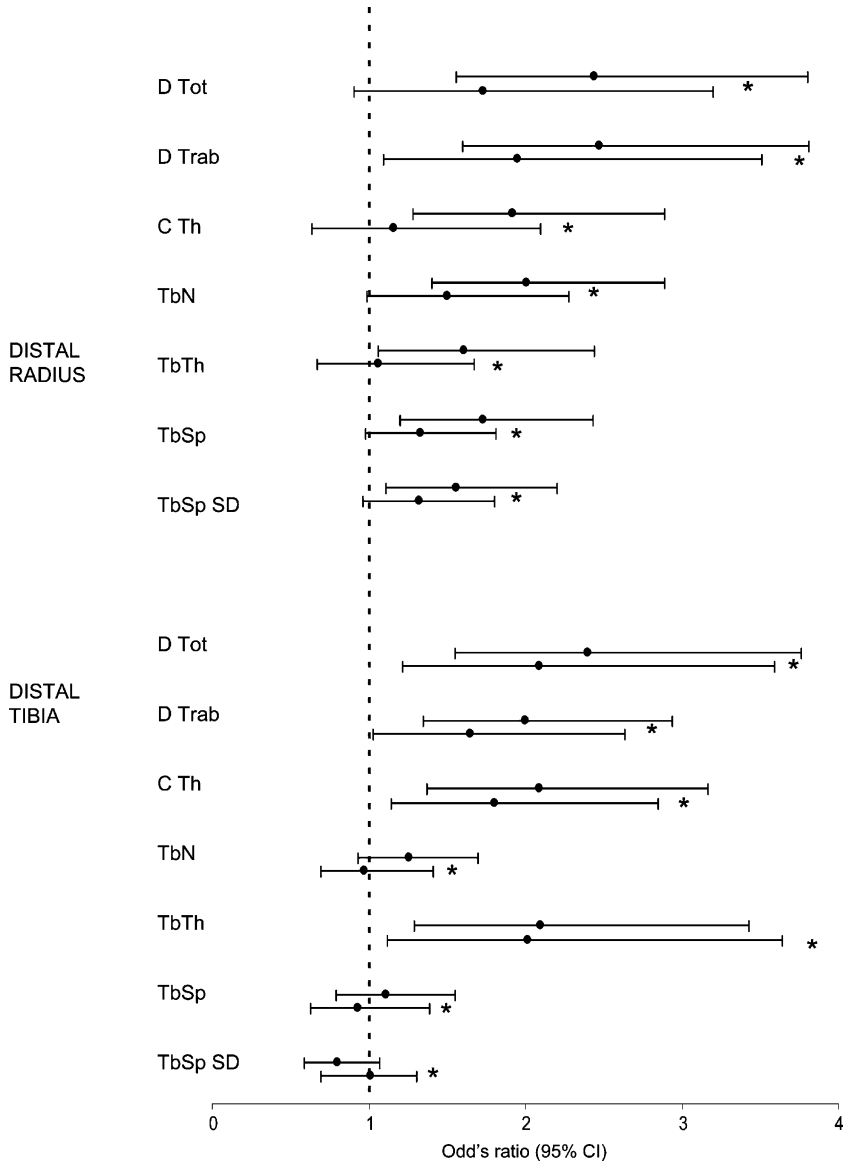

Fig. 4 Association between measurements of bone density/structure and fracture status calculated by conditional logistic regression analysis and expressed as odds ratios and 95% confidence interval, per 1 standard deviation change from the mean of healthy premenopausal women, before and after (*) adjustment for aBMD measured by DXA at the radius (for hr-pQCT measurement of the radius) and hip (for hr-pQCT measurement of the tibia). *Dtot*, total volumetric bone density; *Dtrab*, trabecular volumetric bone density; *CTh*, cortical thickness; *TbN*, trabecular number; *TbTh*, trabecular thickness; *TbSp*, trabecular separation; *TbSpSD*, distribution of trabecular separation

(−14% and −19%, respectively, $p<0.0001$), BV/TV (−19%, $p<0.0001$), cortical thickness (CTh) (−12%, $p<0.001$), trabecular number (TbN) (−14%, $p<0.0001$) and trabecular thickness (−6%, $p=0.02$) and higher trabecular separation (TbSp) (+26%, $p<0.001$) and distribution of trabecular separation (TbSpSd) (+31%, $p=0.004$) than women without fractures. After adjusting for aBMD measured by DXA at the ultradistal radius, differences remained significant for trabecular density and BV/TV, and there was a trend for TbN, TbSp and TbSpSd. At the distal tibia, after adjusting for total hip aBMD, we observed significantly lower values for total and trabecular densities, CTh and TbTh in women with fractures than in controls, but no significant difference for TbN, TbSp and TbSpSd (Table 1).

We then compared the 76 women who sustained a fracture at the most common osteoporotic sites (distal forearm, hip, proximal humerus, spine) with their age-matched controls. Even after adjusting for ultradistal radius aBMD, women with a history of osteoporotic fracture had significantly lower trabecular density, BV/TV, TbN and TbSp. In a conditional logistic regression model, each standard deviation decrease of volumetric total and trabec-

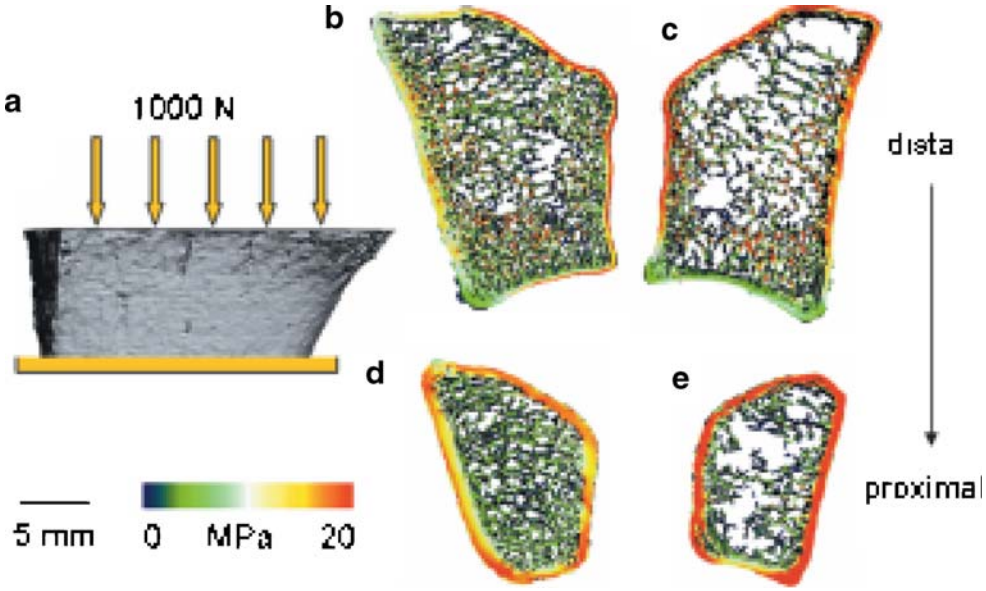

Fig. 5 Boundary conditions and distribution of von Mises stresses in the bone tissue for a control (*left*) and a fracture case (*right*). The colours indicate the stress levels, with *red* for high stresses and *blue* for low stresses. **a** Compression applied in the axial direction; **b**, **d** distribution of von Mises stresses in the first distal (**b**) and last proximal (**d**) slices in a women who had never had a fracture. **c**, **e** Distribution of von Mises stresses in the first distal (**c**) and last (**e**) proximal slices in a woman who had had a wrist fracture. From Boutroy et al. [9], with permission

ular densities at the radius and tibia significantly increased the risk of fracture, with odds ratios (ORs) ranging from 2.00 to 2.47. These ORs were higher than those associated with each SD decrease of ultradistal radius and total hip aBMD (1.46 [1.16–1.83] and 2.03 [1.35; 3.04], respectively). After adjusting for aBMD at the distal radius, differences between cases and controls remained significant for trabecular density, and there was a similar trend for TbN, TbSp and TbSpSd with adjusted ORs ranging from 1.32 to 1.50 (Fig. 4).

Altered microarchitecture and decreased bone strength estimates by micro-finite element analysis in postmenopausal women with prior wrist fracture

Using the same hr-pQCT system, we then compared distal radius aBMD, microarchitecture and bone mechanical parameters assessed by micro-finite element analysis (μFEA) in 33 postmenopausal women with prior history of wrist fracture and their age-matched controls with no history of fracture [9] (Fig. 5). Associations between density, microarchitecture, mechanical parameters and fracture status were evaluated by univariate logistic regression analysis and expressed as ORs (with 95% CIs) per SD change.

We found that, in addition to aBMD, both microarchitecture and bone mechanical properties assessed by FEA, such as estimated failure load, stiffness and the proportion of load carried by the trabecular bone, were significantly associated with wrist fracture (Table 2). Principal components analysis (PCA), performed to highlight differences and similarities in the structural and mechanical parameters, and thus to reduce the large number of variables that were strongly intercorrelated, revealed five independent components that together explained 86% of the variability in bone characteristics at the distal radius. The first principal component included μFEA-estimated failure load, areal and volumetric BMD, and cortical thickness, explaining 51% of the variance with an OR for wrist fracture of 2.49 (95% CI 1.32–4.72). Remaining principal components did not include any density parameters. The

Table 2 Association between BMD, microarchitecture, mechanical parameters at the distal radius and wrist fracture status, expressed as odds ratios (95% confidence interval) per standard deviation change. (From Boutroy et al. [9])

Technique	Variable	OR (95% CI)
DXA	Ultradistal radius aBMD (g/cm^2)	2.98 (1.51–5.89)**
hr-pQCT	Total density (mg HA/cm^3)	5.38 (2.17–13.31)**
	Trabecular density (mg HA/cm^3)	2.54 (1.35–4.80)**
	Trabecular number (mm^{-1})	3.60 (1.73–7.47)**
	Cortical thickness (μm)	5.14 (2.16–12.26)**
μFEA from hr-pQCT	% of load carried by trabecular bone at distal region	1.75 (1.03–2.99)*
	% of load carried by trabecular bone at proximal region	1.86 (1.05–3.29)*
	Stiffness (kN/mm)	3.09 (1.55–6.20)**
	Estimated failure load (N)	3.04 (1.53–6.01)**

*p<0.05; **0.01

second principal component included trabecular architecture, explaining 12% of the variance, with an OR of 1.82 (95% CI 0.94–3.52). The third principal component included the proportion of the load carried by cortical versus trabecular bone, assessed by FEA, explaining 9% of the variance, and had an OR of 1.61 (95% CI 0.94–2.77). Thus, the proportion of load carried by cortical versus trabecular bone seems to be associated with wrist fracture independently of BMD and microarchitecture (included in the first and second principal component, respectively).

Discussion and conclusions

In this series of studies, our group has investigated the relationships among BMD, bone microarchitecture and skeletal fragility using a novel high-resolution, non-invasive imaging technique. Our results confirm and extend previous ex vivo studies on iliac crest bone biopsies that showed alterations of trabecular and cortical microarchitecture in subjects with fractures [3, 5, 6, 12–14], and previous in vivo studies that reported that trabecular bone microarchitecture is significantly associated with non-vertebral [15, 16] and vertebral fractures[17–20]. The slightly better resolution of the hr-pQCT compared to previous techniques allowed us to extend these prior observations with presumably more accurate assessment of cortical and trabecular microarchitecture. We were also able to enhance prior knowledge by examining both weight-bearing and non-weight-bearing sites of the appendicular skeleton with the same technique in the same study population.

There are only few studies showing that BMD measured by DXA, and architecture measured by pQCT, are independently associated with fracture. In one study the association between architectural parameters and fracture status was reported to be similar or higher than that observed with BMD but the independence of both techniques was not analysed [20]. Other studies showed that combining BMD with certain microstructural parameters improved the discrimination capability for vertebral [18], hip [19] and wrist fracture [21] compared to BMD measurement alone, whereas another study showed that differences in trabecular structure parameters between subjects with and without vertebral fractures did not remain significant after adjustment for aBMD [17]. Despite the well-known limitations of the case–control study design, our data consistently showed that even after adjustment for site-matched BMD measurements, parameters of trabecular and cortical architecture differ between postmenopausal women with a history of fragility fracture and those without. We also showed that bone mechanical properties derived from FEA of in vivo hr-pQCT images are associated with wrist fracture. Furthermore, PCA suggested that some of these μFEA-derived mechanical properties provide information about skeletal fragility and fracture risk that is not captured by BMD or architecture measurements alone.

In summary, our findings suggest that in postmenopausal women, vertebral and non-vertebral fractures are associated with low volumetric bone density, architectural alterations of trabecular and cortical bone, and FEA-based mechanical properties that can be assessed non-invasively by hr-pQCT. These alterations are partially independent of aBMD assessed by DXA, suggesting that assessment of bone microarchitecture in vivo may provide improved sensitivity and/or specificity in identifying individuals at greatest risk for fracture. Altogether, these data provide a strong rationale for prospective studies to determine the utility of hr-pQCT and μFEA for predicting the risk of osteoporotic fractures, and monitoring disease progression and the response to treatments.

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