Bone Microarchitecture Assessment by High-Resolution Peripheral Quantitative Computed Tomography in Patients with Systemic Lupus Erythematosus Taking Corticosteroids

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ABSTRACT. ***Objective.*** We assessed the relationship between vertebral fracture and bone microarchitecture in patients with systemic lupus erythematosus (SLE) on chronic corticosteroid therapy using high-resolution peripheral quantitative computed tomography (HR-pQCT).

Methods. Fifty-nine Chinese women with SLE taking corticosteroid were selected to participate in a cross-sectional study. Vertebral fracture was confirmed semiquantitatively by lateral radiographs of the thoracic and lumbar spine. Density and microarchitecture at the distal radius were measured with HR-pQCT. Areal bone mineral density (aBMD) at hip and lumbar spine was measured by dual-energy x-ray absorptiometry (DEXA).

Results. Twelve patients had vertebral fractures. The aBMD of spine or hip did not differ between those with and without vertebral fractures. Measures by HR-pQCT revealed that patients with vertebral fractures had significantly lower level of average bone density ($p = 0.007$), cortical bone density ($p = 0.029$), trabecular bone density ($p = 0.024$), trabecular bone volume to tissue volume ($p = 0.023$), and trabecular thickness ($p = 0.011$) than those without vertebral fractures. Independent explanatory variables associated with higher risk of vertebral fractures were older age ($p = 0.013$) and lower average cortical bone density ($p = 0.029$).

Conclusion. Vertebral fracture in patients with SLE on chronic corticosteroid treatment was associated with alterations of bone density and microarchitectures measured by HR-pQCT and DEXA. However, alterations were more pronounced in measurements by HR-pQCT. Low cortical bone density and old age were significant predictors of vertebral fracture risk. (First Release May 15 2010; J Rheumatol 2010;37:1473–9; doi:10.3899/jrheum.091231)

Key Indexing Terms:
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Patients undergoing chronic corticosteroid therapy are prone to develop pathologic fractures due to reduction of bone mineral density (BMD)[1,2] and change in microarchitecture of trabecular bone[3] and cortical bone[4,5]. Measurement of areal BMD (aBMD) by dual-energy x-ray absorptiometry (DEXA) is the current "gold standard" for clinical assessment of bone fracture risk. However, DEXA has some inherent limitations. DEXA measurements are 2-dimensional, and cannot distinguish between the separate contributions of cortical and trabecular bone, or assess 3-dimensional geometry and microarchitecture. Newer technologies have been developed to examine qualitative bone changes that influence bone strength.

Microcomputed tomography (μCT) is a CT technique with a spatial resolution of about 20 μm. MicroCT is limited to *in vitro* study of cadaveric specimens or biopsies of the iliac crest or other sites[6]. Standard quantitative CT (QCT) techniques generate images with in-plane voxel sizes of 500 μm, and as a result lack the resolution to assess individual trabeculae, which have a thickness of ~400 μm, or to assess the cortical thickness of the vertebral body and femoral neck (< 500 μm) in many osteoporotic individuals[7]. A high-resolution peripheral QCT (HR-pQCT) system with a voxel size of 80 μm has recently been developed that is capable of assessing trabecular and cortical architecture of the distal

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radius and distal tibia. This technique allows excellent precision (2%–4%) for both density and structural parameters[7]. Studies using HR-pQCT have provided unique insight into gender-specific and compartment-specific bone loss in the appendicular skeleton[8,9]. Two cross-sectional studies have reported that bone microarchitecture measured by HR-pQCT at the distal radius is able to discriminate postmenopausal women with and without fragility fracture, partly independent of aBMD[7,10].

We and others have recently reported a high prevalence (20%) of asymptomatic vertebral fractures in patients with systemic lupus erythematosus (SLE) undergoing chronic corticosteroid treatment[11-14]. Consistent with another study, we found that only a modest proportion (29%) of these fractures was attributable to osteoporosis based on the most commonly applied definition of osteoporosis (aBMD T score < –2.5)[15]. A normal aBMD measurement obtained by DEXA in an individual with SLE may not reflect their true risk of fracture, since the aBMD by DEXA combines the measurement of both cortical and trabecular bone, while the bone loss due to inflammation or use of corticosteroid in SLE is mainly in trabecular bone[16]. Also, aBMD does not fully reflect changes in underlying bone architecture that may adversely affect bone strength in the absence of recognizable change in bone density. Thus, it would be of great interest to investigate the relationship between the alteration of cortical and trabecular architecture and fractures in patients with SLE on chronic corticosteroid therapy.

The objective of our study was to investigate alteration of bone microarchitecture in patients with SLE undergoing chronic corticosteroid therapy with vertebral fractures compared with those without vertebral fractures, using HR-pQCT.

MATERIALS AND METHODS

Study design and patients. This was a cross-sectional nonrandomized cohort study. A convenience sample was selected: 59 Chinese women taking corticosteroids with a diagnosis of SLE according to the American College of Rheumatology revised criteria for the classification of SLE[17]. Thirty-seven of these patients were recruited from 152 patients who participated in a previous cross-sectional vertebral fracture prevalence study[11]; 22 patients were recruited from the rheumatology outpatient clinic. Patients were excluded if (1) they had a known metabolic disorder that could affect bone metabolism; or (2) they were currently receiving treatment for osteoporosis (such as bisphosphonates, parathyroid hormone, vitamin D supplements, or hormone replacement therapy). Written informed consents were obtained from all patients and the study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Data collection. Demographic and clinical characteristics were recorded by interview, self-reported questionnaires, chart review, and clinical examination. The following data were collected at interview: age, menstrual status, age of onset and duration of menopause, body weight, body height, and body mass index (BMI). Clinical characteristics included disease duration since diagnosis, comorbidity, history of symptomatic nonvertebral fracture, and disease activity score using the SLE Disease Activity Index (SLEDAI)[18], while accumulated organ damage was assessed with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)[19]. Use of corticosteroids, including past or current use of intravenous (IV) methylprednisolone and use of oral corticosteroids (duration of use, highest dosage ever taken, and cumulative dosage) was documented by chart review. Information about use of other immunosuppressants (i.e., hydroxychloroquine, azathioprine, cyclosporine, methotrexate, IV or oral use of cyclophosphamide, leflunomide and mycophenolate mofetil), calcium supplements, and multivitamin supplements was also recorded.

Assessment of vertebral fracture. Lateral radiographs of thoracic and lumbar spine (T5–L4) were performed in the radiology department by a trained operator according to a standardized protocol. All radiographs were of good quality, with good visibility and reliable identification of all vertebrae. Radiographs were evaluated by a single experienced musculoskeletal radiologist with over 20 years of experience in reporting spine radiographs. The assessment of vertebral fracture was performed using the widely accepted criteria of Genant, *et al*[20]. This is a semiquantitative method of identifying and grading vertebral fracture, which uses a visual estimation of loss of vertebral height relative to adjacent normal-appearing vertebrae. A vertebral fracture was defined as a reduction of at least 20% of the vertebral body height relative to adjacent normal vertebrae. This method grades vertebrae on a scale of 0 to III, where grade 0 = normal, grade I = 20%–25% reduction in height, grade II = 25%–40% reduction in height, and grade III ≥ 40% reduction in height, irrespective of whether the loss of height occurs in a wedge, biconcave, or crush pattern. For the anterior and middle heights, the posterior height of the same vertebra was used as a reference. This straightforward analysis method has been used by other similar studies, with an interrater agreement of 0.78 to 0.89.

aBMD measurement. aBMD measurements of the hip and lumbar spine (L1–L4, anteroposterior view) were performed by a trained technician using the same DEXA equipment (model 4500A; Hologic, Bedford, MA, USA) in all patients, with results expressed in grams per square centimeter. The aBMD values of both lumbar and total hip were compared to the aBMD reference data of normal Chinese subjects in Hong Kong[21].

Assessment of bone microarchitecture. Microarchitecture of bone was measured in the nondominant distal radius using a 3-D HR-pQCT device (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). This system utilizes a 2-D detector array in combination with a 0.08 mm point-focus X-ray tube, enabling simultaneous acquisition of a stack of parallel CT slices with a nominal isotropic resolution (voxel size) of 82 μm. The details of image acquisition and analysis have been described[7]. At the distal radius, 110 CT acquisitions were obtained providing 3-D volumetric representation of total thickness of approximately 9 mm. The entire volume of interest was automatically separated into cortical and trabecular components, yielding average bone density (D100), trabecular bone density (Dtrab), metatrabecular bone density (Dmeta), inner-trabecular bone density (Dinn), and cortical bone density (Dcomp) in mg hydroxyapatite (HA)/cm^3. Mean cortical thickness (Ct.Th) was defined as the mean cortical volume divided by the outer bone surface. Trabecular bone volume fraction (BV/TV) was derived from trabecular density, assuming fully mineralized bone to have a density of 1.2 g HA/cm^3. Using 3-D HR-pQCT datasets, metric indices of topological features of trabecular bone structure could be directly assessed by measuring distances in 3-D space[22]. Trabecular number (Tb.N) was taken as the inverse of the mean distance between the midaxes of the observed trabecular structure. The midaxes of the trabecular structure were assessed from the binary 3-D image dataset using the 3-D distance transformation and extracting center points of nonredundant spheres that filled the structure completely. Combining Tb.N and BV/TV allowed calculation of trabecular thickness [(Tb.Th) = BV/TV divided by Tb.N] and trabecular separation [(Tb.Sp) = (1 – BV/TV) / Tb.N] in analogy to standard histomorphometry[23]. Standard deviation of 1/Tb.N (Tb.1/N.SD) was used to reflect trabecular network inhomogeneity. The *in vivo* precision error of density (total, trabecular, and cortical) measurement, expressed as the coefficient of variation, ranged from 0.7% to 1.5%. The mean duration between the assessment of radiographs and HR-pQCT was 15 (SD 10) days.

Statistical analysis. Statistical analysis was performed using Statistics Package for Social Sciences (SPSS for Windows, version 13.0, 2006; SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD for normally distributed data. For non-normally distributed data, median and IQR were expressed. Variables possibly associated with the presence of vertebral fractures were examined first by univariate tests and subsequently by multiple regression analysis. In view of the relatively small sample size, nonparametric tests (Mann-Whitney U test) were used for comparisons between patients with and without vertebral fractures and in further subgroups. Categorical variables were compared by chi-square test. The following variables were examined in relationship to vertebral fracture by univariate analysis: age, body height, body weight, BMI, menopause status, age of menopause, previous history of nonvertebral fracture, disease duration, SLEDAI and SDI scores, ever-use of IV methylprednisolone, use of corticosteroids (duration of use, highest dosage taken, cumulative dose), aBMD of lumbar spine and hip by DEXA, bone microarchitecture and density measurements by HR-pQCT [D100, Dtrab, Dcomp, Dmeta, Dinn, Ct.Th, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD]. To determine which factors were independently associated with vertebral fracture, variables showing $p < 0.1$ in the univariate analysis were entered into the multiple logistic regression analysis. A p value ≤ 0.05 (2-sided) was considered statistically significant in multiple logistic regression analysis.

RESULTS

Demographic and clinical characteristics and vertebral fracture. The clinical and demographic features of the 59 Chinese female SLE patients are shown in Table 1. Thirty-five (59%) patients were postmenopausal, with normal renal function and mild disease activity. All patients were currently on corticosteroid therapy with a median [interquartile range (IQR)] dose of prednisolone 5 mg/day (IQR 5–7.5) for a mean duration of 13.8 (SD 7.9) years. As shown in Table 1, patients with fracture were older ($p = 0.008$) and were more likely to be postmenopausal ($p = 0.047$). Only 4 patients reported previous nonvertebral fracture, 1 of which was with concurrent radiographic vertebral fracture and 3 without. No patient had osteonecrosis. Other parameters such as disease duration, disease activity and damage, proportion of lupus nephritis, cumulative dosage and duration of corticosteroid, and duration of menopause were not significantly different between patients with and those without fractures. Use of other immunosuppressants, calcium supplements, and multivitamin supplements was also similar between the 2 groups (data not shown).

Lateral spinal radiographs revealed a total of 27 vertebral fractures in 12 (20%) of 59 patients, of which 26 were thoracic fractures and 1 lumbar fracture. Five patients had an isolated fracture, 2 patients had 2 fractures, 4 patients had 3 fractures, and 1 patient had 6 fractures. As for the severity of vertebral fracture, 5 patients had grade I fracture, 2 had grade II fracture, 3 had grade III fracture, and 2 had mixed grade of fracture.

Bone density and microarchitecture by DEXA and HR-pQCT. Of the 59 patients, 22 had normal aBMD, 31 were osteopenic, and 6 were osteoporotic. Of the 12 patients with fractures, 4 had normal aBMD, 5 were osteopenic, and 3 were osteoporotic.

Adjusted for age and body weight, aBMD of both the lumbar spine and the hip were not discriminatory (Table 2). Patients with more than 1 vertebral fracture had a lower aBMD and T score of the lumbar spine compared with those with only 1 fracture (at 0.1 significance level; Table 3). There were no differences in aBMD in patients with grade II or III vertebral fractures compared with those with grade I fractures.

Table 1. Demographic and clinical variables of patients. Results are mean ± SD or median (IQR), unless otherwise specified.

Variables	All Patients, n = 59	Without Fracture, n = 47	With Fracture, n = 12	p
Demographic				
Age, yrs	46.9 ± 9.7	44.9 ± 8.4	54.8 ± 10.1	0.008
Body height, cm	156.4 ± 5.5	156.9 ± 5.4	154.7 ± 5.8	0.181
Body weight, kg	55.8 ± 9.3	54.8 ± 9.2	59.5 ± 9.0	0.085
Body mass index, kg/m^2	22.8 ± 3.7	22.2 ± 3.4	25.0 ± 4.2	0.019
Duration of steroids, yrs	13.8 ± 7.9	13.5 ± 7.0	15.0 ± 10.9	0.821
Highest dose of prednisolone, mg/day	40 (30–60)	40 (30–50)	50 (33–95)	0.138
Cumulative dose of steroid, g	31.0 (21.7–44.2)	31.1 (21.0–44.5)	23.2 (16.1–38.2)	0.265
Menopausal, no. (%)	35 (59)	25 (53)	10 (83)	0.047
Age of menopause, yrs	45 (41–49)	45 (41–48)	43 (40–50)	0.595
Duration of menopause, yrs	4.9 (3.5–9.4)	4.8 (3.1–7.9)	8.5 (3.7–19.6)	0.078
Clinical				
Disease duration, yrs	12.9 (8.7–19.2)	13.0 (8.7–19.2)	12.8 (8.7–20.8)	0.735
SLEDAI	2.1 (0–3)	2 (0–3)	1 (0–3.5)	0.282
SDI	1.1 (0–1)	1 (0–1)	1 (0–2)	0.277
CRP, mg/l	1.0 (1.0–1.9)	1 (1–2)	1 (1–1.7)	0.563
Ever had lupus nephritis, no. (%)	43 (73)	35 (74)	8 (73)	0.427

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CRP: C-reactive protein; IQR: interquartile range.

Table 2. aBMD and microarchitecture characteristics measured by DEXA and HR-pQCT in patients with and without fracture. Values are mean ± SD.

Characteristic	All Patients, n = 59	Without Fracture, n = 47	With Fracture, n = 12	p	Adjusted p*
aBMD					
aBMD of L1-4, g/cm^2	0.879 ± 0.134	0.893 ± 0.134	0.826 ± 0.128	0.342	0.173
T score of L1-4	(–) 1.022 ± 1.273	(–) 0.889 ± 1.262	(–) 1.542 ± 1.230	0.295	0.171
aBMD of hips, g/cm^2	0.813 ± 0.125	0.824 ± 0.122	0.769 ± 0.141	0.175	0.131
T score of hips	(–) 0.685 ± 1.156	(–) 0.579 ± 1.104	(–) 1.100 ± 1.311	0.158	0.118
Microarchitecture					
D100, mg HA/cm^3	340 ± 80	354 ± 79	286 ± 60	0.007	0.023
Dcomp, mg HA/cm^3	906 ± 72	917 ± 68	864 ± 73	0.029	0.059
Dtrab, mg HA/cm^3	136 ± 41	142 ± 42	113 ± 25	0.024	0.087
Dinn, mg HA/cm^3	97 ± 44	102 ± 46	73 ± 28	0.035	0.108
Dmeta, mg HA/cm^3	2.34 ± 1.04	2.28 ± 1.06	2.61 ± 0.94	0.017	0.075
Ct.Th, mm	0.83 ± 0.21	0.85 ± 0.21	0.74 + 0.17	0.101	0.113
BV/TV	0.11 ± 0.03	0.118 ± 0.035	0.094 ± 0.021	0.023	0.088
Tb.N, 1/mm	1.54 ± 0.26	1.56 ± 0.27	1.48 ± 0.22	0.429	0.642
Tb.Th, mm	0.07 ± 0.02	0.08 ± 0.02	0.06 ± 0.01	0.011	0.052
Tb.Sp, mm	0.59 ± 0.13	0.59 ± 0.13	0.63 ± 0.11	0.283	0.648
Tb.1/N.SD, mm	0.27 ± 0.10	0.26 ± 0.11	0.28 ± 0.06	0.258	0.787

* Adjusted for age and body weight. aBMD: areal bone mineral density; DEXA: dual-energy x-ray absorptiometry; HR-pQCT: high resolution peripheral quantitative computed tomography; D100: average bone density; Dtrab: trabecular; Dcomp: cortical bone density; Dinn: inner trabecular bone density; Dmeta: metatrabecular bone density; Ct.Th: Cortical thickness; BV/TV: trabecular bone volume to tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Tb.1/N.SD: standard deviation of 1/ trabecular number. HA: hydroxyapatite.

Measures of HR-pQCT revealed statistically significant differences in several density and morphometric indices of microarchitecture of both trabecular and cortical bone. Women with SLE taking chronic corticosteroids with vertebral fractures had lower levels of average bone density (D100) (p = 0.007), cortical bone density (Dcomp) (p = 0.029), trabecular bone density (Dtrab) (p = 0.024), inner trabecular bone density (Dinn) (p = 0.035), metatrabecular bone density (Dmeta) (p = 0.017), trabecular bone volume to tissue volume (BV/TV) (p = 0.023), Tb.Th (p = 0.011) than those without vertebral fractures (Table 2). After adjusting for age and body weight, only average bone den-

Table 3. Bone density and microarchitecture by number and severity of vertebral fracture. Values are mean ± SD.

Characteristic	With 1 Fracture,	With > 1 Fracture, n = 5	p n = 7	Grade I Fracture,	Grade II/III Fracture*, n = 5	p n = 7
aBMD						
aBMD of L1-4, g/cm^2	0.908 ± 0.054	0.768 ± 0.138	0.088	0.885 ± 0.045	0.784 ± 0.155	0.372
T score of L1-4	(–) 0.74 ± 0.50	(–) 2.11 ± 1.30	0.061	(–) 0.96 ± 0.44	(–) 1.96 ± 1.47	0.370
aBMD of hips, g/cm^2	0.828 ± 0.135	0.727 ± 0.139	0.372	0.827 ± 0.085	0.728 ± 0.164	0.223
T score of hips	(–) 0.56 ± 1.29	(–) 1.49 ± 1.28	0.415	(–) 0.58 ± 0.81	(–) 1.47 ± 1.6153	0.222
Microarchitecture						
D100, mg HA/cm^3	317 ± 58	264 ± 54	0.088	304 ± 57	273 ± 62	0.372
Dcomp, mg HA/cm^3	901 ± 66	837 ± 69	0.167	875 ± 98	855 ± 56	0.570
Dtrab, mg HA/cm^3	125 ± 29	104 ± 20	0.123	129 ± 9	101 ± 27	0.123
Dinn, mg HA/cm^3	89 ± 26	62 ± 25	0.062	91 ± 13	61 ± 30	0.088
Dmeta, mg HA/cm^3	177 ± 33	165 ± 16	0.167	185 ± 8	159 ± 26	0.062
Ct.Th, mm	0.81 ± 0.15	0.70 ± 0.19	0.233	0.77 ± 0.24	0.72 ± 0.13	0.570
BV/TV	0.10 ± 0.02	0.09 ± 0.02	0.123	0.11 ± 0.01	0.08 ± 0.02	0.123
Tb.N, 1/mm	1.61 ± 0.17	1.38 ± 0.21	0.088	1.59 ± 0.06	1.39 ± 0.26	0.233
Tb.Th, mm	0.06 ± 0.01	0.06 ± 0.01	0.684	0.07 ± 0.004	0.06 ± 0.01	0.167
Tb.Sp, mm	0.56 ± 0.08	0.67 ± 0.11	0.088	0.56 ± 0.02	0.68 ± 0.13	0.223
Tb.1/N.SD, mm	0.24 ± 0.04	0.31 ± 0.06	0.062	0.23 ± 0.03	0.31 ± 0.06	0.042

* Two patients with mixed grades of vertebral fractures were categorized according to the most severe grades (grade II and grade III). aBMD: areal bone mineral density; DEXA: dual-energy x-ray absorptiometry; HR-pQCT: high resolution peripheral quantitative computed tomography; D100: average bone density; Dtrab: trabecular; Dcomp: cortical bone density; Dinn: inner trabecular bone density; Dmeta: metatrabecular bone density; Ct.Th: Cortical thickness; BV/TV: trabecular bone volume to tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Tb.1/N.SD: standard deviation of 1/ trabecular number. HA: hydroxyapatite.

sity (D100) was discriminatory between the 2 groups (at 0.05 significance level). Cortical bone density (Dcomp), trabecular bone density (Dtrab), metatrabecular bone density (Dmeta), trabecular bone volume to tissue volume (BV/TV), and Tb.Th differed between patients with and those without vertebral fractures at 0.1 significance level after adjustment for age and body weight.

Patients with more than 1 vertebral fracture had lower average bone density (D100), inner trabecular bone density (Dinn), and Tb.N, and higher Tb.Sp ($p < 0.1$) compared with those with only 1 vertebral fracture (Table 3). Comparing patients with grade II or III vertebral fracture with those with grade I fracture, inner (Dinn) and metatrabecular bone density (Dmeta) differed between these 2 groups at 0.1 significance level, and Tb.1/N.SD differed at 0.05 significance level.

Compared with those with normal aBMD in lumbar spine or hip (T > –1), patients with T score ≤ –1 in lumbar spine or hip had significantly poorer bone microarchitecture measured by HR-pQCT, except that the difference in Tb.Th between patients with T score ≤ –1 in lumbar spine and with normal aBMD in lumbar spine did not reach the significance level (Table 4). The bone density and structure indices of HR-pQCT were significantly correlated with aBMD by DEXA, with all p values < 0.05 (r = 0.27 to 0.61).

Univariate and multivariate analysis. There was significant association between older age (p = 0.002), increased body weight (p = 0.008), higher BMI (p = 0.002), lower average bone density (D100) (p = 0.008), lower cortical bone density (Dcomp) (p = 0.02), lower trabecular bone density (Dtrab) (p = 0.028), lower inner trabecular bone density (Dinn) (p = 0.045), lower trabecular bone volume to tissue volume (BV/TV) (p = 0.029), and less Tb.Th (p = 0.021) and vertebral fracture in the thoracic and lumbar spine. The independent explanatory variables associated with higher vertebral fracture risk were older age (p = 0.013) and lower average cortical bone density (p = 0.029) (Table 5).

DISCUSSION

Our study found deterioration alterations in bone density and microarchitecture among those with vertebral fractures in a group of patients with SLE undergoing chronic corticosteroid therapy. These alterations were more pronounced when measured by HR-pQCT than measured by DEXA. Our results suggest that measurements by HR-pQCT would be valuable in predicting fracture risk in SLE patients receiving chronic corticosteroid therapy.

High prevalence of vertebral fracture in patients with SLE has been reported previously. Both traditional and SLE-related risk factors for fracture have been identified. Corticosteroid use in patients with SLE is associated with reduced BMD, which has been shown to be the strongest risk factor for fracture in patients with SLE[13,24,25]. Previous studies found lower BMD in women with SLE without prior corticosteroid use than in healthy controls, suggesting SLE as a potential risk factor for bone loss[26,27]. Active SLE has been associated with ovarian failure, which may be an

Table 4. Comparison of HR-pQCT measurements in patients with normal (T score > –1) and abnormal (T score ≤ –1) aBMD in spine or hip. Values are mean ± SD.

Characteristic	Lumbar Spine T score ≤ –1, n = 33	Lumbar Spine T score > –1, n = 26	p	Hip T score ≤ –1, n = 29	Hip T score > –1, n = 30	p
D100, mg HA/cm^3	311.6 ± 73.2	376.4 ± 75.1	0.003	303.6 ± 67.3	375.5 ± 76.6	< 0.001
Dcomp, mg/HA/cm^3	879.1 ± 73.3	940.8 ± 54.0	0.002	878.5 ± 74.6	933.2 ± 58.8	0.004
Dtrab, mg HA/cm^3	123.1 ± 30.6	152.2 ± 47.1	0.012	118.1 ± 26.7	153.2 ± 45.4	0.001
Dinn, mg HA/cm^3	81.8 ± 32.9	114.4 ± 50.2	0.013	76.9 ± 28.1	114.7 ± 49.1	0.001
Dmeta, mg HA/cm^3	182.5 ± 29.3	206.5 ± 44.5	0.033	177.3 ± 28.2	208.3 ± 41.1	0.002
Ct.Th, mm	0.8 ± 0.2	0.9 ± 0.2	0.001	0.74 ± 0.2	0.92 ± 0.2	0.001
BV/TV	0.10 ± 0.03	0.12 ± 0.04	0.013	0.1 ± 0.02	0.2 ± 0.04	0.001
Tb.N, 1/mm	1.5 ± 0.2	1.6 ± 0.2	0.008	1.4 ± 0.2	1.6 ± 0.3	0.007
Tb.Th, mm	0.07 ± 0.01	0.08 ± 0.02	0.202	0.07 ± 0.01	0.08 ± 0.02	0.036
Tb.Sp, mm	0.6 ± 0.1	0.5 ± 0.1	0.004	0.6 ± 0.1	0.5 ± 0.1	0.002
Tb.1/N.SD, mm	0.3 ± 0.1	0.2 ± 0.5	0.003	0.3 ± 0.1	0.2 ± 0.1	0.002

HR-pQCT: high resolution peripheral quantitative computed tomography; D100: average bone density; Dtrab: trabecular; Dcomp: cortical bone density; Dinn: inner trabecular bone density; Dmeta: metatrabecular bone density; Ct.Th: Cortical thickness; BV/TV: trabecular bone volume to tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Tb.1/N.SD: standard deviation of 1/ trabecular number.

Table 5. Independent explanatory variables associated with vertebral fracture.

Variable	Coefficient	SE	OR (95% CI)	p
Age (1-year increase)	0.135	0.054	1.145 (1.029–1.273)	0.013
Cortical bone density (1 mg HA/cm^3 increase)	–0.012	0.006	0.988 (0.977–0.999)	0.029

important mechanism of low BMD observed in SLE patients that appears to be independent of corticosteroid use[28,29]. Improved recognition of patients who are at increased risk for bone loss or fracture is essential for prompt initiation of preventive care.

BMD measured by DEXA has commonly been used to diagnose osteoporosis and predict the risk of vertebral fractures. Studies have shown that there are limitations of DEXA in distinguishing between patients with and those without vertebral fracture[12,13]. Our results are in agreement with these findings.

aBMD of the lumbar spine or hip was not significant at the 0.05 level at distinguishing between patients with and those without vertebral fracture. This might be due partly to the small number of patients in our study, and the higher prevalence of osteopenia or osteoporosis in our cohort than in previous cohorts of Asian women[30,31]. A limitation of aBMD is that it measures integral (i.e., cortical and trabecular) BMD and does not assess bone structural factors affecting bone strength beyond BMD. Both these limitations have a bearing on the predictability of DEXA-assessed BMD of vertebral fracture in patients on chronic corticosteroid therapy. This view is supported by the observation that lumbar aBMD is not predictive of vertebral fracture in male patients treated with corticosteroids[32], and that female patients treated with corticosteroids sustain vertebral fractures at a higher aBMD measurement than control subjects not on corticosteroid therapy[33]. Other studies employing standard QCT assessment have shown how chronic corticosteroid treatment in postmenopausal women results in significantly decreased volumetric BMD, with loss of both trabecular and cortical bone[34]. In other words, volumetric BMD assessment by QCT has been shown to be a good predictor of vertebral fracture in subjects receiving chronic corticosteroid treatment[34,35].

This is the first study to apply HR-pQCT in the investigation of steroid-related vertebral fractures. We investigated whether density and architectural findings in the distal radius could discriminate subjects with and those without steroid-related vertebral fractures better than DEXA examination of the lumbar spine and hip. HR-pQCT achieves an isotropic voxel size of about 80 μm at an acceptable radiation dose, yielding high-resolution image data that allow good depiction of trabecular and cortical bone. Using this validated non-invasive new technique, we identified significant deterioration in cortical and trabecular bone density at the distal radius in patients with vertebral fracture, and more importantly were able to detect significant microarchitectural differences between patients with and those without vertebral fracture. The main findings were significant differences in average bone density, cortical bone density, cortical thickness, and trabecular thickness between patients with and without vertebral fractures after adjustment for age and body weight.

It has been reported that severe and multiple vertebral fractures are associated with a greater alteration in cortical bone measures at the radius and tibia[36]. We also found lower aBMD and architectural deterioration of trabecular and cortical bone in patients with multiple and severe vertebral fractures. However, due to the relatively small number of patients with fractures, we were not able to adjust for other confounders and draw definite conclusions. The relevance of trabecular microarchitecture to bone quality has been well documented, and evaluation of both volumetric BMD and microarchitecture alteration of trabecular and cortical bone can provide additional information when predicting fracture risk[10,37]. In our study, we observed deterioration of both cortical and trabecular bone in patients with vertebral fracture using univariate analysis. However, on multivariate analysis, only cortical bone density was identified as an independent explanatory variable associated with increased vertebral fracture risk. No particular features of trabecular microarchitecture were shown to be discriminatory with multivariate analysis. This discrepancy might partly be explained by the small sample size of this study.

There are several limitations in our study. First, participants were of high heterogeneity, regarding severity or activity of disease, menopausal status, or treatment, which decreased the generalizability of our results. Also, no control group of healthy subjects or subjects not receiving corticosteroid therapy was employed. Hence, the effect of SLE or corticosteroid on bone density or microarchitecture could not be established. Second, because of the small number of patients with vertebral fracture, multiple regression analyses and association of vertebral fracture severity or number and microarchitecture deterioration were limited, although significant differences were still apparent. Third, we did not measure the level of 25-hydroxyvitamin D, which is an important bone parameter associated with fracture risk. Fourth, the cross-sectional design of the study did not permit us to establish a causal relationship between microarchitecture deterioration and vertebral fracture. Further, the population was of a single ethnic origin and our findings may not necessarily apply to another ethnic group.

In summary, vertebral fracture in patients with SLE undergoing chronic corticosteroid treatment is associated with reduction in bone density by DEXA and HR-pQCT as well as reduction in specific architectural parameters by HR-pQCT. More pronounced differences are shown by HR-pQCT of the distal radius than by DEXA of the lumbar spine or hip. Both cortical bone density measured by HR-pQCT and age were significant independent predictors of vertebral fracture risk. Overall, HR-pQCT of the distal radius seems to be better than DEXA examination of the lumbar spine or hip at discriminating SLE patients on corticosteroid therapy with or without vertebral fracture.

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