

Increased Organ Damage Associated with Deterioration in Volumetric Bone Density and Bone Microarchitecture in Patients with Systemic Lupus Erythematosus on Longterm Glucocorticoid Therapy

XIAO LIN TANG, TRACY YANER ZHU, VIVIAN W. HUNG, LING QIN, CHUN-KWOK WONG, EMILY W. KUN, LAI SHAN TAM, and EDMUND K. LI

ABSTRACT. Objective. To evaluate bone quality in patients with systemic lupus erythematosus (SLE) who were undergoing longterm glucocorticoid (GC) therapy, and to focus on the correlation between bone quality and organ damage.

Methods. Seventy-eight female patients with SLE and organ damage taking longterm GC, and 72 age-matched SLE patients without damage taking longterm GC were recruited for study. Clinical variables of interest included disease activity, cumulative organ damage (by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SDI), major organ involvement (musculoskeletal damage and neuropsychiatric damage, etc.), and use of medication. Areal bone mineral density (aBMD) was measured by dual-energy X-ray absorptiometry. Bone geometry, volumetric BMD (vBMD), microarchitecture, and biomechanical properties were measured by high-resolution peripheral quantitative computed tomography (HR-pQCT).

Results. Patients were mean age of 45 years (SD 10) and 54% were postmenopausal. The median SDI score of the cohort was 1 (interquartile range 1–2, range 1–5). Compared with patients without damage, the prevalence of osteopenia at either total hip or lumbar spine was significantly higher, and there were trends of deterioration of bone geometry, vBMD, microarchitecture, and biomechanical properties in patients with organ damage. Potential risk factors for bone quality in patients with damage were screened by univariate analysis. During multiple regression analysis, SDI was the only clinical variable consistently associated with deterioration of vBMD and microarchitecture.

Conclusion. Cumulative organ damage consistently correlated with deterioration of vBMD and bone microarchitecture in SLE patients with damage on longterm GC therapy. HR-pQCT provides an insight into the underlying mechanism of bone loss in SLE. (J Rheumatol First Release Aug 15 2012; doi:10.3899/jrheum.120213)

Key Indexing Terms:

BONE MICROARCHITECTURE SYSTEMIC LUPUS ERYTHEMATOSUS ORGAN DAMAGE
HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

From the Department of Medicine and Therapeutics, Department of Orthopedics and Traumatology, and Department of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong; and Department of Medicine and Geriatrics, Tai Po Hospital, Hong Kong.

Supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. CUHK471010).

X.L. Tang, MMS; T.Y. Zhu, PhD, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong; V.W. Hung, MPhil; L. Qin, PhD, Department of Orthopedics and Traumatology, Prince of Wales Hospital, The Chinese University of Hong Kong; C-K. Wong, PhD, Department of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong; E.W. Kun, MBBS, FRCP, Department of Medicine and Geriatrics, Tai Po Hospital; L.S. Tam, MD; E.K. Li, MD, FRCP(C), Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong.

Address correspondence to Prof. E.K. Li, Department of Medicine and Therapeutics, 9/F, Clinical Science Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, NT, Hong Kong.

E-mail: edmundli@cuhk.edu.hk

Accepted for publication July 3, 2012.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a broad range of clinical and laboratory presentations involving almost all organs, including the neuropsychiatric, cardiovascular, and musculoskeletal systems. Women with SLE have higher risk of osteoporosis and fracture than the general population as a result of exposure to direct or indirect risk factors, such as treatment with glucocorticoid (GC), sun avoidance, or premature menopause caused by the disease itself or its treatment with cytotoxic drugs¹. Prevalence of osteoporosis in Chinese patients with SLE ranged from 4% to 6% in premenopausal patients² and 3% to 48% in postmenopausal patients³, depending on different measurement sites.

Many studies using dual-energy X-ray absorptiometry (DEXA) have shown that cumulative organ damage of SLE is a risk factor for decreased areal bone mineral density

(aBMD)^{4,5}. As a 2-dimensional projectional imaging technique, DEXA measures integral aBMD of cortical and trabecular bone and is confounded by bone geometry, and thus cannot truly reflect bone quality including microarchitecture and bone strength⁶. With advances in high-resolution imaging techniques, interest in investigating bone microarchitecture as an important factor in development of osteoporosis has increased. High-resolution peripheral quantitative computed tomography (HR-pQCT) capable of achieving an isotropic voxel size of 80 μm is now available for assessment of trabecular and cortical microarchitecture at the distal radius and tibia⁷. Compared with DEXA, HR-pQCT has the ability to distinguish cortical and trabecular bone with 3-dimensional images, higher resolution, and lower radiation exposure, as well as shorter scanning time. HR-pQCT has been validated against microcomputed tomography, which is usually considered the “gold standard” to assess bone microarchitecture⁸. Further, it is feasible to apply finite-element analysis based on the HR-pQCT images to predict biomechanical properties (bone strength)⁹. In our previous study, we found that the discriminatory power for vertebral fracture was greater for radial volumetric BMD (vBMD) and microarchitecture by HR-pQCT than that for central aBMD in patients with SLE¹⁰.

In this cross-sectional study, we aimed to (1) evaluate various bone quality measurements, including aBMD by DEXA and bone geometric, densitometric, microarchitectural, and biomechanical measures, by HR-pQCT in female Chinese patients with SLE and organ damage who were undergoing longterm GC therapy, compared with age-matched SLE patients with no organ damage; and (2) investigate the risk factors for deterioration of vBMD and microarchitectural and biomechanical variables in SLE patients with organ damage.

MATERIALS AND METHODS

Patients. Consecutive female patients with SLE who regularly attended the outpatient rheumatology clinic at Prince of Wales Hospital or Alice Ho Miu Ling Nethersole Hospital in Hong Kong were screened during September 2010 and July 2011. Patients were eligible if (1) they fulfilled the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE¹¹; (2) they were receiving prednisone at least 5 mg per day continuously for at least 1 year prior to study entry; and (3) they had at least 1 manifestation of organ damage defined as Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) ≥ 1 ¹². Patients were ineligible if (1) they had a known metabolic disorder that could affect bone metabolism; (2) they were receiving treatment that could affect bone metabolism, including antiresorptive drugs, thyroid or parathyroid hormone, hormonal replacement therapy; or (3) they were pregnant or breastfeeding. A total of 180 patients were screened, and 78 fulfilled our criteria. As a comparative group, 72 age-matched (± 5 yrs) female patients with SLE fulfilling the recruiting criteria but with no organ damage (SDI = 0) were chosen. The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. Written informed consent was obtained from all participants.

Data collection and clinical measurement. Demographic data collected from the study interview included age, body weight, body height, menstru-

al status (age and duration of menopause if applicable), smoking habit, aerobic exercise habits for at least 40 min per week, history of fracture after age 25 years, and family history of osteoporosis and fracture. Body mass index (BMI) was calculated for each participant. Disease duration, comorbidities, use of immunosuppressants (mycophenolate mofetil, azathioprine, cyclosporine A, and cyclophosphamide) and supplements (multivitamins and active form of vitamin D) in the preceding year, and use of GC (duration of use, current dose, cumulative dose, and average dose) during the whole disease course up to entry to the study were collected from medical records. Disease activity was assessed by a validated disease activity measure, the SLE Disease Activity Index (SLEDAI)¹³, and organ damage by the SDI¹². It contains 24 descriptors in 9 organ systems, including clinical and laboratory variables, and measures disease activity of the preceding 10 days. The total SLEDAI score ranges from 0 (no activity) to 105 (maximum activity). The SDI is designed to assess organ damage due to the disease itself or the treatment in 12 organ systems occurring since the onset of SLE and presenting for at least 6 months. The total SDI score ranges from 0 (no damage) to 49 (maximum damage).

25-hydroxy vitamin D [25(OH)D] measurement. Serum levels of 25(OH)D were measured with a commercial ELISA kit (Immunodiagnostic Systems Inc.). All samples were collected at the time of the interview. Vitamin D deficiency was defined as serum level < 25 nmol/l (10 ng/ml), and insufficiency as < 75 nmol/l (30 ng/ml)¹⁴.

aBMD measured by DEXA. aBMD measures of left hip, lumbar spine (L1-L4, anteroposterior view), and nondominant ultradistal radius were performed using the same DEXA equipment in all participants (model 4500A; Hologic). Results were expressed in g/cm^2 and T scores calculated with reference to general population norms of Hong Kong¹⁵.

Bone geometry, vBMD, and microarchitecture measurements. Bone geometry, vBMD, and microarchitecture were measured using a 3D HR-pQCT device (XtremeCT) at the nondominant distal radius (dominant distal radius was scanned in 1 patient because of a history of fracture at distal radius). This system uses a 2D 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 resolution (voxel size) of 82 μm . Details of image acquisition and analysis have been described⁷. The arm of the patient was fixed during the examination in an anatomically formed carbon fiber shell. An anteroposterior scout view was used to define the measurement region. A reference line was manually placed at the endplate of the radius. At the distal radius, 110 CT slices were obtained, thus delivering a 3D representation of roughly 9 mm in the axial direction. The first CT slice was 9.5 mm proximal to the reference line for the distal radius. The entire volume of interest was automatically separated into a cortical and trabecular region using a threshold-based algorithm. The threshold used to discriminate cortical from trabecular bone was set to one-third of the apparent cortical bone density value. Mean cortical thickness was defined as the mean cortical volume divided by the outer bone surface. The outcome variables used in our analyses included area for total bone, cortical, trabecular and estimated cross-sectional area; volumetric bone density ($\text{mg hydroxyapatite}/\text{cm}^3$) for total average (D100), trabecular (Dtrab), and cortical bone (Dcomp); cortical thickness (Ct.Th, μm); and trabecular bone volume fraction (BV/TV, percentage), trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, mm^{-1}), and trabecular separation (Tb.Sp, mm). Derivations and definitions of trabecular variables were described in a previous study⁷. The precision of HR-pQCT at the distal radius demonstrates a coefficient of variation of 0.7% to 1.5% for density and 0.9% to 4.4% for trabecular architecture measurements⁷.

Finite-element analysis. The HR-pQCT images were then subjected to 3D finite-element analysis using Image Processing Language software (Scanco Medical) to derive further measures of bone biomechanical properties (bone strength). All images were segmented and only the voxels that represented bone tissue were converted to equal-size brick elements, resulting in models with 1 to 8 million elements. All elements were given a Young modulus of 10 GPa and a Poisson ratio of 0.3¹⁶. A uniaxial compression in the

longitudinal direction, which approximates to the common loading condition for Colle's fracture of radius, was applied to the distal surface of the radius, to simulate a fall from standing height on the outstretched hand for determining bone biomechanical properties, i.e., axial stiffness and strength of radius. The variables used in our study included bone stiffness (kN/mm), apparent modulus (N/mm²), and estimated failure load (N), computed based on a criterion developed by Pistoia, *et al*¹⁷. With this criterion, it is assumed that failure will occur if the bone tissue equivalent strain exceeds 0.7% for > 2% of the bone tissue. Based on the results of the simulated compression tests at 1% strain, a scaling factor is determined such that the calculated bone tissue equivalent strain meets this criterion. The estimated failure load is then calculated by multiplying the total reaction force calculated from the compression test simulation by this scaling factor.

Statistical analysis. Analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as number (percentage) for categorical data, mean \pm SD for normally distributed data, or median and interquartile range (IQR) for non-normally distributed data. Comparisons between continuous variables were performed by independent-samples t test and between categorical variables by chi-square test. Potential variables associated with bone quality and biomechanical measures were examined first by univariate tests and subsequently by multiple linear regression analysis. Tested variables included age, body height, body weight, BMI, menstrual status, disease duration, SLEDAI, SDI, duration of GC use, average GC dose, cumulative GC dose, use of immunosuppressants, and level of 25(OH)D. Univariate correlations for continuous variables were examined by Pearson's or Spearman's correlation for normally or non-normally distributed data, respectively. For categorical variables, Student's t test or Mann-Whitney U test was used, depending on the data distribution. Univariate analysis was used as a screening tool to select the most potential variables in the multiple regression analysis. Variables with $p < 0.05$ in the univariate analysis were then entered into the multiple linear regression analysis to determine the independent explanatory factors for deterioration of bone quality.

RESULTS

Demographic and clinical characteristics and use of medications. SLE patients with organ damage had a mean age of 45.3 years, and over half were postmenopausal, with a mean duration of menopause of 4 years. Patients with damage had a median disease duration of 13.6 years and mild disease activity at the time of study entry. The median SDI score was 1, ranging from 1 to 5. Neuropsychiatric damage (25.6%), ocular damage (24.4%), pulmonary damage (14.1%), and musculoskeletal damage (14.1%) were the most common deficits comprising the SDI. Arthritis and nephritis were the most common features involving major organs in our cohort. Over half the patients with damage had arthritis (51.3%) and nephritis (66.7%). Serum level of 25(OH)D was low, with 98.7% of patients with damage diagnosed as having vitamin D insufficiency, but none as vitamin D deficiency. Table 2 shows the medication use of the study cohort. Patients with damage had a median duration of GC use of 10.4 years, with current dose 5 mg and cumulative dose 22.3 g. Over half the patients with damage had received multivitamins and a certain proportion were treated with immunosuppressant in the preceding year.

Compared with patients with damage, SLE patients with no organ damage had significantly shorter disease duration ($p = 0.01$). Other variables related to demographic and clinical characteristics and use of medications were not significantly different between these 2 groups.

Table 1. Demographic and clinical characteristics of the study cohort. Results are expressed as mean \pm SD or median (interquartile range) unless otherwise indicated.

Variables	Cases (SDI > 0; n = 78)	Comparative Group (SDI = 0; n = 72)	p
Age, yrs	45.3 \pm 9.6	43.1 \pm 8.8	0.15
Height, m	1.6 \pm 0.06	1.58 \pm 0.05	0.17
Weight, kg	55.3 \pm 9.1	57.8 \pm 11	0.13
Body mass index, kg/m ²	22.5 \pm 3.7	23.2 \pm 4.2	0.36
Postmenopausal, n (%)	42 (53.8)	28 (38.9)	0.07
Duration of menopause, yrs	4 (2, 10)	2 (1, 6)	0.06
Currently smoking, n (%)	4 (5.9)	5 (6.9)	0.74
Aerobic exercise \geq 40 min/wk, n (%)	17 (21.8)	25 (34.7)	0.08
History of fracture, n (%)	5 (6.4)	5 (6.9)	0.86
Family history of osteoporosis, n (%)	5 (6.4)	3 (4.2)	0.72
Family history of fracture, n (%)	12 (15.4)	14 (19.4)	0.51
Clinical characteristics			
Disease duration, yrs	13.6 (7.1, 18.6)	10.4 (5.7, 15)	0.01
SLEDAI	2 (0, 4)	2 (0, 4)	0.58
SDI	1 (1, 2)	0	< 0.001
Neuropsychiatric damage, n (%)	20 (25.6)	0	< 0.001
Ocular damage, n (%)	19 (24.4)	0	< 0.001
Pulmonary damage, n (%)	11 (14.1)	0	< 0.001
Musculoskeletal damage, n (%)	11 (14.1)	0	< 0.001
Arthritis, n (%)	40 (51.3)	47 (65.3)	0.08
Nephritis, n (%)	52 (66.7)	48 (66.7)	1
25(OH)d, nmol/l	48.5 \pm 11.1	47.9 \pm 12.5	0.72

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; 25(OH)D: 25-hydroxyvitamin D.

Table 2. Use of medications by study cohort in the preceding year. Results are expressed as median (interquartile range) unless otherwise indicated.

Variables	Cases (SDI > 0; n = 78)	Comparative Group (SDI = 0; n = 72)	p
Glucocorticoid use*			
Duration, yrs	10.4 (4.9, 14.6)	9.4 (5.6, 14.6)	0.16
Current dose, mg/day	5 (5, 7.5)	5 (5, 7.5)	0.57
Cumulative dose, g	22.3 (11.9, 34.7)	17.3 (11.2, 26.8)	0.052
Average dose, mg/day	6.1 (4.6, 8.0)	6 (4.4, 8.8)	0.7
MMF user, n (%)	11 (14.1)	11 (15.3)	0.84
Azathioprine user, n (%)	19 (24.4)	17 (23.6)	0.92
Cyclosporine A user, n (%)	9 (11.5)	12 (16.7)	0.37
Cyclophosphamide user, n (%)	1 (1.3)	0	1
Multivitamin user, n (%)	47 (60.3)	53 (73.6)	0.08
Active vitamin D user, n (%)	8 (10.3)	2 (2.8)	0.1

* Assessed for the whole disease course up to entry to study. MMF: mycophenolate mofetil.

Table 3. Bone geometric, densitometric, microarchitectural, and biomechanical variables by the HR-pQCT. Results are expressed as mean \pm SD.

Variables	Cases (SDI > 0; n = 78)	Comparative Group (SDI = 0; n = 72)	p	p*
aBMD, g/cm ²				
Total hip	0.81 \pm 0.12	0.87 \pm 0.12	0.003	0.003
Lumbar spine (L1-L4)	0.91 \pm 0.15	0.95 \pm 0.14	0.08	0.12
Ultradistal radius	0.43 \pm 0.07	0.42 \pm 0.06	0.67	0.58
Geometry, mm ²				
Total area	207.1 \pm 34.2	213 \pm 30	0.32	0.38
Cortical area	53.4 \pm 11.9	55.8 \pm 9.5	0.16	0.22
Trabecular area	151.1 \pm 34.5	154.4 \pm 30.1	0.53	0.57
Cross-sectional area	277.8 \pm 40.8	287.5 \pm 39.9	0.15	0.16
vBMD, mg HA/cm ³				
D100	359.4 \pm 80.9	367.9 \pm 68.2	0.49	0.47
Dcomp	934.8 \pm 65.1	944.3 \pm 48.4	0.32	0.42
Dtrab	133.7 \pm 44.2	141.6 \pm 39.5	0.25	0.22
Dmeta	192.0 \pm 42.2	200 \pm 37.6	0.23	0.21
Dinn	93.2 \pm 46.7	101 \pm 42	0.28	0.24
Microarchitecture				
Ct.Th, mm	0.9 \pm 0.2	0.92 \pm 0.16	0.33	0.37
BV/TV	0.11 \pm 0.04	0.12 \pm 0.03	0.25	0.22
Tb.N, 1/mm	1.5 \pm 0.3	1.5 \pm 0.3	0.92	0.84
Tb.Th, mm	0.07 \pm 0.01	0.08 \pm 0.02	0.04	0.05
Tb.Sp, mm	0.61 \pm 0.17	0.59 \pm 0.13	0.56	0.52
Biomechanical properties				
Stiffness, kN/mm	66.0 \pm 14.6	69.9 \pm 11.6	0.08	0.08
Estimated failure load, N	2644.1 \pm 547.3	2790.2 \pm 426.8	0.07	0.09
Apparent modulus, N/mm ²	2176.9 \pm 510.7	2225.8 \pm 426.5	0.53	0.52

* Adjusted for disease duration. HR-pQCT: high-resolution peripheral quantitative computed tomography; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; vBMD: volumetric bone mineral density; aBMD: areal BMD; D100: average bone density; Dcomp: cortical bone density; Dtrab: trabecular bone density; Dmeta: metatrabecular bone density; Dinn: inner trabecular bone density; Ct.Th: cortical thickness; BV/TV: trabecular bone volume/tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; HA: hydroxyapatite.

Bone density, microarchitecture, and biomechanical properties by DEXA and HR-pQCT. Table 3 gives data for aBMD measured by DEXA, bone geometry, vBMD,

microarchitecture, and biomechanical properties assessed by HRCT and finite-element analysis in SLE patients with organ damage compared to patients without damage.

Among patients with organ damage, 38 (48.7%) were osteopenic and 9 (11.5%) osteoporotic at either total hip or lumbar spine. The corresponding prevalence in patients without damage was 23 (31.9%) and 4 (5.6%), respectively. The prevalence of osteopenia at either total hip or lumbar spine was significantly higher in patients with organ damage ($p = 0.037$). Patients with damage had trends of deteriorated bone geometry, BMD, microarchitecture, and biomechanical properties compared to patients without damage, and the decrease in aBMD at total hip and trabecular thickness at distal radius achieved a significant difference.

Risk factors for deterioration of bone geometry, vBMD, microarchitecture, and biomechanical properties. Univariate analysis (Tables 4 and 5) was used to screen for selection of the most potential variables that might relate to deterioration of bone quality for the subsequent multiple regression analysis. There was no difference in bone quality between patients with and those without other damage such as neuropsychiatric, ocular, pulmonary, or musculoskeletal damage. As well, no difference of bone quality was found between patients with and those without treatment with immunosuppressant in the preceding year (data not shown).

Variables with $p < 0.05$, such as age, body height, body weight, SLEDAI, SDI, postmenopausal status, nephritis, and arthritis, were then entered into the multiple linear regression analysis to determine the independent explanatory factors for deterioration of bone quality (Tables 6A, 6B). During multiple linear regression, body height was found to be independently associated with bone geometry (total area,

trabecular area, and cross-sectional area), while body weight was associated with cortical area, bone stiffness, and estimated failure load. The influences of age and postmenopausal status were limited to Tb.Sp and apparent modulus, respectively. Cumulative organ damage (SDI) was the only clinical variable that correlated consistently to deterioration of cortical area, vBMD (D100, Dcomp, Dtrab, Dmeta, and Dinn), and bone microarchitecture (Ct.Th, BV/TV, Tb.N, and Tb.Th). However, nephritis seemed to correlate positively with total area and trabecular area. SLEDAI or arthritis did not influence any bone quality during the multiple regression analysis (data not shown).

DISCUSSION

The use of high-resolution imaging techniques such as HR-pQCT allows us to investigate the microarchitectural and biomechanical properties of peripheral bone, which are emerging determinants of bone quality and fracture risks⁷. We previously showed that densitometric and microarchitectural measures assessed by HR-pQCT had greater discriminatory power for fracture in patients with SLE¹⁸. In this study, we evaluated bone geometry, vBMD, microarchitecture, and biomechanical properties by HR-pQCT in SLE patients with organ damage, compared with a group with no damage, and investigated factors correlated with bone quality assessed by HR-pQCT in SLE patients with organ damage. We found that increase in organ damage was independently correlated with densitometric and microarchitectural measures in patients with organ damage.

Table 4. Univariate analysis: correlation between HR-pQCT measures and demographic and clinical variables (continuous variables). Results are expressed as correlation coefficient (r).

Variables	Geometry			vBMD						Microarchitecture				Biomechanical Properties			
	Total Area	Cortical Area	Trabecular Area	CSA	D100	Dcomp	Dtrab	Dmeta	Dinn	Ct.Th	BV/TV	Tb.N	Tb.Th	Tb.Sp	Stiffness	Estimated Failure Load	Apparent Modulus
Age	-0.12	-0.14	-0.08	-0.16	-0.18	-0.19	-0.28*	-0.29	-0.68	-0.12	-0.28*	-0.24*	-0.2**	0.26	-0.32**	-0.31**	-0.22
Body height	0.46**	0.17	0.42**	0.45**	-0.08	0	0.12	0.12	0.11	-0.03	0.12	0.06	0.1	-0.08	0.18	0.16	-0.11
Body weight	0.32**	0.33**	0.24*	0.26*	0.06	0.10	0.11	0.09	0.13	0.18	0.12	0.16	0.05	-0.15	0.26*	0.27*	0.08
Body mass index	0.1	0.21	0.04	0.06	0.04	0.05	0.03	0.01	0.05	0.15	0.04	0.11	-0.01	-0.09	0.13	0.14	0.07
Disease duration	-0.05	-0.02	-0.06	0.02	0.08	-0.06	0.09	0.13	0.07	0.01	0.1	0.04	0.14	-0.04	0.11	0.09	0.06
SLEDAI	0.24*	0.06	0.23*	0.21	-0.04	-0.08	0.18	0.18	0.19	-0.06	0.18	0.22	0.08	-0.22	0.04	0.05	-0.07
SDI	-0.16	-0.32**	-0.08	-0.05	-0.27*	-0.30**	-0.28**	-0.28*	-0.28*	-0.28**	-0.28**	-0.25*	-0.24*	0.27*	-0.27*	-0.28*	-0.22
25(OH)D	0.11	0	0.1	0.2	-0.06	-0.13	0.01	-0.04	0.03	-0.07	0	0.01	0.01	-0.02	-0.11	-0.05	-0.16
Duration of GC use	0.03	-0.15	0.05	0.08	-0.1	-0.18	0	0.04	-0.02	-0.14	0	0	0.03	0.01	-0.05	-0.06	-0.10
Average GC dose	-0.09	-0.04	-0.07	-0.06	0	0.03	-0.03	-0.05	-0.01	0.02	-0.03	-0.01	-0.04	0.02	-0.09	-0.05	-0.07
Cumulative GC dose	-0.01	-0.17	-0.02	0.07	-0.06	-0.15	0.07	0.09	0.06	-0.11	0.07	0.12	0.05	-0.10	-0.13	-0.11	-0.15

* $p < 0.05$. ** $p < 0.01$; HR-pQCT: high-resolution peripheral quantitative computed tomography; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; GC: glucocorticoid; CSA: cross-sectional area; vBMD: volumetric bone mineral density; D100: average bone density; Dcomp: cortical bone density; Dtrab: trabecular bone density; Dmeta: metatrabecular bone density; Dinn: inner trabecular bone density; Ct.Th: cortical thickness; BV/TV: trabecular bone volume/tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation.

Table 5. Relationship between HR-pQCT measures and demographic and clinical variables (categorical variables). Results are expressed as mean \pm SD.

Variables	Postmenopausal		Nephritis		Arthritis	
	Yes (n = 42)	No (n = 36)	Yes (n = 52)	No (n = 26)	Yes (n = 40)	No (n = 38)
Geometry						
Total area	204.5 \pm 32	211.6 \pm 36.6	215.7 \pm 33**	191.7 \pm 31.3	202.0 \pm 33.1	213.8 \pm 34.6
Cortical area	51.2 \pm 10.8	55.8 \pm 12.7	52.9 \pm 11.8	54.4 \pm 12.2	51.6 \pm 11	55.1 \pm 12.7
Trabecular area	149.3 \pm 31.8	153.2 \pm 37.8	159.3 \pm 33.9*	134.8 \pm 30.2	146.7 \pm 31.4	155.7 \pm 37.4
Cross-sectional area	273.2 \pm 37.3	283.5 \pm 44.7	284.6 \pm 38.6*	264.7 \pm 42.5	271.0 \pm 39.5*	285 \pm 41.6
vBMD						
D100	345.1 \pm 81.7	376.0 \pm 77.9	350.1 \pm 83.1	377.9 \pm 74.5	352 \pm 81.1	367.1 \pm 81.1
Dcomp	920.9 \pm 63.4*	950.9 \pm 64.3	925.1 \pm 70	954.2 \pm 49.9	929.7 \pm 68.8	940.1 \pm 61.5
Dtrab	124.9 \pm 46.6	144.0 \pm 39.3	137.0 \pm 46.4	127.1 \pm 39.5	126.3 \pm 46.1	141.4 \pm 41.2
Dmeta	182.5 \pm 43.4*	203 \pm 38.4	195.1 \pm 43.3	185.8 \pm 39.9	185.6 \pm 45.1	198.6 \pm 38.4
Dinn	84.8 \pm 50.2	102.9 \pm 40.7	96.6 \pm 49.2	86.2 \pm 41.3	85.1 \pm 48.4	101.6 \pm 43.8
Microarchitecture						
Ct.Th	0.86 \pm 0.19	0.93 \pm 0.22	0.87 \pm 0.2	0.95 \pm 0.21	0.88 \pm 0.19	0.91 \pm 0.22
BVTV	0.1 \pm 0.04	0.12 \pm 0.03	0.11 \pm 0.04	0.11 \pm 0.03	0.11 \pm 0.03	0.12 \pm 0.03
Tb.N	1.5 \pm 0.3	1.6 \pm 0.3	1.6 \pm 0.3	1.5 \pm 0.3	1.5 \pm 0.3	1.6 \pm 0.3
Tb.Th	0.07 \pm 0.01*	0.08 \pm 0.01	0.07 \pm 0.02	0.07 \pm 0.01	0.07 \pm 0.01	0.07 \pm 0.02
Tb.Sp	0.63 \pm 0.19	0.58 \pm 0.14	0.6 \pm 0.17	0.63 \pm 0.16	0.64 \pm 0.17	0.58 \pm 0.16
Biomechanical properties						
Stiffness	62 \pm 13.2**	71.1 \pm 14.8	66.4 \pm 14.2	65.3 \pm 15.4	63.6 \pm 12.3	68.7 \pm 16.4
Estimated failure load	2472.9 \pm 501.9**	2885.7 \pm 533.7	2665 \pm 530	2604 \pm 588.4	2549.2 \pm 468.9	2744.1 \pm 610.1
Apparent modulus	2070.9 \pm 467.4*	2307.9 \pm 537.9	2143 \pm 526.6	2242.3 \pm 482	2141.9 \pm 441.2**	2213.9 \pm 579

HR-pQCT: high-resolution peripheral quantitative computed tomography; vBMD: volumetric bone mineral density; D100: average bone density; Dcomp: cortical bone density; Dtrab: trabecular bone density; Dmeta: metatrabecular bone density; Dinn: inner trabecular bone density; Ct.Th: cortical thickness; BV/TV: trabecular bone volume/tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation.

Bone loss and fracture in SLE are multifactorial. The traditional risk factors associated with reduced aBMD in SLE include female sex, older age, white or Asian race, lower BMI, early menopause, and a personal or maternal history of fracture and others. SLE-specific risk factors include active disease status, cumulative organ damage, sun avoidance inducing vitamin D deficiency, therapy-related premature menopause, and chronic GC use^{19,20}. It has been documented that organ damage in SLE was significantly associated with reduced aBMD^{21,22}. In our study, we selected SLE patients with at least 1 expression of organ damage, who were at a higher risk of bone loss. This is the first study to investigate the correlation between organ damage in SLE and vBMD, bone microarchitecture, and biomechanical properties. We found that increasing organ damage was the only clinical variable consistently correlated with deterioration of vBMD and bone microarchitecture after adjustment for other risk factors. The correlations between organ damage and vBMD and bone microarchitecture assessed by HR-pQCT demonstrate the potential use of this modality to further our knowledge of the underlying mechanism of bone deterioration in SLE.

Organ damage is a summary of longterm irreversible changes related to the disease itself and to related therapy¹², both of which could be responsible for impairment of bone quality in SLE. As a systemic autoimmune inflammatory disorder, the chronic elevated levels of inflammatory cytokines in active SLE, such as tumor necrosis factor- α

(TNF- α), interleukin 1 (IL-1), and IL-6, could increase the rate of bone resorption through activation of osteoclastogenesis²³, leading to loss of bone density and deterioration of bone microarchitecture. The effect of SLE disease itself on bone quality is supported by the finding that premenopausal patients with early disease and no prior use of GC still had lower aBMD at the spine²⁴. On the other hand, studies have shown that organ damage was one of the risk factors for lower aBMD among SLE patients who were on GC therapy^{5,21,22,25,26}. GC is the mainstay of therapy for SLE, with the dose that is prescribed primarily depending on disease severity and distribution of organ damage. However, numerous adverse side effects may result from GC use. To evaluate the association between GC use and organ damage in patients with SLE, Petri, *et al* investigated patients with SLE from the Hopkins Lupus Cohort and found that cumulative GC dose was significantly associated with many manifestations of organ damage such as osteoporotic fracture, coronary artery disease, cataracts, and avascular necrosis; among these, osteoporotic fracture was the most strongly influenced^{27,28}. The mechanism of GC-induced bone loss is mainly due to its transient increase of osteoclast lifespan and its continual induction of apoptosis of osteoblasts and osteocytes and suppression of osteoblastogenesis, leading to uncoupled resorption rate and formation rate²⁹. Longterm GC therapy significantly and promptly increases bone loss and fracture risk³⁰. Therefore, the predominant role of organ damage (by SDI) in the deterioration of bone

Table 6A. Multiple analysis for independent variables associated with deterioration of bone quality (HR-pQCT measures). Only significant variables are shown. Results are expressed as coefficients (β) and 95% CI and p value.

Variables	Geometry				D100	Dcomp	vBMD Dtrab	Dmeta	Dinn
	Total Area	Cortical Area	Trabecular Area	Cross-sectional Area					
Age									
Body height	169.9 (49.9, 289.9; p = 0.006)		160.1 (37.8, 282.5; p = 0.04)	271.6 (128.1, 415; p < 0.001)					
Body weight		0.31 (0.02, 0.6; p = 0.02)							
Postmenopausal status									
SDI		-3.9 (-6.5, -1.2; p = 0.004)			-36.9 (-71.6, -2.3; p = 0.02)	-20.1 (-35.4, -4.9; p = 0.01)	-10.8 (-21.4, -0.1; p = 0.048)	-10.4 (-20.6, -0.2; p = 0.04)	-13.0 (-23.7, -2.3; p = 0.02)
Nephritis	17.6 (3.1, 32; p = 0.02)		19.5 (4.3, 34.8; p = 0.01)						
R ²	0.3	0.19	0.23	0.26	0.08	0.13	0.1	0.12	0.07
Constant	-104.9	42.2	-90.5	-162.9	398.3	978.4	183.3	244	115

HR-pQCT: high-resolution peripheral quantitative computed tomography; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; vBMD: volumetric bone mineral density; D100: average bone density; Dcomp: cortical bone density; Dtrab: trabecular bone density; Dmeta: metatrabecular bone density; Dinn: inner trabecular bone density.

Table 6B. Multiple analysis for independent variables associated with deterioration of bone quality (HR-pQCT measures). Only significant variables are shown. Results are expressed as coefficients (β) and 95% CI and p value.

Variables	Microarchitecture				Tb.Sp	Stiffness	Biomechanical Properties	
	Ct.Th	BV/TV	Tb.N	Tb.Th			Estimated Failure Load	Apparent Modulus
Age					0.01 (0, 0.01; p = 0.049)			
Body height								
Body weight						0.39 (0.04, 0.78; p = 0.04)	15.2 (0.9, 29.4; p = 0.03)	
Postmenopausal status								-239.4 (-470.2, -8.5; p = 0.04)
SDI	-0.07 (-0.11, -0.02; p = 0.006)	-0.01 (-0.02, 0; p = 0.048)	-0.01 (-0.02, 0; p = 0.048)	-0.004 (-0.007, 0; p = 0.046)				
Nephritis								
R ²	0.1	0.1	0.09	0.12	0.12	0.21	0.24	0.06
Constant	1	0.15	1.9	0.08	-0.39	60.3	2.45	2.35

HR-pQCT: high-resolution peripheral quantitative computed tomography; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; Ct.Th: cortical thickness; BV/TV: trabecular bone volume/tissue volume; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation.

quality might at least in part reflect the negative effect of GC on bone.

Few studies have found a relationship between disease activity or damage and aBMD. Dhillon and colleagues found no correlation between disease activity, measured by British Isles Lupus Assessment Group scores, and lumbar spine aBMD³¹. A similar finding was reported by Hansen, *et al* in a prospective study examining consecutive measurements of aBMD of 37 SLE patients, in which disease activity was measured by SLEDAI, and no correlation was found at baseline or at first and second year followup³². In our study, disease activity (by SLEDAI) had no significant asso-

ciation with bone quality or strength. This finding is not unexpected, since the majority of disease activity measures are limited to assessment of disease status during a short period of time, restricting its utility in predicting longterm outcomes such as bone quality, particularly in a condition such as SLE, which usually has a fluctuating disease course.

Photosensitivity is a common feature of SLE that is usually associated with avoidance of ultraviolet light, which decreases synthesis of vitamin D. Low serum 25(OH)D level predisposes the patient to secondary hyperparathyroidism, an additional risk for osteoporosis in SLE³³. There is a high prevalence of hypovitaminosis D in South Asia³⁴.

The high prevalence of insufficiency of serum vitamin D in our cohort was comparable with that in women of child-bearing age in Hong Kong³⁵, although our patients were older (mean age 45 vs 28 years). We did not find significant correlations between serum 25(OH)D and bone quality. This could be partly explained by the fact that 70% of our patients received vitamin D supplements (multivitamin or active vitamin D) in the preceding year. Disease activity, found to be inversely associated with level of vitamin D³, was relatively low in our cohort. Since patients were recruited over a period of almost a year, the influence of seasonal change of vitamin D level should be considered. Finally, the effects of GC therapy on vitamin D metabolism remain inconclusive³⁰.

Our study has several limitations. First, it was a cross-sectional study. A longitudinal study is needed to determine the cause-effect relationship between organ damage and bone quality. Second, the sample size was relatively small and the number of patients with symptomatic fracture was small, and we did not have data related to asymptomatic vertebral fracture. Therefore, the correlation between organ damage and fracture could not be examined. Since there are no data related to precision of HR-pQCT in patients with SLE, the precision we noted was referred from the study of 256 healthy women by Boutroy, *et al*⁷. However, hand positioning and imaging analysis were acceptable in the patients with SLE. Serum levels of 25(OH)D were measured in different seasons because of the long period of patient recruitment, which limited the prediction ability and interpretation of the influence of 25(OH)D on bone. It would be more reliable to measure the mean 25(OH)D level during a certain time period to accurately determine its effect on a longterm cumulative variable such as bone quality. The lack of information for serum creatinine and glomerular filtration rate in the cohort at time of study entry prevented investigation of correlations between bone quality and renal function. Similarly, the lack of data for erythrocyte sedimentation rate prohibited study of the relationship between bone quality and inflammation. Finally, we could not demonstrate the respective contributions of disease-induced damage and GC therapy-induced damage on bone deterioration, because all patients were receiving GC; GC remains the mainstay of treatment for SLE in Hong Kong, thus a GC-naive group is likely to be a very small sample.

Cumulative organ damage was negatively correlated with vBMD and bone microarchitecture in female patients with SLE with organ damage receiving longterm GC. HR-pQCT provides insight into the underlying mechanism of bone loss in SLE that may be due to disease damage and partly to the chronic use of GC. Therapies without deleterious effect on bone that can effectively control disease activity and at the same time prevent organ damage are needed. Future longitudinal studies, and studies in particular including GC-naive SLE populations in multiple regions, are

needed to monitor bone quality changes during the course of treatment in SLE and to distinguish the respective contribution of disease itself and GC therapy on bone deterioration.

REFERENCES

1. Lee C, Ramsey-Goldman R. Osteoporosis in systemic lupus erythematosus mechanisms. *Rheum Dis Clin North Am* 2005;31:363-85, viii.
2. Li EK, Tam LS, Young RP, Ko GT, Li M, Lau EM. Loss of bone mineral density in Chinese pre-menopausal women with systemic lupus erythematosus treated with corticosteroids. *Br J Rheumatol* 1998;37:405-10.
3. Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. *Lupus* 2005;14:106-12.
4. Pineau CA, Urowitz MB, Fortin PJ, Ibanez D, Gladman DD. Osteoporosis in systemic lupus erythematosus: Factors associated with referral for bone mineral density studies, prevalence of osteoporosis and factors associated with reduced bone density. *Lupus* 2004;13:436-41.
5. Becker A, Fischer R, Scherbaum WA, Schneider M. Osteoporosis screening in systemic lupus erythematosus: Impact of disease duration and organ damage. *Lupus* 2001;10:809-14.
6. Ammann P, Rizzoli R. Bone strength and its determinants. *Osteoporos Int* 2003;14 Suppl 3:S13-8.
7. Boutroy S, Buxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 2005;90:6508-15.
8. MacNeil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 2007;29:1096-105.
9. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Buxsein ML, Delmas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res* 2008;23:392-9.
10. Li EK, Zhu TY, Tam LS, Hung VW, Griffith JF, Li TK, et al. Bone microarchitecture assessment by high-resolution peripheral quantitative computed tomography in patients with systemic lupus erythematosus taking corticosteroids. *J Rheumatol* 2010;37:1473-9.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
12. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363-9.
13. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992;35:630-40.
14. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-81.
15. Lynn HS, Lau EM, Au B, Leung PC. Bone mineral density reference norms for Hong Kong Chinese. *Osteoporos Int* 2005;16:1663-8.
16. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Image-based micro-finite-element modeling for improved distal radius strength diagnosis: Moving from bench to bedside. *J Clin Densitom* 2004;7:153-60.
17. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional

- peripheral quantitative computed tomography images. *Bone* 2002;30:842-8.
18. Li EK, Zhu TY, Tam LS, Hung VW, Griffith JF, Li TK, et al. Bone microarchitecture assessment by high-resolution peripheral quantitative computed tomography in patients with systemic lupus erythematosus taking corticosteroids. *J Rheumatol* 2010;37:1473-9.
 19. Di Munno O, Mazzantini M, Delle Sedie A, Mosca M, Bombardieri S. Risk factors for osteoporosis in female patients with systemic lupus erythematosus. *Lupus* 2004;13:724-30.
 20. Yee CS, Crabtree N, Skan J, Amft N, Bowman S, Situnayake D, et al. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. *Ann Rheum Dis* 2005;64:111-3.
 21. Sinigaglia L, Varena M, Binelli L, Zucchi F, Ghiringhella D, Gallazzi M, et al. Determinants of bone mass in systemic lupus erythematosus: A cross-sectional study on premenopausal women. *J Rheumatol* 1999;26:1280-4.
 22. Almehed K, Forsblad d'Elia H, Kvist G, Ohlsson C, Carlsten H. Prevalence and risk factors of osteoporosis in female SLE patients — Extended report. *Rheumatology* 2007;46:1185-90.
 23. Lacativa PG, Farias ML. Osteoporosis and inflammation. *Arq Bras Endocrinol Metabol* 2010;54:123-32.
 24. Teichmann J, Lange U, Stracke H, Federlin K, Bretzel RG. Bone metabolism and bone mineral density of systemic lupus erythematosus at the time of diagnosis. *Rheumatol Int* 1999; 18:137-40.
 25. Lee C, Almagor O, Dunlop DD, Manzi S, Spies S, Chadha AB, et al. Disease damage and low bone mineral density: An analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. *Rheumatology* 2006;45:53-60.
 26. Lakshminarayanan S, Walsh S, Mohanraj M, Rothfield N. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. *J Rheumatol* 2001;28:102-8.
 27. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801-8.
 28. Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: An update. *Arthritis Care Res* 1995;8:137-45.
 29. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med* 2011;365:62-70.
 30. Lafage-Proust MH, Boudignon B, Thomas T. Glucocorticoid-induced osteoporosis: Pathophysiological data and recent treatments. *Joint Bone Spine* 2003;70:109-18.
 31. Dhillon VB, Davies MC, Hall ML, Round JM, Ell PJ, Jacobs HS, et al. Assessment of the effect of oral corticosteroids on bone mineral density in systemic lupus erythematosus: A preliminary study with dual energy x ray absorptiometry. *Ann Rheum Dis* 1990;49:624-6.
 32. Hansen M, Halberg P, Kollerup G, Pedersen-Zbinden B, Horslev-Petersen K, Hyldstrup L, et al. Bone metabolism in patients with systemic lupus erythematosus. Effect of disease activity and glucocorticoid treatment. *Scand J Rheumatol* 1998;27:197-206.
 33. Arya V, Bhambri R, Godbole MM, Mithal A. Vitamin D status and its relationship with bone mineral density in healthy Asian Indians. *Osteoporos Int* 2004;15:56-61.
 34. Lips P. Vitamin D status and nutrition in Europe and Asia. *J Steroid Biochem Mol Biol* 2007;103:620-5.
 35. Woo J, Lam CW, Leung J, Lau WY, Lau E, Ling X, et al. Very high rates of vitamin D insufficiency in women of child-bearing age living in Beijing and Hong Kong. *Br J Nutr* 2008;99:1330-4.