Lumbar spine bone mineral density predicts endothelial reactivity in patients with systemic lupus erythematosus

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Abstract

Objective

To explore whether endothelial function is related to bone mineral density (BMD) in patients with systemic lupus erythematosus (SLE).

Methods

Consecutive adult SLE patients and age-, sex-, BMI- and smoking-status-matched healthy controls were studied. Subjects with hypertension, hyperlipidemia, diabetes mellitus, renal impairment, dysthyroidism, history of or treatment for cardiovascular and cerebrovascular disorders, antiphospholipid syndrome, positive antiphospholipid antibodies or bone loss were excluded. Endothelial function was assessed by measuring flow-mediated dilatation (FMD) at the brachial artery and carotid intima-media thickness (IMT) by ultrasound. Lumbar and hip BMD were measured by dual-energy x-ray absorptiometry. Fasting blood samples were assayed for atherogenic index and high sensitivity C-reactive protein (hsCRP). Regression models were constructed to study the relationship between FMD and BMD.

Results

One hundred and ten subjects (55 SLE and 55 matched healthy controls) were studied. While there were no differences between SLE patients and controls in menopausal status, blood pressure, atherogenic index, carotid IMT and BMD, SLE patients had significantly poorer FMD even after adjustment for age, gender, smoking and baseline brachial artery diameter. Also, SLE patients with lumbar osteopenia had significantly lower FMD than those with normal BMD. Multivariate regression revealed that lower FMD was associated with lower lumbar BMD and higher serum hsCRP in SLE patients, but these relationships were absent amongst healthy controls.

Conclusions

Lumbar vertebral BMD predicted endothelial reactivity in SLE patients without clinically-overt bone loss and atherosclerosis. Thus, early atherosclerotic disease should be considered in lupus patients especially if vertebral bone loss is evident.

Key words

osteoporosis, inflammation, bone loss, endothelial dysfunction, atherosclerosis, SLE

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Introduction

The association between atherosclerosis and bone loss has been increasingly studied in the past few years. Emerging data from a number of biological studies has led to the belief that atherogenesis and bone turnover are inter-related and tightly regulated processes (1, 2). Recently, a few clinical observational studies have echoed these biological observations by demonstrating an association between increased cardiovascular events and low bone mineral density (BMD) in different patient cohorts and in the general population (3, 4). Intriguingly, carotid intima-media thickness (IMT), a surrogate marker of cardiovascular events, has been shown to independently predict BMD in a cohort of apparently healthy postmenopausal women (5). This finding underscores the plausibility that physiological alterations leading to both pathological processes may have set in even before the occurrence of clinical cardiovascular and bone loss events.

Osteoporosis and cardiovascular disease are two major categories of damage accrued in patients with systemic lupus erythematosus (SLE). Although aging, use of glucocorticoids and other immunosuppressive agents and possibly inflammation (6) and oxidative stress (7) are believed to be partially responsible for bone loss and cardiovascular disease in SLE, few studies have explored the relationship between these two sequelae. First reported in a subgroup analysis of 13 lupus patients who underwent electron-beam computed tomography scanning, coronary artery calcium score was shown to be significantly associated with lower lumbar spine BMD without adjustment for potential confounders (8). To extend this observation, a recent cross-sectional analysis of 94 lupus patients demonstrated that the degree of coronary calcification was associated with lower whole body BMD and disease duration of SLE (9).

While these uncontrolled clinical observations suggest that common pathological processes lead to bone loss and atherosclerosis in SLE patients, vascular calcification occurs relatively late in the process of atherogenesis (10) and coincidental bone loss may have resulted from chronic exposure to predisposing factors. Further elucidation of the association between these complications requires correlation of early pathophysiological changes in the vascular system to subclinical bone loss in SLE patients without clinically overt cardiovascular and bone disease, and comparison with healthy controls matched for cardiovascular risk factors. Accordingly, we measured in these patient groups indexes of bone loss and premature vascular disease, including endothelial reactivity, a non-invasive measure of endothelial dysfunction and established surrogate biophysical marker of early atherosclerosis (10-12). With proper control of potential confounding factors such as age, sex, duration of the illness, smoking, menopausal state, body mass index (BMI) and certain immunosuppressant use including glucorticoids, cyclophosphamide (CYC) and cyclosporine, the existence of a correlation between endothelial dysfunction and bone loss will be informative for clinicians to be alerted to early vascular pathology if SLE patients have suboptimal bone density.

Patients and methods

Adult patients (age ≥21) who satisfied the American College of Rheumatology (ACR) classification criteria for SLE were identified. Patients with a history of and/or treatment for cerebrovascular and cardiovascular disease, hyperlipidaemia, hypertension, diabetes mellitus, dysthyroidism, renal impairment (serum creatinine >120 μmol/L), positive anti-phospholipid antibodies (anticardiolipin and anti-β2-glycoprotein I IgG/IgM antibodies and lupus anticoagulant) and anti-phospholipid antibody syndrome were excluded. Patients on anticoagulation, antiplatelet agents, anti-osteoporotic agents except calcium and vitamin D were not also eligible.

We assessed endothelial reactivity by measuring flow-mediated dilatation (FMD) at the brachial artery using the Prosound Alpha-10 ultrasound system (Aloka Inc., Tokyo, Japan). A 10 MHz linear array probe, steadied by a stereotactic clamp which allowed fine positional adjustment, was used to image

the brachial artery and position electronic tracking gates at the media-adventitia interface of opposing arterial walls. eTRACKING implemented in this equipment uses radiofrequency signals from the tracked B-mode images to provide measurement of vessel distension in real time to 0.01 mm accuracy (13). Reactive hyperemia was induced by inflation of a pneumatic cuff placed around the proximal forearm to a pressure of 50 mmHg above the systolic blood pressure for 5 minutes. Rapid inflation and deflation was achieved using the E20 Rapid Cuff Inflator (D. E. Hokanson Inc., Bellevue, WA). Proprietary FMD software provided a continuous graphical display of minute vasodilatation from baseline, cuff occlusion, vasodilation and recovery, and automatically calculated parameters such as vessel diameter at maximum dilatation and % FMD. Thus, manual measurements of brachial artery diameter were not required, and no post-processing of the raw data was required. All FMD studies were performed after abstention from food and exercise for 12 hours, coffee and tea for 24 hours and alcohol for 48 hours. Although commonly used vasoactive drugs may not significantly influence brachial reactivity, patients were nevertheless asked to discontinue calcium channel and beta blockers, angiotensin converting enzyme inhibitors, where applicable, for 36 hours prior (14). Female subjects were studied at least 7 days after cessation of their last menstrual periods to minimise any effect of progesterone on endothelial reactivity.

Carotid intima media thickness (IMT) was determined by B-mode ultrasonography of the common carotid arteries using the equipment, in accordance with American Society of Echocardiography guidelines (15). Carotid plaque was defined as localised wall thickening ≥50% of the surrounding vessel wall or as a focal region with carotid IMT >1.5 mm protruding into the lumen (15). All FMD and IMT studies were performed by a single trained technologist blinded to the clinical and other laboratory data.

BMD of the lumbar spine (L2-4) and hips was measured on the same day after the vascular studies using the Hologic® dual energy x-ray absorptiometry scanner. Fasting venous blood samples were taken immediately before both vascular and bone densitometry scans and stored at -80°C until analysis for atherogenic index (total cholesterol/high-density lipoprotein ratio), serum C3, glycosylated haemoglobin (HbA1c) and high sensitivity C-reactive protein (hsCRP). Healthy volunteers from the surrounding community were recruited and matched with patients for age, sex, BMI, menopausal and smoking status. These controls underwent the same test procedures as the lupus patients. The study was approved by the local ethics committee and written informed consent was obtained from all study participants.

Statistical analyses

Unless otherwise specified, values are expressed as mean ± standard deviation (SD). Categorical data were compared using the chi-square or Fisher's exact test, and continuous data using the Student's *t*-test or Mann-Whitney U-test as appropriate. ANCOVA of the general linear model was used for adjustment for confounders when required. To explore the relationship between FMD and bone loss, univariate and multiple linear regression models were constructed. Additionally, as a secondary analysis, a multiple logistic regression model was fitted to explore predictors for osteopenia (T-score between -2.5 and -1.5) and osteoporosis (T score <-2.5) of the lumbar spine and both hips (16). To avoid too many variables in the regression equation, only variables satisfying $p<0.2$ in univariate analysis were entered into the multiple regression model. Tests of good fit and analyses of residuals and Hosmer-Lemeshow tests were performed in order to ascertain the validity of the multiple regression models. Multicollinearities within these models were detected by the tolerance test and a tolerance value ≥0.6 was accepted.

Statistical significance was defined as 2-tailed p-value <0.05. All statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL).

Results

Fifty-five SLE patients and 55 age-, sex- and BMI-matched healthy controls were studied. There were no significant differences between lupus patients and controls in age, sex, race and menopausal status. Patients and controls were also comparable with regard to mean arterial pressure, fasting lipid atherogenic index, carotid IMT, baseline brachial artery diameter and presence of carotid plaque. However, FMD was significantly depressed in patients with SLE than the normal healthy subjects (3.48±2.3% versus 4.90±3.1%, p=0.008). After adjustment for age, sex, BMI, baseline brachial diameter and smoking status, FMD remained significantly lower in the lupus group (3.39±0.4% versus 4.99±0.3%, p=0.002). In addition, patients with SLE had significantly higher serum hsCRP than healthy controls (2.77±3.8mg/dL *versus* 1.54±2.2mg/dL, p=0.046). No significant differences in lumbar and hip BMD and in proportion of osteoporosis and osteopenia were observed between groups. Table I summarises the demographic data of the SLE patients and controls. Table II lists the patterns of drug use, disease activity and damage in our patients with SLE.

Within the SLE group, it was only possible to compare those with osteopenia of the lumbar spine and hips against those with normal BMD since no patient had lumbar spinal and right hip osteoporosis, and only one had left hip osteoporosis (Table I). Patients who were osteopenic at the lumbar spine had significantly lower BMI (19.54±3.2 versus 23.40±4.9, p=0.039) and lower FMD (2.26±1.6% *versus* 3.68±2.3%, p=0.048) compared with SLE patients with normal lumbar BMD. No significant difference however was noted between patients with osteopenia of both hips and those with normal BMD (data not shown). Identical analyses confined to the control group revealed no significant difference in FMD between those who were osteoporotic, osteopenic and normal in BMD (data not shown). Table 3 summarises the observed difference in demographic and clinical variables in SLE patients with and without osteopenia of the lumbar spine.

Table I. Comparison of demographics and clinical characteristics between patients with SLE and matched healthy controls.

	Mean±SD; number(%)		
	SLE (n=55)	Control (n=55)	*p*-value
Age, year	40.40 ± 12.9	40.69 ± 13.4	0.908
Gender, Women	48 (87)	48 (87)	1.000
Race			
Chinese	40 (73)	46 (84)	
Malay	8 (15)	3 (6)	0.418
Indian	4 (7)	3 (6)	
Others	3 (6)	3 (6)	
BMI	22.84 ± 4.9	22.85 ± 4.2	0.985
Menopause	12 (22)	13 (24)	1.000
Duration of illness, month	54.27 ± 69.7	NA	NA
Smoker (ever or current)	2 (4)	2 (4)	1.000
MAP, mmHg	84.31 ± 16.1	85.89 ± 9.5	0.535
hsCRP, mg/dL	2.77 ± 3.8	1.54 ± 2.2	0.046
TC/HDL ratio	3.57 ± 1.1	3.52 ± 0.9	0.808
HbA1c, %	5.51 ± 0.8	NA	NA
FMD, %	3.48 ± 2.3†	4.90 ± 3.1†	0.008†
	3.39 ± 0.4‡	4.99 ± 0.34‡	0.002‡
Baseline brachial artery diameter, mm	3.55 ± 0.6	3.63 ± 0.6	0.477
Carotid IMT¶, mm	0.56 ± 0.1	0.55 ± 0.1	0.913
Presence of carotid plaque	9 (16)	11 (20)	0.805
Lumbar BMD, g/cm^2	1.00 ± 0.1	1.01 ± 0.2	0.629
Left hip BMD, g/cm^2	0.81 ± 0.1	0.83 ± 0.1	0.403
Right hip BMD, g/cm^2	0.82 ± 0.1	0.84 ± 0.1	0.383
Osteopenic at lumbar spine	9 (16)	8 (15)	1.000
Osteoporotic at lumbar spine	0 (0)	0 (0)	NA
Osteopenic at left hip	9 (16)	7 (13)	0.788
Osteoporotic at left hip	1 (2)	3 (6)	0.618
Osteopenic at right hip	5 (9)	8 (15)	0.556
Osteoporotic at right hip	0 (0)	1 (2)	1.000

SD: Standard deviation; SLE: systemic lupus erythematosus; BMI: body mass index; NA: not applicable; MAP: mean arterial pressure; hsCRP: high sensitivity C-reactive protein; TC/HDL: total cholesterol/high-density lipoprotein; FMD: flow-mediated dilatation; IMT: intima media thickness; BMD: bone mineral density.
†Unadjusted values; ‡Values adjusted for age, sex, BMI, smoking and baseline brachial artery diameters by ANCOVA using the general linear model; ¶Averaged left and right carotid IMT.

Table II. Drug use, serology, disease activity and damage index in patients with SLE.

	Number (%); Mean±SD (range)
Current drug use	
Prednisolone	48 (87)
Azathioprine	13 (24)
Hydroxychloroquine	47 (86)
Cyclosporine	5 (9)
Tacrolimus	1 (2)
Mycophenolate mofetil	11 (20)
Methotrexate	2 (4)
CYC (past and current)	15 (27)
Prednisolone dose, mg/day	13.28 ± 14.4 (0-60)
Cumulative prednisolone dose, gm	8.38 ± 9.3 (0-40.4)
Serology	
Serum C3, mg/dL	80.46 ± 33.4 (27-201)
Serum anti-dsDNA, IU	100.01 ± 95.2 (1-250)
SLE disease activity and damage	
SLEDAI	7.02 ± 5.9 (0-25)
SLICC-SDI	0.31 ± 0.7 (0-4)

SLE: systemic lupus erythematosus; SD: standard deviation; CYC: cyclophosphamide; SLEDAI: systemic lupus erythematosus disease activity index; SLICC-SDI: Systemic lupus Internaional Collaboration Clinics-Damage Index.

Univariate linear regression involving the SLE group revealed that older age (r=–0.36; p=0.006), menopause (r=–0.28; p=0.037), higher serum hsCRP level (r=–0.29; p=0.034), higher carotid IMT (r=–0.33; p=0.014) and lower lumbar BMD (r=0.31; p=0.021) were associated with lower FMD. No association between FMD and smoking, use of cyclophosphamide (CYC), cyclosporine, hydroxychloroquine and glucocorticoids, atherogenic index, presence of carotid plaque and hip BMD was noted. After multivariate adjustment, higher serum hsCRP level (r=–0.26; p=0.037) and lower lumbar BMD (r=0.27; p=0.025) were found to be independently associated with lower FMD. Separate regression analyses revealed no relationship between FMD and BMD among healthy controls (by univariate linear regression, FMD & lumbar BMD, p=0.520; FMD & left-hip BMD, p=0.901; FMD and right-hip BMD, p=0.951). Table III summarises the results of the linear regression analyses in the SLE group. Figure 1 is a scatter plot of the association between FMD and lumbar BMD.

As for predictors for vertebral osteopenia, multiple logistic regression involving clinically relevant covariates with p<0.2 in the univariate analysis (from Table III) revealed an independent association between lower FMD and lumbar osteopenia (p=0.045) (see Table V).

Discussion

Besides extending previous observations that endothelial function is impaired in patients with SLE (17-23), we demonstrated for the first time that endothelial dysfunction is related to lower lumbar BMD in patients with SLE.

While a number of recent case-control studies have shown impaired endothelial function in SLE patients compared with healthy controls (17-23), factors associated with endothelial dysfunction have not been well explored. A limited number of case-control studies demonstrated that established cardiovascular risk factors such as carotid IMT (17), menopause (18), total (18) and HDL-cholesterol (19) and BMI (19) were associated with FMD in lupus patients.

Table III. Comparison of demographics and clinical characteristics between those with osteopenia of the lumbar spine in patients with SLE.

	Mean±SD; number (%)		
	Osteopenia (n=8)	No osteopenia (n=47)	*p*-value
Age, year	40.50 ± 14.7	40.38 ± 12.7	0.981
Gender, Women	8 (100)	40 (85)	0.310
Race			
Chinese	7 (88) 33	(70)	
Malay	1 (13)	4 (15)	0.369
Indian	0 (0)	4 (9)	
Others	0 (0)	3 (6)	
BMI, kg/m^2	19.54 ± 3.2	23.40 ± 4.9	0.039
Menopause	2 (25)	11 (23)	0.615
Duration of illness, month	88.38 ± 69.7	48.47 ± 69.5	0.136
Current prednisolone dose, mg/day	8.75 ± 11.2	14.05 ± 14.9	0.314
Cumulative prednisolone, gm	13.25 ± 11.2	7.55 ± 8.8	0.111
Medication use			
Azathioprine	1 (13)	12 (26)	0.664
Prednisolone	7 (88)	41 (87)	0.983
Hdroxychloroquine	8 (100)	39 (83)	0.587
MMF	2 (25)	9 (19)	0.654
Cyclophosphamide*	2 (25)	13 (28)	0.876
Cyclosporine	3 (38)	2 (4)	0.002
Tacrolimus	0 (0)	1 (2)	1.000
Methotrexate	0 (0)	2 (4)	1.000
Smoker (ever or current)	1 (13)	1 (2)	0.272
MAP, mmHg	82.79 ± 14.4	84.58 ± 16.6	0.775
hsCRP	2.87 ± 2.7	2.87 ± 4.0	0.997
TC/HDL ratio	3.33 ± 1.6	3.61 ± 1.0	0.518
HbA1c,%	5.28 ± 0.4	5.55 ± 0.9	0.395
FMD, %	2.26 ± 1.6	3.68 ± 2.3	0.048
Baseline diameter, mm	3.71 ± 0.8	3.52 ± 0.5	0.477
Serum C3	92.13 ± 52.7	78.43 ± 29.2	0.495
Serum anti-dsDNA	97.00 ± 109.4	100.57 ± 93.83	0.923
SLEDAI, unit	5.63 ± 7.2	7.26 ± 5.7	0.477
SLICC, unit	0.13 ± 0.4	0.34 ± 0.8	0.437
Carotid IMT, mm	0.57 ± 0.1	0.49 ± 0.1	0.134
Presence of arterial plaque	1 (13)	10 (21)	0.492
BMD, g/cm^2			
Lumbar	0.80 ± 0.0	1.04 ± 0.1	<0.001
Left hip	0.68 ± 0.1	0.83 ± 0.1	0.001
Right hip	0.69 ± 0.1	0.84 ± 0.1	0.001

SD: standard deviation; BMI: body mass index; MMF: mycophenolate mofetil; MAP: mean arterial pressure; hsCRP: high sensitivity C-reactive protein; TC/HDL: total cholesterol/high density lipoprotein; FMD: flow-mediated dilatation; SLEDAI: SLE disease activity index; SLICC/SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; IMT: intima medial thickness; BMD: bone mineral density.
*past or current use.

Although conventional vascular risk factors are important causes for poor cardiovascular outcome, they cannot account fully for the increased cardiovascular disease burden in SLE patients (24). Additional drivers such as metabolic, inflammatory, immunological and therapeutic factors may have an equally important role in atherogenesis in SLE patients (24). Since these factors may also trigger bone loss, it is reasonable to hypothesize that bone loss and cardiovascular disease are pathologically and phenotypically linked in SLE. In keeping with this hypothesis, we found that lower lumbar BMD independently predicted poorer endothelial function even after adjustment for major confounders such as age, gender, menopause, use of CYC and serum hsCRP level. Owing to the cross-sectional nature of this study, we cannot address the cause-effect relationship between bone loss and endothelial dysfunction in our SLE patients. Nevertheless, we theorize a concurrent role for endothelial nitric oxide synthease (eNOS) and its product nitric oxide (NO), thus generated from L-arginine (10). NO is produced by intact endothelial cells which diffuses into the vascular myocytes and triggers cyclic guanosine monophosphate (cGMP)-induced vasodilatation in response to circulatory shear stress (10). Current evidence strongly indicates that endothelial dysfunction reflects the propensity for development of consequent atherosclerotic disease and is therefore a surrogate indicator of early vascular failure (10). Interestingly, an emerging body of evidence suggests that eNOS is also constitutively expressed in bone, and that production of NO is crucial in supporting osteoblast differentiation and proliferation and modulating anabolic effects of oestrogen on bone homeostasis by restraining osteoclast-mediated bone resorption (25, 26), in addition to its potential anti-inflammatory effects (27). There therefore exists a possible biological link where alteration in eNOS expression in SLE (28, 29) could lead to concurrent dysfunction of the endothelium and osteoblasts. In addition to eNOS, other mechanisms such as oestrogen deficiency (30), high osteopontin (31), osteoprotegerin (OPG) and bone-associated proteins expression may contribute to bone loss and atherosclerosis (32). Oxidised lipids have also been shown to promote concomitant atherosclerosis and inhibit mineralisation of osteoid (33, 34). Further experimental studies are needed to validate this hypothesis.

Intriguingly, significant relationships between endothelial dysfunction and hip BMD were not observed in our SLE patients. The reason is unclear but one explanation could be less severe bone loss in cortical-rich femoral sites vis-à-vis trabecular-rich vertebra in SLE patients taking glucocorticoids (35, 36). If so, expansion of the sample size and recruitment of patients with longer disease duration may increase the power to detect a significant relationship between peripheral bone mineral density and endothelial dysfunction.

Aside from the relationship with BMD, endothelial dysfunction was also associated with higher serum hsCRP level. While it is well recognised that inflam-

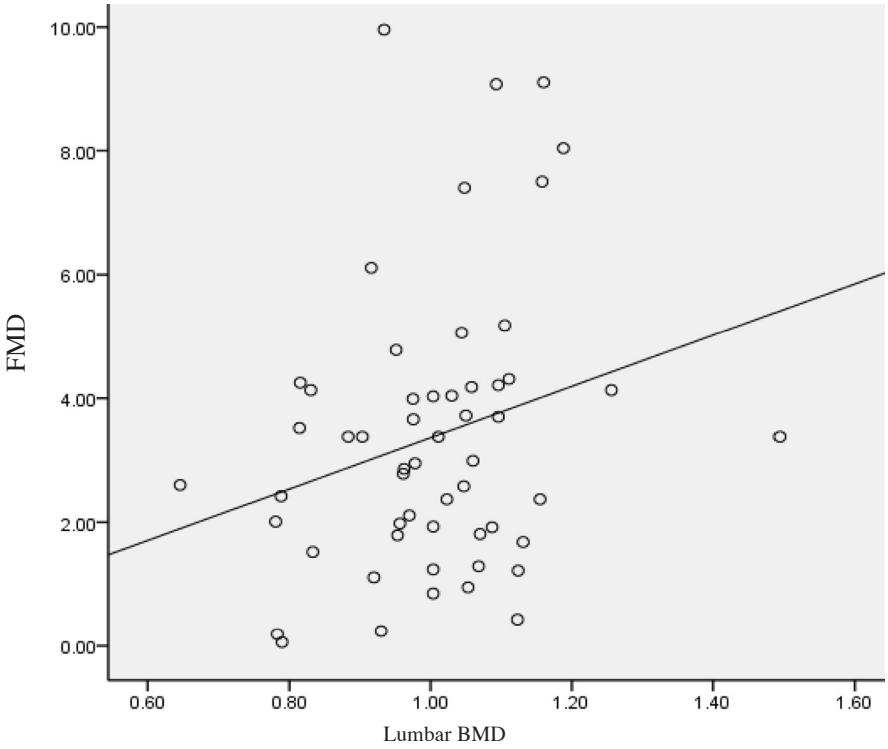

Fig. 1. Scatter plot of the association between FMD and lumbar BMD.

Table IV. Predictors for endothelial reactivity in SLE patients as assessed by flow-mediated dilatation of the brachial artery.

	Univariate			Multivariate			
	Slope (SE)	r	*p-value*	Slope (S E)		r	*p-value*
Age, years	-0.064 (0.023)	-0.364	0.006	-0.061	(0.040)	-0.345	0.13
Gender, female	1.470 (0.904)	0.218	0.110	1.356	(0.822)	0.201	0.105
Duration of SLE	0.002 (0.004)	0.050	0.719	--		--	--
Menopause	-1.489 (0.697)	-0.282	0.037	0.721	(1.040)	0.136	0.491
Smoking	-0.162 (1.648)	-0.013	0.922	--		--	--
BMI, kg/m^2	-0.072 (0.063)	-0.156	0.256	--		--	--
Mean arterial pressure	0.007 (0.019)	0.048	0.727	--		--	
Ever use of CYC	1.214 (0.672)	0.241	0.077	1.164	(0.609)	0.231	0.062
Ever use of CSA	0.609 (1.070)	0.078	0.572	--		--	--
Non-use of HCQ	0.392 (0.874)	0.061	0.656	--		--	--
Current prednisolone, mg/day	0.004 (0.022)	0.028	0.838	--		--	--
Cumulative prednisolone dose, gm	0.024 (0.033)	0.099	0.471	--		--	--
hsCRP, mg/dL	-0.171 (0.079)	-0.286	0.034	-0.154	(0.071)	-0.257	0.037
TC/HDL ratio	0.113 (0.284)	0.054	0.693	--		--	--
Presence of carotid plaque	-0.717 (0.765)	-0.128	0.353	--		--	--
Carotid IMT, mm	-5.688 (2.237)	-0.330	0.014	-1.369	(2.757)	-0.079	0.622
SLEDAI, unit	0.026 (0.052)	0.067	0.625	--		--	--
SLICC, unit	-0.143 (0.434)	-0.045	0.742	--		--	--
BMD – lumbar spine	5.056 (2.126)	0.311	0.021	4.419	(1.915)	0.271	0.025
BMD – left hip	0.853 (2.589)	0.045	0.743	--		--	--
BMD – right hip	4.165 (2.804)	0.200	0.143	*		*	*

SE: Standard error; r: Correlation coefficient; SLE: Systemic lupus erythematosus; BMI: Body mass index; CYC: Cyclophosphamide; CSA: Cyclosporine; HCQ: hydroxychloroquine; hsCRP: high-sensitive C-reactive protein; TC/HDL: Total cholesterol/High-density lipoprotein cholesterol; IMT: intima media thickness; SLEDAI: SLE disease activity index; SLICC: SLE damage index; BMD: bone mineral density.

*Due to significant correlation between BMD – lumbar spine and BMD – right hip (r=0.577, $p<0.001$), BMD – right hip was entered as the independent variable in another multiple regression model together with the same confounding variables. This regression model yielded Slope (SE) =1.958(2.725); r=0.094; $p=0.476$, for BMD-right hip, and for hsCRP, they are: Slope (SE) =-0.161(0.075); r=-0.270; $p=0.036$. Other independent variables remain statistically insignificant.

mation is closely related to endothelial dysfunction especially in the setting of chronic inflammation in SLE, this is one of the very few studies which is able to demonstrate a correlation between hsCRP and endothelial dysfunction in patients with SLE. We cannot however conclude that hsCRP mediates bone loss and endothelial dysfunction because a separate analysis revealed no bivariate correlation between serum hsCRP level and lumbar spine BMD (r=–0.025, $p=0.863$) and hip BMD (left hip: r=0.135, $p=0.332$; right hip: r=0.022, $p=0.882$). Nonetheless, serum hsCRP level in lupus must be interpreted with caution because its level fluctuates during SLE disease course (increasing with infection, serositis or arthritis), a single measurement is therefore not necessarily representative of the general health status of the endothelium (37).

In contrast to the SLE group, no significant relationship between endothelial reactivity and BMD was evident in the control group. Since the control subjects were extensively matched for age, sex, BMI, smoking and menopausal status with the SLE patients, and their ethnicity, blood pressure, and atherogenic index were comparable (see Table I), it is likely that SLE-related factors were operant in effecting bone loss and endothelial dysfunction in our lupus patients. Further studies are necessary to identify the factors which maintain this association.

A few limitations exist in our study. First, while the sample size is powered enough to detect a difference between SLE and healthy controls regarding FMD, a larger sample size may demonstrate difference in other less sensitive biophysical markers of atherosclerosis such as carotid IMT. A larger sample size also enables more confounding variables to be adjusted for during multivariate regression modelling. Second, this cross-sectional study can determine an association but not the casual relationship between bone loss and endothelial dysfunction, or the mechanistic factors mediating these processes. Third, blood sugar level in normal healthy controls was not ascertained. Nevertheless, our control subjects were mainly nursing

Table V. Predictors for lumbar osteopenia in patients with SLE.

	Multivariate		
	Slope (SE)	OR (95% CI)	*p-value*
Duration of SLE, months	0.031 (0.020)	1.031 (0.991-1.073)	0.125
BMI, kg/m^2	-0.248 (0.203)	0.780 (0.525-1.161)	0.221
Use of CSA	-4.576 (2.325)	0.014 (0.000-1.008)	0.052
Cumulative glucocorticoid dose, gm	0.077 (0.124)	1.080 (0.847-1.378)	0.535
FMD, %	-1.914 (0.953)	0.147 (0.023-0.955)	0.045
Carotid IMT, mm	-18.66 (12.33)	0.000 (0.000)	0.130

SLE: systemic lupus erythematosus; SE: Stand error; OR: Odds ratio; CI: confidence interval; BMI: body mass index; CSA: cyclosporine; FMD: flow mediated dilatation; IMT: intima media thickness. Hosmer-Lemeshow test: p=0.925.

staff of our clinic, were generally more health conscious and were never diagnosed with glucose intolerance. Indeed, they had less endothelial dysfunction than SLE patients. Finally, while we attempted to increase the robustness of the current study by selecting patients with less advanced SLE and confounding co-morbidities compared to previous studies (17-23), it is impossible to eliminate all factors which may impact bone and cardiovascular health, such as subtle renal dysfunction and differences in level of exercises and diet. These confounding factors may be mitigated by prospective recruitment of a more homogeneous population with similar disease duration, treatment and cumulative disease burden.

In conclusion, we found that in SLE patients, low lumbar bone mineral density and high serum hsCRP level are independent predictors for endothelial dysfunction. Although potential drivers leading to this relationship remain to be identified, our findings serve to alert physicians to the presence of early atherosclerotic disease in lupus patients, particularly those with low lumbar BMD or lumbar vertebral osteopenia.

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