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ORIGINAL ARTICLE

Prevalence of and risk factors for low bone mineral density in Japanese female patients with systemic lupus erythematosus

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Abstract To examine the prevalence of and risk factors for low bone mineral density (BMD) (osteoporosis or osteopenia) in Japanese female patients with systemic lupus erythematosus (SLE). We performed BMD measurements by dual X-ray absorptiometry at the lumbar spine and the hip and collected basic and lifestyle-related, clinical and treatment characteristics among 58 SLE patients. Odds ratios (ORs) and their 95% confidence intervals (CIs) were assessed for associations between low BMD and selected factors among SLE patients. The mean BMD ± SD was 0.90 ± 0.17 g/cm^2 at the lumbar spine and 0.76 ± 0.17 g/cm^2 at the hip. The prevalence of osteopenia (2.5 SD < *T* score < 1 SD) was 50.0% and that of osteoporosis (*T* score < 2.5 SD) was 13.8% in our SLE patients. After adjustment for age and disease duration, we found the number of deliveries (OR = 5.58, 95% CI = 1.31–26.06; $P = 0.02$) to be a risk factor for overall low BMD (*T* score < 1 SD) and a maximal dosage of >50 mg/day of oral corticosteroids (OR = 0.25, 95% CI = 0.07–0.91; $P = 0.035$) as a preventive factor for low BMD at the lumbar spine. Reduced BMD, especially in spinal trabecular bone, was pronounced in Japanese female patients with SLE, particular in those with a history of delivery. A history of high-dose oral corticosteroids was associated with the preservation of BMD at the lumbar spine, however, further study is needed considering the limited sample size.

Keywords Systemic lupus erythematosus · Bone mineral density · Female · Lumbar spine · Deliveries · Corticosteroids

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Introduction

Over the last few decades, the survival of patients with systemic lupus erythematosus (SLE) has improved dramatically thanks to improved treatment [1], and the morbidity pattern has shown a shift toward long-term complications, including osteoporosis. Osteoporosis is characterized by low bone mass and damaged structural integrity leading to increased risk of fracture. While SLE occurs predominantly in women during their child-bearing years, the disease often persists into the postmenopausal period [2]. Several studies have demonstrated a high prevalence of low bone mineral density (BMD) in patients with SLE, especially in female patients [3–8].

Exposure to corticosteroids is generally considered to be a major factor contributing to the development of osteoporosis, although the net effect is still a matter of debate. Several studies have reported the association of low BMD with corticosteroid use in SLE patients, demonstrating a relationship between osteoporosis and use of steroids, mean dose of steroids and cumulative dose of steroids [4, 7,

9, 10]. On the other hand, no association has been demonstrated between corticosteroids and osteoporosis in SLE patients [11–14]. Therefore, factor(s) other than corticosteroids may be involved in the development of osteoporosis in SLE patients. Factors directly related to SLE could be involved in the development of osteoporosis in SLE patients. Reportedly inflammatory mediators such as IL-6, IL-1, and TNF-α can promote bone resorption [15]. In addition, there might be other factors predisposing to lower BMD, such as premature menopause, menstrual irregularity, sun avoidance leading to reduced vitamin D, reduced physical activity, and amenorrhea in SLE patients.

In this study, we carried out BMD measurements in 58 Japanese female patients with SLE and collected basic and lifestyle-related, clinical, and treatment data of them. The aims of this study were as follows (1) to assess the prevalence of osteopenia and osteoporosis and (2) to investigate risk factors associated with low BMD that will contribute to the identification of SLE patients who are likely to benefit from BMD measurement.

Patients and methods

Patients

Fifty-eight consecutive female patients with a diagnosis of SLE were included in the study. All patients regularly attended the rheumatology clinic of Kyushu University Hospital. All patients fulfilled the 1997 ACR revised criteria for the classification of SLE [16] and were informed of the objectives of the study and provided written consent. This study was approved by the ethical review board of Kyushu University Hospital.

Data collection and measurement

All measurements were performed from January to August 2006. Data were collected by questionnaire survey. Basic and lifestyle-related data were obtained regarding age, BMI, and menstrual (presence of regular menstruation and menopause) and obstetric history (number of deliveries). In addition, we inquired about smoking; intake of alcohol; exercise; going out; intake of milk, dairy products, fish, small fish, soybean products, coffee, tea, and Japanese green tea; use of sunscreen; and sleeping habits (bed or Japanese futon).

Clinical data of SLE patients were assessed for disease duration, renal involvement (presence of persistent proteinuria of >0.5 g/24 h or cellular casts: lupus nephritis), photosensitivity, osteoporosis, bone and vertebral fractures, diabetes mellitus, hyperlipidemia, aseptic necrosis of the femoral bone, and family history of osteoporosis or femoral neck fracture. We used the questionnaire survey to obtain information regarding family history. Laboratory data were obtained including complete blood count, urinary sediment, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, urinary creatinine (Ucr), urinary protein (Up), serum level of bone-specific alkaline phosphatase (BAP), type I collagen cross-linked N-telopeptide (NTx), 25-hydroxyvitamin D, anti-double stranded DNA antibodies, and complement components. We calculated creatinine clearance from serum creatinine using the Cockcroft and Gault equation [17] and used Up/Ucr to calculate urinary protein excretion per day [18]. A high titer of NTx was defined as a serum level >16.5 nmol BCE/l during premenopause and >24.0 nmol BCE/l during postmenopause, while low BAP titer was defined as a serum level <9.6 U/l, based on the laboratory reference value. Disease activity was scored using the systemic lupus erythematosus disease activity index (SLEDAI) [19] by the physicians in charge of the patients.

A history of corticosteroids and other immunosuppressant use was also obtained. We investigated past and current use of corticosteroids, duration of their use in years, maximal dosage taken orally, actual current prednisone use, and past intravenous (IV) methylprednisolone use. In addition, we investigated past and current use of cyclosporin, methotrexate, cyclophosphamide, azathioprine, mizolibin, mycophenolate mofetil (MMF), rituximab, and IV administration of cyclophosphamide. We also inquired about current use of major or minor tranquilizers, antispasmodics, vitamin D supplements, hormone replacement therapy, vitamin K_2 supplements, warfarin, bisphosphonates (alendronates or risedronates), calcium supplements, oral contraceptive and vitamin C supplements, drugs prescribed in other hospitals and supplements taken by the patients by themselves.

BMD measurements

We performed BMD measurements of the lumbar spine (LS) (L2–L4) and the hip [total hip: femoral neck (FN), trochanter and intertrochanter]. Measurements were performed using the same dual energy X-ray absorptiometry equipment (model QDR-4500A; Hologic) by trained technicians. Measurement of the hip was not performed in nine patients because of bilateral hip replacements. In this study, we used the standard definitions of osteoporosis (T score < -2.5 SD) and osteopenia (-2.5 SD $< T$ score < -1 SD). BMD with a T score < -1 SD was defined as low. Z score is equivalent to the SD from mean BMD of age- and sex-matched controls.

Statistical analysis

We first examined all variables to determine an association with low BMD overall, at the LS and at the hip by

univariate tests. The analysis of categorical (dichotomous) variables included a presentation of frequency distributions, proportions, and statistical comparisons using Pearson's tests. We used the Student t test for the analysis of continuous variables. Predictor variables from Table 1 with a level of significance less than or equal to 10% ($P = 0.10$) for the univariate tests were included as candidate predictors in the multivariable tests. Univariate and multivariate unconditional logistic regression analyses were used to obtain the crude and adjusted odds ratios (ORs) for the risk of low BMD and the corresponding 95% confidence intervals (95% CIs). Multivariate adjustments were made for age and disease duration because low BMD is associated with advanced age and prolonged disease duration. A P value less than or equal to 0.05 (two-sided) was considered statistically significant. We identified the risk factors and predictors of overall low BMD and low BMD at the spine and hip. All of the calculations were performed using STATA Version 8.2 (Stata Corporation, College Station, TX, USA) software.

Results

The characteristics of the study patients

The characteristics of 58 Japanese female patients with SLE are shown in Table 1. Mean age ± SD was 44.0 ± 13.6 years and mean BMI ± SD was 22.4 ± 3.88. Nineteen patients (33.3%) were postmenopausal. Mean disease duration ± SD was 16.5 ± 8.55 years, and mean SLEDAI was 6.95 ± 5.76. Twenty-six (48.2%) patients had renal involvement while 56 patients (96.6%) had a history of corticosteroid use. Among those, 54 patients (93.1%) currently used corticosteroids with a median daily dose of 9.0 ± 5.5 mg. For the treatment or prevention of osteoporosis, vitamin D was used in 65.5% ($n = 38$) and bisphosphonates were administered in 41.4% ($n = 24$) of the patients.

These characteristics were compared between SLE patients with normal and low BMD. Patients with low BMD were significantly older by an average of 7.3 years ($P = 0.049$). Smoking was more prevalent in patients with normal BMD (33.3%) than in patients with low BMD (8.1%) ($P = 0.006$). The number of deliveries was significantly higher in patients with low BMD than in those with normal BMD ($P = 0.006$). Creatinine clearance was significantly lower in patients with low BMD than in patients with normal BMD ($P = 0.042$). However, a history of renal involvement was more prevalent in patients with normal BMD than those with low BMD ($P = 0.039$). Although there was no association between low BMD and current use of corticosteroids, treatment duration, or a history of IV methylprednisolone, the maximal dosage of oral corticosteroids was significantly higher in normal BMD patients (51.8 mg/day) than in low BMD patients (38.5 mg/day) ($P = 0.021$). There was no association between other medicines including immunosuppressants and low BMD.

The results of the BMD measurements are shown in Table 2. The mean BMD ± SD was 0.90 ± 0.17 g/cm^2 at LS and 0.76 ± 0.17 g/cm^2 at the hip. The mean T score ± SD was −0.99 ± 1.51 SD at LS and −0.95 ± 1.47 SD at the hip. The frequency of osteopenia (T score < −1.0 SD at LS and/or at the hip) was 50.0%. The frequency of osteoporosis (T score < −2.5 SD at LS and/or at the hip) was 13.8%.

Characteristics of SLE patients with normal or low BMD at the LS or at the hip were assessed separately, as shown in Table 3. Postmenopausal status was significantly associated with low BMD at the hip ($P = 0.046$), but not at the LS ($P = 0.132$). A history of smoking was more prevalent in patients with normal BMD both at the LS ($P = 0.039$) and at the hip ($P = 0.028$). Going out everyday was more prevalent in patients with low BMD at the total hip ($P = 0.044$), but not at the LS ($P = 0.555$). The number of deliveries was significantly higher in patients with low BMD at the LS ($P = 0.005$), but not at the hip ($P = 0.464$). Regular menstruation was more prevalent in patients with normal BMD at the total hip than in those with low overall BMD ($P = 0.05$), but not at the LS ($P = 0.077$). High NTx was associated with normal BMD at the LS ($P = 0.043$), but not at the total hip ($P = 0.602$). A history of renal involvement was more prevalent in patients with normal BMD than in those with low BMD at the LS ($P = 0.048$), but the relationship was not observed at the total hip ($P = 0.28$). As for treatment variables, maximal dosage of corticosteroids was significantly higher in patients without low BMD than in those with low BMD at the LS ($P = 0.023$), but not at the hip. Current use of vitamin K_2 was more prevalent in patients with low BMD than in individuals with normal BMD at the LS ($P = 0.036$), but not at the hip ($P = 0.202$).

Association between low BMD and selected factors

Odds ratios and 95% CIs for the association with low BMD (overall, at the LS, or at the hip) were further examined for the factors selected based on the data in Tables 1 and 3. As shown in Table 4, crude ORs (95% CI) of overall low BMD, history of smoking, use of bed and history of renal involvement were 0.18 (0.04–0.78, $P = 0.022$), 0.28 (0.08–0.98, $P = 0.047$) and 0.28 (0.08–0.98, $P = 0.043$), respectively. Number of deliveries (more than one vs. null) was associated with an increased risk of overall low BMD (crude OR = 4.4, 95%

Table 1 Characteristics of the SLE patients with normal and low BMD

Variable	All patients ($n = 58$)	SLE patients				P
		Normal BMD ($n = 21$)	Data missing for patients (n)	Low BMD ($n = 37$)	Data missing for patients (n)	
Basic and lifestyle-related						
Age, mean (SD)	44.0 (13.6)	39.3 (11.2)		46.6 (14.2)		0.049
BMI, mean (SD)	22.4 (3.88)	23.4 (4.05)		21.78 (3.70)		0.128
Postmenopausal status, n (%)	19 (33.3)	4 (19.0)		15 (41.7)	1	0.083
History of smoking, n (%)	11 (19.0)	7 (33.3)		3 (8.1)		0.006
Alcohol drinking more than three times weekly, n (%)	6 (10.7)	2 (10)	1	4 (11.1)	1	0.898
Exercise more than twice weekly, n (%)	16 (28.1)	6 (28.6)		10 (27.8)	1	0.949
Going out daily, n (%)	26 (52.0)	11 (61.1)	3	15 (46.9)	5	0.333
Daily milk intake, n (%)	21 (36.8)	6 (28.6)		15 (41.7)	1	0.323
Dairy product intake more than twice weekly, n (%)	47 (81.0)	1 7 (81.0)		30 (81.1)		0.990
Fish intake more than twice weekly, n (%)	50 (87.7)	18 (90)	1	32 (86.5)		0.700
Small fish intake more than twice weekly, n (%)	33 (58.9)	9 (42.9)		14 (40.0)	2	0.833
Soybean product intake more than twice weekly, n (%)	53 (91.4)	19 (90.5)		34 (91.9)		0.854
Daily coffee or (black) tea intake, n (%)	45 (77.6)	19 (90.5)		26 (70.3)		0.076
Daily green tea intake, n (%)	34 (58.6)	11 (52.4)		23 (62.1)		0.467
Number of deliveries, mean (SD)	0.89 (1.11)	0.35 (0.75)	1	1.19 (1.18)		0.006
Regular menstruation, n (%)	21 (38.2)	15 (75.0)	1	19 (54.3)	2	0.128
History of falls, n (%)	22 (41.5)	8 (44.4)	3	14 (40.0)	2	0.756
Use of bed, n (%)	36 (62.1)	16 (76.2)		20 (54.1)		0.071
History of surgery, n (%)	44 (75.9)	17 (81.0)		27 (73.0)		0.499
Clinical						
Disease duration, mean (SD) years	16.5 (8.55)	13.8 (8.20)	1	18.03 (8.47)	1	0.076
Low bone-specific alkaline phosphatase (BAP), n (%)	2 (5.2)	1 (5.3)	2	1 (2.8)	1	0.640
High type I collagen cross-linked N-telopeptide (NTx), n (%)	3 (5.2)	2 (10.5)	2	1 (2.8)	1	0.229
Erythrocyte sedimentation rate, mean (SD) mm/h	21.7 (16.8)	21.5 (16.6)	2	21.9 (17.7)	3	0.935
C-reactive protein, mean (SD) mg/dl	0.24 (0.62)	0.14 (0.12)		0.30 (0.78)	1	0.334
SLEDAI, mean (SD)	6.95 (5.76)	6.67 (6.26)		7.10 (5.54)		0.782
25-hydroxyvitamine D, mean (SD) pg/ml	54.63 (18.76)	51.27 (20.90)	2	56.40 (17.58)	1	0.339
Creatinine clearance, mean (SD) ml/min	93.76 (36.1)	106.41 (41.3)		86.40 (30.97)	1	0.042
Urine protein, mean(SD) g/day	0.47 (0.91)	0.29 (0.63)	2	0.57 (1.03)	3	0.282
History of photosensitivity, n (%)	24 (41.4)	8 (42.1)	2	16 (44.4)	1	0.868
Use of sunscreen, n (%)	42 (73.7)	15 (71.4)		27 (75.0)	1	0.768
History of renal involvement, n (%)	26 (48.2)	12 (70.6)	2	14 (40.0)	2	0.039
History of Diabetes Mellitus, n (%)	3 (5.2)	2 (9.5)		1 (2.7)		0.260

Table 1 continued

Variable	All patients ($n = 58$)	SLE patients				P
		Normal BMD ($n = 21$)	Data missing for patients (n)	Low BMD ($n = 37$)	Data missing for patients (n)	
History of hyperlipidemia, n (%)	26 (44.8)	10 (47.6)		16 (44.4)	1	0.816
History of aseptic necrosis of femoral bone, n (%)	16 (27.6)	7 (35.0)	1	9 (26.5)	3	0.507
History of previous osteoporosis, n (%)	14 (25.5)	4 (20.0)	1	10 (28.6)	2	0.483
History of previous bone fracture, n (%)	16 (0.3)	4 (19.1)		12 (32.4)		0.273
History of previous vertebral fracture, n (%)	5 (9.3)	1 (5.0)	4	4 (11.8)	7	0.408
Family history of osteoporosis or femoral neck fracture, n (%)	6 (10.3)	2 (9.5)		4 (10.8)		0.877
Treatment						
History of corticosteroid use, n (%)	56 (96.6)	21 (100)		35 (94.6)		0.278
Treatment duration of corticosteroids, mean (SD) years	15.6 (8.6)	13.7 (8.8)		16.7 (13.7)	4	0.256
Maximal dosage of oral corticosteroids, mean (SD) mg/day	43.3 (20.3)	51.8 (22.0)	2	38.5 (17.9)	3	0.021
History of IV methylprednisolone, n (%)	16 (27.6)	8 (38.1)		8 (21.6)		0.177
Current use of corticosteroids, n (%)	54 (93.1)	21 (100)		33 (89.2)		0.118
Actual prednisone dosage, mean(SD) mg/day	9.0 (5.5)	9.5 (6.1)		8.8 (5.2)	4	0.648
History of cyclosporine, n (%)	11 (19.0)	4 (19.0)		7 (18.9)		0.990
Current use of cyclosporine, n (%)	9 (15.5)	4 (19.0)		5 (13.5)		0.576
History of methotrexate, n (%)	1 (1.7)	0 (0)		1 (2.7)		0.447
Current use of methotrexate, n (%)	1 (1.7)	0 (0)		1 (2.7)		0.447
History of cyclophosphamide, n (%)	16 (27.6)	4 (19.0)		12 (32.4)		0.273
History of IV cyclophosphamide, n (%)	9 (15.5)	4 (19.0)		5 (13.5)		0.576
Current use of cyclophosphamide, n (%)	1 (1.7)	0 (0)		1 (2.7)		0.447
History of azathioprine, n (%)	10 (17.2)	4 (19.0)		6 (16.2)		0.784
Current use of azathioprine, n (%)	3 (5.2)	1 (4.8)		2 (5.4)		0.915
History of mizolibin, n (%)	6 (10.3)	3 (14.3)		3 (8.1)		0.458
Current use of major tranquilizer, n (%)	2 (3.5)	2 (9.5)		0 (0)	1	0.059
Current use of minor tranquilizer, n (%)	14 (24.1)	5 (23.8)		9 (24.3)		0.965
Current use of antispasmodic, n (%)	3 (5.2)	0 (0)		3 (8.1)		0.180
Current use of vitamin D supplements, n (%)	38 (65.5)	15 (71.4)		23 (62.2)		0.476
Current use of vitamin K_2 supplements, n (%)	14 (24.6)	3 (14.3)		11 (30.6)	1	0.169
Current use of warfarin, n (%)	9 (16.4)	2 (10.5)	2	7 (19.4)	1	0.395
Current use of bisphosphonates, n (%)	24 (41.4)	6 (28.6)		18 (48.6)		0.136
Current use of alendronates, n (%)	8 (13.8)	1 (4.8)		7 (18.9)		0.133
Current use of risedronates, n (%)	16 (27.6)	5 (23.8)		11 (29.7)		0.628
Current use of calcium supplements, n (%)	16 (27.6)	5 (23.8)		11 (29.7)		0.628
Current use of vitamin C supplements, n (%)	7 (12.1)	3 (14.3)		4 (10.8)		0.696

Table 2 BMD measures at the lumbar spine and at the total hip

Variable	
BMD, mean ± SD	
Lumbar spine	0.9 ± 0.17
Total hip*	0.76 ± 0.17
T score, mean ± SD	
Lumbar spine	−0.99 ± 1.51
Total hip*	−0.95 ± 1.47
Z score, mean ± SD	
Lumbar spine	−0.49 ± 1.37
Total hip*	−0.25 ± 1.50
Osteopenia	
Lumbar spine and/or total hip, *n* (%)	29 (50.0)
Lumbar spine, *n* (%)	24 (41.4)
Total hip*, *n* (%)	22 (37.9)
Osteoporosis	
Lumbar spine and/or total hip, *n* (%)	8 (13.8)
Lumbar spine, *n* (%)	8 (13.8)
Total hip*, *n* (%)	3 (5.2)

* Data missing for nine patients

CI = 1.32–14.7; $P = 0.016$). Maximal dosage of oral corticosteroids (more than 50 mg/day vs. less than or equal to 50 mg/day) was associated with decreased risk of overall low BMD (crude OR = 0.29, 95% CI = 0.08–0.98; $P = 0.047$). After adjustment for age and the disease duration, there remained no significant association of these factors with low BMD.

As for low BMD at the LS, number of deliveries (crude OR = 4.29, 95% CI = 1.39–13.25; $P = 0.012$) and current use of vitamin K_2 (crude OR = 4.22, 95% CI = 1.03–17.28; $P = 0.046$) were associated with an increased risk of low BMD at the LS. Maximal dosage of oral corticosteroids (crude OR = 0.25, 95% CI = 0.07–0.86; $P = 0.028$) was associated with a decreased risk of low BMD at the LS. Use of a bed (crude OR = 0.34, 95% CI = 0.11–1.07; $P = 0.065$) and a history of renal involvement (crude OR = 0.32, 95% CI = 0.10–1.01; $P = 0.051$) was marginally associated with a decreased risk of low BMD at the LS. After adjustment for age and disease duration, the number of deliveries (adjusted OR = 5.85, 95% CI = 1.31–26.06; $P = 0.02$) was significantly associated with an increased risk of low BMD at the LS and maximal dosage of oral corticosteroids (adjusted OR = 0.25, 95% CI = 0.07–0.91; $P = 0.035$) was significantly associated with a decreased risk of low BMD at LS.

As for low BMD at the hip, postmenopausal state (crude OR = 3.51, 95% CI = 1.0–2.36; $P = 0.51$) was marginally associated with increased risk of low BMD at the hip. Going out daily (crude OR = 0.34, 95% CI = 0.11–1.08; $P = 0.067$) and regular menstruation (crude OR = 0.30, 95% CI = 0.09–1.02; $P = 0.054$) were marginally associated with a decreased risk of low BMD at the hip. However, after adjustment for age and the disease duration, no significant associations remained.

When the number of deliveries and maximal dosage of oral corticosteroids were included in the same model with age and the disease duration, the significant association between the two factors and low BMD persisted. For example, maximal dosage of oral corticosteroids was significantly associated with a decreased risk of overall low BMD (adjusted OR = 0.26, 95% CI = 0.07–0.98, $P = 0.047$) and low BMD at LS (adjusted OR = 0.22, 95% CI = 0.05–0.85, $P = 0.028$). In contrast, the number of deliveries was associated with an increased risk of overall low BMD (adjusted OR = 5.32, 95% CI = 1.05–26.74; $P = 0.043$) (data not shown).

In order to further clarify the preventive effect of corticosteroids, we set up an alternative cut-off dosage of corticosteroids (equivalent to 40 mg/day of prednisolone) (Table 5). The risk for low BMD was compared. In contrast to the results obtained when the patients were divided by the dosage equivalent to 50 mg/day prednisolone, there was no difference in the risk for low BMD between the patients with a maximal dosage >40 mg/day and those with a maximal dosage of ≤40 mg/day. When the patients were subdivided into the groups taking, 0 mg/day ≤ maximal dosage < 20 mg/day, 20 mg/day < maximal dosage ≤ 40 mg/day and maximal dosage > 40 mg/day, there was no significant difference in the low BMD either overall, at the LS or at the hip (Table 5). Similarly, there was no significant difference in the risk for low BMD when the patients were subdivided into six ranges (0 ≤ ever maximal dosage < 10, 10 < dosage ≤ 20, 20 < dosage ≤ 30, 30 < dosage ≤ 40, 40 < dosage ≤ 50, and dosage > 50) when assessed by using 0 ≤ dosage < 10 as a reference (data not shown).

Discussion

Several studies have demonstrated a high prevalence of osteopenia (25–46%) [3–5] and a high prevalence of osteoporosis (1–23%) [6–8] among SLE patients. We observed a prevalence of osteopenia of 50% and a prevalence of osteoporosis of 13.8% among our female Japanese patients. These figures were relatively high, but within the range reported in previous studies of SLE patients. Almost all previous studies focusing on the low BMD in SLE patients have been carried out in Caucasian populations. The prevalence of osteopenia ((50%) [20] or (33% at LS and 74% at FN) [21]) and the prevalence of osteoporosis ((20%) [20] or (48% at LS and 3% at FN) [21]) have been reported in two Asian studies. Racial difference in the prevalence of low BMD between Caucasians and Asians may be small.

Table 3 Characteristics of SLE patients with normal and low BMD at the spine and the hip

Variable	Spine				*P*	Hip				*P*
	Normal BMD ($n = 26$)	Data missing for patients (n)	Low BMD ($n = 32$)	Data missing for patients (n)		Normal BMD ($n = 24$)	Data missing for patients (n)	Low BMD ($n = 25$)	Data missing for patients (n)	
Basic and lifestyle-related										
Age, mean (SD)	41.2 (13.5)		46.2 (13.5)		0.166	40.7 (11.2)		48.0 (15.3)		0.064
BMI, mean (SD)	23.2 (4.1)		21.7 (3.7)		0.147	22.2 (2.9)		21.4 (3.4)		0.406
Postmenopausal status, *n* (%)	6 (23.1)		13 (41.9)	1	0.132	5 (20.8)		12 (48.0)		0.046
History of smoking, *n* (%)	8 (30.8)		3 (9.4)		0.039	8 (33.3)		2 (8.0)		0.028
Going out daily, *n* (%)	10 (43.5)	3	14 (51.9)	3	0.555	6 (28.6)	3	13 (59.1)	3	0.044
Small fish intake more than twice weekly, *n* (%)	10 (38.5)		13 (43.3)	2	0.712	13 (56.5)	1	9 (37.5)	1	0.191
Soybean product intake more than twice weekly, *n* (%)	3 (11.5)		2 (6.3)		0.475	4 (16.7)		1 (4.0)		0.143
Daily coffee or (black) tea intake, *n* (%)	5 (19.2)		8 (25.0)		0.600	3 (12.5)		8 (32.0)		0.102
Number of deliveries, mean(SD)	0.4 (0.8)	1	1.3 (1.2)		0.005	0.74 (1.0)	1	0.96 (1.1)		0.464
Regular menstruation, *n* (%)	18 (75.0)	2	16 (51.6)	2	0.077	17 (73.9)	1	11 (45.8)	1	0.050
History of falls, *n* (%)	14 (60.9)	3	17 (56.7)	2	0.758	14 (66.7)	3	12 (55.0)	1	0.259
Use of bed, *n* (%)	18 (75.0)	2	17 (53.1)	3	0.094	16 (72.7)	2	13 (52.0)		0.145
Clinical										
Disease duration, mean (SD) years	14.7 (7.7)	1	18.0 (9.0)	1	0.150	14.7 (7.4)	1	17.9 (9.1)	1	0.195
Low bone-specific alkaline phosphatase (BAP), *n* (%)	1 (4.2)	1	1 (3.2)	2	0.853	1 (4.3)	1	1 (4.0)		0.952
High type I collagen cross-linked N-telopeptide (NTx), *n* (%)	3 (12.5)	1	0 (0)	2	0.043	1 (4.3)	1	2 (8.0)		0.602
Creatinine clearance, mean (SD) ml/min	102.4 (38.1)		86.5 (33.2)	1	0.100	96.0 (28.1)		84.1 (25.5)	1	0.126
Urine protein, mean (SD) g/day	0.27 (0.56)	2	0.63 (1.10)	3	0.149	0.48 (0.96)	2	0.46 (0.87)	1	0.932
History of renal involvement, *n* (%)	14 (66.7)	5	12 (38.7)	1	0.048	12 (60.0)	4	10 (43.5)	2	0.280
History of previous bone fracture, *n* (%)	4 (15.4)		12 (37.5)		0.061	6 (25.0)		6 (24.0)		0.935
Treatment										
History of corticosteroid use, *n* (%)	26 (100)		30 (93.8)		0.195	23 (95.8)		24 (96.0)		0.976
Treatment duration of corticosteroids, mean (SD) years	13.6 (8.1)	5	17.3 (9.8)	6	0.145	13.8 (7.9)	5	16.4 (8,7)	6	0.345
Maximal dosage of oral corticosteroids, mean (SD) mg/day	50.2 (21.6)	2	37.6 (17.6)	3	0.023	40.9 (21.9)	1	43.4 (16.7)	3	0.665
History of IV methylprednisolone, *n* (%)	10 (38.5)		6 (18.8)		0.095	7 (29.2)		5 (20.0)		0.456
Current use of corticosteroids, *n* (%)	25 (96.2)		29 (90.6)		0.409	23 (95.8)		22 (88.0)		0.317
Actual prednisone dosage, mean (SD) mg/day	9.1 (6.0)		9.0 (5.1)		0.972	9.1 (3.9)	1	8.6 (6.3)	3	0.770

Table 3 continued

Variable	Spine				*P*	Hip				*P*
	Normal BMD ($n = 26$)	Data missing for patients (n)	Low BMD ($n = 32$)	Data missing for patients (n)		Normal BMD ($n = 24$)	Data missing for patients (n)	Low BMD ($n = 25$)	Data missing for patients (n)	
History of cyclophosphamide, *n* (%)	5 (19.2)		11 (34.3)		0.199	4 (16.7)		8 (32.0)		0.212
History of IV cyclophosphamide, *n* (%)	5 (19.2)		4 (12.5)		0.481	3 (12.5)		4 (16.0)		0.726
Current use of cyclophosphamide, *n* (%)	0 (0)		1 (3.1)		0.363	0 (0)		1 (4.0)		0.322
Current use of major tranquilizer, *n* (%)	2 (7.7)		0 (0)	1	0.116					
Current use of antispasmodic, *n* (%)	0 (0)		3 (9.4)		0.109	0 (0)		2 (8.0)		0.157
Current use of vitamin K_2 supplements, *n* (%)	3 (11.5)		11 (35.3)	1	0.036	3 (13.0)	1	7 (28.0)		0.202
Current use of warfarin, *n* (%)	2 (8.3)	1	7 (22.6)	2	0.157	2 (8.7)	1	5 (21.7)	2	0.218
Current use of bisphosphonates, *n* (%)	9 (34.6)		15 (46.9)		0.346	8 (33.3)		11 (44.0)		0.444
Current use of alendronates, *n* (%)	2 (7.7)		6 (18.8)		0.225	2 (8.3)		3 (12.0)		0.672

A higher proportion of osteopenia and osteoporosis at the LS when compared with the hip was observed in our study (Table 2). Our finding may be caused by a reduced spinal trabecular bone mass, which was frequently observed in SLE patients. The predominant trabecular loss in corticosteroid-treated SLE patients may be partly explained by the differential effects of glucocorticoids on bone mineral. Most studies showed that LS is more severely affected by corticosteroids than various hip [11, 22] or distal radius [23] subregions. The rapid loss of spinal trabecular bone in corticosteroid-treated patients seems well established.

We observed a negative association between the number of deliveries and low BMD at LS. As shown in Table 4, the patients with more than one delivery had a significantly increased risk of low BMD at the LS (adjusted OR = 5.85, 95% CI = 1.31–26.06). We also observed a marginally negative association between the number of deliveries and overall low BMD. There are no studies reporting the association between number of deliveries and low BMD in SLE patients. As for pregnancy-associated osteoporosis, there has been a controversy about the presence or absence of pre-existing bone disease [24]. This type of osteoporosis also seems to be observed in SLE patients who frequently use corticosteroids.

In this study, we identified intake history of more than 50 mg oral steroids as a preventive factor of low BMD at LS. This outcome at the spine was rather unexpected. Glucocorticoids are considered to cause symptomatic osteoporosis, which results mainly from reduced bone formation due to direct inhibition of osteoblasts [25], enhanced urinary loss and decreased intestinal absorption of calcium, and possibly increased bone resorption [26]. A randomized study reported significantly decreased markers of bone formation in patients using 5 mg prednisone per day for 6 weeks [27]. Bone loss in patients treated with corticosteroids may be reversible and transient [27–29]. In the above study, the changes of bone formation markers were reversed during the 2-week recovery phase [27]. In a cross-sectional study, no permanent reduction in BMD was seen in patients using daily oral low dose corticosteroids when compared with controls [29]. We have used preventive continuous treatment of calcium and/or vitamin D and recently bisphosphonates for patients who have ever taken high-dose oral corticosteroids. These treatments could have played a protective role in minimizing the effect of steroids on bone density particularly at the LS; however, this cannot explain the increased protection from low BMD in patients who have taken a maximal dosage of >50 mg/day of prednisolone. In contrast, many reports have indicated independence of SLE osteoporosis on glucocorticoid intake [11–14]. Some studies have suggested that corticosteroid has a more

Table 4 Odds ratios and 95% confidence intervals for the association of low BMD and various factors

Factors	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
Overall low BMD				
History of smoking	0.18 (0.04–0.78)	0.022	0.27 (0.06–1.28)	
Going out daily	0.62 (0.21–1.82)		0.82 (0.25–2.62)	
Daily use of black tea or coffee	0.25 (0.05–1.26)		0.28 (0.05–1.52)	
Use of bed	0.28 (0.08–0.98)	0.047	0.31 (0.08–1.18)	
Postmenopausal	3.04 (0.85–10.87)		1.62 (0.20–13.10)	
Regular menstruation	0.40 (0.12–1.33)		0.67 (0.11- 3.89)	
Number of deliveries, more than one	4.4 (1.32–14.70)	0.016	4.45 (0.93–21.34)	0.062
History of IV methylprednisolone	0.45 (0.14–1.46)		0.36 (0.10–1.30)	
Maximal dosage of oral corticosteroids, more than 50 mg/day	0.29 (0.08–0.98)	0.047	0.30 (0.08–1.06)	0.060
Current use of vitamin K_2	2.64 (0.64–10.85)		2.28 (0.52–10.01)	
History of previous bone fracture	2.04 (0.56–7.40)		1.50 (0.39–5.81)	
Creatinine clearance (CCR), 88 > CCR or 128 < CCR	1.05 (0.35–3.12)		0.94 (0.30–2.99)	
Renal involvement	0.28 (0.08–0.96)	0.043	0.27 (0.07–1.03)	0.055
Low BMD at the spine				
History of smoking	0.28 (0.06–1.22)		0.41 (0.09–1.90)	
Going out daily	0.68 (0.24–1.94)		0.84 (0.28–2.56)	
Daily use of black tea or coffee	0.71 (0.20–2.52)		0.86 (0.23–3.21)	
Use of bed	0.34 (0.11–1.07)	0.065	0.38 (0.11–1.26)	
Postmenopausal	2.41 (0.76–7.66)		2.13 (0.31–14.61)	
Regular menstruation	0.36 (0.11–1.4)		0.47 (0.09–2.52)	
Number of deliveries, more than one	4.29 (1.39–13.25)	0.012	5.85 (1.31–26.06)	0.020
History of IV methylprednisolone	0.37 (0.11–1.21)		0.30 (0.08–1.08)	
Maximal dosage of oral corticosteroids, more than 50 mg/day	0.25 (0.07–0.86)	0.028	0.25 (0.07–0.91)	0.035
Current use of vitamin K_2	4.22 (1.03–17.28)	0.046	3.90 (0.92–16.55)	0.065
History of previous bone fracture	3.30 (0.91–11.91)		2.83 (0.75–10.65)	
Creatinine clearance (CCR), 88 > CCR or 128 < CCR	1.36 (0.47–3.90)		1.27 (0.42–3.82)	
Renal involvement	0.32 (0.10–1.01)	0.051	0.31 (0.09–1.05)	0.061
Low BMD at the hip				
History of smoking	0.21 (0.04–1.15)		0.32 (0.05–1.86)	
Going out daily	0.34 (0.11–1.08)	0.067	0.40 (0.12–1.39)	
Daily use of black tea or coffee	0.30 (0.07–1.32)		0.33 (0.07–1.53)	
Use of bed	0.36 (0.11–1.21)		0.48 (0.13–1.70)	
Postmenopausal	3.51 (1.0–2.36)	0.051	2.17 (0.33–14.17)	
Regular menstruation	0.30 (0.09–1.02)	0.054	0.34 (0.06–1.91)	
Number of deliveries, more than one	1.41 (0.45–4.40)		0.84 (0.21–3.36)	
History of IV methylprednisolone	0.61 (0.16–2.27)		0.53 (0.13–2.15)	
Maximal dosage of oral corticosteroids, more than 50 mg/day	1.06 (0.28–3.98)		1.14 (0.29–4.46)	
Current use of vitamin K_2	2.59 (0.58–11.56)		2.47 (0.53–11.56)	
History of previous bone fracture	0.95 (0.26–3.48)		0.65 (0.16–2.67)	
Creatinine clearance (CCR), 88 > CCR or 128 < CCR	0.92 (0.30–2.82)		0.75 (0.22–2.52)	
Renal involvement	0.51 (0.15–1.73)		0.58 (0.16–2.08)	

*Adjusted for age, disease duration

P values > 0.1 were omitted for simplicity

pronounced inhibitory effect on the low BMD at the LS [30, 31], whereas the low BMD at the LS may also be due to the effects of the proinflammatory cytokines involved in the pathogenesis of SLE itself [32]. Spontaneous production of bone-resorbing lymphokines was demonstrated in SLE patients in the absence of corticosteroid therapy [33].

Table 5 Odds ratios and 95% confidence intervals for the association of low BMD and maximal dosage of oral corticosteroids

Maximal dosage of oral corticosteroids	Crude OR (95% CI)	P	Adjusted OR* (95% CI)	P
Overall low BMD				
Dosage > 40 versus dosage ≤ 40	0.36 (0.11–1.12)	0.094	0.32 (0.09–1.09)	0.078
20 < dosage ≤ 40 versus 0 ≤ dosage < 20	0.75 (0.06–8.83)		2.16 (0.14–33.24)	
Dosage > 40 versus 0 ≤ dosage < 20	0.30 (0.03–2.98)		0.69 (0.06–8.34)	
Low BMD at the lumbar spine				
Dosage > 40 versus dosage ≤ 40	0.35 (0.11–1.09)	0.070	0.34 (0.11–1.01)	0.071
20 < dosage ≤ 40 versus 0 ≤ dosage < 20	1.47 (0.18–11.71)		4.33 (0.39–47.78)	
Dosage > 40 versus 0 ≤ dosage < 20	0.56 (0.08–3.77)		1.36 (0.15–12.08)	
Low BMD at the total hip				
Dosage > 40 versus dosage ≤ 40	1.58 (0.48–5.12)		1.50 (0.43–5.23)	
20 < dosage ≤ 40 versus 0 ≤ dosage < 20	1.29 (0.16–10.45)		6.09 (0.40–93.88)	
Dosage > 40 versus 0 ≤ dosage < 20	2.00 (0.29–13.91)		6.68 (0.53–84.70)	

*Adjusted for age and disease duration

P values > 0.1 were omitted for simplicity

In fact, patients who had never treated with corticosteroid showed a lower hip BMD than controls, indicating that the disease per se might induce bone loss [34]. Almehed et al. [35], therefore, hypothesized that a low dose of corticosteroids may protect from osteoporosis by diminishing systemic inflammation known to accelerate bone loss while higher doses may decrease BMD by different mechanisms such as reducing bone formation by negative effects on the osteoblasts. Based on these findings, high-dose oral corticosteroid intake in the acute phase may protect bone mass at the LS by reducing inflammation due to proinflammatory cytokines in SLE patients. Dhillon et al. [14] reported the possibility that lupus patients may be protected from osteoporosis in view of the work where Lahita et al. [36] showed increased rates of 16-α-hydroxylation of estradiol in lupus patients, with the formation of 'estrogenic' metabolites such as 16-α-hydroxyestrone and estriol. Bhattoa et al. [6] suggested that the measured bone mass could be a result of both positive and negative effects of corticosteroids on body mass. Our finding was supported by this hypothesis although our small sample size prevents us from drawing a definite conclusion.

We investigated the lifestyles of our SLE patients, and found that the use of a bed had a marginal negative association with low overall BMD and low BMD at the LS and going out everyday had a marginal negative association with low BMD at the hip before adjustment for age and disease duration (Table 4). Body weight is thought to affect BMD in pre- and postmenopausal women by affecting the mechanical stress placed on the skeleton leading to osteogenesis [37, 38]. It is reported that weight-bearing exercise like regular walking has no significant effect on preservation of BMD at the spine in postmenopausal women, while significant positive effects at FN are evident [39, 40]. Co-twin control studies have revealed that FN BMD is more sensitive to environmental factors, such as physical loading than lumber BMD, which is more strongly influenced by genetics [41]. It is important that use of a bed and light activity like going out could preserve BMD in SLE patients, and such lifestyle modification might be useful to prevent bone loss in SLE patients.

An inverse relationship between smoking and bone density is well established [42], and is due to multiple factors including an earlier menopause in females, reduced body weight, and enhanced metabolic breakdown of exogenous estrogens. Cigarette smoke extract inhibited in vitro differentiation of osteoprogenitor cells to osteoblast-like cells. In premenopausal women, bone density is similar in smokers and non-smokers, however, postmenopausal bone loss is greater in current smokers than non-smokers [43]. In the present study, a history of smoking was associated with a decreased risk of low overall BMD, which turned out to be not significant after adjustment for age and disease duration. It is possible that smokers in our study might be younger and in better health than the non-smokers. Current use of vitamin K_2 was marginally associated with an increased risk of low BMD at the LS ($P = 0.064$). We prescribe vitamin K_2 to SLE patients with severely low BMD in our hospital. Vitamin K_2 treatment for osteoporosis has been shown to reduce the risk of new vertebral fractures, although it fails to increase BMD [44].

In conclusion, reduced BMD, especially in the spinal trabecular bone, was pronounced in Japanese female patients with SLE, particular in those who have ever delivered. Therefore, these patients should be considered a high-risk group deserving regular BMD scans and therapy

to prevent vertebral fractures. We showed that a history of oral corticosteroids (equivalent to more than 50 mg/day of prednisolone) was associated with the preservation at the lumbar spine although the strength of this evidence is limited by our small sample size. Additional studies with larger sample size will undoubtedly lead to a more thorough understanding of the preservative role of high-dose oral corticosteroids on BMD in female patients with SLE.

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