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**Shogo Banno · Yoshifuji Matsumoto · Taio Naniwa
Yoshihito Hayami · Yoshiki Sugiura · Takeo Yoshinouchi
Ryuzo Ueda**

Reduced bone mineral density in Japanese premenopausal women with systemic lupus erythematosus treated with glucocorticoids

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Abstract We evaluated bone mineral density (BMD) in Japanese female patients with systemic lupus erythematosus (SLE) and assessed the influence of the use of glucocorticoids. Lumbar BMD was measured by dual x-ray absorptiometry (DXA) in 60 premenopausal females who previously had been receiving glucocorticoid therapy. Therapeutic- and disease-related variables for SLE were analyzed and bone resorption or formation markers were measured. Osteoporosis was defined as a T-score below 2.5 SD by DXA; 12 patients (20%) showed osteoporosis, and 30 (50%) had osteopenia. Compared with the nonosteoporotic group ($n = 48$), the osteoporotic group ($n = 12$) had a significantly longer duration of glucocorticoid treatment ($P = 0.01$), a cumulative prednisolone dose ($P = 0.002$), and an SLE damage index (SLICC/ACR). There was no difference in the incidence of osteoporosis either with or without the previous use of methyl-prednisolone pulse or immunosuppressive drugs. There was a significant positive correlation between urinary type I collagen cross-linked N-telopeptides (NTx) and serum bone-specific alkaline phosphatase (BAP) ($r = 0.404$, $P = 0.002$), but these bone metabolic markers showed no difference between the osteoporotic and nonosteoporotic groups. A good significant negative correlation was shown between BMD and the cumulative glucocorticoid dose ($r = -0.351$, $P = 0.007$). Stepwise logistic regression analysis showed that the cumulative glucocorticoid intake was independently associated with osteoporosis. Glucocorticoid-induced osteoporosis was frequently observed in Japanese SLE patients, as in Caucasian populations. The cumulative glucocorticoid dose was associated with an increased risk for osteoporosis. Bone metabolic markers such as NTx and BAP were not influenced by glucocorticoid treatment and could not predict current osteoporosis in SLE patients.

S. Banno (✉) · Y. Matsumoto · T. Naniwa · Y. Hayami · Y. Sugiura · T. Yoshinouchi · R. Ueda
Second Department of Internal Medicine, Medical School, Nagoya City University, 1 Kawasumi, Mizuho-ku, Nagoya 467-8601, Japan
Tel. +81-52-853-8216; Fax +81-52-852-0849

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease resulting in multisystem damage, and the clinical course is characterized by periods of remission and relapse. Most SLE patients need glucocorticoid therapy to control the disease activity. However, numerous adverse effects may result from glucocorticoid use.

Glucocorticoid-induced osteoporosis is one of the major adverse effects resulting from chronic oral glucocorticoid use.[1] In particular, osteoporotic fractures lead to a reduced quality of life and diminished daily life activity in premenopausal patients. A UK consensus group recommended a treatment algorithm for adults receiving a glucocorticoid dose of more than 7.5 mg/day or for more than 6 months according to T-scores measured by bone mineral density (BMD).[2] To our knowledge, there are few reports about glucocorticoid-induced osteoporosis in Japanese premenopausal women with SLE. We determined the prevalence of reduced BMD in Japanese premenopausal women with SLE and identified factors predictive of reduced BMD. In addition, bone resorption or bone formation biochemical markers were measured to evaluate whether these bone metabolic markers could estimate glucocorticoid-induced osteoporosis.

Materials and methods

Sixty consecutively glucocorticoid-treated premenopausal Japanese women with SLE were recruited for this study. All were ambulatory at Nagoya City University Hospital and

fulfilled the American Rheumatism Association's revised criteria for the diagnosis of SLE. Recorded patient data included age, body mass index, disease activity of SLE, and medical treatment history. Therapeutic variables for SLE were the duration of glucocorticoid therapy, cumulative glucocorticoid dose, maximum or current prednisolone dose, and previous use of glucocorticoid pulse or immunosuppressive agents from a detailed review of medical records. The cumulative glucocorticoid dose was calculated as the total prednisolone dose, in which methyl-prednisolone pulse therapy, (defined as a methyl-prednisolone dose of more than 500 mg/day for 3 consecutive days) was converted to prednisolone, given the pharmacological action.

Disease activity in patients with SLE was scored by the SLE disease activity index (SLEDAI), and accumulated organ damage by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage index (SLICC/ACR). The SLEDAI served for the model of global assessment of activity at the time of BMD measurement. Otherwise, the SLE damage index (DI) (SLICC/ACR) is designed to assess cumulative organ damage due to SLE since the onset of the disease, caused by the disease itself or by the treatment. No patients were receiving estrogen replacement therapy. Patients who were administered bisphoshanate or vitamin K_2 were excluded from this study.

Lateral radiographs of the lumbar spine were obtained to estimate the vertebral bone deformity in all patients. The vertical heights of the anterior margin (A), central portion (C), and posterior margin (P) of each vertebral body were measured, and the vertebral bone deformity was defined by a reduced A/P value (less than 0.75), or reduced C/A, C/P values (less than 0.8).[3]

BMD of the lumbar spine (L1–4) was measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR 1000 densitometer (Hologic, Waltham, MA, USA) in a spine position with straightening of the lordotic curvature by elevating the legs; BMD was expressed in g/cm^2. The mean lumbar spine BMD was used in this study. All scans were obtained and reviewed by radiologists to exclude calcification and osteoarthritic change according to the standard procedures. Severe compression fracture of vertebral bone can cause aberrations in BMD data, and these vertebral bone data were excluded. Osteoporosis was defined according to the WHO criteria (-2.5 SD below the mean value obtained in healthy women between the ages of 20 and 40 years: T-score < -2.5 SD). Patients were determined to be either normal (T-score $\geqq -1.0$ SD) or to have osteopenia (-2.5 SD $\leqq$ T-score < -1.0 SD) based on these criteria.

Biochemical parameters of bone metabolism were determined within 1 month of BMD measurement. Urinary excretion of type I collagen cross-linked N-telopeptides (NTx) and serum bone-specific alkaline phosphatase (BAP) were measured by ELISA kit, Osteomark (Ostex, Seattle, WA USA)[4] and Alphatase B (Quidel, CA, USA)[5], respectively. The former is known to be a sensitive bone resorption marker, the latter as a bone formation marker.

The between-group Mann-Whitney *U* test was used when appropriate to compare differences among continuous variables. *P* values $\leqq 0.05$ were deemed to be statistically significant. Pearson's correlation coefficient was used to calculate the relationship between continuous variables. Statistically significant variables were entered in a stepwise logistic model in which the presence of osteoporosis was the dependent variable.

Results

The clinical characteristics of patients are shown in Table 1. All patients were previously receiving glucocorticoids, and all but one patient received it at the time of DXA measurement. The mean cumulative dose of prednisolone was 31.9 $\pm$ 19.8 g, and the mean duration of glucocorticoid treatment was 121 $\pm$ 67 months. Twenty-eight patients (47%) were

Table 1. Clinical characteristics in 60 premenopausal patients with SLE

Continuous variables	Mean $\pm$ SD	Range
Age (years)	34.8 $\pm$ 8.1	20–48
Body mass index (BMI)	20.6 $\pm$ 2.6	16.2 $\pm$ 28.5
Duration of glucocorticoid therapy (months)	121 $\pm$ 67	11–302
Cumulative glucocorticoid dose (g)	31.9 $\pm$ 19.8	4.1 $\pm$ 21.8
Mean daily prednisolone dose (mg/day)	9.6 $\pm$ 4.3	2.1–21.8
Maximum prednisolone dose (ever used) (mg/day)	45.6 $\pm$ 14.5	20–80
SLEDAI score	1.7 $\pm$ 2.2	0–8
SLE damage index (SLICC/ACR)	0.9 $\pm$ 1.2	0–4
Categorical variables	**Number**	**%**
Methyl-prednisolone pulse therapy (ever used)	28	47
Immunosuppressive drugs (ever used)	19	32
Vitamin D_3 therapy (ever used)	26	43
SLE damage index (SLICC/ACR) $\geqq$1	26	43

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology

Table 2. Disease- and treatment-related variables according to the presence of osteoporosis in patients with SLE

Variable	Osteoporosis $n = 12$ medium ± SD	No osteoporosis $n = 48$ medium ± SD	P
BMD (g/cm^2)	0.693 ± 0.067	0.875 ± 0.088	
T-score	−3.2 ± 0.6	−1.4 ± 0.8	
Z-score	−2.5 ± 0.9	−1.0 ± 0.8	
Age (years)	36.0 ± 8.7	35.5 ± 7.9	NS
Body mass index	19.9 ± 1.9	20.2 ± 2.7	NS
Duration of glucocorticoid treatment (months)	164 ± 65	108 ± 64	0.01
Cumulative glucocorticoid dose (g)	44.0 ± 21.5	24.4 ± 17.2	0.002
Mean daily prednisolone dose (mg/day)	9.7 ± 5.0	8.3 ± 4.1	NS
SLEDAI score	1.4 ± 1.7	1.8 ± 2.3	NS
SLE damage index (SLICC/ACR)	1.4 ± 1.4	0.7 ± 1.1	0.05
Urinary NTx (nMBCE/mMCr)	36.6 ± 16.7	34.6 ± 20.6	NS
Serum BAP (U/l)	17.9 ± 5.9	19.8 ± 6.6	NS

BMD, bone mineral density; NTx, type I collagen cross-linked N-telopeptides; BAP, bone-specific alkaline phosphatase; NS, Not significant. For other abbreviations, see Table 1

previously treated with methyl-prednisolone pulse therapy, and 19 patients (32%) had used immunosuppressive drugs such as azathioprine, mizoribine, or cyclophosphamide. Twenty-six patients (43%) were treated with vitamin D_3 (alfacalcidol, 0.5 μg/day) for more than 12 months. The SLEDAI score at the time of the study showed that most patients had little disease activity.

Thirty patients (50%) had osteopenia and 12 (20%) had osteoporosis of the lumbar spine. The other 18 patients had normal T-scores. Bone deformity of the lumbar spine was determined in 10 patients. To further characterize glucocorticoid–induced osteoporosis in SLE, patients were then classified into two groups: osteoporosis group ($n = 12$) and nonosteoporosis group ($n = 48$) (Table 2). The nonosteoporosis group had osteopenia and normal a T-score. There was a significantly lower BMD in the 12 osteoporotic patients (0.693 ± 0.067 g/cm^2) than in the 48 nonosteoporotic patients (0.875 ± 0.088 g/cm^2). When compared with the nonosteoporotic group, the osteoporotic group had a significantly longer duration of glucocorticoid treatment ($P = 0.01$) and cumulative prednisolone dose ($P = 0.002$), whereas the mean daily prednisolone dose was not statistically different. The SLE damage index (SLICC/ACR) was significantly higher in the osteoporotic group than in the nonosteoporotic group, but the SLEDAI score showed no difference between the two groups. Moreover, there were no differences in urinary NTx or serum BAP between them.

There was no difference in the frequency of osteoporosis and BMD regardless of whether a patient previously used methyl-prednisolone pulse, immunosuppressive drugs, or vitamin D_3 (Table 3). Patients with persistent organ damage (SLICC/ACR score >1) showed a significantly higher frequency of osteoporosis and a more increased BMD than did patients without damage (SLICC/ACR score, 0). The prior occurrence of a flare-up of SLE and high-dose prednisolone (maximum dose ≧ 40 mg/day) tended to decrease in BMD, but not statistically. Otherwise, both urinary NTx and serum BAP levels showed no difference among all categorized variables used in Table 3. The SLE damage index was not influenced by urinary NTx or serum BAP.

Linear correlation analysis (Table 4) showed a significantly weak association between BMD and the duration of glucocorticoid therapy ($r = -0.284$), SLE damage index (SLICC/ACR) ($r = -0.246$) or body mass index ($r = 0.278$). A better significant negative correlation was found between BMD and the cumulative glucocorticoid dose ($r = -0.351$). A statistically positive correlation was confirmed between NTx and BAP ($r = 0.404$, $P = 0.002$), whereas these bone metabolic markers showed no association with clinical variables in SLE.

The presence of osteoporosis was analyzed by a multivariate logistic regression test in which the independent variables were age, cumulative glucocorticoid intake, mean daily prednisolone dose, the presence of methyl-prednisolone pulse, immunosuppressive drugs, and vitamin D_3 (Table 5). This stepwise logistic regression analysis showed that the cumulative glucocorticoid intake was independently associated with osteoporosis ($P = 0.02$), although the odds ratio was low at 1.06 [95% confidence interval (CI), 1.01–1.11].

Discussion

This study at a single rheumatology institution, performed on young premenopausal glucocorticoid-treated patients with SLE, showed that glucocorticoid-induced osteoporosis was a frequent disease manifestation. In our sample, osteoporosis and osteopenia were found in 20% and 30% of the subjects, respectively. Several previous studies agreed that BMD in patients with SLE was significantly decreased compared with healthy controls.[6,7] The prevalence of osteoporosis in the lumbar spine, defined as BMD less than −2.5 SD according to WHO criteria, was reported in about

Table 3. Frequency of osteoporosis and univariate relationships of BMD (g/cm^2) with categorical variables

		Number	Osteoporosis *n* (%)	BMD medium ± SD	*P*
Vertebral bone deformity	Yes	10	9 (90%)	0.704 ± 0.120	0.005
	No	50	4 (8%)	0.865 ± 0.100	
Methyl-prednisolone pulse therapy (ever used)	Yes	28	6 (21%)	0.830 ± 0.116	NS
	No	32	6 (19%)	0.840 ± 0.121	
Immunosuppressive drugs (ever used)	Yes	19	5 (26%)	0.835 ± 0.125	NS
	No	41	4 (10%)	0.834 ± 0.112	
Vitamin D_3 therapy (ever used)	Yes	26	5 (19%)	0.814 ± 0.126	NS
	No	34	7 (21%)	0.859 ± 0.109	
SLE flare up (ever)	Yes	38	11 (29%)	0.833 ± 0.125	NS
	No	22	1 (5%)	0.851 ± 0.097	
SLE damage index (SLICC/ACR)	≧1	26	8 (31%)	0.807 ± 0.133	0.05
	0	34	4 (12%)	0.859 ± 0.017	
Maximum prednisolone dose (ever used) (mg/day)	≧40	45	12 (27%)	0.845 ± 0.126	NS
	<40	15	0 (0%)	0.833 ± 0.089	
Current prednisolone dose (mg/day)	≧7.5	30	6 (20%)	0.827 ± 0.119	NS
	<7.5	30	6 (20%)	0.847 ± 0.116	
Urinary NTx (nMBCE/mMCr)	≧40	23	6 (26%)	0.852 ± 0.134	NS
	<40	36	6 (17%)	0.835 ± 0.109	

For abbreviations, see Tables 1 and 2

Table 4. Univariate relationships with BMD and multivariate logistic regression analysis associated with osteoporosis

Correlation coefficient for BMD and continuous variables

	BMD	
	R	*P*
Age	−0.217	0.11
BMI	0.278	0.03
Duration of glucocorticoid treatment	−0.284	0.02
Cumulative glucocorticoid dose	−0.351	0.007
Mean prednisolone dose per day	−0.038	0.78
SLEDAI score	−0.046	0.73
SLE damage index	−0.246	0.06
Urinary NTx	0.003	0.83
Serum BAP	−0.038	0.39

Table 5. Multivariate logistic regression analysis associated with osteoporosis

	Coefficient	Odds ratio	95% CI	*P*
Cumulative glucocorticoid dose	0.056	1.06	1.01–1.11	0.02

Dependent variable, presence of osteoporosis; independent variables, cumulative glucocorticoid dose, age, mean daily prednisolone dose, presence of methyl-prednisolone pulse therapy, immunosuppresive drugs, and vitamin D_3

CI, confidence interval. For other abbreviations, see Tables 1 and 2

10%–25% of Caucasian subjects in a cohort of recent studies.[8–12] Moreover, several studies indicated that reduced total BMD in SLE was associated with glucocorticoid intake, whereas in some reports bone loss was not due to glucocorticoid treatment.[6–8] The wide distribution in the frequency and the discrepancies in the relationship with glucocorticoid influence in these studies were considered to be due to differences in sample size and mixing of male and female patients, premenopausal and postmenopausal together in the populations studied, or because patients with SLE never treated with glucocorticoids were included.

In an analysis resembling our study populations that examined 84 Italian premenopausal young ambulatory patients receiving glucocorticoid treatment, osteoporosis was found in 22.6% of the patients, and significant differences in BMD were detected in cumulative glucocorticoid intake and higher SLICC/ACR scores.[12] On the other hand, Li et al.[13] showed that the frequency of osteoporosis in 52 Chinese premenopausal patients with SLE was only 4%, a much lower prevalence than in Caucasian patients. In addition, from examining such factors as cumulative dose, mean daily dose, or treatment duration, no correlation was found between BMD and glucocorticoid therapy. The same authors reported that the lower rate and no correlation with glucocorticoid therapy compared with Caucasians were caused by an interethnic difference in calcium homeostasis. However, our results from a Japanese population suggested that the high prevalence of osteoporosis was similar to the results of a study of Caucasians.[12] A comparison was reported using the same DXA measuring instrument among Asian people including Japanese, Koreans, and Taiwanese having no history of chronic illness. An age-dependent loss of BMD was clearly observed in Japanese and Koreans but not in Taiwanese women, particularly in the third and fourth decades of life.[14] These data may suggest that the difference in bone loss among Japanese or Koreans was caused by their Westernized lifestyle, although DNA polymorphisms such as vitamin D_3 receptor, estrogen receptor, or TGF-β were thought to be associated with the racial differences of osteoporosis.[15]

Our data indicated that highly cumulative glucocorticoid intake, longer disease duration, and high SLICC/ACR scores were correlated with lower BMD. Stepwise logistic regression analysis showed that a cumulative glucocorticoid dose was associated with osteoporosis independently of other variables. These results confirm those of Lakshminarayanan et al.[16] in premenopausal patients with SLE, which also showed a correlation between the cumulative glucocorticoid dose and BMD. However, some reports[6,13] indicated no relationship between them. Interestingly, our results showed no relationship of the daily prednisolone dose or previously administered methyl-prednisolone pulse. In addition, a history of previously used immunosuppressive drugs or vitamin D_3 supplement did not influence BMD. The risk of osteoporosis was associated with cumulative doses of glucocorticoids and the organized damage from SLE. These data suggested that the key to prevention of glucocorticoid-induced osteoporosis in patients with SLE was a reduction in the cumulative glucocorticoid intake together with methyl-prednisolone pulse therapy to decrease the organ damage in a short time.

In several clinical studies, biochemical markers of bone metabolism, representing urinary NTx and serum BAP, have been used to assess the treatment of osteoporosis.[17]

In a recent study[18] among Japanese women without any treatment affecting bone metabolism, both NTx and BAP values in postmenopausal women were significantly higher than those in premenopausal women, showing that NTx inversely correlated with BMD ($r = -0.408$), and that there was a markedly high correlation between NTx and BAP ($r = 0.756$). In another report, the levels of NTx discriminated between normal, osteopenic, and osteoporotic BMD levels in female subjects, aged 50 to 98 years, particularly with nonestrogen users.[19] We found that a correlation coefficient existed between NTx and BAP ($r = 0.404$), although there was no difference between these bone metabolic markers and BMD. We concluded that the levels of these markers could not be used to predict current osteoporosis. A single baseline measurement of urinary collagen cross-links (pyridinoline and deoxypyridinoline), namely, bone resorption markers, was not predictive of bone loss in premenopausal women with SLE.[20] Changes in bone markers may be demonstrated within weeks of beginning administration of glucocorticoid.[21] It is thought that bone markers play a limited role in the detection of osteoporosis, but may have a major application in monitoring responses to osteoporosis treatments. The bone markers were dependent on the effect of a recently increased glucocorticoid dose, whereas BMD was influenced by the total cumulative bone loss induced by total glucocorticoid intake over the long term.

In conclusion, the prevalence of glucocorticoid-induced osteoporosis in Japanese premenopausal women with SLE was similar to the high ratio among Caucasians but differed from that in a Chinese population. Our data demonstrated that osteoporosis was associated with cumulative glucocorticoid intake, that patients with SLE undergo increased glucocorticoid intake for a long time because of the severity and distribution of organ damage, and that these patients needed more aggressive prevention and treatment measures against osteoporosis.

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