Bone Mineral Density in Premenopausal Women with Systemic Lupus Erythematosus

SOMCHAI UARATANAWONG, UTIS DEESOMCHOKE, SOMRAT LERTMAHARIT, and SOMSRI UARATANAWONG

ABSTRACT. ***Objective.*** To study bone mineral density (BMD) in premenopausal women with systemic lupus erythematosus (SLE) and to evaluate the influence of disease activity and use of corticosteroids.

Methods. A cross-sectional study on BMD of 118 premenopausal women with SLE. Patients were divided into 2 groups, 74 who had been treated with corticosteroids and 44 who had not. BMD at lumbar spine, femoral neck, and trochanter was measured.

Results. BMD in patients without and with corticosteroid treatment was 1.13 ± 0.13 vs 1.05 ± 0.14 g/cm^2 (p = 0.005) at lumbar spine, 0.92 ± 0.12 vs 0.86 ± 0.12 g/cm^2 (p = 0.005) at femoral neck, and 0.78 ± 0.13 vs 0.72 ± 0.12 g/cm^2 (p = 0.014) at trochanter, respectively. Stepwise multilinear regression analysis showed that corticosteroid exposure was independently associated with decreased BMD in the corticosteroid treated patients (r^2 = 7% for lumbar and 6.6% for trochanter model). No significant difference in BMD in corticosteroid treated patients appeared when they were subgrouped according to whether they were taking calcium supplements. Prevalence of osteoporosis at lumbar spine in corticosteroid treated patients was 1.4%, and was lower than reported for age and sex matched Caucasians.

Conclusion. BMD measurements were significantly lower in premenopausal SLE patients who had had corticosteroid treatment than those who had not. There was a negative correlation between BMD and corticosteroid therapy, but not disease activity. Prevalence of osteoporosis, based on lumbar spine BMD, was lower than that reported in Caucasians. (J Rheumatol 2003;30:2365–8)

Key Indexing Terms:
BONE MINERAL DENSITY
CORTICOSTEROIDS
SYSTEMIC LUPUS ERYTHEMATOSUS
OSTEOPOROSIS

Over recent decades, the life expectancy of patients with systemic lupus erythematosus (SLE) has improved dramatically[1]. This raises new concerns about drug induced side effects including premature menopause, late malignancy, accelerated atherosclerosis, and osteoporosis. Bone loss leading to fracture is associated with longterm morbidity and increased mortality[2]. Prolonged steroid therapy is known to increase the development of osteoporosis and fractures[3,4]. Research conducted predominantly in rheumatoid arthritis (RA) has shown that corticosteroids have a significant role in the loss of bone mass[5-7]. Although the effect of disease activity and corticosteroid therapy on bone mineral density (BMD) in patients with SLE has been assessed, most studies have been confined to the Caucasian population and the conclusions have been conflicting[8-12].

Evidence is now growing that calcium homeostasis and the effects of declining BMD are affected by ethnicity[13-16]. Further, the decline in BMD varies among different ethnic groups[14]. To evaluate the effects of longterm corticosteroid therapy on BMD and the prevalence and severity of bone loss, we studied a group of premenopausal women of Thai descent with SLE.

MATERIALS AND METHODS

Patients. A group of 118 premenopausal Thai women with SLE were clinically evaluated and underwent BMD measurement. They attended the rheumatology outpatient clinic at the Bangkok Metropolitan Administration Medical College and Vajira Hospital. All patients fulfilled the revised criteria of the American College of Rheumatology for the classification of SLE[17]. They were ambulatory, physically active, and in functional class 1 or 2 using the criteria of Steinbrocker[18]. The duration of disease, daily and cumulative prednisolone doses, and the duration of prednisolone therapy were obtained through comprehensive review of medical records. All patients were nonsmokers. Exclusion criteria were as follows: renal impairment (serum creatinine > 2 mg/dl); use of any medication known to affect bone metabolism, with the exception of calcium supplements and corticosteroids (i.e., anticoagulants, barbiturates, calcitonin, thiazides, estrogenic hormones); transient amenorrhea lasting > 2 months; or hyperthyroidism. Lupus disease activity and severity also were evaluated[19] by the SLE Disease Activity Index[20] and a simple severity of disease index for SLE[19], respectively. The patients were divided into 2 groups. Group 1 included 44 patients who had never taken prednisolone. Group 2

From the Rheumatology Unit, Department of Medicine, Bangkok Metropolitan Medical College and Vajira Hospital, Bangkok, Thailand.

S. Uaratanawong, MD, Rheumatology Unit, Department of Medicine, Bangkok Metropolitan Administration Medical College and Vajira Hospital; U. Deesomchoke, Professor, Rheumatology Unit, Department of Medicine, Faculty of Medicine, Chulalongkorn University;
S. Lertmaharit, Assistant Professor, Department of Preventive and Social Medicine, Chulalongkorn University; S. Uaratanawong, BSc, Division of Nuclear Medicine, Department of Radiology, Bangkok Metropolitan Administration Medical College and Vajira Hospital.

Address reprint requests to Dr. S. Uaratanawong, Rheumatology Unit, Department of Medicine, Bangkok Metropolitan Administration Medical College and Vajira Hospital, 681 Samsen Road, Dusit, Bangkok 10300, Thailand.

Submitted June 20, 2001; revision accepted April 17, 2003.

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

included 74 patients who had been treated with prednisolone. Thirty-one of the 74 prednisolone treated patients had been arbitrarily receiving calcium supplement (calcium carbonate 1000 mg/day) before commencement of this study (mean duration 6 ± 2.5 mo). The effect of calcium supplementation on BMD was analyzed separately by subgrouping prednisolone treated patients into those receiving (n = 31) and not receiving (n = 43) calcium supplement.

Bone density measurements. BMD (g/cm^2) of the lumbar spine (L2–L4) and left hip (femoral neck, trochanter) was measured by dual energy x-ray absorptiometry (DEXA) with a Lunar DPX-L (Lunar Radiation Corp., Madison, WI, USA). The coefficients of variation in a phantom were 0.5% for lumbar spine and 1.3% for the hip. Osteoporosis was defined using WHO criteria[21]. Multivariable data analysis determined factors related to BMD at lumbar, neck, and trochanteric area. All treated patients were included to determine the strength of association between BMD and other factors, i.e., daily dose of prednisolone, duration of treatment, cumulative dose, disease duration, disease activity and severity, and calcium supplement.

Statistical analysis. Data were expressed as mean ± standard deviation. Demographic and clinical characteristics of patients were compared using unpaired t tests for continuous variables and the chi-square statistic for proportions. Correlations between clinical and demographic characteristics with lumbar spine and proximal femur (femoral neck and trochanter) BMD were evaluated using Pearson correlation coefficient for continuous variables. A stepwise multiple linear regression model assessed the independent effects of corticosteroid related variables (mean daily dose, duration of treatment, cumulative dose) and disease related variables (disease duration, disease activity, disease severity, calcium supplements) on the change in the lumbar spine and proximal femur BMD. P value < 0.05 was considered statistically significant. All analyses were performed using SPSS for Windows v.10 (SPSS, Chicago, IL, USA).

RESULTS

Demographic data of the 74 SLE patients with prednisolone therapy and 44 patients without prednisolone as controls are shown in Table 1. The clinical characteristics of the patients did not differ significantly between the groups. Disease activity was greater in the non–prednisolone patients. This was probably related to the absence of glucocorticoid therapy. BMD measures in prednisolone treated patients were significantly lower at the lumbar spine and proximal femur than the non-prednisolone patients. Pearson correlation coefficient in prednisolone treated patients showed BMD was correlated to prednisolone treatment (average daily dose, cumulative dose, or duration of treatment), but not to duration of disease, severity of disease, and disease activity (Table 2). The stepwise method was used to select significant variables affecting BMD. The results (Table 3) showed that only cumulative dose was significant and entered in the model for BMD at lumbar spine, and duration of treatment was the only variable to be selected in the model for BMD at trochanter. No variable was significant to be selected into the model for BMD at the neck. However, the coefficient of determination (r^2) in both models was very low, only 7% for lumbar spine and 6.6% for trochanter.

We further compared BMD in prednisolone treated patients subgrouped according to calcium supplement status. There was no difference in BMD between both subgroups. There was only one prednisolone treated patient with lumbar spine BMD 2.5 below that of healthy young controls. It was not present in any of the 44 non-prednisolone treated patients. The frequency of osteoporosis at the lumbar spine in prednisolone treated patients was 1.4% and frequency of osteopenia according to WHO criteria[21] was 6.8–32.4%.

DISCUSSION

Consistent with the majority of studies evaluating Caucasians, this study has shown that BMD is significantly lower in both cortical and trabecular sites in premenopausal Thai patients with SLE taking chronic prednisolone therapy. Meaningful comparison between our study and others is limited because of differences in populations with respect to

Table 1. Characteristics of patients with SLE (mean ± SD).

	SLE without Prednisolone, n = 44	SLE with Prednisolone, n = 74	p
Age, yrs (range)	33.98 ± 7.88 (18–49)	31.82 ± 8.08 (16–49)	0.161
Weight, kg	51.89 ± 7.99	53.70 ± 10.31	0.318
Height, m	1.54 ± 5.44	1.54 ± 0.06	0.929
BMI, kg/m^2	22.06 ± 3.03	22.77 ± 4.38	0.342
Disease duration, mo (range)	17.08 ± 25.77 (4.5–120)	30.34 ± 31.58 (4.5–120)	0.015*
Duration of pred, mo (range)	—	19.00 ± 23.37 (0.5–120)	
Mean dose, mg/day (range)	—	18.73 ± 15.89 (2.5–60)	
Cumulative dose, mg (range)	—	5228 ± 5172 (140–27,000)	
Disease activity† (range)	7.93 ± 5.97 (0–24)	2.88 ± 4.12 (0–16)	< 0.001*
Disease severity†† (range)	2.20 ± 1.29 (1–6)	2.11 ± 0.97 (1–5)	0.646
Function class			
1	33	55	0.804
2	11	19	
Lumbar BMD, g/cm^2	1.126 ± 0.126	1.053 ± 0.140	0.005*
Femoral BMD, g/cm^2			
Neck	0.918 ± 0.118	0.859 ± 0.115	0.005*
Trochanter	0.777 ± 0.125	0.717 ± 0.120	0.014*

† SLE Disease Activity Index (SLEDAI)[20]. †† Severity of disease index for SLE[19].

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

Table 2. Correlations between corticosteroid and BMD.

	Lumbar Spine	Femoral Neck	Trochanter
Daily dose	0.230	0.102	0.242
p	0.048	0.392	0.042
n	74	73	71
Drug duration	–0.202	–0.206	–0.256
p	0.085	0.081	0.031
n	74	73	71
Cumulative dose	–0.264	–0.157	–0.219
p	0.023	0.186	0.067
n	74	73	71
Disease duration	–0.038	–0.163	–0.117
p	0.745	0.169	0.333
n	74	73	71
Disease activity	0.060	–0.029	0.032
p	0.612	0.808	0.788
n	74	73	71
Disease severity	–0.020	–0.032	–0.008
p	0.868	0.786	0.950
n	74	73	71

disease variables (activity and duration of disease), prednisolone therapy (indication for treatment, dose and duration), and type of controls. Many studies show that SLE patients taking prednisolone have decreased BMD compared with controls[9,10,12,22-24]. In the study of Pons, *et al*[11] no difference could be found for BMD at either lumbar spine or femoral neck between controls, SLE patients who had never received corticosteroids, and SLE patients taking corticosteroids. In our study, trabecular (lumbar spine, trochanter) and cortical (neck) bone mass was significantly reduced in prednisolone treated patients compared with controls, in agreement with studies by Formiga, *et al*[10] and Li, *et al*[24], but not Houssiau, *et al*[12] (only trabecular bone).

The effects of corticosteroids on bone loss observed in SLE have been widely studied, yet several studies[9,10,24] have failed to find a correlation between BMD and steroid therapy. In contrast, our data support the negative effect of corticosteroids on bone mass in patients with SLE (Table 2). We found that both cumulative dose and duration of prednisolone treatment significantly and negatively affected BMD at lumbar spine and trochanter. However, our multivariable models were only able to predict a small proportion of the overall variance. Short duration of treatment (only 19 months), lack of habitual exercise, and insufficient sample size likely influenced this finding. Importantly, trabecular bone is much more sensitive to corticosteroid than cortical bone[25], which probably explains the correlation we observed between BMD and both steroid duration and cumulative corticosteroid intake at the lumbar and trochanteric sites, but not at the neck site (Table 3).

In our study in prednisolone treated patients with SLE, using standard criteria based on lumbar spine BMD, prevalence of osteoporosis was low at only 1.4%. This was lower than results reported by Formiga, *et al*[10] (12%) and Pons, *et al*[11] (18%) in similar-aged groups, yet comparable to findings from Li, *et al*[24] (4–6%). Osteoporosis in prednisolone treated patients was found only at the lumbar spine. In contrast, the frequency of osteopenia in this study (6.8–32.4%) is comparable to those reported in Caucasian populations (25%)[9] and Chinese (32%)[24]. The lower frequency of osteoporosis in our study compared to earlier reports is unlikely to be due to differences in daily prednisolone treatment (18.7 vs 15 mg/day, respectively), but may be due to differences in cumulative doses (5.2 g vs 25.2 g)[19] or duration of treatment (19.0 mo vs 59.9 mo). In the study of Li, *et al*[24], a lower frequency than that reported in Caucasians was observed in steroid treated SLE patients. There was no difference in prednisolone therapy with respect to mean daily dose and duration of treatment[10,11]. Moreover, there are several factors showing that calcium hemostasis is different in Thais compared to other ethnic groups[14-16,26]. It is possible that the interethnic difference in calcium homeostasis, through effects on BMD, may in part explain the lower rate of osteoporosis in Thai SLE patients using corticosteroids compared with those reported in Caucasians.

In our study, prednisolone treated SLE patients arbitrarily receiving calcium supplements did not have significantly different BMD measures compared with patients not receiving calcium in unmatched and matched groups. First, this may be due to the duration of calcium treatment in our study, which was only 6 months and which is significantly shorter than most treatment periods for interventional trials in BMD[27]. Second, the duration of prednisolone treatment in both groups was 22.4 ± 26.7 and 14.3 ± 17.1 mo when corticosteroid-related bone loss was greatest in the Caucasian population after 12–18 months[11,28]. Third, Thai people have a low calcium intake, about one-third that reported in Caucasians[26]. Fourth, studies have shown that rates of bone loss may be affected by ethnicity[13-16]. Finally, the lack of association between calcium supplements and BMD might

Table 3. Regression coefficient from stepwise multiple linear regression for BMD at lumbar spine and trochanter.

Selected Variable	Lumbar Spine	Femoral Neck	Trochanter
Constant	1.090	—	0.742
Cumulative glucocorticoid dose	-7.13×10^{-6}	—	—
Duration of glucocorticoid treatment	—	—	-1.31×10^{-3}
R^2	0.070	—	0.066

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

also be a result of the sample size not being large enough to reveal a small difference.

In summary, consistent with studies in Caucasians, we found that premenopausal SLE patients that had been treated with prednisolone had significantly lower BMD than controls. Based on preliminary data, our findings of only modest prevalence of corticosteroid induced osteoporosis compared to Caucasians provide further evidence of ethnic and geographic differences in the factors controlling BMD. Further studies are needed to examine this hypothesis.

ACKNOWLEDGMENT

The authors thank Dr. Wanchai Buppanharun, Assistant Professor, Department of Preventive Medicine, Srinakarintaravirot University and Dr. Varodom Boonvisuth, Division of Nuclear Medicine, Department of Radiology, Bangkok Metropolitan Administration Medical College and Vajira Hospital.

REFERENCES

1. Reveille JD, Bartolucci A, Alarcon GS. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as cause of death. Arthritis Rheum 1990;33:37-48.
2. Devogelaer JP, Nagant de Deuxchaisnes C. Therapy in the 1990s. Osteoporosis. Br J Rheumatol 1993;32 Suppl 4:48-55.
3. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 1990;112:352-64.
4. Sambrook P, Birmingham J, Kempler S, et al. Corticosteroid effects on proximal femur bone loss. J Bone Miner Res 1990;5:1211-6.
5. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993;36:1510-6.
6. Mateo L, Nolla JM, Rozadilla A, et al. Bone mineral density in patients with temporal arteritis and polymyalgia rheumatica. J Rheumatol 1993;20:1369-73.
7. Laan RF, van Riel PL, van de Putte LB. Bone mass in patients with rheumatoid arthritis. Ann Rheum Dis 1992;51:826-32.
8. Dhillon VB, Davies MC, Hall ML, 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.
9. Khalla AA, Fataar AB, Jessop SJ, Bewerunge L. Loss of trabecular bone mineral density in systemic lupus erythematosus. Arthritis Rheum 1993;36:1726-34.
10. Formiga F, Moga I, Nolla JM, Pac M, Mitjavila F, Roig-Escofet D. Loss of bone mineral density in premenopausal women with systemic lupus erythematosus. Ann Rheum Dis 1995;54:274-6.
11. Pons F, Peris P, Guanabens N, et al. The effect of systemic lupus erythematosus and long term steroid therapy on bone mass in premenopausal women. Br J Rheumatol 1995;34:742-6.
12. Houssiau FA, Lefebvre C, Depresseux G, Lambert M, Devogelaer JP, Nagant de Deuxchaisnes C. Trabecular and cortical bone loss in systemic lupus erythematosus. Br J Rheumatol 1996;35:244-7.
13. Lee WT, Leung SS, Fairweather–Tait SJ, et al. True fractional calcium in Chinese children measured with stable isotopes (^{42}Ca and ^{44}Ca). Br J Nutr 1994;72:883-97.
14. Sugimoto T, Tsutsumi M, Fujii Y, et al. Comparision of bone mineral content among Japanese, Koreans and Taiwanese assessed by dual-photon absorptiometry. J Bone Miner Res 1992;7:153-9.
15. Hegsted DM. Calcium and osteoporosis. J Nutri 1986;116:2316-9.
16. Luz Villa M, Nelson L. Race, ethnicity and osteoporosis. In: Marcus R, Feidman P, Keisy J, editors. Osteoporosis. San Diego: Academic Press; 1996.
17. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-5.
18. Steinbrocker O, Traeger CH, Batterman RE. Therapeutic criteria in rheumatoid arthritis. JAMA 1947;140:659-67.
19. Katz JD, Senecal JL, Rivest C, Goulet JR, Rothfield N. A simple severity of disease index for SLE. Lupus 1993;2:119-23.
20. 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.
21. WHO Study Group. Osteoporosis. In: Technical report series 843. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization; 1994:2-25.
22. Sels F, Dequeker J, Verwilghen J, Mbuyi-Muamba JM. SLE and osteoporosis: dependence and/or independence on glucocorticoids. Lupus 1996;5:89-92.
23. Petri M. Osteoporosis in SLE: prednisolone affects lumbar spine more than other areas [abstract]. Arthritis Rheum 1996;39 Suppl:S667.
24. 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.
25. Kipen Y, Buchbinder R, Forbes A, Strauss B, Littlejohn G, Morand E. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. J Rheumatol 1997;24:1922-9.
26. Komindr S, Piaseu N, Pattamakom V, et al. Calcium status and factors relating to bone mineral content in normal Thais living in Bangkok. Proceedings of the 10th Annual Scientific meeting of the Royal College of Physicians of Thailand, April 22-26, 1996:61.
27. Ringe JD, Welzed D, Schmid K. Therapy of corticoid-induced osteoporosis with salmon calcitonin. In: Christiansen C, Johanson JS, Riis BJ, editors. Osteoporosis. Copenhagen: Osteopress; 1987:1074-6.
28. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid osteoporosis. A 3 year followup. J Rheumatol 1996;23:995-1000.

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org