Four Years Follow-up of Bone Mineral Density Change in Premenopausal Women with Systemic Lupus Erythematosus

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Objective : *To measure the change in bone mineral density (BMD) in premenopausal women with systemic lupus erythematosus (SLE) during 4 years of follow-up, and to identify the role of glucocorticoid and disease related variables.*
Method : *Premenopausal women with SLE were clinically evaluated and underwent BMD measurement of the lumbar spine, femoral neck and trochanter by dual energy x-ray absorptiometry.*
Results : *106 SLE patients were evaluated with a mean age of 31.7 ± 7.5 years, duration of SLE 2.5 ± 2.6 years, mean daily dose 17.1 ± 14 mg/d, duration of prednisolone treatment 16.3 ± 19.9 months during 4 years of follow-up. There was no significant change in BMD at the lumbar spine (1.051 ± 0.15 vs 1.052 ± 0.14 vs 1.056 ± 0.17 vs 1.056 ± 0.19; p = 0.27), femoral neck (0.861 ± 0.12 vs 0.867 ± 0.12 vs 0.846 ± 0.12 vs 0.844 ± 0.12; p = 0.28) and trochanter (0.718 ± 0.12 vs 0.726 ± 0.13 vs 0.717 ± 0.13 vs 0.709 ± 0.14; p = 0.26) at the baseline, first, second and fourth year follow-up study. Furthermore, annual percentage BMD changes were not significant in lumbar BMD (p = 0.37), femoral neck BMD (p = 0.65) and trochanteric BMD (p = 0.47) during the 4 years follow-up study. The average annual percentage change of BMD was not significantly associated with change in age, body mass index (BMI), disease activity, disease severity, disease duration and prednisolone treatment. In addition, there were no significant bone changes between subgroups treated with ≤ 7.5 mg and > 7.5 mg daily dose of prednisolone as indicated by BMD at the lumbar spine, femoral neck and trochanter as well as annual percentage BMD changes over the study period.*
Conclusion : *There was no significant change of lumbar spine, femoral neck or trochanteric BMD in premenopausal SLE women treated with corticosteroid. These findings suggest that low dose prednisolone may not be detrimental to bone in premenopausal women with SLE during longterm treatment.*

Keywords : *Bone mineral density, Systemic lupus erythematosus, Glucocorticoids*

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Systemic lupus erythematosus (SLE) is a chronic, systemic inflammatory disease of unknown etiology characterized by damage to multiple organs including the musculoskeletal system. Several studies have shown that osteoporosis and reduced bone mineral density (BMD) are prevalent in SLE[1-8]; however, it is unclear whether bone loss is progressive. Follow-up studies of BMD in SLE are limited in number and small in size. Most studies have been confined to Caucasian populations and did not confirm ongoing bone loss[5,6,9].

The role of corticosteroid therapy in causing bone loss in SLE has not been clearly defined. Although several studies have revealed an association of reduced BMD with corticosteroid therapy[3-5,7], others have not [1,2]. Furthermore, follow-up studies have not shown corticosteroid exposure to be associated with progressive bone loss[5,9,10]. To assess these issues, the authors

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measured the change in BMD in Thai premenopausal SLE patients over 4 years follow-up and identified the role of corticosteroid and disease related variables.

Patients and Method

Patients

106 Thai premenopausal women (fertile women with regular menstruation) with prednisolone treated 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 [11]. All subjects underwent a standardized interview, examination, medical record review by the same clinician during the 4 years follow-up. BMD measurement was performed by dual energy x-ray absorptiometry (DEXA) by a medical technician.

Data collected from interviews included body mass index and menstrual history. All patients were nonsmokers. They were ambulatory, physically active and in functional class 1 or 2 using the criteria of Steinbrocker[12]. The duration of disease, daily and cumulative prednisolone doses and the duration of prednisolone therapy were obtained through comprehensive review of medical records during the follow-up study. Disease activity of SLE patients was evaluated using the systemic lupus erythematosus disease activity index (SLEDAI)[13] and severity of disease was assessed by the severity of disease index for SLE[14]. Exclusion criteria in the present study were: renal impairment (serum creatinine > 2 mg/dl), 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 more than 2 months or hyperthyroidism.

Corticosteroid exposed subjects were subdivided into 2 groups according to whether they were receiving $\leq$ 7.5 or > 7.5 mg per day of prednisolone.

Bone density measurements: BMD (g/cm^2) of the lumbar spine (L2-L4) and the left hip (femoral neck, trochanter) were measured by dual-energy x-ray absorptiometry (DEXA) with a Lunar DPX-L, (Lunar Radiation Corporation, Madison, WI, USA). The machine was calibrated daily using a quality assurance phantom. The precision error of the technique expressed as a coefficient of variation (CV) was 0.5% for the lumbar spine and 1.3% for the hip phantom.

Statistical analysis

Demographic and clinical characteristics of patients at baseline and follow-up were compared using the Mann Whitney-u test for categorical quantities, repeated ANOVA test for continuous variables.

Univariate associations of clinical and demographic characteristics with lumbar spine, femoral neck and trochanteric BMD were evaluated using Pearson correlation coefficients for continuous quantities.

Results are expressed as mean (SD) unless otherwise specified. All statistical tests performed were 2 sided, with a nominal p value of 0.05 used to judge statistical significance. All analyses were performed using SPSS version 10.

Results

The baseline and the 4 years follow-up study demographic and clinical characteristics of 106 prednisolone treated SLE patients are displayed in Table 1. The mean age, mean disease duration, mean daily dose of prednisolone, mean cumulative dose and mean drug duration during the follow-up study were 31.7 $\pm$ 7.5 years, 2.5 $\pm$ 2.6 years, 17.1 $\pm$ 14 mg/d, 4.98 $\pm$ 46.1 g, 16.3 $\pm$ 19.9 months respectively. There were no significant changes in body mass index (BMI), disease activity and disease severity over the study period. Similarly, there were no significant changes in lumbar spine, femoral neck BMD and trochanteric BMD respectively. In addition, annual percentage BMD changes were not significantly different in lumbar BMD, femoral neck BMD and trochanteric BMD during the 4 years follow-up study (Table 1). The average annual percentage change in lumbar, femoral neck and trochanteric BMD was 0.45%, -0.19% and 0.05% respectively during the 4 years follow-up study.

A univariate analysis of baseline study demographic and clinical characteristics of prednisolone treated SLE patients with an average annual percentage change in lumbar, femoral neck and trochanteric BMD was performed. The average annual percentage change of BMDs were not significantly associated with changes in age, BMI, disease activity, disease severity, disease duration and prednisolone treatment.

The prednisolone treated SLE patients were subdivided into patients receiving a daily dose of $\leq$ 7.5 mg (n= 38) and > 7.5 mg (n= 68) during the 4 year study period. There were no significant differences in each group and between the two groups with respect to baseline and the 4 years follow-up BMDs (Table 2). Similarly, the annual percentage change in lumbar, femoral neck and trochanteric BMD were not significantly

Table 1. Baseline demographic and clinical characteristics of prednisolone treated SLE patients(mean± SD)

	Baseline (n=106)	1st year (n=88)	p	2nd year (n= 82)	p	4th year (n=50)	p
Age(yrs)	31.7±7.5	32.0±7.5		34.5±7.8		36.9±7.5	<0.001
BMI, kg/m2	23.23±4.2	22.94±4.27		22.61±5.45		22.77±5.19	0.16
Disease durations (yrs)	2.52±2.62	3.04±2.25		4.29±2.48		6.22±2.32	
Disease activity*	2.16±3.60	1.61±2.84	0.360	1.08±2.53	0.087	1.16±2.19	0.696
Disease severity*	1.93±0.73	1.94±0.32	0.838	1.96±0.38	0.422	1.76±0.56	0.695
Corticosteroid use							
Duration (mo)	16.26±19.86	23.85±18.02		38.67±20.76		62.97±22.93	
Cumulative dose(g)	4982±46.09	7048.37±50.13		9989.57±61.9		15034.14±95.47	
Mean daily dose(mg)	17.08±14.28	11.05±11.75		8.08±9.76		5.55±6.28	<0.001
LS BMD, g/cm^2	1.051±0.15	1.052±0.14		1.056±0.17		1.056±0.19	0.27
% Change of LS BMD/y		0.87±4.31		0.28±4.43		-0.11±0.52	0.37
FN BMD, g/cm^2	0.861±0.12	0.867±0.12		0.846±0.12		0.844±0.12	0.28
% Change of FN BMD/y		0.53±4.83		-1.30±4.59		0.29±3.24	0.65
Tro BMD, g/cm^2	0.718±0.12	0.726±0.13		0.717±0.13		0.709±0.14	0.26
% Change of Tro BMD/y		0.82±6.30		-0.24±5.69		-0.94±4.88	0.47

LS= Lumbar spine, FN= Femoral neck, Tro= Trochanter, BMD= Bone mineral density, y=year
Repeated ANOVA test for continuous variables

Table 2. Baseline and follow-up bone mineral density of prednisolone exposed SLE patients categorized according to daily prednisolone dose during the study period (mean± SD)

	Baseline (n = 106)	1st year (n = 88)	p	2nd year (n = 82)	p	4th year (n = 50)	p
LS. BMD, g/cm^2							
≤7.5 mg/day	1.037±0.12	1.038±0.14		1.047±014		1.063±0.19	0.66
(n)	(38)	(50)		(57)		(37)	
>7.5 mg/day	1.049±0.16	1.068±0.16		1.075±0.19		1.048±0.23	0.21
(n)	(68)	(38)		(25)		(13)	
p	0.48	0.65		0.67		0.44	
FN. BMD, g/cm^2							
≤7.5 mg/day	0.827±0.11	0.851±0.12		0.835±0.11		0.849±0.12	0.65
(n)	(38)	(50)		(57)		(37)	
>7.5 mg/day	0.879±0.12	0.889±0.12		0.876±0.14		0.829±0.13	0.31
(n)	(68)	(38)		(25)		(13)	
p	0.98	0.97		0.87		0.57	
Tro. BMD, g/cm^2							
≤7.5 mg/day	0.678±0.11	0.700±0.10		0.707±0.12		0.706±0.12	0.51
(n)	(38)	(50)		(57)		(37)	
>7.5 mg/day	0.738±0.13	0.761±0.14		0.751±0.17		0.719±0.17	0.58
(n)	(68)	(38)		(25)		(13)	
p	0.95	0.97		0.79		0.49	

LS= Lumbar spine, FN= Femoral neck, Tro= Trochanter, BMD= Bone mineral density, y=year

different between the two groups over the follow-up study. In addition, there were no significant differences between the two groups with respect to baseline disease related variables, patient related variables, or drug variables except the daily dose of prednisolone (Table 3).

Discussion

Studies of musculoskeleton involvement in SLE have focused increasingly on the prevalence of reduced BMD and osteoporosis. These studies have largely been cross sectional in design and have revealed significantly reduced lumbar spine and femoral neck BMD in patients with SLE[1-8]. Follow-up of bone change in SLE, however, have been scarce[5,9,10,15]. The presented 4 years follow-up study of BMD in 106 SLE patients, which is the largest to date, found no signifi-

Table 3. Baseline and follow-up bone mineral density change of prednisolone exposed SLE patients categorized according to daily prednisolone dose during the study period (mean± SD)

	≤7.5 mg/day	>7.5 mg/day	p
At baseline(n=38, 68)			
Age, yrs	31.0±7.77	32.21±7.8	0.65
BMI at baseline	22.09±5.66	23.25±4.32	0.74
Disease duration at baseline	3.43±2.35	2.15±2.34	0.91
Disease activity (SLEDAI) at baseline	1.25±2.12	2.44±3.91	0.96
Disease severity at baseline	1.89±0.69	1.95±0.75	0.48
Corticosteroid use at baseline			
Duration, mo	26.71±22.28	11.95±17.17	0.98
Cumulative dose, g	4699±388	5231±494	0.64
Daily dose (mg)	5.13±0.75	22.28±14.50	<0.001
%LS BMD change/y : y1-0 (n=38,38)	0.02±0.19	-0.02±0.23	0.65
: y2-1(n=50,25)	0.03±0.02	0.02±0.21	0.45
: y4-2(n=37,13)	0.02±0.28	-0.01±0.03	0.46
%FN BMD change/y : y1-0(n=38,38)	0.03±0.18	0.02±0.20	0.45
: y2-1(n=50,25)	0.03±0.18	0.03± 0.21	0.58
: y4-2(n=37,13)	0.04±0.17	-0.04±0.22	0.76
%Tro BMD change/y : y1-0(n=38,38)	0.03±0.18	0.01±0.20	0.56
: y2-1(n=50,25)	0.04±0.18	0.04±0.57	0.35
: y4-2(n=37,13)	0.04±0.19	0.01±0.51	0.54

LS = Lumbar spine, FN = Femoral neck, Tro = Trochanter, BMD = Bone mineral density, y =year, mo = month, g = gram
Unpaired T- test for comparing continuous variables

cant change in lumbar spine, femoral neck and trochanteric BMD throughout the study period. In addition, annual percentage BMD changes were small (-0.19% to 0.45%) and no significant differences in lumbar BMD, femoral neck BMD and trochanteric BMD were found during the 4 years follow-up study. This finding is consistent with 3 previous follow-up studies in Caucasian that found no significant bone loss of BMD in premeno-pausal females. Pons, et al studied 21 SLE patients and found no significant reduction in lumbar spine and femoral neck BMD over a mean duration of 36.6 months (mean daily dose of prednisolone 15 ± 6.8 mg/d, cumulative dose 25.2 ± 21.5 g) of follow-up study. Formiga, et al were unable to confirm a significant change in BMD in 25 SLE patients after 18 months of follow-up study (mean age 31.7 years, mean disease duration 7.5 years, mean daily dose 9.2 mg/d). Kipen, et al studied 32 SLE patients and found no significant change over 3 years in BMD at the lumbar spine and the femoral neck for the group as a whole and for the 21 corticosteroid treated SLE patients (mean age 35.6 ± 1.5 years, mean disease duration 7.7 ± 0.9 years, mean daily dose of prednisolone 11.05 mg, cumulative dose of prednisolone 9.9 g.) during follow-up study.

Several factors may explain why the present study did not find ongoing bone change. First, all SLE patients were premenopausal, with a mean age of 31.7 years and 36.9 years at the baseline and the fourth year follow-up respectively, about the age at which peak BMD is attained. Postmenopausal women were deliberately excluded to eliminate the confounding effect of menopause on bone loss. Second, rapid bone loss may occur at the onset of the disease, as has been reported in RA[16,17]. Third, it has been postulated that patients with SLE may be protected from loss of BMD due to an increased formation of estrogenic metabolites. Lahita, et al described increased rates of 16 alpha hydroxylation of estradiol in SLE, with the formation of estrogenic metabolites such as 16 alfa hydroxyestrone and estriol[18,19]. Forth, BMD was not measured at the time of first prednisolone treatment which was the most pronounced corticosteroid induced bone loss period (first 6-12 months of therapy)[20]. Another possible explanation is that the size of the study population was small at the conclusion of the 4 year follow-up study. However, the present study is the largest to date, and the difficulty in following large groups of eligible patients with SLE is well recognized.

In Kipen, et al, the patients receiving > 7.5 mg/d of prednisolone lost bone compared to an increase in BMD in those receiving < 7.5 mg/d at the lumbar spine. In contrast, there were no significant bone changes between the subgroups treated with ≤ 7.5 mg and > 7.5 mg daily dose of prednisolone as indicated by BMD at the lumbar spine, femoral neck

and trochanter as well as annual percentage BMD changes over the study period in the present study. It may be due to differences in sample size (n = 21)[10].

Previous cross sectional studies on the role of corticosteroids in SLE bone mineral change are conflicting. While some have shown an association of reduced BMD with corticosteroid therapy[3-5,7], others have not[1,2,19,21]. The present follow-up study showed no significant associations between average annual percentage change in the lumbar spine, femoral neck and trochanteric BMD at baseline with corticosteroid use, disease activity, disease severity, and patient related factors (age, BMI) which is consistent with previous follow-up studies[9,10,15]. It has been suggested that a multifactorial action could explain the lack of association between the dose of prednisolone and BMDs. Regular exercise was protective against bone loss at the femoral neck in corticosteroid exposured subjects[10] and glucocorticoids may paradoxically inhibit bone resorption that has been stimulated by PGE_2 or cytokines[20,22-24]. However, the duration, cumulative and mean daily doses of prednisolone in the present study was lower than previous studies[5,19].

In summary, after a follow-up period of 4 years, there was no significant change of lumbar spine, femoral neck or trochanteric BMD in premenopausal women with treated corticosteroid SLE. These findings suggest that low dose prednisolone may not be detrimental to bone in premenopausal women with SLE over a long period of treatment. Nevertheless, further studies to demonstrate change of bone mineral density in SLE during longterm treatment will probably require at the first corticosteroid treatment, more patients and a longer period of study.

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การเปลี่ยนแปลงความหนาแน่นของกระดูกในผู้ป่วยโรคลูปุส

สมชาย เอื้อรัตนวงศ์, อุทิศ ดีสมโชค, นรินทร์ หิรัญสุทธิกุล, สมศรี เอื้อรัตนวงศ์

วัตถุประสงค์ *: เพื่อศึกษาการเปลี่ยนแปลงความหนาแน่นของกระดูกในผู้ป่วยโรคลูปุส ระยะเวลาติดตาม 4 ปี และปัจจัยที่เกี่ยวข้อง*

วิธีการศึกษา *: ทำการศึกษาข้อมูลทางคลินิกและความหนาแน่นของกระดูกในผู้ป่วยสตรีโรคลูปุสที่ยังมีประจำเดือน ที่ตำแหน่งกระดูกสันหลังและกระดูกสะโพกที่วัดด้วยวิธี dual energy x-ray absorptiometry*

ผลการศึกษา *: ผู้ป่วยสตรีโรคลูปุส 106 ราย มีอายุเฉลี่ย 31.7 $\pm$ 7.5 ปี ระยะเวลาการเป็นโรคเฉลี่ย 2.5 $\pm$ 2.6 ปี ได้รับยาเพรดนิโซโลนขนาดเฉลี่ย 17.1 $\pm$ 14 มก/วัน ระยะเวลาได้รับยาเฉลี่ย 16.3 $\pm$ 19.9 เดือน ไม่พบการเปลี่ยนแปลงของความหนาแน่นกระดูกและอัตราการเปลี่ยนแปลงอย่างมีนัยสำคัญที่ตำแหน่งกระดูกสันหลังและกระดูกสะโพกตลอดระยะเวลา 4 ปี นอกจากนี้ยังไม่พบมีความแตกต่างของความหนาแน่นกระดูกที่ตำแหน่งกระดูกดังกล่าวในกลุ่มที่ได้ยาเพรดนิโซโลนน้อยกว่าหรือเท่ากับ 7.5 มก/วันและกลุ่มที่ได้มากกว่า 7.5 มก/วัน อัตราการเปลี่ยนแปลงของกระดูกโดยเฉลี่ยไม่สัมพันธ์กับตัวโรคและยาเพรดนิโซโลนที่ใช้รักษา*

สรุป *: ไม่พบมีการเปลี่ยนแปลงของความหนาแน่นกระดูกในสตรีโรคลูปุสที่ยังมีประจำเดือน และได้รับยาเพรดนิโซโลนขนาดต่ำอย่างมีนัยสำคัญ*