Bone Mineral Density Change in Systemic Lupus Erythematosus: A 5-year Followup Study

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ABSTRACT. ***Objective.*** To determine changes of bone mineral density (BMD) over a 5-year period in a cohort of female patients with systemic lupus erythematosus (SLE) and to identify factors predictive of BMD loss.

Methods. Our longitudinal study involved 125 female patients with SLE with a mean (SD) age of 46.5 years (10.1) and a median disease duration of 10.4 years. Demographics and clinical data were collected and BMD at the femoral neck, total hip, and lumbar spine (L1-4) was performed by using dual-energy x-ray absorptiometry at baseline and followup.

Results. Average percentage changes of BMD over a mean followup of 5 years were –2.41% at the femoral neck, –1.63% at the total hip, and –0.62% at the lumbar spine, with significant changes at both the femoral neck ($p < 0.0001$) and total hip ($p < 0.0005$), but not at the lumbar spine ($p = 0.128$). Disease flare, new organ damage, and use of glucocorticoids during followup were significantly associated with larger decreases in BMD. BMD loss was arrested at the femoral neck and BMD increased at the total hip and lumbar spine in patients receiving antiosteoporosis therapy. In multivariate analyses, use of antiosteoporosis therapy was independently associated with increased BMD at any site and new organ damage was an independent predictor of BMD loss at the femoral neck.

Conclusion. Significant BMD loss at the hip over a period of 5 years was found in patients with SLE. Disease activity, disease damage, and use of glucocorticoids are the disease-specific variables that contribute to bone loss in SLE. (First Release July 1 2014; J Rheumatol 2014;41:1990–7; doi:10.3899/jrheum.131190)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by periods of exacerbations that can affect any organ system. Organ damage in SLE is the result of the disease itself and/or a consequence of its treatment. With the improved survival seen in SLE, more emphasis has been placed on the prevention and treatment of its comorbidities. Osteoporosis is one of the most common comorbidities in SLE[1]. Recent cross-sectional studies have demonstrated a high frequency of osteoporosis in SLE[2,3,4,5]. These are associated with longer disease duration[6], organ damage[6,7], markers of inflammation[7], and use of glucocorticoids[8,9]. Only a few longitudinal studies have investigated longitudinal changes in bone mineral density (BMD) in patients with SLE and most of those studies were limited by a small cohort and relatively short followup time[10,11,12,13,14,15]. Significant change in BMD at the hip or lumbar spine was found only in 2 of these studies with followup duration of 21 and 24 months, respectively[10,14]. Significant association between glucocorticoid use and decrease in BMD was seen in some[10,12,13,14] but not all of those studies[11,15]. The relative contribution of both traditional and disease-associated factors to bone loss in SLE is not well understood. The primary aim of our study was to determine changes in BMD over a 5-year period in a cohort of female patients with SLE. The secondary aim was to identify factors predictive of bone loss in patients with SLE, including demographic and clinical variables at baseline and during followup.

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MATERIALS AND METHODS

Patients. A consecutive cohort of 152 female Chinese patients with SLE was recruited in 2007 for evaluation of frequency of osteoporosis and vertebral fracture. All patients regularly attended the outpatient rheuma-

tology clinic at Prince of Wales Hospital in Hong Kong and fulfilled the American College of Rheumatology (ACR) revised criteria for the classification of SLE[16]. The cross-sectional baseline results from this cohort have been described[3]. In 2012, patients examined at baseline were invited to receive a followup examination. At followup, 9 patients were dead, 15 patients refused to participate, and 3 patients failed to attend for assessment of BMD. The prospective cohort for the current study therefore consisted of 125 patients. The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and written informed consent was obtained from all participants.

Clinical assessment. Participants underwent clinical examination and assessment on BMD at baseline and followup. Demographics documented included age, body weight, body height, disease duration, menstrual status, age of menopause, drinking and smoking habits, and history of symptomatic fragility fractures after the age of 25. Menopause was defined as amenorrhea for at least 1 complete year and the age of menopause as the age of the last menstrual flow of any amount. Patients' menstrual status during followup was further categorized as premenopausal or post-menopausal if their menstrual status remained in the respective stage throughout the followup period, and as transitional if they had undergone change from premenopausal to postmenopausal. Current drinking was defined as taking 3 or more units of alcohol daily. History of fragility fracture at baseline was defined as a fracture arising from trauma that would not normally be expected to result in fracture, such as a fall from less than or equal to standing height, excluding skull or digit fractures. Serum levels of 25-hydroxy Vitamin D [25(OH)D, in µg/l] at baseline were measured by radioimmunoassay (DiaSorin Inc.).

Disease activity was scored with the SLE Disease Activity Index (SLEDAI)[17]. Disease flare during followup period was recorded by a revised Safety of Estrogens in Lupus Erythematosus: National Assessment flare tool that excluded the component of physician's global assessment[17,18]. Mild/moderate flares were defined as 1 or more of the following: (1) change in SLEDAI score of > 3 points but ≤ 12 points; (2) new/worse discoid lesions, photosensitivity, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, and/or fever; (3) increase in glucocorticoids not to exceed 0.5 mg/kg/day; or (4) added nonsteroidal antiinflammatory drugs or hydroxychloroquine sulfate for SLE. Severe flares were defined as 1 or more of the following: (1) change in SLEDAI score of > 12 points; (2) new/worse neuropsychiatric SLE, vasculitis, nephritis, myositis, platelet count < 60,000/mm^3, or anemia (hemoglobin level < 7 mg/dl), which required either a doubling of or increase in glucocorticoid dosage to > 0.5 mg/kg/day; (3) increase in glucocorticoids to > 0.5 mg/kg/day; (4) new immunosuppressants for SLE activity; or (5) hospitalization for SLE. To reflect cumulative disease activity, we recorded the total number of disease flares during the followup period. Flares with only serologic manifestations (increased anti-dsDNA titer and depressed complement level) without medical intervention were not recorded. Accumulated organ damage was assessed with the Systemic Lupus International Collaborating Clinics/ACR damage index (SDI), a validated physician-rated index that consists of 41 items in 12 organ systems/domains[19]. New organ damage during followup period was recorded.

Use of medications during followup period, including glucocorticoid (oral or intravenous), hydroxychloroquine (HCQ), immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, or leflunomide), calcium and vitamin D supplements, and antiosteoporosis therapies, was recorded by chart review. Use of oral glucocorticoids, HCQ, or immunosuppressants was defined as consecutive use of ≥ 3 months of any dose. Cumulative dose and duration of oral glucocorticoids during followup were calculated. All doses of oral glucocorticoids were prednisolone equivalent. To ensure adequate antiresorptive effect, use of antiosteoporosis therapy was defined as consecutive use of ≥ 24 months.

BMD by dual-energy x-ray absorptiometry (DEXA). BMD measurements of the hip (left femoral neck and total hip) and the lumbar spine (L1–L4; anteroposterior view) were performed by a single trained technician at baseline and followup using the same DEXA (model Hologic Delphi W; Hologic). Hip BMD measurement could not be performed on 2 patients at baseline and 3 patients at followup because of hip replacement. Our short-term precision error of BMD by DEXA, expressed as the coefficient of variance[20], was 1.5% at the femoral neck, 1.31% at the total hip, and 0.72% at the lumbar spine, and was based on healthy subjects receiving DEXA scans at the center[21]. BMD values, expressed in g/cm^2, were compared to the reference norms of the Chinese population in Hong Kong for calculation of T scores[21]. Osteoporosis was defined as a T score ≤ –2.5 at the femoral neck, total hip, or lumbar spine and low bone mass as a T score between –1.0 and –2.5. Changes in BMD at the femoral neck, total hip, and lumbar spine were expressed as percentage change during followup period.

Statistical analyses. Statistical analyses were performed using the Statistics Package for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0). Results were expressed as mean (± SD) for normally distributed data. For non-normally distributed data, median and interquartile range was used. Comparison of baseline and followup BMD value and T score was performed using paired-sample t test. Comparison of percentage of patients with osteoporosis or low bone mass at baseline and followup was performed using McNemar's test. Comparison in percentage change in BMD between 2 groups (such as those using or not using oral glucocorticoids) was performed by Student's t test and comparison between ≥ 3 groups was performed by analyses of variance with Bonferroni adjustment. Correlation between percentage change in BMD and continuous variables (such as age and disease duration) was performed by Pearson and Spearman correlation, depending on data distribution. Variables significantly associated with change in BMD in univariate analyses ($p < 0.05$) were further tested by multiple linear regression analysis with change in BMD as a dependent variable. All hypotheses were 2-tailed, and $p < 0.05$ were considered statistically significant.

RESULTS

Characteristics of participants. Table 1 shows the characteristics of the study participants. The mean followup duration for the 125 patients was 5.0 years (SD: 0.26 yrs, median: 4.9 yrs, range: 4.37–5.29 yrs). Compared to those who attended a followup visit, patients who refused to participate were significantly older (mean ± SD age: 55.3 ± 11.7 yrs vs 46.5 ± 10.1 yrs, $p = 0.001$) and more likely to be postmenopausal (88.9% vs 63.2%, $p = 0.031$). However, BMD values did not differ significantly between the 2 groups (data not shown). The majority of the study cohort was middle-aged females (range: 19–72 yrs) with a median disease duration of 10 years and mild disease activity and organ damage. Seventy-eight patients (62.4%) were postmenopausal and 76 patients (60.8%) had a history of lupus nephritis.

During the followup period, 90 episodes of disease flare were recorded in 44 patients (35.2%). Twenty of 44 patients (45.5%) had 1 flare, 11 (25%) had 2 flares, and 13 (29.5%) had ≥ 3 flares. At baseline, 70 patients (56%) had organ damage. Ocular (21 patients), neuropsychiatric (16 patients), and musculoskeletal (14 patients) systems were the most commonly involved systems at baseline. At followup, new organ damage had developed in 41 patients (32.8%), 25 patients of whom did not have damage at baseline. The most

Table 1. Baseline demographic and characteristics of participants.

Variables	Participants, n = 125
Age, yrs	46.5 ± 10.1
Body height, m	1.56 ± 0.06
Body weight, kg	53.7 ± 9.0
Body mass index, kg/m^2	22.1 ± 3.5
Postmenopausal, no. (%)	79 (63.2)
Age of menopause, yrs	45 (41, 49)
Duration of menopause, yrs	5.7 (2.2, 9.8)
Current drinker, no. (%)	0
Current smoker, no. (%)	2 (1.6)
History of fragility fracture, no. (%)	6 (4.8)
Disease duration, yrs	10.4 (5.4, 16.0)
SELENA-SLEDAI score	1 (0, 3.5)
SDI score	1 (0, 1)
Lupus nephritis, no. (%)	76 (61.3)
25[OH]D, µg/l	17.9 (14.2, 21.3)
Baseline BMD, g/cm^2	
Femoral neck	0.668 ± 0.105
Total hip	0.802 ± 0.128
Lumbar spine	0.866 ± 0.149

Results are mean ± SD or median (interquartile range) unless otherwise indicated. SELENA-SLEDAI: the Safety of Estrogens in Lupus Erythematosus, National Assessment version of the SLE Disease Activity Index; SDI: the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; 25[OH]D: 25-hydroxy Vitamin D; BMD: bone mineral density.

Table 2. Treatment variables during followup.

Variables	All Patients, n = 125
Hydroxychloroquine, ≥ 3 mos	
Current user	55 (44.0)
Ever user	14 (11.2)
Other immunosuppressants*, ≥ 3 mos	
Current user	29 (23.2)
Ever user	17 (13.6)
Oral glucocorticoids ≥ 3 mos	
Current user	86 (68.8)
Ever user	7 (5.6)
User of ≥ 7.5 mg for ≥ 3 mos	52 (41.6)
Cumulative dose#, g	9.6 ± 4.3
Cumulative duration of use#, mos	55.2 ± 10.3
Intravenous methylprednisolone	
Ever user	6 (4.8)
Antiosteoporosis therapies	
Bisphosphonates	
Current user	17 (13.6)
Ever user	19 (15.2)
Use for ≥ 24 mos	20 (16)
Hormone replacement therapy, ≥ 24 mos	
Current user	1 (0.8)
Ever user	1 (0.8)
Calcium supplement	
Current user	89 (71.2)
Ever user	10 (8)
Vitamin D supplement	
Current user	78 (62.4)
Ever user	8 (6.4)

Results are mean ± SD or number (percentage). * Includes azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, and leflunomide. # Among patients who used oral glucocorticoids and in prednisolone-equivalent dose.

common new sites of organ damage were the musculoskeletal (11 patients), renal (10), and ocular (9) systems. During followup, 94 patients (75.2%) used oral glucocorticoids, with a mean (SD) cumulative dose of 9.6 g (4.3 g; Table 2). Fifty-two patients (41.6%) had used glucocorticoids at a dose ≥ 7.5 mg for ≥ 3 months. Use of immunosuppressants was recorded in 46 patients (36.8%), among which only 2 patients had not used glucocorticoids during followup. The most commonly used immunosuppressants (current or ever use) were azathioprine (25 patients), cyclosporine (11), and mycophenolate mofetil (10). Six patients had used cyclophosphamide, including 4 oral and 2 intravenous uses. Bisphosphonates (alendronate and ibandronate) and hormone replacement therapies, which were used by 38 patients, were the only antiosteoporosis therapies recorded. Only 22 patients had used antiosteoporosis therapies for ≥ 24 months.

Changes of BMD. Mean (SD) percentage changes of BMD of the whole study cohort over 5 years were –2.41% (5.60%) at the femoral neck, –1.63% (5.10%) at the total hip, and –0.62% (7.32%) at the lumbar spine. Significant decreases in BMD and T score were seen at both the femoral neck ($p < 0.0001$) and total hip ($p < 0.0005$), but not at the lumbar spine ($p = 0.128$; Table 3). Frequency of low bone mass or osteoporosis did not change significantly over time.

Variables associated with changes of BMD. There was no significant association between percentage changes of BMD at any site and age or body mass index at baseline, with correlation coefficient (r) ranging from –0.085 to 0.047 (all $p > 0.05$). BMD change at any site was not associated with patients' menstrual status at baseline (Table 4). Patients of transitional menstrual status during followup had significantly larger decreases in BMD at all sites than those who remained postmenopausal or premenopausal.

Flare during followup was significantly associated with larger decrease in BMD at the total hip and lumbar spine (Table 4). Among patients who had flare, the number of flares did not correlate with changes of BMD at any site, with r ranging from –0.251 to –0.209 (all $p > 0.05$). Compared to those without flare (n = 78), patients who had ≥ 3 flares (n = 13) had significantly larger decrease in BMD at the total hip (Bonferroni-adjusted $p = 0.009$), and decrease in BMD at the lumbar spine was marginally significant (adjusted $p = 0.053$). Changes of BMD at any site did not differ between patients without flare and patients with 1–2 flares (n = 31), or between patients with 1–2 flares and patients with ≥ 3 flares.

New organ damage was associated with larger decrease in BMD at the femoral neck and total hip (Table 4).

Table 3. Bone mineral density variables at baseline and followup.

Variables	Femoral Neck			Total Hip			Lumbar Spine		
	Baseline	Followup	p	Baseline	Followup	p	Baseline	Followup	p
BMD, g/cm^2	0.668 ± 0.105	0.652 ± 0.109	< 0.0001*	0.802 ± 0.128	0.790 ± 0.131	< 0.0005*	0.866 ± 0.149	0.858 ± 0.148	0.128
T score	–1.08 ± 1.16	–1.25 ± 1.19	< 0.0001*	–0.79 ± 1.19	–0.91 ± 1.22	< 0.0005*	–1.15 ± 1.41	–1.22 ± 1.40	0.183
Low bone mass	57 (46.3)	66 (54.1)	0.078	44 (35.2)	52 (41.6)	0.064	48 (38.4)	53 (42.4)	0.383
Osteoporosis	10 (8.1)	14 (11.5)	0.219	10 (8)	9 (7.2)	1.000	19 (15.2)	18 (14.4)	1.000

Results are mean ± SD or n (%). *Statistically significant. BMD: bone mineral density.

Table 4. Percentage changes of bone mineral density over followup period by menstrual status, disease flare, new organ damage, use of glucocorticoids, hydroxychloroquine, immunosuppressants, and antiosteoporosis therapies.

Variables	Femoral Neck	Total Hip	Lumbar Spine
Menstrual status at baseline			
Postmenopausal, n = 79	–2.31 ± 5.10	–1.40 ± 4.58	–0.55 ± 6.84
Premenopausal, n = 46	–2.57 ± 6.38	–2.00 ± 5.91	–0.74 ± 8.15
p	0.801	0.553	0.893
Transitional menstrual status during followup			
Yes, n = 16	–5.80 ± 6.13	–5.26 ± 5.23	–5.38 ± 6.06
No, n = 109	–1.89 ± 5.36	–1.08 ± 4.88	0.08 ± 7.24
p	0.009*	0.002*	0.005*
Flare during followup			
Yes, n = 44	–3.48 ± 5.47	–3.44 ± 4.75	–3.10 ± 6.35
No, n = 81	–1.80 ± 5.61	–0.60 ± 5.04	0.72 ± 7.49
p	0.112	0.003*	0.005*
New organ damage			
Yes, n = 41	–4.22 ± 5.35	–3.30 ± 4.83	–1.84 ± 7.09
No, n = 84	–1.55 ± 5.53	–0.84 ± 5.06	–0.03 ± 7.39
p	0.013*	0.012*	0.194
New renal damage			
New renal damage, n = 10	–8.03 ± 4.02	–6.10 ± 3.90	–5.16 ± 5.00
New other damage, n = 31	–2.91 ± 5.17	–2.34 ± 4.80	–0.77 ± 7.39
p **	0.031*	0.118	0.293
Hydroxychloroquine			
Yes, n = 68	–2.29 ± 5.25	–1.88 ± 4.91	–0.44 ± 7.11
No, n = 56	–2.55 ± 6.05	–1.31 ± 5.36	–0.85 ± 7.61
p	0.798	0.540	0.756
Immunosuppressants			
Yes, n = 46	–2.79 ± 6.55	–2.59 ± 6.06	–1.20 ± 8.32
No, n = 79	–2.18 ± 4.99	–1.06 ± 4.40	–0.29 ± 6.69
p	0.568	0.112	0.503
Oral glucocorticoids			
Yes, n = 93	–2.73 ± 5.90	–2.13 ± 5.31	–1.47 ± 7.55
No, n = 32	–1.50 ± 4.61	–0.21 ± 4.24	1.83 ± 6.03
p	0.289	0.067	0.027*
Daily oral glucocorticoids ≥ 7.5 mg for ≥ 3 mos			
Yes, n = 52	–3.34 ± 5.51	–3.35 ± 4.75	–2.82 ± 7.09
No, n = 41	–1.93 ± 6.35	–0.54 ± 5.62	0.25 ± 7.86
p	0.265	0.012*	0.051
Antiosteoporosis therapies			
Yes, n = 22	0.33 ± 5.67	1.93 ± 5.34	4.41 ± 7.51
No, n = 103	–2.97 ± 5.43	–2.37 ± 4.75	–1.70 ± 6.84
p	0.013*	< 0.0005*	< 0.0005*

Results are mean ± SD. *Statistically significant difference. ** p value was Bonferroni-adjusted.

Analyses excluding the 11 patients with new musculoskeletal damage showed similar findings (data not shown). Patients with new renal damage had a larger decrease in BMD than did patients with other new damage, with significant difference seen at the femoral neck (Bonferroni-adjusted p = 0.031). New musculoskeletal damage or ocular damage was

not associated with larger decrease in BMD (data not shown). Baseline SLEDAI score and SDI score did not correlate with changes in BMD at any site, with r ranging from –0.010 to –0.251 (all $p > 0.05$). Use of HCQ or immunosuppressants was not associated with changes of BMD at any site. Higher baseline level of 25[OH]D was significantly associated with less BMD loss at the lumbar spine ($r = 0.209$, $p = 0.019$) but not at the femoral neck ($r = 0.137$, $p = 0.133$) or the total hip ($r = 0.124$, $p = 0.173$).

BMD at the femoral neck and total hip decreased to a lesser extent and BMD at the lumbar spine increased in patients who did not use oral glucocorticoids during followup, in comparison with their counterparts (Table 4). Significant difference in changes of BMD between these 2 groups was seen only at the lumbar spine. Patients who used glucocorticoids ≥ 7.5 mg for ≥ 3 months had significantly larger reduction in BMD at the total hip than did patients who did not use glucocorticoids ≥ 7.5 mg for ≥ 3 months (–3.35% vs –0.54%, Bonferroni-adjusted $p = 0.025$) or patients who did not use glucocorticoids during followup (–3.35% vs –0.21%, adjusted $p = 0.017$). Use of daily glucocorticoids ≥ 7.5 mg for ≥ 3 months was also associated with a larger decrease in BMD at the lumbar spine, in comparison with patients who did not use glucocorticoids (–2.82% vs 1.83%, adjusted $p = 0.013$). Higher cumulative dose of oral glucocorticoids was significantly associated with BMD loss at the total hip ($r = –0.230$, $p = 0.011$) and lumbar spine ($r = –0.228$, $p = 0.011$) but not at the femoral neck ($r = –0.101$, $p = 0.268$). Longer cumulative duration of use of glucocorticoids was also significantly associated with BMD loss at the total hip ($r = –0.178$, $p = 0.0499$) but not at the femoral neck ($r = –0.078$, $p = 0.396$) or lumbar spine ($r = –0.152$, $p = 0.091$). In patients who had received anti-osteoporosis therapies ≥ 24 months, BMD loss was arrested at the femoral neck and total hip, and BMD increased at the lumbar spine. In contrast, BMD decreased at all sites in patients not treated for osteoporosis.

Subgroup analyses by use of glucocorticoids, flare, and use of antiosteoporosis therapies. Compared to patients without flare, use of glucocorticoids (91% vs 65%, $p = 0.002$) or immunosuppressants (66% vs 25%, $p < 0.0001$) was significantly more common, and cumulative dose of glucocorticoids during followup significantly higher (median: 11.2 g vs 5.5 g, $p < 0.0001$) in patients who had flare. Use of glucocorticoids (59% vs 78%, $p = 0.070$) or immunosuppressants (27% vs 39%, $p = 0.307$) did not differ significantly between patients who used and patients who did not use antiosteoporosis therapies.

In patients who used glucocorticoids during followup, decrease in BMD at any site was higher in patients who had flare than in those who did not have flare, with significant difference at the total hip (Figure 1A). This between-group difference remained significant ($p = 0.038$) after adjustment for the cumulative dose of glucocorticoids during followup. In patients who did not use glucocorticoids during followup, flare did not further increase BMD loss significantly. Use of antiosteoporosis therapies arrested BMD loss at all sites, especially at the total hip and lumbar spine, in patients who used glucocorticoids during followup (Figure 1B). A particularly high increase in BMD (5.87%) was seen at the lumbar spine in patients who used antiosteoporosis therapies but did not use glucocorticoids during followup.

Multivariate analyses for variables associated with changes of BMD. Table 5 shows the results of the multivariate linear regression analyses. Use of antiosteoporosis therapies was independently associated with increased BMD at any site. New organ damage was an independent predictor for BMD loss at the femoral neck while transitional menstrual status was predictive of BMD loss at the lumbar spine. The correlation between cumulative dose of glucocorticoids and BMD loss at the lumbar spine failed to reach statistical significance ($p = 0.062$).

DISCUSSION

Our study is one of the largest longitudinal studies investigating BMD changes in patients with SLE. Significant decreases in BMD at the hip were found after an average followup of 5 years. Bone loss in SLE increased in patients with transitional menstrual status and patients with more active and severe disease. Use of glucocorticoids was also associated with increased bone loss, particularly at the lumbar spine. Our results suggest that bone loss in SLE could be prevented by antiosteoporosis therapy.

In previous longitudinal studies, annual BMD changes in patients with SLE ranged from –0.2% to –0.32% at the femoral neck, –0.2% to –3.59% at the total hip, and –0.08% to –4.2% at the lumbar spine[10,11,12,13,14,15]. The magnitude of annual bone loss at the femoral neck (–0.43%) and total hip (–0.27%) reported in our studies was similar to that in most previous studies. But annual bone loss at the lumbar spine generally appears less (–0.13%). Besides difference in ethnicity, such discrepancy could be attributable to the relatively higher percentage of patients using antiresorptive therapies in our study, which generally increases BMD to a greater degree at the spine than at the hip[22,23,24,25].

Our study demonstrates that apart from traditional risk factors for osteoporosis such as the onset of menopause, a more active and severe course of disease contributes to bone loss in SLE. Disease flare during followup was associated with bone loss at the hip and lumbar spine. The presence of flare further increased the bone loss in patients receiving glucocorticoids, particularly at the hip, and its effect was independent of the cumulative dose of glucocorticoids. New organ damage during followup was associated with bone loss at the hip and it remained one of the independent predictors for decrease in BMD at the femoral neck. Renal damage appeared to have a more deleterious effect on the bone than did other organ damage, particularly at the hip.

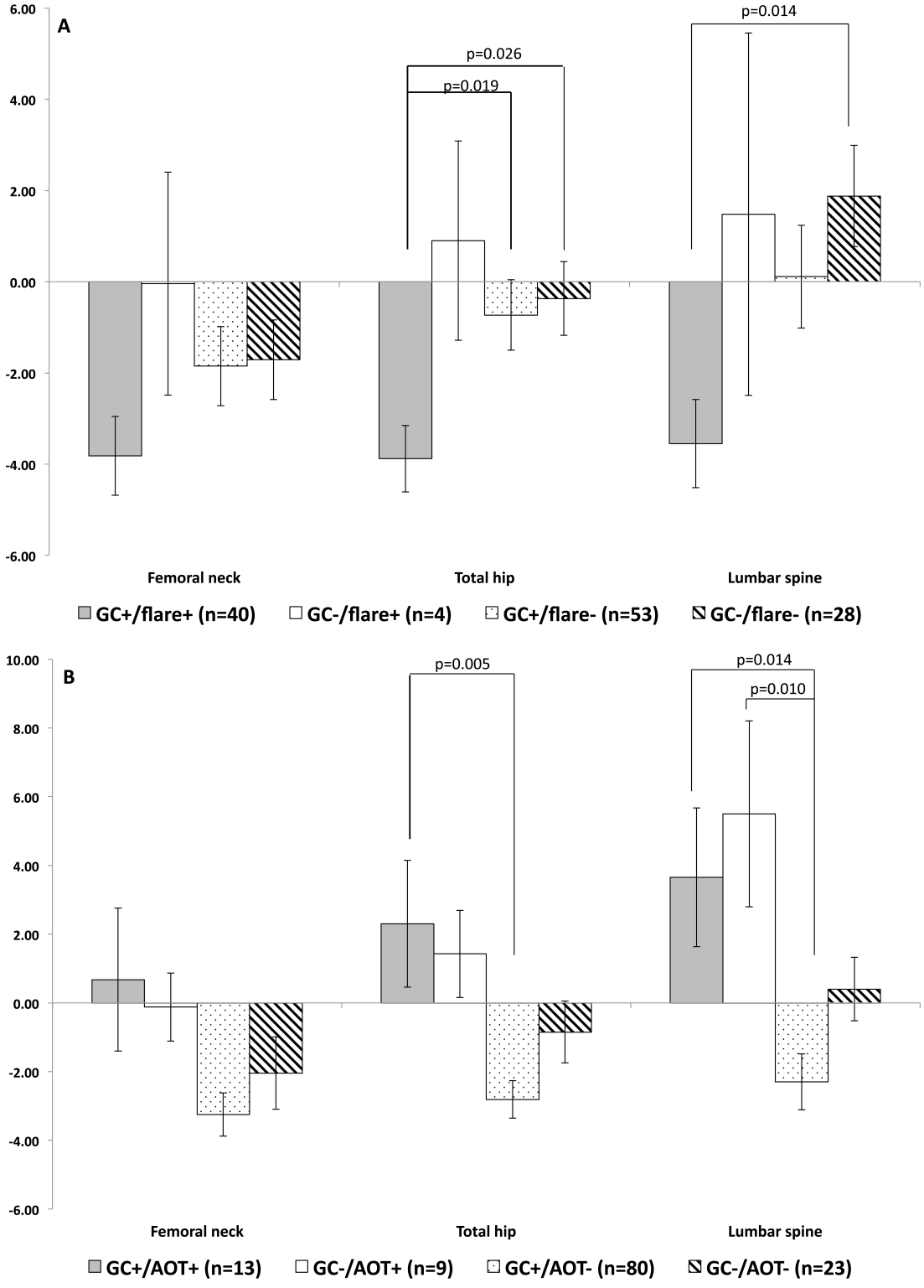

Figure 1. Percentage changes of bone mineral density over followup period in subgroups of patients according to use of glucocorticoid (GC) during followup (GC+: user, GC–: non-user) and disease flare during followup (panel A, flare+: patients with flare, flare–: patients with no flare), and use of antiosteoporosis therapies (AOT) for ≥ 24 months (panel B, AOT+: user, AOT–: non-user). Bars represent mean percentage change over followup period and error bars represent the standard error of mean. Grey bars: users of GC with disease flare/use of AOT; white bars: nonusers of GC with disease flare/use of AOT; dotted bars: users of GC without disease flare/use of AOT; striped bars: nonusers of GC without disease flare/use of AOT. All p values were derived from between-group comparisons by ANOVA with Bonferroni adjustment.

Table 5. Multivariate linear regression analyses with percentage changes of bone mineral density over followup period as dependent variables.

Characteristic	β (95% CI)	p
Femoral neck		
Transitional menstrual status	–0.460 (–1.632, 0.712)	0.439
New organ damage	–2.417 (–4.526, –0.308)	0.025*
Antiosteoporosis therapies	3.397 (0.797, 5.996)	0.011*
Total hip		
Transitional menstrual status	–0.526 (–1.570, 0.517)	0.319
Flare during followup	–1.262 (–3.662, 1.138)	0.300
New organ damage	–1.667 (–3.607, 0.274)	0.092
Daily oral glucocorticoids ≥ 7.5 mg for ≥ 3 mos	–0.614 (–3.406, 2.178)	0.664
Cumulative dose of glucocorticoids	–0.073 (–0.286, 0.141)	0.502
Antiosteoporosis therapies	3.729 (1.389, 6.070)	0.002*
Lumbar spine		
Transitional menstrual status	–1.808 (–3.259, –0.357)	0.015*
25[OH]D level	0.116 (–0.021, 0.254)	0.097
Flare during followup	–1.342 (–4.390, 1.584)	0.385
Oral glucocorticoids	–6.307 (–14.197, 1.584)	0.116
Cumulative dose of glucocorticoids	–0.432 (–0.887, 0.022)	0.062
Cumulative duration of glucocorticoids	0.150 (–0.010, 0.310)	0.065
Antiosteoporosis therapies	6.048 (2.796, 9.301)	< 0.0005*

*Statistically significant. 25[OH]D: 25-hydroxy Vitamin D.

Musculoskeletal damage was not associated with decrease in BMD, probably because over half (54.5%) of these patients were treated with antiosteoporosis therapies during followup. These results suggest that the disease course itself, characterized by chronic systemic inflammation[26], is a major contributor to the bone loss in SLE. Treatments that effectively control disease activity and prevent organ damage but without deleterious effects on the bone may reduce the risk of osteoporosis in SLE. Screening for osteoporosis should be considered in patients with SLE and a more active and severe course of disease even in the absence of use of glucocorticoids.

Several cross-sectional and longitudinal studies have linked the use of glucocorticoids to bone loss in patients with SLE, particularly at the spine[11,13,14]. Our findings were in line with these previous observations. Use of glucocorticoids significantly increased BMD loss at the lumbar spine and there was a dose-dependent relationship between glucocorticoids and bone loss at both the lumbar spine and the hip. These findings concur with the recognized effect of glucocorticoid to particularly affect trabecular rich areas, such as the spine[27,28,29]. BMD loss could be prevented in patients with SLE. In our study, use of potent antiresorptive therapies arrested BMD loss at the hip and significantly increased BMD at the spine. Such therapeutic effect was maintained in patients treated with glucocorticoids and appeared to be greater at the spine.

Our study has several limitations. First, in the absence of a matched control group, we could not distinguish the bone loss attributable to the disease course of SLE and the bone loss attributable to aging. A previous longitudinal study on Chinese females aged 45 to 55 years in Hong Kong reported an annual BMD loss of about 0.5% among premenopausal females, 2% to 2.5% among females with transitional menstrual status, and about 1.5% in postmenopausal women[30]. These figures are higher than those in our study. However, direct comparison between studies cannot be made because of the obvious difference in age profile. Second, compared with randomized controlled study design, our observational study design did not provide strong evidence for the effect of various treatments of SLE on the bone. Third, given the small number of patients in each subgroup, we could not fully explore the interaction between glucocorticoid use, disease characteristics, and BMD loss in SLE. Fourth, our study cohort was dominated by postmenopausal patients and included only Chinese females, limiting the generalizability of our results. Finally, we assessed BMD changes alone and did not study fragility fracture prevalence. While BMD is the best available surrogate marker of reduced bone strength, fragility fracture is a more definite marker of osteoporosis.

Significant BMD loss at the femoral neck and hip over a period of 5 years was found in patients with SLE. Disease activity and damage, as well as glucocorticoid use, contribute independently or synergistically to bone loss in SLE. Potent antiresorptive therapy can potentially arrest bone loss in SLE, especially at the spine. Our results underpin the importance of trying to minimize disease activity, disease damage, and glucocorticoid use in patients with SLE. Screening for osteoporosis should be considered in patients with SLE, especially if they have a more active and severe course of disease, even without glucocorticoid treatment.

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