Homocysteine, Bone Mineral Density, and Fracture Risk Over 2 Years of Followup in Women with and without Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To examine the relationship of baseline homocysteine levels with bone mineral density (BMD) and incidence of fractures over 2 years in women with and without systemic lupus erythematosus (SLE).

Methods. Women with SLE (n = 100) and without SLE (n = 100) were matched according to age (± 5 yrs), race, and menopausal status. Data were collected from 1997 to 2004, including hip, lumbar spine (L-spine), and distal forearm BMD, serum homocysteine levels, and a self-administered questionnaire on osteoporosis risk factors, medications and symptomatic fractures at baseline and 2-year followup. Analyses were performed to compare homocysteine levels, BMD, and incident fractures and to evaluate the relationship of homocysteine with BMD and incident fractures in both groups.

Results. Mean homocysteine ± SD was higher ($p < 0.001$) in women with SLE (9.88 ± 3.8 μmol/l) than in women without SLE (7.98 ± 2.6 μmol/l). Women with SLE had significantly lower L-spine BMD Z-scores, while hip BMD Z-scores and distal forearm BMD T-scores were nonsignificantly lower than in women without SLE. No significant correlations were observed between homocysteine and BMD in either group. Thirteen women with SLE experienced new fractures, while 4 women without SLE had new fractures over 2 years ($p = 0.035$); however, there was no association between homocysteine levels and incident fractures in either group.

Conclusion. Women with SLE had significantly greater baseline homocysteine, lower L-spine BMD, and more new fractures over 2 years, compared with women without SLE. Homocysteine levels were not significantly associated with BMD and did not predict new fractures in women with or without SLE over 2 years. (First Release Jan 15 2008; J Rheumatol 2008;35:230–6)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
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As survival has improved for patients with systemic lupus erythematosus (SLE), increased attention is being focused on the longterm causes of morbidity in these individuals. Patients with SLE are at increased risk of bone loss, and even premenopausal women with lupus may develop osteoporosis[1-6]. Moreover, women with SLE have nearly a 5-fold increased risk for fractures as compared with women in the general population[7].

The pathogenesis of low bone mineral density (BMD) and fractures in patients with SLE is likely to be multifactorial. Contributing factors likely include traditional or lifestyle-related risk factors, as well as SLE disease/treatment-related risk factors. There is a need to ascertain the relative contributions of these various risk factors in order to target the appropriate intervention strategies to prevent fractures in these patients.

In the general population, elevated levels of homocysteine are associated with an increased risk of fractures in older men and women[8,9], but the evidence supporting a relationship between homocysteine and BMD is less consistent[8,10-12]. While homocysteine has been shown to be elevated in those with SLE as compared with healthy con-

trols[13,14], the relationship of homocysteine with BMD and fracture events in women with SLE is unknown. Our objective was to examine the relationship between baseline homocysteine levels and BMD, as well as with the incidence of fractures over a 2-year followup period in women with and without SLE matched for age, race, and menopausal status.

MATERIALS AND METHODS

Our study was derived from a parent study designed to examine osteoporosis risk factors and BMD outcomes in women with and without SLE. For the purposes of our study, fracture risk was added as a secondary outcome to conduct an exploratory analysis to assess the relationship between baseline homocysteine levels and incidence of new fractures in these groups.

Study population and data collection. A total of 100 pairs of women with and without SLE who had BMD measurements performed at 3 anatomical sites (hip, spine, and/or forearm) and returned for a 2-year followup visit after the baseline visit were included in this cross-sectional and longitudinal study conducted from 1997 to 2004. Women with SLE were recruited from the Chicago Lupus Database, a registry that was established at Northwestern University in 1991. It is a cohort of 508 participants, aged 20–94 years (95% women and 5% men; 63% Caucasian, 22% African American, 4% Asian, 9% Hispanic, and 1% other), who meet the 1982 or updated 1997 American College of Rheumatology classification for SLE[15,16]. The participants in our study had characteristics similar to those who are in the Chicago Lupus Database. Eighty-eight of the 100 women met at least 4 criteria from the American College of Rheumatology (ACR) classification criteria for SLE. Of the remaining 12% of women having 3 ACR classification criteria for SLE, all had a clinical diagnosis of SLE and the spectrum of ACR classification criteria fulfilled for SLE included mucocutaneous, musculoskeletal, immunologic, hematologic, renal, and cardiopulmonary manifestations.

One hundred healthy women without SLE were matched by age (± 5 yrs), self-reported race/ethnicity, and menopause status to the women with SLE. These control women were volunteers recruited from the general population using flyers and advertisements. They were then matched to the SLE cases sequentially based on their age, race/ethnicity, and menopause status. The 100 pairs attended a study visit at baseline and at 24 months. All women completed a self-administered questionnaire at each visit on osteoporosis risk factors, medication use, and symptomatic fractures. The visits included an examination, laboratory testing, and BMD measurements using dual-energy x-ray absorptiometry (DEXA). The institutional review board of Northwestern University approved the protocol, and all study participants provided informed consent prior to enrollment.

Measurement of risk factors. Information on age (age at SLE diagnosis and age at menopause), self-reported race/ethnicity (African American, Caucasian, or Hispanic), SLE disease duration, and presence of renal disease was obtained from the Chicago Lupus Database. Menopause status was confirmed by follicle-stimulating hormone (FSH) measurements if the subject's status was uncertain (e.g., irregular menses or hysterectomy without oophorectomy). Medication and supplement use was obtained via questionnaire at each study visit, with particular attention to corticosteroid use. Mean current daily dose of corticosteroids and duration of use were calculated for women reporting past and/or current corticosteroid use. Potential risk factors for osteoporosis in women with and without SLE were assessed via self-administered questionnaire and included questions about participant's smoking habits, alcohol consumption, caffeine intake, dietary calcium intake, and menopausal status. Cumulative disease damage in patients with SLE was assessed by a physician who completed the American College of Rheumatology/Systemic Lupus International Collaborating Clinics cumulative disease damage index (ACR/SLICC-DI), a validated measure of damage in the disease course regardless of attribution, modified by excluding the one point for osteoporosis and fracture item from the total score of 47. Renal disease was defined as having met ACR criteria for renal involvement during the course of SLE disease.

Measurement of BMD. BMD of hip, lumbar spine (L-spine), and distal forearm were measured by DEXA using a Hologic QDR-4500 densitometer (Hologic Inc., Waltham, MA, USA). The L-spine was measured from L1 to L4, and the mean lumbar BMD was reported. BMD results for the spine and total hip were expressed as BMD Z-scores using the DEXA scanner manufacturer's age and race/ethnicity-specific female reference database, because the majority of our subjects were premenopausal. A reference database was not available for distal forearm BMD; therefore BMD T-scores were reported instead.

To assess intra-instrument variation we measured spine and femur phantoms on the machine used for scanning. Block phantoms of standardized densities were performed daily to test variation in system linearity. The intra-instrument coefficients of variation were less than 0.56% for the spine, 0.46% for the femur, and 0.44% for the block phantoms.

Measurement of serum homocysteine. Blood samples for all assays were collected from the arm or hand by standard venipuncture, allowed to clot, and centrifuged at 760 g, 4°C for 10 min. Then serum was removed and stored at –80°C until the assays were performed. Homocysteine was measured from nonfasting sera collected at the baseline visit using an enzyme immunoassay (Biorad). The assay had a sensitivity of 1.0 μmol/l and intra- and interassay coefficients of variation (CV) of 7%–8% and 7%, respectively. The reference range based on 95% confidence interval (95% CI) is 3.6–15.0 μmol/l.

Determination of fractures. Baseline history of fractures and incident fractures were ascertained using a self-administered questionnaire at the baseline visit and at 2-year followup. Only symptomatic fractures were assessed. Fractures in the following sites were included: hip, spine, upper arm, lower arm, hand, leg, fingers, foot, heel, pelvis, ribs, shoulder, wrist, and ankle. Analyses were done using the number of women with at least one fracture, rather than the absolute number of fractures. Symptomatic incident fractures were verified through radiographic reports and clinic notes. We were able to verify incident fractures reported by 3 of the 4 controls and 11 of the 13 women with lupus. Of the 3 fractures not verified, 2 women were lost to followup and there were no available records for the remaining one. All 14 women with available records had verified fractures.

Data analysis. Statistical analyses were performed using paired t-tests for comparisons of means for continuous variables and McNemar's test for comparison of dichotomous variables between the matched cases and controls. Associations between homocysteine and BMD values were assessed using the Pearson product-moment correlation coefficient, and the 2-sample t-test was used to evaluate differences in homocysteine levels in women with SLE based on their fracture status. Chi-square and t-tests were used to compare potential risk factors for SLE women with and without incident fractures. Statistical analyses were completed using Stata version 9.2 (Stata, College Station, TX, USA).

RESULTS

Characteristics of study subjects with and without SLE. The baseline demographic characteristics and osteoporotic risk factors for the 100 women with SLE and the 100 women without SLE are shown in Table 1. The 2 groups were successfully matched for age, race, and menopausal status and were similar with respect to all demographic variables and risk factors for osteoporosis except past or present use of osteoporosis medications, which included bisphosphonates and calcitonin, and past or present use of oral contraceptives.

Table 1. Baseline characteristics: demographics, lifestyle factors, medication use, concomitant diseases, bone mineral density, and self-reported symptomatic fractures in 100 pairs of women with and without systemic lupus erythematosus (SLE).

Feature	SLE, n = 100	Non-SLE, n = 100	p
Patient characteristics			
Age*, yrs	44.1 (11.1)	44.5 (10.7)	
Caucasian, %	80	80	
Non-Caucasian, %	20	20	
Menstruating, %	64	64	
Body mass index*, kg/m^2	26.6 (6.9)	25.9 (5.7)	0.445
Followup*, yrs	2.1 (0.17)	2.1 (0.26)	0.547
Lifestyle factors			
Caffeine*, mg/day	86.4 (96.0)	113.8 (148.3)	0.114
Alcohol*, g/wk	3.4 (6.0)	3.2 (5.6)	0.865
Calcium*, mg/day	765.6 (463.4)	659.4 (374.1)	0.071
Current tobacco use, %	9	13	0.481
Medications			
Current folic acid use†, %	9	2	0.065
Oral contraceptive use‡, %	37	56	0.008
Estrogen use‡, %	28	23	0.359
Osteoporosis medications‡, %	9	1	0.022
Concomitant diseases			
Thyroid disease, %	11	10	1.000
Diabetes, %	5	0	0.063
Bone mineral density			
Lumbar spine*, Z-score	–0.221	0.356	0.001
Hip*, Z-score	–0.107	0.125	0.130
Distal forearm*, T-score††	–0.052	0.153	0.137
			OR (95% CI)
Baseline fractures**			
Spine, n	8	1	8.0 (1.0, 64.0)
Nonvertebral, n	36	34	1.1 (0.7, 1.7)
Any, n	41	35	1.2 (0.8, 1.8)
Incident fractures over 2 yrs**			
Spine, n	1	0	NA
Nonvertebral, n	12***	4***	3.0 (1.0, 9.3)
Any, n	13	4	3.3 (1.1, 10.0)

* Mean (SD). † Present use. ‡ Past or present use of these medications. Osteoporosis medications included bisphosphonates and calcitonin. †† Reference database not available for calculation of appropriate Z-score at distal forearm site. ** Fracture data presented as number of women with at least one fracture, rather than the absolute number of fractures. *** Incident nonvertebral fractures in SLE women included: foot (8), ribs (1), wrist (1), shoulder (1), ankle (1); and in non-SLE women included: foot (1), leg (1), ribs (1), wrist (1).

SLE disease characteristics. For the 100 women with SLE, the mean age ± SD at SLE diagnosis was 35.2 ± 11.9 years and the mean disease duration at study visit was 8.8 ± 8.3 years. A history of renal disease defined by ACR criteria was reported by 24% of the women. Seventy-seven percent reported ever having taken corticosteroids, while 49% were still taking corticosteroids. Of the women who were currently taking corticosteroids the mean daily dose was 10.9 ± 10.8 mg/day and the mean duration of use was 6.5 ± 7.1 years. The mean SLICC-DI score was 1.2 ± 1.8, with 51% having a score of zero, indicating a relatively low disease burden in this group of patients with SLE.

Homocysteine levels in women with and without lupus. Mean serum homocysteine levels were significantly higher in lupus patients compared with controls (9.88 ± 3.8 vs 7.98 ± 2.6 μmol/l; $p < 0.001$), consistent with prior reports[13,14]. Homocysteine levels were not significantly different among women with SLE when stratified by race, menopausal status, estrogen use, or corticosteroid use. In contrast, among women without SLE, homocysteine was higher in postmenopausal compared with premenopausal women (8.70 ± 2.3 vs 7.58 ± 2.7 μmol/l; $p < 0.05$). There were no significant differences in homocysteine levels for the women without SLE when stratified by race or estrogen use.

BMD and fractures in women with and without SLE. BMD Z-scores at the L-spine were significantly lower in the SLE subjects compared with those without SLE (p = 0.001). Hip BMD Z-scores (p = 0.13) and distal forearm T-scores (p = 0.14) were lower in the SLE women, but results did not reach statistical significance (Table 1). There were no significant differences in the total number of women who reported fractures at baseline between those with and without SLE (41 vs 35 women with fractures), but more women with SLE reported baseline spinal fractures compared with those without SLE (8 vs 1 fracture; Table 1). Over the 2-year followup period, 13 women with SLE and 4 women without SLE reported incident fractures. The number of incident fractures was low in both groups, but there were still significantly more women with fractures in the SLE group.

Homocysteine, BMD, and fractures. In women with and without SLE, no significant correlations were found between homocysteine levels and BMD Z-scores at the L-spine or hip and BMD T-scores at the distal forearm. Homocysteine levels were significantly associated with age in women with SLE (r = 0.236, p = 0.018). Multivariate analyses were performed for each group using various models which included potential confounders, such as age, race, menopausal status, caffeine intake, alcohol intake, calcium intake, estrogen use, birth control pill use, and body mass index (BMI), in order to explore the possibility that one of these factors may be causing differential effects on homocysteine and BMD, thereby masking a relationship. This was not the case and adjustment for these other variables only served to further diminish the significance of the homocysteine coefficient in women both with and without SLE (data not shown).

Increased homocysteine levels were not associated with an increased number of baseline fractures in either group (Table 2). Further, baseline homocysteine levels were not predictive of incident fractures over the 2-year followup period in either group. In the control group, homocysteine was higher in women with incident fractures compared with those without fractures, but the difference was not statistically significant (9.85 ± 2.7 μmol/l vs 7.91 ± 2.5 μmol/l; p = 0.14).

Fracture risk factors in women with SLE. We assessed those factors at baseline that were predictive of incident fractures over the 2-year followup period in the women with SLE (Table 3). Only higher alcohol intake — but not current age, BMI, current steroid dose, duration of steroid use, calcium and caffeine intake, menopausal status, race, current osteoporosis medication use, smoking status, or history of prior fracture — was significantly associated with an increased risk of fractures.

DISCUSSION

Our results indicate that women with SLE have significantly higher levels of homocysteine, lower BMD at the L-spine, and a higher number of vertebral fractures, and are 3 times as likely to have a fracture over a 2-year period compared with healthy women without SLE. These findings are consistent with data on homocysteine levels in relation to vascular disease in patients with SLE[13,14], and on BMD and the risk of fractures in this population[1,2,5-7,17-19]. However, our study is the first to describe the relationship of homocysteine with BMD or fractures in women with SLE. In this exploratory study, we have shown that baseline homocysteine levels were not associated with bone density at any of the 3 anatomical sites (L-spine, hip, and distal forearm), and further, were not predictive of incident fractures in women either with or without SLE.

Hyperhomocysteinemia is associated with various disease states including cardiovascular disease and cognitive impairment[20-23]. Several large population-based studies have also linked homocysteine levels with fractures, with what appears to be a threshold effect. Van Meurs, *et al* and McLean, *et al* reported a 2-fold increased risk of fractures in older women with homocysteine in the highest quartile compared with the reference group[8,9]. Supporting this association further, Sato, *et al* determined that treatment with folate and vitamin B12 over 2 years in elderly stroke patients not only lowered homocysteine levels, but also decreased the incidence of fractures with a relative risk of 0.20 (95% CI 0.08–0.50)[24].

There are limited investigative data supporting an association between homocysteine and BMD, and in some instances the existing evidence has been conflicting[8,10-12]. Although there were increased rates of fractures in patients with higher homocysteine levels, both van Meurs, *et al* and Sato, *et al* found no differences in BMD based on homocysteine levels[8,24], raising the possibility that bone quality, rather than bone density, is playing a role in the differential fracture risk based on homocysteine levels. We know that BMD is a strong predictor of fractures, but there are other characteristics of bone, such as microarchitecture and collagen cross-linking, as well as non-bone related factors, such as muscle strength and factors predisposing toward falls, that are important in determining the risk of fractures. Homocysteine thiolactone, a metabolite of homocysteine, can inhibit lysyl oxidase, the enzyme required to produce collagen cross-links[25]. Correspondingly, patients with homocystinuria, a rare autosomal recessive disorder, characterized by markedly elevated homocysteine levels, skeletal abnormalities, early onset osteoporosis, and accelerated atherosclerosis[26,27], have decreased collagen cross-links[28]. In a recent study, Saito, *et al* found impaired collagen cross-linking in both low and high mineralized bone from cases who had sustained fractures compared with bone from controls without fractures. The subjects with fractures also has elevated plasma homocysteine levels compared with controls[29]. These data suggest that homocysteine has an effect on bone structure that may in part explain the propensity to

Table 2. Comparison of homocysteine levels in systemic lupus erythematosus (SLE) and non-SLE women with and without fractures.

	Baseline Fractures			Incident Fractures		
	+	–	p	+	–	p
Homocysteine, μmol/l*						
SLE	9.6 (3.4)	10.1 (4.0)	0.54	9.8 (4.8)	9.9 (3.7)	0.88
Non-SLE	7.8 (2.1)	8.2 (2.8)	0.44	9.8 (2.7)	7.9 (2.5)	0.14

* Homocysteine levels reported as mean (SD).

Table 3. Factors associated with incident fractures in 100 women with SLE.

	+ Incident Fractures	– Incident Fractures	p
Age*, yrs	45.3 (13.9)	43.7 (10.8)	0.657
Body mass index*, kg/m^2	28.4 (9.3)	26.4 (6.6)	0.335
Current steroid dose*, mg	2.3 (2.7)	5.9 (9.9)	0.190
Calcium intake*, mg/d	828.0 (494.9)	765.0 (461.4)	0.651
Caffeine intake*, mg/d	89.6 (107.8)	86.4 (95.3)	0.913
Alcohol intake*, g/wk	9.2 (9.4)	2.5 (4.9)	< 0.001
Menopausal status: post, %	54	33	0.143
Race: Caucasian, %	92	77	0.222
Current smoking, %	7.7	8.2	0.947
History of prior fracture, %	54	39	0.305
Osteoporosis medication use†, %	7.7	9.4	0.842
Folic acid use†, %	15	8.2	0.406

* Mean (SD). † Current use. On average, a 12 ounce can of beer, a 5 ounce glass of wine, and 1.5 ounces of 80-proof distilled liquor contains approximately 12 g alcohol[17].

fracture despite having an unappreciable effect on measured BMD.

In this exploratory study, we were unable to demonstrate any association between homocysteine and BMD or fractures. One potential explanation may be that although women with SLE have higher homocysteine levels compared with non-SLE women, the majority of subjects had homocysteine levels that were within the normal range, and thus the threshold effect for fracture risk, which was suggested by both van Meurs, *et al*[8] and McLean, *et al*[9] was not reached. The difference in homocysteine levels between women with and without SLE was consistent in magnitude with previous studies, which reported differences in the 2–3 μmol/l[13,14] range. Yet these differences may not be clinically significant in relation to BMD and fracture risk. In addition, the subjects in our study were relatively young, with a mean age of 44.1 and 44.5 years in the women with and without SLE, respectively, whereas the studies finding positive associations between homocysteine levels and fracture risk were studying older individuals. Further, over the 2 years of followup, there was a relatively small number of incident fractures, with only 13 in the lupus patients and 4 in the controls. This may have precluded detecting an association between homocysteine and fracture risk, even if one existed. Longer followup may be needed in order to detect any meaningful associations. Finally, given the exploratory design of our study, it is possible that we were unable to find an association between homocysteine and fractures due to type II error from lack of power.

The women with lupus who participated in our study had relatively "mild" lupus disease, as evidenced by their low SLICC damage scores. The mean current dose of corticosteroids (10.8 mg/day) also indicates only mild to moderate SLE disease activity. The women with SLE in our study may not have represented the full range of disease activity, particularly those who were very ill with more severe SLE disease; this limitation may have created a bias toward the null hypothesis.

Asymptomatic fractures were not identified, since spinal radiographs were not performed. This may have led to an underestimation of total fractures in women with and without SLE. There were significantly more symptomatic self-reported spinal fractures at baseline in the women with SLE compared to those without. The women with SLE also had lower spine BMD compared with controls, consistent with previous reports[1,2,5,6,17-19], which would be an important predisposing factor for fractures. Therefore, there may have been disproportionately more asymptomatic spinal fractures in the women with SLE than in those without, and not identifying these may have also contributed to the negative findings in our study.

Although our study was exploratory and had limited

power, it did have several strengths. Foremost, our study is the first to explore the relationship between homocysteine and bone health in women with SLE. In addition, it is known that age and estrogen deficiency are associated with increased levels of homocysteine[30-33] and can serve as confounding factors. In our study, the women with and without SLE were successfully matched by age, race, and menopausal status, which would have precluded confounding based on these factors.

The timing of this observational study was another strength for examining the relationship of homocysteine with BMD and fractures in women with SLE. Data were collected between 1997 and 2004, with 95% of women with SLE having had their baseline visits during 1997 and 2000. In our study, relatively few women with SLE were treated with bisphosphonates to prevent glucocorticoid-induced osteoporosis, which allowed us to evaluate the natural course of bone disease in these women, unhindered by use of bisphosphonates. One reason so few women were taking bisphosphonates during the study period is the controversy over the safety of bisphosphonate use in young premenopausal women of childbearing age[34]. Additionally, routine use of bisphosphonate medications for the treatment of glucocorticoid-induced bone loss was not widespread or common until 1999-2000, which coincided with the end of the enrollment period for the baseline visits.

Women with SLE have higher homocysteine levels, lower BMD in the spine, and an increased frequency of fractures over 2 years. Despite the link seen between homocysteine and fracture risk in large population-based studies of elderly men and women, we were unable to demonstrate such a relationship in this relatively young group of women with SLE or their matched controls in this exploratory study. Larger studies with longer followup are needed to more definitively assess the relationship between homocysteine levels and bone density and fracture risk in women with SLE.

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