Factors Associated with Low Bone Mineral Density in Female Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To study risk factors for low bone mineral density (BMD, g/cm) in patients with systemic lupus erythematosus (SLE).

Methods. Ninety-two consecutive patients with SLE followed by rheumatology faculty between 1997 and 1999 completed a questionnaire regarding lifestyle during the clinic visit, a chart review was performed, and data were collected for the time of the first dual energy x-ray absorptiometry (DXA) examination. Univariate and multivariate statistical analyses were used to assess relationships between various risk factors and BMD.

Results. Ninety-eight percent of patients had received prednisone, 51% were postmenopausal (9 of whom received hormone replacement therapy), 68% had received hydroxychloroquine, and 15% were osteoporotic. The following factors were found to be significantly related to lower BMD by univariate analysis: Caucasian race, older age at diagnosis, higher age at the time of the first DXA, longer disease duration, higher cumulative corticosteroid dose, higher SLE Damage Index score, and postmenopausal status. In the multivariate analysis only the following factors were significant: Caucasian race, increased number of pregnancies, postmenopausal status, higher SLE Damage Index, and higher cumulative corticosteroid dose. An unexpected finding was that taking hydroxychloroquine was the only factor associated with higher BMD of the hip and spine in the univariate analysis, and it remained predictive of higher BMD of the hip and spine in the multivariate analysis.

Conclusion. Hydroxychloroquine appears to protect against low BMD in corticosteroid treated patients with SLE. (J Rheumatol 2001;28:102–8)

Key Indexing Terms:
BONE DENSITY SYSTEMIC LUPUS ERYTHEMATOSUS HYDROXYCHLOROQUINE

Female patients with systemic lupus erythematosus (SLE) have increased risk of developing low bone mineral density (BMD)[1-6], and this has been reported to be exacerbated by corticosteroid therapy[4-8]. These reports consisted of studies of premenopausal patients with the exception of the studies of Hansen, *et al*[8] and Kipen, *et al*[4]. Since patients with SLE are now living longer and are treated during the postmenopausal periods, they face increased risk for developing low BMD. In addition, previous studies have failed to address the confounding influences of many factors using multivariate regression analysis. Although some have used this type of analysis, factors such as the use of drugs commonly prescribed for SLE were not considered[3,4,7,8].

In our study of a large group of patients with SLE, including a large number of postmenopausal patients untreated with estrogens, we analyzed the data using a stepwise multivariate regression strategy. This allowed us to take all variables into account in determining factors that are associated with the development of low BMD.

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MATERIALS AND METHODS

Patients. Ninety-two consecutive nonpregnant female patients with a diagnosis of SLE followed by faculty of the Division of Rheumatic Diseases, University of Connecticut Health Center, who had a baseline dual energy x-ray absorptiometry (DXA) performed were included in the study. All patients with SLE seen between July 1997 and March 1999 were asked to participate in the study: all agreed to participate. Patients were followed by our faculty since the time of diagnosis of SLE. Patients fulfilled at least 4 of the American College of Rheumatology classification criteria for SLE[9]. Patients answered an oral questionnaire administered by their physician and their medical records were reviewed by one of us. Data collected from the questionnaire included the patient's current age, race, age at menarche, menopausal status, age at menopause, duration since menopause, number of pregnancies, family history of osteoporosis, alcohol and tobacco intake, and exercise status. The duration of calcium supplements, vitamin D supplements, estrogen supplements or oral contraceptive pills were recorded as well. Patients were asked about the usage of any medication to treat osteoporosis (nasal calcitonin, etidronate, alendronate). A history of smoking habits was determined by calculating the total number of pack-years. Alcohol usage was determined as positive if a minimum of one standard alcoholic drink (10 g ethanol) was consumed per day[4]. Partaking in regular exercise was noted as positive if a minimum of 40 min of aerobic exercise was performed at least 3 times a week[4]. Medication usage reported by the patient was checked by chart review.

Data from the questionnaire and chart review were entered into a database. Disease variables recorded included duration of disease calculated from the time of diagnosis to the time of the first DXA and activity of disease at time of the first DXA, assessed via the SELENA SLEDAI (SLE Disease

Activity Index) score[10] and severity measured using the SLE Damage Index[11]. Cumulative prednisone dose, average daily prednisone dose, and duration of prednisone therapy were calculated and recorded from each patient's medical record. It has been routine for the past 30 years to prescribe hydroxychloroquine (HCQ) for all patients with mucocutaneous involvement (rashes, alopecia, mucosal ulcers, etc). Based on data from the experience of one of us (NFR) with a different SLE cohort showing the efficacy of antimalarials in reducing all SLE flares[12], HCQ has been recommended to all SLE patients over the past 25 years. Some patients refused to take HCQ and others refused to continue the drug after experiencing gastrointestinal side effects. A total of 14 patients either refused HCQ or took the drug for less than 2 mo and these 14 patients were considered to have not taken HCQ. Usage and duration of HCQ, methotrexate, cyclophosphamide, and other drugs were recorded from the time of diagnosis to the time of the first DXA. Subjects' age at diagnosis and age at the time of the first DXA were also extracted from the medical records. Bone mineral density (BMD, g/cm^2) of the left femoral neck and lumbar spine (L1–L4) were measured by DXA using a Lunar DPX densitometer with Lunar software version 3.6Y (Lunar Radiation Corp., Madison, WI, USA). The reproducibility of the Lunar DPX is ± 0.010 g/cm^2 for the spine and ± 0.015 g/cm^2 for the hip. The physical and mathematical principles have been described[13-15]. The mean lumbar BMD (L2–L4) was used. Based on the World Health Organization criteria for osteoporosis, patients were determined to be either normal (T score > –1.0), osteopenic (T score < –1.0), osteoporotic (T score < –2.5), or severely osteoporotic (T score < –2.5 with fracture)[16].

Univariate statistical analyses were performed to assess associations between patient variables and BMD of the hip or spine. For variables that were dichotomous, a 2 sample t test was used to compare mean BMD across categories. For continuous variables, simple linear regression was used to calculate slopes for change in mean BMD, and correlation analysis was used to assess strength of association with BMD. Before performing the simple linear regressions, it was necessary to transform the scale of some continuous variables to adjust for overt skewness in their distributions.

To determine which variables are associated with changes in BMD while adjusting for the potential effects of other variables, multivariate linear regression was used in conjunction with a mixed backward and forward variable selection strategy. The mixed stepwise strategy began with all independent variables entered into the regression equation. Nonsignificant variables were eliminated sequentially based on statistical testing results for each variable. Once this "backward" procedure was completed, a "forward" stepwise strategy was applied to see if any of the variables that were eliminated could be added to the regression equation to produce a statistically significant component. Identification of best fitting models for hip and spine BMD was followed by regression diagnostics in which residual, leverage, and influence measures for all observations were evaluated. Results from the multivariate regressions are reported as differences in mean BMD relative to dichotomous variables and as slopes relative to continuous variables. Partial correlation coefficients that show the adjusted strength of association between BMD and other variables are also reported. P values ≤ 0.05 were deemed to be statistically significant.

Ordinal logistic regression was used to identify variables that alter the probability of moving from normal bone density to osteopenia or from osteopenia to osteoporosis. Three different dependent variables were used in these regressions — osteopenia/osteoporosis status of the hip, of the spine, and of either location. Best fitting, multivariate ordinal regression models were determined by applying a mixed stepwise strategy similar to that described above. Effect estimates from the ordinal regressions are reported as odds ratios relative to dichotomous variables and as multiplicative factors that alter the odds of osteopenia or osteoporosis relative to a unit change in continuous variables.

RESULTS

Clinical characteristics. The clinical and demographic characteristics of patients are shown in Table 1. The SLEDAI at time of study revealed that most patients had little disease activity. Characteristics found in 10 or fewer patients are not shown and were not included in the analyses (patients taking methotrexate, patients taking cyclophosphamide, patients consuming alcohol).

Table 1. Demographic and clinical characteristics of subjects.

Categorical Variables	Number (%)
Race	
Caucasian	69 (75.0)
Non-Caucasian	23 (25.0)
Family history of osteoporosis	23 (25.0)
Ever pregnant	65 (70.7)
Oral contracetive use (ever)	12 (13.0)
Postmenopausal	48 (52.2)
Hormone replacement therapy (ever)	9 (9.8)
Exercise (at bone density scan)	46 (50.0)
Smoking (ever)	20 (21.7)
Alcohol (at bone density scan)	10 (10.9)
Prednisone use (ever)	90 (97.8)
Cyclophosphamide use (ever)	4 (4.3)
Methotrexate use (ever)	10 (10.9)
Hydroxychloroquine use (ever)	78 (84.8)

Continuous Variables	Mean ± SD	Median	Range
Age at diagnosis, yrs	32.8 ± 12.2	31	11–67
Duration SLE, yrs	14.5 ± 8.5	13.5	1–37
SLEDAI (at bone density scan)	2.4 ± 3.0	2	0–13
SLE Damage Index	1.2 ± 1.7	0	0–9
Age at hone density scan, yrs	45.9 ± 12.4	45.5	21–75
Age at menarche, yrs	2.9 ± 1.8	13	9–21
Number of pregnancies (ever pregnant only)	3.0 ± 1.8	3	1–9
Oral contraceptive duration, mo, users only	49.0 ± 40.1	36	12–120
Age at menopause, yrs, postmenopausal only	43.7 ± 8.6	46	13–57
Hormone replacement therapy*, mos	64.2 ± 53.0	48	18–168
Cigarette consumption (packs, smokers only)	4626 ± 3872	3193	250–13,690
Prednisone, cumulative dose*, mg	41,031 ± 36,431	31,658	483–194,951
Prednisone, average daily dose*, mg/day	11.9 ± 6.8	10.3	0.5–31.5
Cyclophosphamide duration*, mo	7.3 ± 3.2	6	5–12
Methotrexate duration*, mos	31.0 ± 26.9	27	2–75
hydroxychloroquine duration*, mos	69.1 ± 65.6	48	1–293

*Data only on subjects for whom drug was ever prescribed.

Prevalence of low BMD (Table 2). Thirty patients (34.5%) had osteopenia and 10 patients (11.5%) had osteoporosis of the femoral neck. Twenty-eight patients (31.5%) had osteopenia, 12 (13.5%) had osteoporosis, and one (1.1%) had severe osteoporosis of the lumbar spine.

Univariate analyses (Tables 3, 4). There was a significantly higher mean BMD of the hip in the 23 non-Caucasian patients

Table 2. Frequency of osteopenia and osteoporosis in patients with SLE.

WHO Classification*	Femoral Hip** n, %	Lumbar Spine*** n, %	Either n, %
Normal	47, 54.0	48, 53.9	32, 36.0
Osteopenia	30, 34.4	28, 31.5	39, 43.8
Osteoporosis	10, 11.5	12, 13.5	17, 19.1
Severe osteoporosis	0, 0.0	1, 1.1	1, 1.1
Total	87	89	89

*World Health Organization (WHO) criteria for osteoporosis. Patients were determined to be either normal (T score > –1.0), osteopenic (T score < –1.0), osteoporotic (T score < –2.5), or severely osteoporotic (T score < –2.5 with fracture).
**T scores for femoral hip were not assigned to 5 patients. For 2 of these patients, a BMD could not be determined due to total hip replacement.
***T scores for the lumbar spine were not assigned to 3 patients.

Table 3. Univariate relationships of categorical variables to BMD measurements (g/cm^2).

	BMD Hip Mean ± SD	p*	BMD Spine Mean ± SD	p*
Race				
Caucasian	0.85 ± 0.16	0.02	1.08 ± 0.20	0.88
Non-Caucasian	0.95 ± 0.12		1.09 ± 0.17	
Family history of osteoporosis				
No	0.88 ± 0.16	0.47	1.08 ± 0.19	0.83
Yes	0.85 ± 0.16		1.09 ± 0.20	
Prior pregnancy				
No	0.90 ± 0.15	0.31	1.09 ± 0.16	0.98
Yes	0.86 ± 0.16		1.09 ± 0.20	
Oral contraceptive use				
No	0.87 ± 0.16	0.67	1.08 ± 0.19	0.45
Yes	0.89 ± 0.19		1.13 ± 0.19	
Postmenopausal				
No	0.92 ± 0.14	0.005	1.14 ± 0.17	0.005
Yes	0.83 ± 0.16		1.03 ± 0.20	
Exercise				
No	0.88 ± 0.16	0.89	1.08 ± 0.20	0.72
Yes	0.87 ± 0.16		1.09 ± 0.19	
Smoking				
No	0.89 ± 0.16	0.24	1.09 ± 0.20	0.64
Yes	0.84 ± 0.17		1.07 ± 0.17	
Hydroxychloroquine				
No	0.77 ± 0.16	0.009	1.02 ± 0.24	0.19
Yes	0.89 ± 0.15		1.10 ± 0.18	

*Based on 2 sample t test.

(0.95 ± 0.12 g/cm^2) than in the 69 Caucasian patients (0.85 ± 0.16 g/cm^2) (p = 0.01), although there was no difference in BMD of the spine in the 2 racial groups (p = 0.56). Forty-four (47.9%) of the patients were premenopausal and 48 (52.2%) were postmenopausal. Three patients had had surgical or chemical menopause at ages 13, 27, and 30. An additional 12 patients had menopause between the ages of 31 and 39. The mean BMD of the hip was significantly higher in the premenopausal patients (0.92 ± 0.14 g/cm^2) than the postmenopausal patients (0.83 ± 0.16 g/cm^2) (p = 0.005). Similarly, there was a statistically significant difference in the mean BMD of the spine, with higher BMD in the premenopausal patients (1.14 ± 0.17 g/cm^2) than in postmenopausal patients (1.03 ± 0.20 g/cm^2) (p = 0.005).

As shown in Table 4, there was no significant correlation between age at the time of diagnosis and BMD of the spine (p = 0.13), although there was a significant negative correlation between age at the time of diagnosis and BMD of the hip (p = 0.03). There was also a significant correlation between longer disease duration and lower BMD of the hip but not of the spine (p = 0.006; p = 0.21). There was a significant correlation between higher SLE Damage Index and lower BMD for both hip (p = 0.002) and spine (p = 0.02). There was a significant correlation between age at the time of BMD and lower BMD of both the hip and the spine (p < 0.001; p = 0.05).

Table 4. Univariate slopes (± standard errors) of bone density measures relative to continuous patient variables.

	Hip BMD Slope (SE)	R	p*	Spine BMD Slope (SE)	R	p*
Age at diagnosis	–0.003 (0.001)	–0.23	0.03	–0.002 (0.002)	–0.16	0.13
Duration of disease	–0.006 (0.002)	–0.29	0.006	–0.003 (0.002)	–0.13	0.21
SLEDAI	–0.001 (0.006)	–0.02	0.85	0.0002 (0.007)	+0.004	0.97
SLE Damage Index†	–0.032 (0.010)	–0.33	0.002	–0.034 (0.014)	–0.25	0.02
Age at bone density	–0.005 (0.001)	–0.39	< 0.001	–0.003 (0.002)	–0.21	0.05
Age at menarche	–0.001 (0.009)	–0.02	0.88	–0.009 (0.01)	–0.08	0.45
Number of pregnancies+	–0.016 (0.011)	–0.18	0.16	–0.024 (0.014)	–0.21	0.09
Oral contraceptive duration+†‡	0.213 (0.160)	+0.41	0.21	0.199 (0.127)	+0.46	0.15
Age at menopause+†	–0.0004 (0.003)	–0.02	0.91	0.002 (0.004)	+0.08	0.57
Cigarettes+‡	–0.044 (0.078)	–0.13	0.58	0.030 (0.078)	+0.09	0.70
Cumulative prednisone+‡	–0.084 (0.031)	–0.28	0.008	–0.017 (0.038)	–0.05	0.66
Prednisone, average daily+#	–0.032 (0.017)	–0.20	0.06	–0.005 (0.021)	–0.02	0.82
Hydroxychloroquine+‡	-0.026 (0.036)	–0.08	0.49	0.089 (0.042)	0.24	0.03

*t test on slope and correlation coefficient. + Based only on persons with the characteristic. †Slope estimate reflects removal of one or more outlying, influential observations. ‡Slope estimated after transformation of the independent variable to a logarithmic scale. #Slope estimated after transformation of the independent variable to a square root scale.

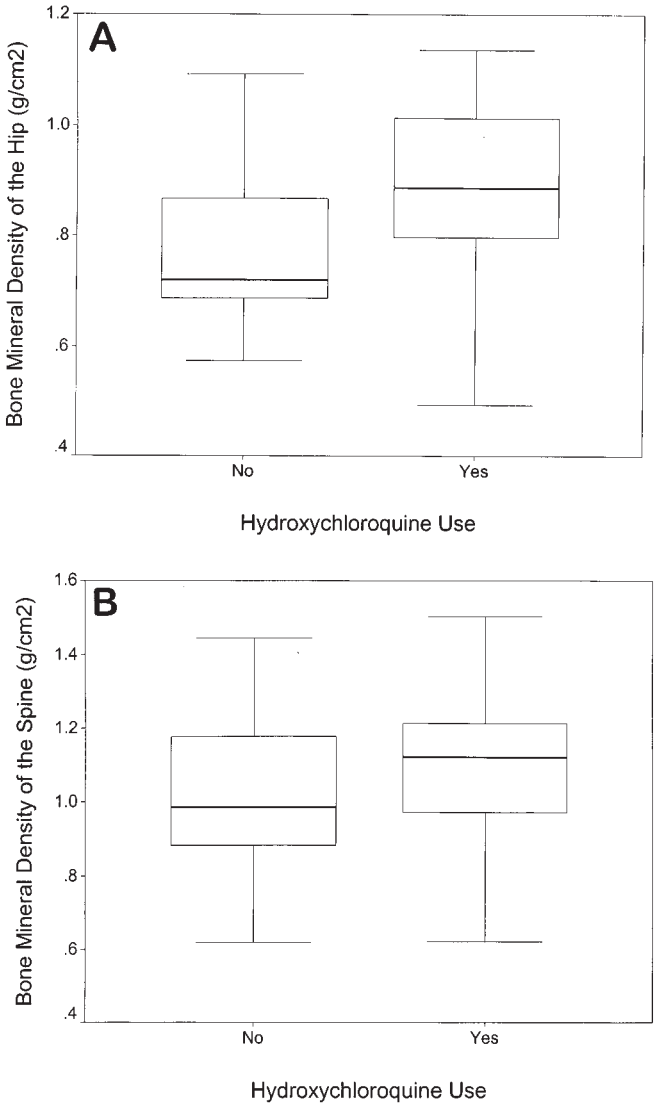

Figure 1. Box plots of BMD (A, femoral neck; B, lumbar spine) in patients with SLE divided by HCQ therapy (yes, no) prior to bone density scan. Boxes represent the interquartile ranges (25th through 75th percentiles). Horizontal lines within the boxes represent the medians and horizontal lines outside the boxes represent actual ranges (minimum and maximum observations). Patients taking HCQ had significantly higher mean BMD of the femoral neck ($p = 0.009$), but not of the lumbar spine ($p = 0.19$).

Two patients did not take prednisone from the time of their diagnosis to the time of their bone density scan. A higher cumulative prednisone but not a higher mean dose of prednisone correlated with a lower BMD of the hip ($p = 0.008$; $p = 0.06$). Neither the cumulative prednisone dose nor the mean prednisone dose had a significant effect on the BMD of the spine ($p = 0.66$; $p = 0.82$).

As shown in Table 3 and Figure 1, the mean BMD of the hip (0.89 ± 0.15 g/cm^2) was significantly higher in the 78 patients who took HCQ compared with the mean BMD of the hip (0.77 ± 0.16 g/cm^2) in the 14 patients who never took HCQ ($p = 0.009$). HCQ had no significant effect on the mean BMD of the spine, but duration of HCQ was significantly correlated with higher BMD of the spine ($p = 0.03$).

The duration of HCQ therapy had no significant effect on the mean hip and lumbar spine BMD when the data were analyzed comparing the 47 patients taking HCQ for ≤ 5 years with the 31 patients who had taken the drug for > 5 years (data not shown).

A family history of osteoporosis, prior pregnancy, exercise, and taking estrogen or oral contraceptives had no significant effect on the mean lumbar spine or hip BMD. Additionally, age at menarche, SLEDAI at time of study, and smoking history were not significantly correlated with the presence of low BMD.

Multivariate analyses (Tables 5, 6). To determine which factors had a significant influence on BMD, the clinical characteristic variables were entered into a stepwise multivariate regression analysis. All variables evaluated in the univariate analyses, regardless of the outcome, were entered into the multivariate analysis. The following factors were found to have a significant effect on the BMD of either the hip or spine: number of pregnancies, postmenopausal status, cumulative prednisone dose, race, SLE Damage Index, and use and duration of use of HCQ.

BMD of the hip was significantly lower in patients who took a higher cumulative prednisone dose, were of the Caucasian race, had a larger number of pregnancies, and had a higher SLE Damage Index. On the other hand, patients who took HCQ had significantly higher BMD of the hip.

Similarly to the effect on the hip, our data also showed that duration of taking HCQ had a statistically significant effect on increasing the BMD of the spine. The only other variable that was associated with the BMD was postmenopausal status. Postmenopausal women had lower BMD of the spine.

The results of the ordinal regression analyses (Table 6) show that the variables that affect the odds of progressing from normal bone density to osteopenia or from osteopenia to osteoporosis vary by site. Risk of osteopenia or osteoporosis of the hip increased relative to age at diagnosis, SLE Damage Index, Caucasian race, and average daily dose of prednisone. The odds of osteopenia or osteoporosis of the spine increased in relationship to menopausal status and number of pregnancies, but decreased in relationship to the occurrence of any pregnancy and the length of time taking HCQ. In combination, the effect of any pregnancy and the number of pregnancies is generally to reduce the risk of osteoporosis/osteopenia, but the magnitude of the beneficial effect became smaller as the number of pregnancies increased. Menopausal status was the only variable that affected the odds of osteopenia or osteoporosis at either site; postmenopausal women were at 3 times greater risk of disease.

When patients were grouped according to T scores, there was no significant difference in mean disease duration among the 41 normal patients (13.4 yrs), the 37 osteopenic patients (15.2 yrs), and the 14 osteoporotic patients (15.6 yrs) ($p = 0.54$).

Table 5. Results of the stepwise multivariate regression analysis.

Hip BMD (g/cm^2) Independent Variable	Slope (SE)	R*	p
Race (Caucasian vs non-Caucasian)	–0.131 (0.035)	–0.38	0.0004
Prednisone, cumulative dose†	–0.083 (0.027)	–0.32	0.0003
Number of pregnancies	–0.023 (0.007)	–0.33	0.003
SLE Damage Index	–0.020 (0.009)	–0.23	0.03
Hydroxychloroquine use (ever vs never)	+0.105 (0.042)	+0.27	0.01
Spine BMD (g/cm^2)			
Independent Variable	**Slope (SE)**	**R**	**p**
Postmenopausal (yes vs no)	–0.107 (0.038)	–0.29	0.006
Hydroxychloroquine duration, mo†	+0.061 (0.027)	+0.24	0.02

*Partial correlation coefficients. †Slope estimated after transformation of the independent variable to a common logarithmic scale.

Table 6. Results of multivariate ordinal logistic regression to identify factors associated with osteopenia and osteoporosis in patients with SLE.

Osteopenia or Osteoporosis of the Hip Independent Variable	Odds Ratio	95% CI	p
Race (Caucasian vs Non-Caucasian)	4.68	(1.44, 15.20)	0.01
Prednisone, average daily dose, mg‡	1.93	(1.17, 3.17)	0.01
SLE Damage Index	1.32	(1.02, 1.71)	0.03
Age at diagnosis, yrs	1.06	(1.02, 1.10)	0.003
Osteopenia or Osteoporosis of the Spine			
Independent Variable	**Odds Ratio**	**95% CI**	**p**
Post-menopausal (yes vs no)	3.96	(1.59, 9.85)	0.003
Number of pregnancies	1.44	(1.07, 1.94)	0.02
Hydroxychloroquine duration, mo†	0.46	(0.25, 0.84)	0.01
Ever pregnant (yes vs no)	0.15	(0.04, 0.62)	0.009
Osteopenia or Osteoporosis in Either Location			
Independent Variable	**Odds Ratio**	**95% CI**	**p**
Post-menopausal (yes vs no)	3.32	(1.45, 7.62)	0.005

†Slope estimated after transformation of the independent variable to a common logarithmic scale. ‡Slope estimated after transformation of the independent variable to a square root scale.

Factors influencing cumulative prednisone level. Stepwise multivariate regression analysis in which cumulative prednisone was used as a dependent variable revealed that a higher cumulative dose of prednisone was dependent on only 2 factors: disease duration and duration of HCQ therapy. Interestingly, even after adjusting for disease duration, the duration of HCQ therapy had an independent effect on increasing the cumulative prednisone dose. Despite the positive correlation between cumulative prednisone dose and duration of HCQ therapy, the duration of HCQ therapy was still associated with a higher BMD of the spine.

DISCUSSION

Our cohort of patients with SLE differs from those reported previously in 3 respects. First, the mean disease duration of 14 years reported here is more than 4 years longer than that of prior studies[1-8,17] and the average age of our patients at the time of study was 45 years. Second, only 9 (10%) were taking hormone replacement therapy and only 12 (13%) additional patients had ever used oral contraception. It has been our general practice that estrogen use should be avoided in patients with SLE. Therefore we were surprised to note that 44.6% of the patients had normal T scores and that 33.3% of the 48

postmenopausal patients had normal T scores. The third unique characteristic of our cohort is the use of HCQ in 68% of the patients.

The factors significantly related to lower BMD in the univariate analysis were Caucasian race, increasing age at diagnosis, increasing age at bone density, duration of disease, cumulative prednisone dose, and postmenopausal status. When all variables were taken into account, using multivariate analysis, Caucasian race, cumulative prednisone dose, number of pregnancies, and postmenopausal status significantly correlated with lower BMD.

HCQ was the only factor found to be related to higher BMD in the univariate analysis and remained predictive of higher BMD in the multivariate regression analysis. The effect was found for the hip and the spine in both the univariate and the multivariate analyses. Consistent with these results, ordinal regression analysis also showed that HCQ reduced the risk of osteopenia and osteoporosis of the spine.

Our findings of an association between Caucasian race and low BMD is supportive of the data showing that for non-SLE patients, Caucasian individuals have a higher prevalence of low bone density than in other races[18]. Thus, it is not surprising that these findings were upheld in our patients with SLE. Many of the reports on SLE BMD do not address the effect of race of the patients on BMD[1-8] and, in most instances, do not describe the race of the patients studied. There were only 2 Asian patients in our group and the predominant race was Caucasian (69 patients). We studied a total of 24 factors considered to be important in predicting osteoporosis including the drugs used to treat SLE. Of these, only HCQ use was found to be related to higher BMD.

This report represents one of the largest groups of patients with SLE studied to date[1-8,17]. Kipen, *et al* reported on 97 Australian women with SLE, but the racial characteristics of the study group were not noted[4]. It is of interest that our study is one of very few based on patients from a United States population. Kalla, *et al* measured BMD by DXA in 46 premenopausal South African SLE patients without renal disease[3]. No information on the racial distribution of the patients was provided. Patients were divided into those taking corticosteroids at the time of the study and those who were not taking corticosteroids. There was a lower hip BMD in the entire group of patients compared with 108 healthy premenopausal females. The prevalence of osteopenia in the entire lupus group was 25% (no comparable percentage was given for the controls). Dhillon, *et al* in England studied the lumbar spine BMD in 26 premenopausal lupus patients, 10 of whom had never taken corticosteroids, and found no significant difference in the mean BMD between the 2 groups[1]. Formiga, *et al* in Barcelona studied 74 premenopausal lupus patients whose mean disease duration was 86 months and found that 12% had osteoporosis[2]. Pons studied 43 premenopausal Spanish patients and found that 18% of the patients taking corticosteroids had osteoporosis[5]. Houssiau, *et al* studied 47 premenopausal Belgian patients with SLE and found that 2 patients were osteoporotic. Of interest was their finding that their group of 11 SLE patients not taking corticosteroid had significantly reduced hip BMD[6]. The effect of the mean corticosteroid dose varies from no effect[1-3,17] to a BMD lowering effect[4-8]. Multivariate analysis was done in only 4 studies and these investigators took into consideration relatively few variables[3,4,7,8].

Gourley, *et al*[19] studied 60 lupus patients and found that the lower BMD in lupus patients was not related to presence of active versus inactive disease, duration of lupus, or presence of nephritis. We also found no relationship in multivariate analysis between disease activity or disease duration and lower BMD.

Ramsey-Goldman, *et al* studied self-reports of fractures in a cohort of 702 SLE patients. Eighty-five percent of the patients were white and thus similar to our patients. They found that age at diagnosis and duration of corticosteroid therapy were associated with fractures, but did not find that race was associated with fractures. The mean dose of corticosteroid was not studied, but duration of use was significantly correlated to fracture in both the univariate and multivariate analyses[20]. In their analysis, only factors that were found to be significant in the univariate analysis were entered into the multivariate analysis, whereas in our study all factors, whether statistically significantly associated with low BMD or not, were entered into the multivariate analysis.

HCQ use was associated with higher BMD in our patients. We are unaware of studies on bone loss in SLE in which the effects of HCQ were investigated. This effect was apparent in both the univariate analysis and the multivariate regression analysis. The effect was on both hip and lumbar spine, and was apparent even when all other clinical and demographic factors were taken into account. In addition, patients taking HCQ were significantly less likely to have osteoporosis. The reason for this association is unclear. We found that the proportion of patients with severe arthritis did not differ in the HCQ treated group (3/78) and the nontreated group (0/14). Similarly, the proportion of patients with avascular necrosis was similar in the treated (8/78) and nontreated (2/14) groups. Only 4 patients in the treated group and one in the nontreated group had either endstage renal disease or severe renal disease. There was no statistically significant difference in SLE Damage Index between patients who did and did not receive HCQ. The percentage of the patients taking HCQ who took vitamin D was similar to those who did not take HCQ (46.2% vs 57.1%) and the percentage taking alendronate was similar (7.7% vs 7.1%). It is of interest that the percentage of patients taking calcium was lower in the HCQ group (46.2%) than in the non-HCQ group (78.6%), so that calcium ingestion does not explain the greater BMD in the HCQ treated group.

The mechanisms of action of antimalarials have been variously reported to be related to their effect on cytokines, especially interleukin 6 (IL-6), IL-1α, stabilizing lysosomal membranes, effect on DNA, on antigen processing, and other

mechanisms that might lead to loss of bone[21,22]. Others have suggested that chloroquine inhibits T cell proliferation partly due to suppression of the production of IL-2, or that there is inhibition of production of interferon gamma, IL-1, or tumor necrosis factor *in vitro*[23-25]. In addition, Wallace, *et al* have shown that HCQ therapy in SLE patients results in a decrease in circulating IL-6[26]. Thus, the protective effects we observed due to HCQ may be due to their action of reducing the production or the effect of cytokines (IL-1 and/or tumor necrosis factors) that by themselves have a deleterious effect on bone. Our data suggest that in our patients with an average of 14 years' disease duration, patients taking HCQ were less likely to develop osteoporosis or osteopenia than patients not taking HCQ.

Our data describe our patients at one point in time. Since the disease duration was very long at the time of study (mean 14 years), it is impossible from this report to determine the rate at which bone loss occurred in these patients. It is well recognized that significant bone loss occurs during the first 6 months of corticosteroid therapy[27]. Our multivariate analysis revealed that disease duration was not a significant predictor of bone loss. To determine the effect of longterm corticosteroid therapy, we are now studying our patients prospectively with yearly DXA scans. The interesting finding that HCQ predicts higher bone density should be confirmed by studies carried out on other cohorts of patients with SLE as well as on patients with other diseases treated with antimalarials.

Our study of a large cohort of patients with SLE of long duration revealed that despite the lack of estrogens, one-third of the postmenopausal patients and more than half (55%) of the premenopausal patients had normal BMD. In addition, it appears that hydroxychloroquine has a protective effect on both cortical and trabecular bone.

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