EXTENDED REPORT

Prevalence and predictors of fragility fractures in systemic lupus erythematosus

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Objective: To establish the prevalence of reduced bone mineral density (BMD) and fractures, and risk factors for fractures, in a cross sectional study of a large cohort of patients with systemic lupus erythematosus (SLE).

Methods: All SLE patients willing to take part in the study had bone densitometry in 1999/2000 and completed a questionnaire on risk factors for osteoporosis and on drugs used. Accumulated damage was scored using the SLICC/ACR damage index (SDI). Only fractures occurring since the onset of SLE and unrelated to trauma were included, and the SDI score was modified to exclude osteoporotic fractures. Statistical analysis was by χ^2 test, Fisher's exact test, and binary logistic regression.

Results: 242 patients were studied, median age 39.9 years (range 18 to 80), median disease duration 7.0 years (range 0 to 42). Of these, 123 (50.8%) had reduced BMD (T score <-1.0) and 25 (10.3%) were in the osteoporotic range (T score <-2.5). Fragility fractures had occurred in 22 patients (9.1%) since diagnosis of SLE. Of these, two (9.1%) had normal BMD and 20 (90.9%) had reduced BMD, while seven (31.8%) were within the osteoporotic range. Non-Afro-Caribbean race and exposure to prednisolone >10 mg daily were significantly associated with reduced BMD, while age and menopause were associated with osteoporosis. The risk factors for fractures were reduced BMD and age.

Conclusions: Reduced BMD, osteoporosis, and fragility fractures appear to be prevalent in patients with SLE. Steroids were not an independent risk factor for fractures, although their effect could be mediated through reduced bone mineral density.

Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disorder which predominantly affects women in the prime of their life. As survival improves in SLE, it is anticipated that reduced BMD and fragility fractures will become a major form of morbidity, as corticosteroids remain the mainstay of treatment. However, there have been few studies on reduced BMD and fragility fractures in SLE,[1–8] and they have tended to involve small numbers of patients or have only examined premenopausal patients.

Our objectives in this cross sectional study were to determine the prevalence of reduced BMD and fragility fractures and the risk factors for these conditions in a large cohort of SLE patients.

METHODS

Subjects and setting

All patients who fulfilled the American College of Rheumatology criteria for SLE[9] and were attending lupus clinics at Queen Elizabeth Hospital and City Hospital in Birmingham were invited to participate in this cross sectional study. This large cohort of SLE patients was set up by one of us (CG) in 1989. The local ethics committees approved the study, and written consent was obtained from patients before their inclusion. During follow up, detailed clinical and drug use information was recorded at each visit and entered into a specific lupus database (BLIPS).[10] Damage was scored using Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) every six months and this has been in use since 1993.[11] Ethnicity was classified into white, Afro-Caribbean (black), Asian (Indian subcontinent), or others.

Patients willing to participate were required to complete a questionnaire on risk factors for osteoporosis, details about any fractures sustained, family history of any fractures, and drugs used (current and previous), with particular reference to glucocorticoids, the oral contraceptive pill, hormone replacement therapy (HRT), calcium/vitamin D, and bisphosphonates. Bone mineral densitometry was done in 1999/2000, measuring BMD of the femoral neck and lumbar spine by dual energy *x* ray absorptiometry using a Lunar DPX-L pencil beam scanner with software version 1.3 g (GE Medical Systems, Madison, Wisconsin, USA). BMD results were computed into a T score, which compared the patient's observed BMD with an expected value for a young adult (expressed as number of standard deviations). Definitions of osteopenia and osteoporosis used were according to the World Health Organisation (WHO) criteria.[12] Only fractures occurring since the onset of SLE and unrelated to trauma were included. A modified SDI score excluding osteoporotic fractures was used in the analysis.

Statistical analysis

Analysis was carried out using the χ^2 test, Fisher's exact test, or binary logistic regression where appropriate. The model for logistic regression was tested for goodness of fit with the Hosmer and Lemeshow test. Probability (p) values of less than 0.05 were considered statistically significant. Statistical calculations were done using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

In all, 318 patients were invited to participate in the study, and 242 agreed to take part (response rate 76.1%). The demographic characteristics of this cohort are shown in table 1. There were 106 patients (56.2%) with a modified

Abbreviations: BMD, bone mineral density; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus

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Table 1 Demographic characteristics of 242 patients with systemic lupus erythematosus

Age (years), median (range)	39.9 (18 to 80)
Female sex (%)	231 (95.5)
Race (%)	
White	153 (63.2)
Afro-Caribbean	40 (16.5)
Asian	37 (15.3)
Others	12 (5.0)
Disease duration (years), median (range)	7 (0 to 42)
Body mass index (%)	
Underweight (<18.5)	9 (3.7)
Normal (18.5 to 24.9)	107 (44.2)
Overweight (≥25.0)	126 (52.1)

damage index of 1 or more at the time of bone mineral densitometry. The menopausal status of the 231 female patients was: 126 (54.5%) premenopausal, 39 (16.9%) premature menopause, 64 (27.7%) normal menopause. The menopausal status of two female patients was not known as the questionnaire was incompletely filled in. The prevalence of other known risk factors for osteoporosis in this cohort is shown in table 2.

Fourteen patients (5.8%) were taking bisphosphonates, nine (3.7%) had previous exposure to bisphosphonates, and 89 (36.8%) were taking calcium and vitamin D supplements at the time of bone densitometry. There was history of exposure to HRT in 32 patients (13.2%), while 16 were still on it at the time of the scan. There were 138 patients (57.0%) who had exposure to the oral contraceptive pill: 88 with combined oestrogen-progestogen, 16 with progestogen only, and 34 uncertain of the type.

Bone mineral densitometry

In all, 123 patients (50.8%) had reduced BMD (T score less than −1.0) and 25 (10.3%) were in the osteoporotic range (T score less than −2.5). Ten patients (8.1%) with reduced BMD were taking bisphosphonates at the time of the scan, while only three (12%) of those patients in the osteoporotic range were taking bisphosphonates at that time.

Univariate analysis showed that age, non-Afro-Caribbean race, low body mass index (underweight, <18.5 mg/m^2), menopause, disease duration, modified SDI >0, and exposure to prednisolone >10 mg/day were associated with reduced BMD, while exposure to the oral contraceptive pill was protective against reduced BMD. Further analysis of exposure to oral contraceptives did not show any difference between combined oestrogen-progestogen or progestogen-only preparations. Age, menopause, disease duration, and modified damage index >0 were significantly associated with osteoporosis in univariate analysis. Similarly, exposure to oral contraceptives was protective against osteoporosis.

Table 2 Prevalence of risk factors for osteoporosis in 242 patients with systemic lupus erythematosus

Risk factor	Prevalence (%)
Currently taking oral corticosteroids	176 (72.7)
Ever had intravenous pulse steroids	63 (26)
Ever had prednisolone >10 mg/day	179 (74)
Ever had prednisolone >29 mg/day	61 (25.2)
Ever smoked	85 (35.1)
Ever had alcohol >20 units/week	4 (1.7)
Ever avoided dairy products	28 (11.6)
Ever confined to bed for >2 months	28 (11.6)

With multivariate analysis, non-Afro-Caribbean race and exposure to prednisolone >10 mg/day were significantly associated with reduced BMD. Age and menopause were associated with osteoporosis in multivariate analysis (table 3). However, the 95% confidence interval of the odds ratio for menopause was large, reflecting the small number of patients with osteoporosis in this cohort.

Fragility fractures

There were 22 patients (9.1%) with fragility fractures since the diagnosis of SLE. All of them were female. Of these, two (9.1%) had normal BMD and 20 (90.9%) had reduced BMD, with seven (31.8%) within the osteoporotic range. Most of these patients (81.8%) were menopausal. Only three patients (13.6%) were taking bisphosphonates at the time of the scan.

Univariate analysis showed that age, disease duration, menopause, non-Afro-Caribbean race, modified SDI, and reduced BMD were associated with fractures, while exposure to oral contraceptives was protective. Only reduced BMD and age were predictors of fractures in multivariate analysis (table 4). Steroid exposure was not significantly associated with fragility fracture.

DISCUSSION

We found a high prevalence of reduced BMD (50.8%), osteoporosis (10.3%), and fragility fracture (9.1%) in our SLE cohort, considering that 70.7% of our patients were not more than 50 years of age. Our figures were similar to previous studies by Kipen *et al*,[5] who found a prevalence of 44.3% for reduced BMD and 13.4% for osteoporosis, and by Ramsey-Goldman *et al*,[8] who reported low trauma fractures in 12.3% of their cohort. Although our study had a relatively large number of patients in the cohort, one of its limitations is the small number with osteoporosis and fragility fracture.

We did find a significant association between steroid exposure and reduced BMD. This is not surprising, as steroids are a well recognised cause of osteoporosis and fractures. Previous studies by Kipen *et al*[5] and the Hopkins Lupus Cohort[13] have found that cumulative steroid dose is associated with reduced BMD or osteoporosis. Unfortunately, we did not have the cumulative steroid dose in our study. It is also not unexpected that Afro-Caribbean race is protective against reduced BMD, as Afro-Caribbeans tend to have higher BMD than whites.[14]

In our study, reduced BMD appeared to be the strongest risk factor for fragility fractures. We did not find a significant association on multivariate analysis between exposure to different glucocorticoid doses and fractures. There has been only one previous study, by Ramsey-Goldman *et al*, looking at low-trauma fractures following the diagnosis of SLE.[8] These investigators found that longer exposure to steroid was independently associated with fractures, which is in contrast to our result. However, in that study they looked at the duration of exposure (rather than the dose) and data on BMD were not collected, which may explain the difference. It is likely that the

Table 3 Predictors of reduced bone mineral density and osteoporosis

	Odds ratio (95% CI)	
Predictor	Reduced BMD	Osteoporosis
Non-Afro-Caribbean	2.5 (1.2 to 5.4)	–
Ever taken prednisolone >10 mg/day	2.1 (1.1 to 4.2)	–
Menopause	–	13.3 (1.6 to 111.1)
Age	–	1.0 (1.0 to 1.1)

BMD, bone mineral density; CI, confidence interval.

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Table 4 Predictors of fragility fractures since onset of lupus

Predictor	Odds ratio (95% CI)
Reduced BMD	8.1 (1.7 to 40.0)
Age	1.2 (1.1 to 1.3)

BMD, bone mineral density; CI, confidence interval.

effect of steroids on fractures is mediated predominantly by reduction in bone density in susceptible individuals.

There is some evidence that steroid induced fractures occur at higher BMD than age related or postmenopausal osteoporotic fractures.[15 16] This may explain the rather high prevalence of low trauma fractures in patients whose BMD is not in the osteoporotic range. However, the bone mineral densitometry was not done at the time of the fracture in this study. Nevertheless, it may be reasonable to start preventive treatment against fragility fractures at a lower BMD threshold in patients on steroids, as has been recommended recently in the United Kingdom.[15] Despite the overall high prevalence of fragility fractures in this cohort, the prevalence of these fractures in premenopausal women remains low (3.1% in this cohort). Therein lies the difficulty in the management of such patients as SLE predominantly affects premenopausal women, while bisphosphonates—which are teratogenic in animal studies—are the only class of drug that has shown efficacy in the treatment and prevention of corticosteroid induced osteoporosis.[17–19] In view of its prolonged skeletal half life, bisphosphonates should be used with great caution in women who intend to get pregnant at some future time. Further studies would be required to address these issues. In the meantime, we recommend bisphosphonates only in those premenopausal SLE patients with osteopenia or osteoporosis who require long term high dose steroids. Bisphosphonates with the least evidence of persistence in the skeleton should be used.

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