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Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus

L Carli,[1,2] C Tani,[2] V Spera,[2] R Vagelli,[2] S Vagnani,[2] M Mazzantini,[2] O Di Munno,[2] M Mosca[2]

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[1]Department of Genetic Oncology and Clinical Medicine (GenOMeC) PhD, University of Siena, Siena, Italy
[2]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Correspondence to
Dr Marta Mosca; marta.mosca@med.unipi.it

ABSTRACT

Osteoporosis (OP) and fragility fractures (FFx) are a known comorbidity in patients with systemic lupus erythematosus (SLE). This work aimed at evaluating (1) the prevalence of OP and FFx in a cohort of SLE and (2) the risk factors associated with both OP and FFx. The following data were collected from clinical charts: age, sex, menopausal status (MP), body mass index, smoking habits, disease duration, daily dose and cumulative glucocorticoids (GCs), type of organ involvement, comorbidities and medications. Data on bone metabolism, calcium and vitamin D supplementation and treatment with bisphosphonates, teriparatide or denosumab were collected, together with bone mineral density (BMD) values (measured by dual-energy X-ray absorptiometry (DXA)) and history of FFx (occurred after the onset of SLE and unrelated to trauma). OP and reduced BMD were defined according to the WHO. 186 patients were included (women 175, men 11; mean age 46.4±13 years, mean disease duration 14.9±9 years). At their last visit, 97 patients (52.2%) had a reduced BMD and 52 (27.9%) had OP. 22 patients (11.8%), all women, had at least one FFx; six patients (27.3%) were pre-menopausal. On univariate analysis, age, cumulative dose of GC, MP, therapy with antiepileptics and chronic renal failure (CRF) were correlated with OP ($p<0.03$); age, total amount of GC, MP, CRF, anticoagulants (AC) and antiepileptic therapy were correlated with FFx ($p<0.05$). The multivariate logistic model confirmed a direct association of OP and age, MP and antiepileptic therapy ($p\leq0.01$) and of FFx and age, chronic therapy with AC and antiepileptics ($p<0.03$). In conclusion, low BMD is frequently observed in SLE, and FFx are observed also in premenopausal patients. Together with traditional risk factors (age, MP and GC), CRF and chronic treatments with AC or antiepileptics seem to be associated with a higher risk profile for OP and FFx occurrence.

KEY MESSAGES

- A low bone mineral density is frequently observed in patients with systemic lupus erythematosus chronically treated with glucocorticoids.
- Fragility fractures are observed also in pre-menopausal patients.
- A higher risk profile for osteoporosis and fragility fractures seems to be related, together with traditional risk factors (age, disease duration, post-menopausal status and cumulative glucocorticoids dose) with the presence of a chronic renal failure and with a chronic treatment with AC or antiepileptics.

INTRODUCTION

The occurrence of osteoporosis (OP) and fragility fractures (FFx) in patients with systemic lupus erythematosus (SLE) has been widely described in the literature.

Among the various factors predisposing to OP in SLE, glucocorticoid (GC) therapy certainly plays a central role.[1–12]

It has been shown that the thresholds of vertebral bone mineral density (BMD) for FFx are higher in women under chronic GC treatment at any site, compared with postmenopausal subjects.[3 6 10 13 14]

The aim of the present work is to evaluate (1) the prevalence of OP and clinical FFx in a cohort of patients with SLE under chronic GC therapy and (2) the risk factors associated with both OP and FFx.

PATIENTS AND METHODS

Patients with a diagnosis of SLE according to the American College of Rheumatology classification criteria[15] regularly followed at our unit were enrolled in the study. Only patients under chronic GC therapy (more than 6 months) were considered eligible. At study enrolment, the following data were collected for each patient from both clinical charts and discharge documents: age, sex, ethnicity, menopause (defined as amenorrhoea for the 12 months following the final menstrual period[16]), body mass index (BMI), smoking habits (former and current smoking and

number of packets per year), disease duration, follow-up duration, daily dose and total amount of GC (expressed as prednisone equivalent), presence and type of organ involvement. Concomitant diseases (chronic renal failure (CRF), either hyperthyroidism or hypothyroidism) and concomitant medications (GC, ciclosporin A (CyA), anticoagulants (AC), antiepileptic drugs), potentially affecting bone metabolism were also recorded. In particular, CRF was defined as a glomerular filtration rate of <60 mL/min, based on the definition of the Kidney Disease: Improving Global Outcomes (KDIGO) study group.[17]

The history of FFx at various skeletal sites and bone metabolism parameters (calcium, 25OH-Vitamin D and parathyroid hormone (PTH)) at the last observation were also evaluated; data on calcium and vitamin D supplementation were also collected. Only FFx occurring after the onset of SLE and unrelated to trauma (such as falling from a standing position) were included. Self-reporting by the patients of clinical FFx was considered valid only in the presence of an X-ray confirmation.

BMD of lumbar spine (L1–L4) and non-dominant hip (total hip, femoral neck) measured by DXA and expressed as T-scores and in gram per square centimetre were recorded. In particular, a cross-sectional evaluation of BMD of all patients was performed at the last visit; in addition, previous BMD measurements were also recorded. OP was defined according to the WHO criteria.[18]

For the descriptive analysis, continuous variables were expressed as mean±SD; categorical variables were reported as proportions; univariate and multivariate analysis were used in order to analyse the associations of both OP and FFx with possible risk factors. For both the univariate analysis and the multivariate analysis, a logistic regression model was built.

RESULTS

A total of 186 patients were included in the analysis, all Caucasians. All the patients had been treated with GC, at a mean daily dose of 5.4±2.3 mg, with a mean cumulative dose of 34.9±25.3 g. In total, 155 patients (83.3%) were regularly taking calcium (500 mg/day) and vitamin D (cholecalciferol), while no treatment with calcium and vitamin D was reported in the clinical charts of 31 patients (16.7%).

Demographic data and clinical characteristics of the cohort at the last observation are summarised in table 1, while the impact of OP risk factors is summarised in table 2.

Bone metabolism

A cross-sectional evaluation of bone metabolism parameters showed that, at last observation, the mean value of 25OH-D was 21.8±15.7 ng/mL, serum calcium was 9.3 ±0.4 mg/dL and PTH was 47.4±43.1 pg/mL. A total of 147 patients (79%) had experienced hypovitaminosis D (25OH-D levels <30 ng/mL) at least once in their clinical history; in particular, 97 patients (66% of patients with hypovitaminosis D and 52.2% of the total) had a 'deficiency' of vitamin D (<20 ng/mL) and 50 patients (34% of patients with hypovitaminosis D and 26.9% of the total) had an 'insufficiency' (from 20 to 30 ng/mL). The remaining 39 patients (21%) had never had hypovitaminosis D during their follow-up.[19]

OP and FFx

Mean values of vertebral, femoral neck and total femur BMD were 0.921±0.142, 0.750±0.139 and 0.818±0.140 g/cm^2, respectively, with mean T-score values at each site of −1.43±1.20, −1.38±1.15 and −1.29±0.97. At their last observation, 97 patients (52.2%) had a reduced BMD and 52 patients (27.9%) had BMD values (either lumbar or femoral) defined as OP. In 31 patients (59.6%) a T-score lower than −2.5 was present only at the vertebrae, in 13 (26%) only at the femoral site, while in 8 (15.3%) at both sites; in particular, seven of them experienced values of BMD corresponding to OP at the vertebral site before that femur and only one of them had BMD values of OP earlier at the femoral site (figure 1). The mean age at the time of OP diagnosis was 49.9±11.9 years and the mean disease duration was 22.3±8 years.

T-score values at femur and vertebrae were inversely associated with age (p<0.0001) and disease duration (p=0.05/0.007), while only vertebral T-score was inversely correlated with the total amount of GC (p=0.05). Post-menopausal patients had a significantly lower T-score at both sites (p=0.003/0.001).

Univariate analysis showed a correlation between OP and age (p<0.0001), total amount of GC (p=0.001), post-menopausal status (p<0.0001), therapy with antiepileptics (p=0.005), CRF (p=0.01) and duration of therapy with AC (p=0.05); the multivariate logistic model confirmed a direct association of OP and age, post-menopausal status and antiepileptic therapy (respectively, p<0.0001, p=0.01 and p=0.01).

25OH-D values at the last observation were not associated with BMD values at the last observation nor with the presence of OP, FFx or the total dose of GC.

At least one FFx was observed in 22 out of 186 patients (11.8%), all of whom were women. Sixteen of them had more than one FFx, for a total of 40 FFx; the most common FFx sites were vertebrae (n=29), followed by costae (n=6), femur (n=3) and ribs (n=2). Sixteen women were post-menopausal at the time of FFx, while six were pre-menopausal.

The first FFx occurred at a mean age of 53.4 ±9.4 years, after a mean disease duration of 23.4±7 years and a cumulative dose of GC of 26.5±9.4 g.

At the time of FFx, 10 patients (45.5%) were treated with AC, 6 (27.3%) with antiepileptics and 6 (27.3%) had a diagnosis of CRF.

At the univariate analysis, the occurrence of FFx was associated with age (p<0.0001), total amount of GC

Table 1 Demographic and disease characteristics of the cohort at the last observation

	No OP (134)	With OP (52)	With FFx (22)	p value
Female/male	128/6	47/5	22/0	NA
Mean age at last observation	42.3±10.9 years	56.9±12 years	61.3±10.3 years	<0.0001*
Mean disease duration	16.5±7.7 years	22.5±8 years	23.4±7.1 years	<0.01*
Cutaneous involvement	108/134 (80.6%)	19/52 (36.5%)	8/22 (36.4%)	Ns
Joint involvement	97/134 (72.4%)	18/52 (34.6%)	12/22 (54.5%)	Ns
CNS involvement	34/134 (25.4%)	13/52 (25%)	6/22 (27.3%)	Ns
Renal involvement	71/134 (53%)	30/52 (57.7%)	14/22 (63.6%)	Ns
Chronic renal failure	14/134 (10.4%)	12/52 (23.1%)	6/22 (27.3%)	<0.05*

*OP and FFx versus no OP.
CNS, central nervous system; FFx, fragility fractures; OP, osteoporosis.

(p=0.0002), post-menopausal status (p=0.0002), CRF (p=0.04), antiepileptic therapy (p=0.0005) and its duration (p=0.05), both vertebral and femoral BMD (p≤0.05), AC therapy (p=0.0009) and its duration (p=0.05). The multivariate analysis showed age, antiepileptic therapy, vertebral BMD and therapy with AC as the best independent risk factors of FFx (respectively, p=0.003, p=0.008, p=0.02 and p=0.03).

DISCUSSION

SLE is a chronic autoimmune disorder predominantly affecting young women. About 25% of patients develop organ damage attributed to the musculoskeletal system (including OP and FFx), within the first 10 years of the disease.[2 8 9 11 12]

We have observed that more than 50% of our patients chronically treated with GC had low BMD and 28% had OP. These results appear consistent with previous reports.[8 9 11 12]

While a correlation was observed between T-score values and age, disease duration and menopausal status, only vertebral T-score was associated with the total amount of GC.

These findings are reasonably related to the mechanism of bone damage of GC characterised by a preferential loss of the trabecular bone of the spine, which typically precedes that which occurs in the cortical bone of the hip, thus causing an increased prevalence of vertebral FFx, and occurring earlier with respect to the population not treated with GC.[13 14]

In accordance with the literature, in our cohort, traditional risk factors such as age, GC use, postmenopausal status and chronic antiepileptic therapy showed an association with OP occurrence.

Similarly for the development of FFx, our data confirmed the association with vertebral and femoral BMD, age, post-menopausal status and the cumulative GC dose (p<0.01); moreover, FFx also appeared to be associated with CRF and a chronic treatment both with AC and antiepileptics (p<0.05). In particular, our data showed that vertebral BMD, AC and antiepileptics were the best independent risk factors of FFx development.

On the contrary, two previous studies on large SLE cohorts have failed to show an association with antiepileptic therapy. This discrepancy could be attributed to a number of factors such as ethnicity, disease severity and clinical manifestations that in both these cohorts were different from the characteristics of our patients.[20 21]

Indeed, all our patients were Caucasians; while Lee *et al* described a cohort of Caucasians, African

Table 2 Risk factors for OP and FFx

	No OP (134)	With OP (52)	With FF (22)	p Value
Mean BMI	23.8±6 kg/m^2	23.2±3 kg/m^2	23.7±3 kg/m^2	Ns
Former smoking	26/134 (19.4%)	9/52 (17.3%)	2/22 (9%)	Ns
Current smoking	25/134 (16.4%)	8/52 (15.3%)	3/22 (13.6%)	Ns
Postmenopausal status	30/128 (23.4%)	28/47 (59.6%)	16/22 (72.7%)	0.0001*
Thyroid disorders	48/134 (35.8%)	21/52 (40.4%)	10/22 (45.5%)	Ns
Mean total dose of GC	24.4±16.6 g	37.1±25.5 g	48.9±28.8 g	<0.001*
GC pulses	85/134 (63.4%)	28/52 (53.8%)	14/22 (63.6%)	Ns
AC therapy	24/134 (17.9%)	13/52 (25%)	10/22 (45.5%)	0.003†
Mean duration	7.5±5.2 years	13.3±9.2 years	14.4±9.7 years	0.05*
Antiepileptic therapy	7/134 (5.2%)	10/52 (19.2%)	6/22 (27.3%)	<0.01*
Mean duration	9.7±7.8 years	13.4±11.9 years	11.5±6.4 years	Ns
CyA therapy	38/134 (28.4%)	10/52 (19.2%)	4/22 (18.1%)	Ns

*OP and FFx versus no OP.
†No OP- OP versus FFx.
AC, anticoagulants; BMI, body mass index; CyA, ciclosporin A; FFx, fragility fractures; GC, glucocorticoids; OP, osteoporosis.

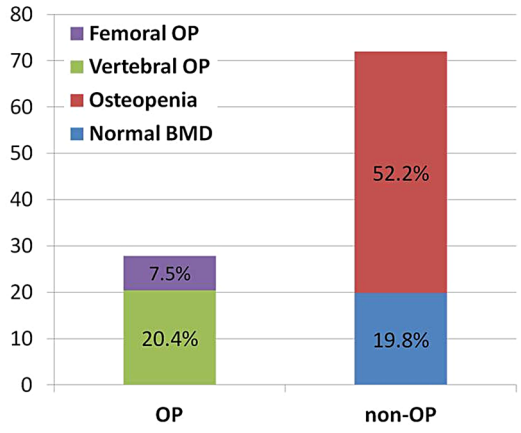

Figure 1 Distribution of bone mineral density (BMD) values in our cohort. OP, osteoporosis.

Americans and Hispanic patients, Bultink *et al* described a cohort in which 31% of the patients were Caucasians.

In the study of Bultnik *et al*, patients with SLE were selected from a general practitioners registry and may therefore represent patients with a milder disease. Lee *et al* reported a prevalence of renal involvement in 36.8% in the fractured group and in 18.1% in the non-fractured group. Our data show a higher prevalence of renal involvement (63.6% in the fractured group vs 55% in the non-fractured group). Finally, AC therapy was not included in the analysis in either of the two studies.[20 21]

It is known that the prevalence of hypovitaminosis D tends to be higher in patients with SLE than in the general population and actually a great debate is ongoing about this association to clarify whether low levels of vitamin D are the consequence or whether they anticipate SLE onset.[22–25]

Indeed, although in therapy, a high percentage of our patients showed low values of 25OHVitD, with normal values of both serum calcium and PTH. In particular, we found a higher prevalence of vitamin D deficiency, in comparison with some already published data.[22 23 25 26]

Considering that more than 80% of patients were regularly taking supplementation with calcium and vitamin D (from the analysis of hospitalisation documents and clinical charts), this finding might be explained throughout an incorrect uptake (eg, uptake on an empty stomach), or a low compliance to the medical indications. Recent data show that a concomitant GC assumption might compromise the serum concentration of 25OHD and suggest that patients chronically treated with GC should be supplemented with higher doses than those reported in glucocorticoid-induced osteoporosis (GIO) treatment recommendations; of note, in our cohort, no direct relationship between 25OHD levels and the total amount of GC was observed.[27] Finally, some genetic polymorphisms seem to interfere with serum levels of 25OHD; in particular, Monticielo *et al*[28] observed that Fok I vitamin D receptor polymorphism seems to interfere with serum concentrations of 25OHD in patients with SLE, but further studies are needed to better analyse all these data.

Taking into account the association we found between hypovitaminosis D and renal impairment, we could speculate that this subgroup of patients with SLE might benefit from a more aggressive supplementation scheme. Additional data, however, are needed to define guidelines for vitamin D supplementation in patients with a chronic kidney disease.[29]

Hypovitaminosis D is a well known risk factor for OP[23]; however, it did not show any significant correlation with BMD values in our cohort. This apparently discordant data could be explained by the wide distribution of hypovitaminosis in our population that could mask the effect of this condition in increasing the risk of bone loss in our patients with SLE.

It is known that heparin and oral AC might increase the risk of bone mass loss and consequently of FFx. Many data suggest that heparins cause increased bone loss in a time- and dose-related manner, with a minor effect of low-molecular-weight heparins compared with unfractionated heparin. Vitamin K is a crucial factor for the carboxylation of bone matrix proteins and low levels might be associated with a reduction in BMD; the antagonising effects of oral AC on vitamin K might be one of the mechanisms through which these drugs have a deleterious effect on BMD.[30 31]

All antiepileptics, both enzyme inducers (phenytoin, phenobarbital, carbamazepine) and enzyme non-inducers, such as valproate, are associated with accelerated bone loss and subsequent increased risk of osteoporotic FFx. A meta-analysis found antiepileptic therapy to be associated with increased risk of FFx, with the relative risk of 2.2 (95% CI 1.9 to 2.5). The risk of FFx seems to be dependent on treatment duration and cumulative dose of antiepileptics. Newer antiepileptics, including topiramate and lamotrigine, also seemed to be associated with increased risk of FFx. Another meta-analysis including 22 studies found a significant increase in FFx for both enzyme-inducing and non-enzyme-inducing antiepileptics. Even if long-term studies with the newer agents are needed to better assess FFx risk, the majority of the studies about this topic showed that antiepileptics are associated with a moderate to severe risk of FFx with prolonged use.[32]

Nearly one-third of women with FFx were premenopausal. In our analysis we found that five of six were taking AC or antiepileptics, while two of them had a CRF, thus confirming the potential role of these conditions in increasing the risk of developing FFx in patients with SLE.

If we consider that our patients were treated chronically with low doses of GC (<6 mg/day, mean 5.4 mg/day) recently considered as 'safe',[33] it is important to observe how our results confirm that, at least with respect to bone health, there is no safe GC dose and that withdrawal of steroids should be attempted in patients with SLE, particularly in the presence of additional risk factors, as recommended by GIO prevention and treatment guidelines.[13]

Limitations of this retrospective study includes the likelihood of an underestimation of the real prevalence of FFx since the diagnosis of vertebral FFx in our cohort does not take into account the occurrence of all asymptomatic FFx, given that the patients underwent an x-ray examination of the spine only in the presence of back pain.

In conclusion, low BMD is frequently observed in patients with SLE chronically treated with GC, with FFx additionally observed also in premenopausal patients. A higher risk profile for OP and FFx seems to be related with age, disease duration, post-menopausal status and the cumulative GC dose as well as the presence of CRF and a chronic treatment with AC or antiepileptics.

Contributors LC designed the study, collected data from clinical charts and hospitalisation documents of the patients, performed the analysis of the data and drafted the manuscript. CT, VS, RV and SV collected data from clinical charts and hospitalisation documents. MM and ODM revised the manuscript. MMo extensively edited the article.

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