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ORIGINAL RESEARCH

Incidence of Vertebral Fractures in Women with Systemic Lupus Erythematosus After 8 Years of Follow-Up

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Abstract The aim of this study was to evaluate possible associations between potential risk factors and the occurrence of established vertebral fractures (VF) in Mexican patients with systemic lupus erythematosus (SLE). Consecutive patients with SLE were enrolled in a prospective, observational study from 2006 to 2015. Information on potential risk factors, including demographics, clinical data, and bone mineral density (BMD) at the lumbar spine and hip on dual-energy X-ray absorptiometry was collected at baseline and follow-up. Semiquantitative analysis was used to determine incident VF on lateral thoracic and lumbar radiographs, defined as any vertebral body graded normal at baseline and at least mildly deformed (20–25% reduction or more in any vertebral height) during follow-up. Differences in baseline characteristics were assessed in patients with and without new radiographic VF. Of 110 SLE patients included, with a median follow-up of 8 (IQR 8–9) years, 22 (20%) had radiographic VF at baseline; 35 (32%) patients had a new VF. The annual incidence rate of new morphometric VF was 3.5 (95% CI 2.4–4.91) per 100 patient/years. Most fractures were mild or moderate and biconcave shaped. Incident VF were significantly associated with baseline BMD at the total hip and longer disease duration. Cumulative glucocorticoid dose, postmenopausal status, and previous prevalent VF were not associated with VF. In this SLE cohort in daily clinical practice, new VF were frequently present in SLE patients, especially those with longer disease duration and low-hip BMD.

Keywords Systemic lupus erythematosus · Vertebral fractures · Bone mineral density · Risk factors · Incidence

Introduction

Vertebral fractures (VF) are the hallmark of bone fragility [1], causing severe back pain, impaired spinal mobility, height loss, and disability. In general, prevalent VF have a

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strong predictive value for more vertebral or non-vertebral fractures, even after adjustments for age and bone mineral density (BMD) [2, 3].

Patients with systemic lupus erythematosus (SLE) are at high risk of VF [4, 5]. A case–control study in 136 Swedish patients with SLE showed that an increased risk for symptomatic VF, with an OR of 2.2 [5]. Although low BMD is a known major risk factor for VF in the general population, the relationship between BMD and fracture in patients with SLE is not yet fully clear [6–8]. Moreover, identification of other established risk factors is required to better predict patients at increased risk of VF. Although several risk factors for VF in patients with SLE have been suggested [9, 10], there is limited reported longitudinal supporting data [11]. The detection of individuals at high risk is important, because bisphosphonates, active vitamin D 3, teriparatide, and denosumab have been shown to increase spine BMD and reduce bone turnover in patients with corticoid-induced osteoporosis (GIOP), including SLE patients [12–18]. Therefore, these pharmacological therapies may have benefits for SLE patients.

In a previous cross-sectional study, we reported on some risk factors for VF in Mexican women with SLE [7]. The analysis, made between 2006 and 2008, found a prevalence of VF of 26.1% in the 210 women included. The present study reevaluates the possible associations between potential risk factors and VF in Mexican women with SLE.

Patients and Methods

Patients

All 210 patients from the original study were eligible to participate in this prospective, longitudinal, observational cohort study. The inclusion and exclusion criteria for the baseline study have previously been described in detail [7]. In short, SLE subjects attending the Autoimmune Systemic Diseases outpatient clinic (Hospital General Regional 36, IMSS) were consecutively enrolled. Patients aged $\geq$18 years who fulfilled the American College of Rheumatology (ACR) revised classification criteria for SLE were included [19]. Patients were excluded if they were pregnant or had renal impairment (creatinine >2 mg/dL) or untreated thyroid disease. All patients gave written informed consent and the local ethics committee approved the study.

Clinical Assessments

Data at baseline and during follow-up were collected by interview, clinical examination, questionnaires, and medical records and included age, disease duration, height, weight, BMI (weight [kg] divided by height [meters] squared), calcium intake, fractures (anatomical site and cause), current and previous use of anti-osteoporotic therapies and immunosuppressant drugs, daily glucocorticoid dose, cumulative glucocorticoid dose and ever use of intravenous (IV) methylprednisolone. The different preparations were converted to milligrams of prednisolone equivalents using a conversion formula for anti-inflammatory potency (prednisone 5 mg is equivalent to methylprednisolone 4 mg).

Clinical assessments were made of disease activity (mexSLEDAI) [20] and accumulated organ damage using the Systemic Lupus International Collaborating Clinics/ACR damage index (SDI) [21]. A modified DI score was derived by excluding the osteoporosis/fracture item (1 point).

25-hydroxyvitamin D (25OHvitD) levels were assessed at baseline. Serum levels of 25OHvitD were measured by chemiluminescent immunoassay (Abbot Architect, Wiesbaden, Germany). Vitamin D deficiency was defined as 25OHvitD levels <20 ng/mL [22].

BMD was measured by dual-energy X-ray absorptiometry (DXA) using Hologic densitometry equipment (Hologic QDR Explore, Bedford, MA, USA) at the lumbar spine (anterior-posterior projection at L1–L4), total hip, and femoral neck; the same equipment was used for all patients. The Z-score (number of SD from the normal mean corrected for age) and T-score (number of standard deviations (SD) from the normal mean obtained from young healthy adults) were interpreted according to World Health Organization (WHO) definitions to define osteopenia (T-score -1 to 2.5) and osteoporosis (T-score ≤ -2.5). The 2013 International Society for Clinical Densitometry consensus (ISCD) was used to define low BMD (Z-score ≤ -1) and very low BMD (Z-score ≤ -2) [23].

Least significant changes (LSC) were calculated according to the ISCD. The LSC for the spine was 0.027 g/cm^2 at the 95% confidence level. The LSC for the hip ranged from 0.026 to 0.041 g/cm^2 at the 95% confidence level.

Vertebral fractures

All spinal X-rays were made according to local protocol; the same protocol was used at baseline and during follow-up. Lateral radiographs of the thoracic and lumbar spine were scored according to the semiquantitative method described by Genant et al. [24]. One trained radiologist performed a radiograph, scoring individually. The reader was blinded to age, clinical data including absorptiometry images and previous radiographic evaluations. Scoring of follow-up radiographs was blinded for the baseline image, and the results were compared with baseline X-rays and

scores to determine whether new VF were detected. The scores corresponded to the following reductions in height ratios: grade 0 (normal), 20% or less; grade 1 fracture (mild), >20 to 25%; grade 2 fracture (moderate), >25 to 40%; grade 3 fracture (severe), >40%. A prevalent VF was defined as a ≥20% reduction in any vertebral height (grade ≥1). A fracture was scored as an incident VF if not present at baseline or if there was a significant increase in height loss (>20%) in a vertebra already fractured at baseline. Degenerative changes were not scored as VF. In addition to the prevalence and incidence, the location and shape of VF were reviewed. The kappa value for classification of an SLE patient having any vertebral fracture was 0.73.

Statistical Analysis

Descriptive statistics were used to describe the prevalence, incidence, localization, and shape of radiographic vertebral fractures. Results were expressed as number of patients (%), mean ± SD or median (IQR) for categorical, normally distributed and non-normally distributed data, respectively. The Chi-square or Fisher's exact test, independent samples *t* test, and Mann–Whitney *U*-test were used as appropriate to compare baseline characteristics of patients with and without ≥1 incident VF.

Patients with incident VF were compared with those without new fractures with respect to demographic variables, clinical variables, and BMD using two-sided t tests for continuous variables and χ^2 tests. Possible risk factors for incident VF were assessed by multivariate logistic regression. The criteria for entering independent variables in the logistic regression analysis were a p value <0.2 in the univariate analysis and a supposed clinical relevance for the dependent variable. p values ≤0.05 were considered as statistically significant. The statistical analysis was made using IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

Results

Demographic and Clinical Variables

A total of 110 of the original 210 patients had radiographs available at baseline and follow-up (Fig. 1). Baseline characteristics were similar between patients included and excluded, except for age at menopause (41.9 ± 7.2 vs. 44.9 ± 6.7; $p = 0.02$) and mexSLEDAI scores (0.65 ± 1.5 vs. 1.28 ± 2.0; $p = 0.01$) (Supplementary file).

The demographic and clinical characteristics of the 110 SLE patients included are shown in Table 1. Most patients were postmenopausal (63.6%) with a median (IQR) disease duration of 6 (3–13) years at inclusion. Overall, patients had mild disease activity at study inclusion. Median (IQR) follow-up was 8 (8–9) years, with a total of 985 patient-years. Mean BMI change during follow-up was +0.63 ± 2.7. The mean cumulative dose of glucocorticoids, including equivalent dose i.v. methylprednisolone during follow-up was 31.7 ± 18.6 g.

Most patients used calcium and/or vitamin D supplements at inclusion and during the follow-up, while 35.5% were treated with bisphosphonates.

Prevalence of Vertebral Fractures at Baseline

At baseline, 29 radiographic VF were found in 22 (20%) patients (1.3 fractures per patient). Of these, 15 (52%) were defined as mild (grade 1), 11 (38%) as moderate (grade 2), and 3 (10%) as severe (grade 3). Most VF were found in the mid-thoracic and thoracolumbar regions of the spine.

Incident Vertebral Fractures During Follow-Up

After 8 years follow-up, 35 (31.8%) patients developed ≥1 new radiographic VF, of whom only 26% had presented symptomatic VF (chronic back pain) during the follow-up. No fracture with acute-onset back pain occurred. The annual incidence rate of new morphometric VF was 3.5 (95% CI 2.4–4.91) per 100 patient/years. Nineteen patients had one new fracture, 6 had two, and 9 had ≥3. In total, 80 new VF were found after 8 years of follow-up. The location of the new VF is shown in Fig. 2.

Fifty-one VF were biconcave shaped, 27 wedge shaped, and 2 crush shaped. One severe (grade 3) fracture at L2 and L3 occurred in a postmenopausal woman with osteoporosis

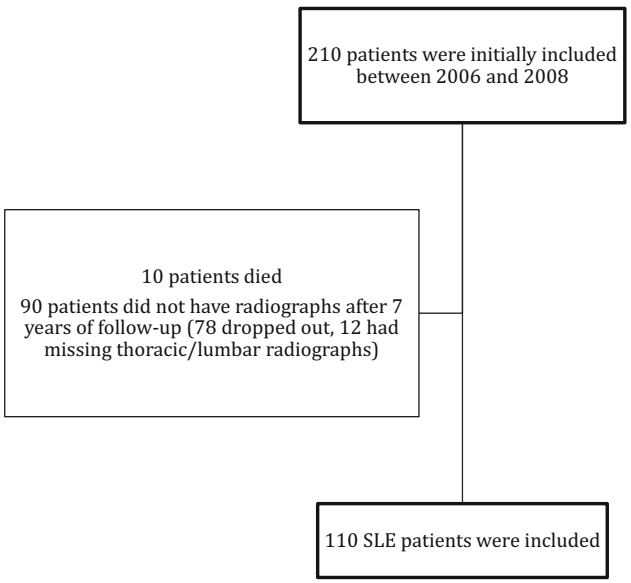

Fig. 1 Flow chart of SLE patients included

Table 1 Characteristics of 110 patients with SLE included

	Baseline	Follow-up
Age (years)		
Mean (SD)	42.3 ± 11.6	n.a.
Disease duration (years)		
Median (IQR)	6 (3–13)	n.a.
BMI (kg/m^2)		
Mean (SD)	27.2 ± 4.4	27.4 ± 4.4
Smokers		
n (%)	13 (11.8)	11 (10)
Postmenopausal		
n (%)	52 (47.3)	70 (63.6)
Previous self-reported non-vertebral fractures		
n (%)	10 (9.1)	n.a.
mexSLEDAI, score		
Mean (SD)	3.5 ± 2.1	3.2 ± 1.8
SLICC/ACR DI, score		
Median (IQR)	0 (0–1)	1 (0–1)
Glucocorticoids, ever use		
n (%)	88 (80)	105 (95.4)
Prednisone daily dose (mg/days)		
Mean (SD)	11.0 ± 8.7	15.5 (25.1)
Cumulative glucocorticoids dose (g)		
Mean (SD)	19.6 ± 21.9	37.6 ± 24.9
Calcium and vitamin D supplementation		
n (%)	104 (94.5)	100 (90.9)
Bisphosphonates		
n (%)	11 (10)	39 (35)
25OHvitD levels (ng/mL)		
Mean (SD)	19.6 ± 6.9	22.9 ± 6.8
Vitamin D deficiency		
n (%)	38 (34.5)	33 (30)
BMD lumbar spine (g/cm^2)		
Mean (SD)	1.020 ± 0.219	0.860 ± 0.140
BMD total hip (g/cm^2)		
Mean (SD)	1.260 ± 0.125	1.137 ± 0.128
Osteoporosis, T-score <-2.5[a]		
n (%)	10 (9.0)	26 (23.6)
Osteopenia, T-score <-1.5[a] and >-2.5		
n (%)	28 (25)	38 (34.5)
Low BMD, Z-score ≤ -1[b]		
n (%)	6 (5.4)	8 (7.2)

a only postmenopausal patients, *b* only premenopausal patients, *25OHvitD* 25-hydroxyvitamin D, *BMD* bone mineral density, *BMI* body mass index, *IQR* interquartile range, *mexSLEDAI* the Mexican Systemic Lupus Erythematosus Disease Activity Index, *n.a.* not applicable, *SLICC/ACR DI* the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index, *S.D* standard deviation

who already had a moderate baseline fracture at T8. The remaining new VF were mild or moderate.

Differences Between Patients With and Without Incident Vertebral Fractures

Patients with a new VF had a lower mean BMD at baseline compared with those without (Table 2). This was significant only for baseline BMD at the hip ($p = 0.011$). Patients with new VF had a longer disease duration and higher cumulative glucocorticoid dose at baseline ($p = 0.005$ and $p = 0.037$, respectively) were more often menopausal (RR = 1.57, 95% CI 1.07–2.28; $p = 0.018$) and were more prone to have disease damage evaluated by SDI at baseline (RR = 1.55, 95% CI 1.04–1.2.29; $p = 0.028$) than patients without new VF. Surprisingly, ever use of IV methylprednisolone was non-significantly less frequent in patients with incident VF than in those without ($p = 0.056$).

There were no significant between-group differences with respect to previous 25OHvitD levels or antiresorptive therapy during follow-up.

Patients with new VF had non-significantly more prevalent VF at baseline ($p = 0.317$).

Of the postmenopausal patients who were osteopenic or osteoporotic at baseline, 10 (36%) and 4 (40%) sustained a new VF, respectively, during follow-up. In premenopausal patients with low BMD at baseline, there was 1 (17%) new VF during follow-up.

Possible Risk Factors for Incident Vertebral Fractures

In the multivariate logistic analysis, BMD at the total hip and longer disease duration were independent risk factors for incident VF (≥1 new VF). Postmenopausal status, BMD at the spine, cumulative glucocorticoid use, and SDI

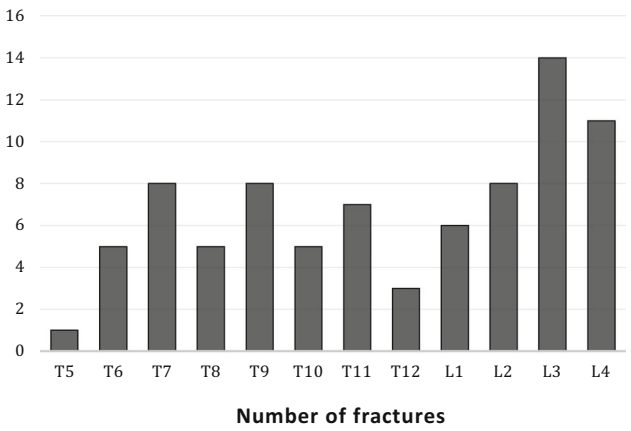

Fig. 2 Distribution of new vertebral fractures

Table 2 Demographics and disease variables for patients with and without new vertebral fractures at baseline or during follow-up

	Vertebral fractures		*p*
	Yes ($n = 35$)	No ($n = 75$)	
Age (years)			
Mean (SD)	44.1 ± 11.0	41.4 ± 11.8	0.272
BMI (kg/m^2)			
Mean (SD)	27.1 ± 5.3	27.3 ± 3.9	0.871
Postmenopausal at baseline			
***n* (%)**	**22 (63)**	**30 (40)**	**0.021**
Disease duration (years)			
Median (IQR)	**9.0 (5–14)**	**5.0 (3–12)**	**0.005**
Previous non-vertebral fractures at baseline			
n (%)	3 (8.5)	7 (9.3)	0.602
Vertebral deformity at baseline			
n (%)	9 (26)	13 (17)	0.317
25OHvitD levels, ng/mL at baseline			
Mean (SD)	20.8 ± 6.6	19.1 ± 7.0	0.407
SLICC/ACR DI, ≥ 1			
***n* (%)**	**21 (60)**	**29 (39)**	**0.042**
Mean prednisone daily dose (mg)			
Mean (SD)	9.5 ± 6.4	11.7 ± 9.6	0.123
Cumulative dose of glucocorticoids at baseline (g)			
Median (IQR)	**16.2 (7–41)**	**9.9 (6–24)**	**0.037**
Ever use of IV methylprednisolone			
n (%)	7 (20)	25 (33.3)	0.056
BMD lumbar spine (g/cm^2)			
Mean (SD)	0.981 ± 0.222	1.039 ± 0.217	0.205
BMD total hip (g/cm^2)			
Median (IQR)	**0.884 (0.844–1.025)**	**0.981 (0.914–1.055)**	**0.011**
Use of bisphosphonates during follow-up			
n (%)	15 (43)	24 (32)	0.185

25OHvitD 25-hydroxyvitamin D, *BMD* bone mineral density, *BMI* body mass index, *IQR* interquartile range

Bolded values indicate statistical significance at $p < 0.05$

Table 3 Significant variables for incident vertebral fractures in the multivariate analysis

	B	OR (95%)	*p* value
BMD at total hip	−4.7	0.015 (0.001–0.404)	0.022
Disease duration (years)	0.006	1.006 (1.001–1.011)	0.029
Constant	1.69	5.434	0.369

≥1 were entered into the model, but were eliminated as not significant (Table 3).

Discussion

This observational cohort study of SLE patients with mild disease activity on glucocorticoid therapy showed that new VF were frequently observed on radiographs of the thoracic and lumbar spine during follow-up. 20% of patients had radiographic VF at baseline and 32% developed new radiographic VF during the 8-year follow-up, an annual incidence of 3.5/100 patients/year. As this is an observational study, there are no data from a control group for comparison. However, comparison with other historical cohorts is possible. In the European Prospective Osteoporosis Study (EPOS) of fractures in the general population aged ≥50 years, the annual incidence rate of morphometric VF in females was 1.07 per 100 patient-years [25]. However, our patients were younger (mean age 62.2 years). In a 5-year follow-up study in rheumatoid arthritis (RA) women (mean age 61 years) the annual incidence of new VF identified on spinal X-ray was 3.7 per 100 patient-years [26]. Although comparisons between studies should be taken with caution, these studies give a clear indication of

the high incidence rate of VF in our study in a younger population. Similarly, the annual incidence rate was lower (0.94 per 100 patient-years) in a recent study in Chinese SLE female patients with a mean age of 47 years, which is comparable to our study. A possible explanation for the differences in this risk between studies may be the fact that differences in fracture risk between races have largely been attributed to differences in BMD. Although some Asian studies have shown a lower BMD compared with other racial groups [27–29], mainly due to weight or bone size, Asians have a relatively low risk of hip fracture [30, 31], while the prevalent VF rate is similar to that of Caucasians [32]. Moreover, Asian women had a lower risk of osteoporotic fracture of the forearm compared with Caucasian, Hispanic and Native American women [33]. There is a lack of longitudinal studies comparing the risk of VF in Asian and Hispanic populations. However, ethnic differences in the prevalence of low BMD in SLE patients may partially explain differences between the Chinese study and our study [34].

Mild or moderate, biconcave-shaped fractures were those most frequently found in our study. Most VF at baseline were clustered in the mid-thoracic and thoracolumbar region of the spine, in agreement with studies in SLE patients [11], postmenopausal women [24], and the general population aged ≥50 years [35, 36]. Unexpectedly, most incident VF in our study were located at L3. It is unclear why, but there might be a "VF cascade" phenomenon, in which, after an initial VF, the risk of subsequent VF increases significantly. The mechanisms underlying this fracture cascade are inadequately understood, creating clinical uncertainty with respect to the prevention of further fractures. The "cascade" cannot be explained by low BMD alone, suggesting that other factors are involved [37].

Our results show that only baseline BMD of the hip and longer disease duration were risk factors for incident VF. A cross-sectional study reported that low BMD in the total hip but not in the spine was associated with prevalent VF [38]. Other traditional risk factors, such as previous VF or non-vertebral fractures, menopause and glucocorticoid therapy were not risk factors for new VF. Although SLE patients with incident VF were more likely to be menopausal, have a higher cumulative glucocorticoid dose and have more disease damage measured by SDI, these were not independent risk factors for future VF. In addition, 25OHvitD levels at baseline were not associated with new VF. Some 34.5 and 30% of SLE patients in our cohort had vitamin D deficiency at baseline and at 8 years of follow-up, respectively. Vitamin D in patients with rheumatic conditions has been shown to be highly prevalent despite oral supplementation [39]. The possible reasons why vitamin D supplementation does not work adequately in those patients might that the current recommended dietary allowance of vitamin D is low to increase 25OHvitD to >30 ng/mL in this kind of patients, and that inadequate compliance with supplementation might be also be a factor [40].

Glucocorticoid therapy has been associated with prevalent [41] and incident VF [42]. Glucocorticoids are extensively used for the treatment of SLE disease flares and complications and might have beneficial effects by reducing the adverse effects of systemic inflammation on bone. The beneficial effects produced by suppressing the impact of inflammation on bone turnover might outweigh the harmful effects of glucocorticoids. Cross-sectional studies on the relationship between glucocorticoid use and BMD in SLE show conflicting results [43]. We found no association in the multivariate analysis. Similarly, studies in RA patients found no correlation between cumulative prednisone dose and the prevalence of vertebral deformities [44, 45].

The reasons for these conflicting results are unclear. First, it might be because we measured the cumulative rather than the daily dose, as suggested in a study in postmenopausal women [42]. Secondly, a wide range of definitions have been used to attribute fractures to glucocorticoid exposure. A study in SLE patients found that ever use of IV methylprednisolone was associated with prevalent VF [9]. However, when we analyzed this variable in our cohort, patients with incident VF had less-frequently used IV methylprednisolone than patients without incident VF. A possible explanation might be that methylprednisolone pulse therapy may suppress inflammation, preserving bone mass [46], since systemic inflammation is supposed to contribute to bone loss in SLE by increasing osteoclastic bone resorption and reducing osteoblastic bone formation [47]. Finally, a possible limitation of the present study is that although it is a longitudinal study, attrition bias cannot be not ruled out, which might have affected the power of the study which may not have been sufficient to detect such an association, although the clinical significance of the cumulative glucocorticoid dose between patients with or without incident VF in the univariate analysis would then be questionable. Irrespective of this, our data suggest that VF are highly prevalent and incident in patients with SLE once glucocorticoids are initiated.

Studies have found that a history of osteoporotic fracture is a risk factor for subsequent fractures. Approximately 19 percent of patients with a vertebral compression fracture will have another fracture in the next year. A systematic review found that women with preexisting VF had an approximately four-fold higher risk of subsequent VF than women without prior fractures [3]. Surprisingly, in our study, although preexisting VF was more frequent in patients with new VF compared with those without (26 vs.

17%), this difference was not significant. We have no plausible explanation for the fact that, in our study, the incidence of VF was not related to prevalent VF. The lack of a sufficient sample size and the possibility of attrition bias may mean our conclusions are not valid. However, non-vertebral fractures have also been associated with subsequent radiographic VF, particularly in studies including postmenopausal patients [48]. In SLE patients, a previous history of fracture was associated with prevalent VF [8]. However, we found no association between self-reported non-vertebral fractures at baseline and new radiographic VF. This might have been because we measured non-vertebral fractures according to self-report, with verification by medical records, thus making this factor subject to recall error (underreporting/overreporting) [49].

Our study had several limitations. First, most our patients in our cohort were on glucocorticoid therapy at baseline and during follow-up. The cumulative dose and daily dose were used as definitions for the evaluations of glucocorticoid therapy. Both definitions have limitations. The "cumulative dose" method assumes that all current and prior glucocorticoids have an equal impact on fracture risk regardless of how recently they were taken. However, calculating the cumulative dose can be difficult and may lead to misclassification and imprecise estimates. On the other hand, the daily dose does not consider historical exposure to glucocorticoids, particularly in SLE patients, who have different manifestations from mild-to-severe during the SLE follow-up, requiring different glucocorticoid doses. Secondly, attrition bias cannot be ruled out, since patients lost during follow-up were older and had more active disease and more prevalent vertebral compression (31 vs. 20%). Thirdly, measurements were made at baseline and at 8 years. This is a quite long period and measurements such as vitamin D levels or bisphosphonate use at baseline and during follow-up will probably not correctly reflect fluctuations in those variables during the study period. Thirdly, vitamin D and calcium supplementation compliance was not assessed during follow-up. Finally, the semiquantitative fracture grading method provides highly reproducible diagnoses of VF using a fracture-nonfracture dichotomy. To assess incident fractures, a high degree of agreement can be reached. Even relatively inexperienced readers can assess vertebral fractures using this grading scheme with relatively good results [50]. However, normal variations may be misinterpreted as mild vertebral deformities using the semiquantitative fracture method. Generally, incident fractures are easily identified qualitatively on serial radiographs, since a direct comparison with baseline radiographs is possible. Using Genant's semiquantitative grading scheme to assess incident fractures, however, the reader may sometimes feel that even though a further height reduction is seen in a vertebra, assigning a higher grade to the incident fracture in comparison with the preexisting prevalent fracture may not be justified, since some degree of settling or remodeling generally occurs.

In conclusion, this prospective longitudinal observational cohort study showed that radiographic new VF occurred frequently in SLE women. VF may easily be missed due to lack of symptoms or poor recognition on radiographs. Therefore, imaging is important during follow-up, especially in long-term SLE patients with previous low BMD.

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Compliance with ethical standards

Conflict of interest Mario García-Carrasco, Claudia Mendoza-Pinto, María de la Luz León-Vázquez, Socorro Méndez-Martínez, Ivet Etchegaray-Morales, Álvaro Montiel-Jarquín, Miguel Angel Enriquez-Guerra, Margarita Muñóz-Guarneros, José Luis Gálvez-Romero, Pamela Soto-Santillán and Ricard Cervera declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent The study was reviewed and approved by our local institutional ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

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