



# A Retrospective Analysis of Longitudinal Changes in Bone Mineral Density in Women with Systemic Lupus Erythematosus

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## Abstract

Most prospective studies of bone mineral density (BMD) in systemic lupus erythematosus (SLE) patients have been of relatively short duration, with a maximum of 6 years. To describe long-term changes in BMD in women with SLE and identify risk factors associated with BMD loss. We retrospectively evaluated 132 adult Mexican-Mestizo women with SLE who underwent dual X-ray absorptiometry (DXA). Demographic and clinical data were collected and BMD at the lumbar spine (L1–L4) and total hip were collected at baseline and during the follow up. At baseline, the mean age of participants was  $43.4 \pm 12.5$  years, 50.8% had osteopenia and 11% osteoporosis. The median follow-up was 13 (IQR 10.2–14.0) years. During follow up, 79% of patients used glucocorticoid (GCT). The mean percentage of changes in BMD during follow up were:  $-14.03 \pm 11.25\%$  ( $-1.49\%/year$ ) at the lumbar spine, and  $-15.77 \pm 11.57\%$  ( $-1.78\%/year$ ) at the total hip, with significant changes ( $p < 0.001$  for both comparisons). Multivariate analysis showed older age, GCT use at baseline, and transition to the menopause during the follow-up were significantly associated with greater reductions in BMD. This retrospective longitudinal study found significant BMD loss at the lumbar spine and hip. Older age, menopausal transition and GCT use were independently associated with BMD decline in women with SLE.

**Keywords** Systemic lupus erythematosus · Bone mineral density · Osteoporosis · Cohort

## Introduction

International experts recommend that all individuals with systemic lupus erythematosus (SLE) should be screened and monitored for bone loss according to present guidelines for postmenopausal women and/or patients on glucocorticoid (GCT) therapy [1, 2]. Cross-sectional studies of bone mineral density (BMD) have reported that low BMD

and osteoporosis are frequent in SLE patients [3–7]. However, few longitudinal cohort studies have evaluated BMD changes over time [8–11], with most being of short to medium duration.

Subjects with SLE, especially those with a long disease duration, are at risk of several factors such as persistent inflammation, low levels of vitamin D, decreased physical activity and GC exposure that adversely affect bone health [12]. Likewise, SLE survival rates have improved in recent decades, meaning an increase in accumulated organ damage.

Longitudinal studies of SLE patients show short-term accelerated BMD loss of 1.22–5.54% per year [8, 9], while medium-term (5–6 years) follow-up studies demonstrated relative BMD stability, with a percentage of loss ranging from 0.08 to 0.20% per year [10] and a mean overall loss of up to 2.41%, depending on the site evaluated [11]. Although the short- and medium-term effects of SLE on BMD are well described, there are no reports on the long-term effect. Therefore, the aims of the present study were to evaluate longitudinal changes in BMD in women with SLE and identify determinants associated with BMD changes.

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## Patients and Methods

### Study Population

The study methods, particularly the baseline inclusion and exclusion criteria are described in detail in other reports [7, 13, 14]. Briefly, in this observational, longitudinal cohort study, Mexican-Mestizo women with SLE attending our outpatient clinic were consecutively enrolled. Adult patients who fulfilled the American College of Rheumatology revised classification criteria [15] and the 2012 Systemic Lupus International Collaborating Clinic (SLICC) validated criteria [16] were recruited. Exclusion criteria were renal impairment (creatinine > 2 mg/dl), pregnancy and untreated thyroid disease. The study was approved by our local ethical research committee, and informed consent acquired from participants.

### Clinical Measurements

Patients were entered between 2006 and 2016. Follow-up evaluations were made between 2009 and 2020. Demographic and clinical data were documented at inclusion and during follow up by structured interview and clinical examinations. Demographic and clinical characteristics included age, body mass index (BMI), smoking (yes or no) and drinking ( $\geq 3$  U of alcohol per day), self-reported fractures (vertebral and non-vertebral), menstrual status, disease duration and medications. Menopause was stated as amenorrhea for at least 1 year and transitional menstrual status (whether women had undergone a permanent change in menstrual status) during the follow up was also recorded. Premature menopause was defined as amenorrhea for at least 12 months at age < 40 years [17].

Disease activity was measured using the Mexican Systemic Lupus Erythematosus Disease Activity Index (mex-SLEDAI), which is a validated activity index adjusted for the Mexican-Mestizo population [18]. Cumulated organ damage was evaluated using the Systemic Lupus International Collaborating Clinic/ACR Damage Index (SLICC/ACR DI) [19]. Organ damage was collected at baseline and new organ damage during the follow up was recorded. Use of medications during the follow up, including the cumulative dose of GCT, antimalarials, immunosuppressive drugs, calcium and vitamin D supplements and anti-osteoporotic agents, were collected by chart review. Oral GCT use was collected in milligram (mg)/day. The cumulative dose of GCT at baseline and follow-up were calculated as the total milligrams (mg) of prednisone plus intravenous methylprednisolone (IV MP). The dose of IV MP, in mg was multiplied by 1.25 to convert the quantity to prednisone counterparts.

At baseline, circulating levels of 25-hydroxyvitamin D (25[OH]D in  $\mu$ /ml) were assessed by chemiluminescent immunoassay (Abbot Architect, Wiesbaden, Germany). 25(OH)D serum level of < 20  $\mu$ /ml defined vitamin D deficiency [20].

### BMD Measurements

BMD measurements at the lumbar spine and total hip were made using the same dual X-ray absorptiometry equipment (DXA) (Lunar, Prodigy densitometer, Madison, WI, USA) at baseline and during follow up. All determinations were made by experienced operators using standardised methods for patient positioning. The coefficients of variation of precision in all sites were < 1%. BMD evaluations at the lumbar spine (anteroposterior projection at L1–L4) and total hip were expressed as the grams of bone mineral per square centimetre ( $g/cm^2$ ). The World Health Organization (WHO) definitions to define osteopenia and osteoporosis were used to interpret the *T*-score (number of standard deviations [SD] from the normal mean obtained from young healthy adults) for menopausal women. Osteopenia and osteoporosis were defined as a *T*-score ranging from  $-1$  to  $-2.5$  and a *T*-score  $\leq -2.5$ , respectively. A *Z*-score number of SD from normal of  $-2.0$  or lower is defined as below the expected range for age and a *Z*-score above  $-2.0$  is within the expected age range for females prior to menopause according to the 2019 International Society of Clinical Densitometry (ISCD) consensus [21].

### Statistical Analysis

Normally distributed continuous variables were expressed as mean  $\pm$  SD and non-normally distributed variables as median and interquartile range. Categorical variables were described in percentages. Comparisons of baseline and follow-up BMD values, *Z* and *T* scores were made using a paired-sample *t* test. McNemar's test was used to compare the percentages of patients with osteopenia, osteoporosis and low BMD at baseline and during follow-up. Annual BMD change was calculated in each participant as  $[(BMD2 - BMD1)/BMD1] * 100 / \text{time (in years)}$  between assessments. Relationships between the percentage of change in BMD and numerical variables such as age, BMI, and cumulative GCT were made using Pearson correlations. Risk factors with bivariate associations of  $p < 0.2$  were entered in a multiple linear regression analysis. A two-tailed  $p$  value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Mac V25.0 (SPSS Inc, Chicago, Ill, USA).

## Results

### Characteristics of Women with SLE

Of the 225 original participants, 132 had BMD measurements available at the end of follow up (Online Resource 1). The median follow up was 13.0 years (IRQ 10.2–14.0) from the first BMD measurement to the second. Baseline demographic and clinical characteristics of patients lost and those who completed the follow up are shown in Online Resource 2. Attrition analysis shows that participants who had significantly more prevalent vertebral fractures and bisphosphonate use at baseline were more likely to be lost to follow-up. However, BMD measurements were not significantly different between the two groups.

Table 1 shows the main characteristics of the 132 women with SLE included in the final analysis. Nearly half the participants were postmenopausal, with mild disease activity and a median (IQR) disease duration of 6.0 years (1.0–9.7) at inclusion. At the end of follow up, 71.6% of the participants were postmenopausal. Twenty-five patients (18.9%) had premature menopause (before 40 years). At baseline, 44.7% had organ damage and new organ damage during the follow-up was recorded in 70 patients (either no previous organ damage or increased organ damage). At

inclusion, 50.8% and 11.7% of patients had osteopenia and osteoporosis, respectively. During follow-up, 79% were taking oral GCT, with a mean (SD) cumulative dose of 39.8 (22.7) g. Use of antimalarials and immunosuppressive drugs were recorded in 87.3% and 50% of patients, respectively. The most common immunosuppressants used (current or ever) were azathioprine (28%), methotrexate (18%), cyclophosphamide (8%) and mycophenolic acid (5%). Bisphosphonates (alendronate and risedronate) were administered in 20 patients, of whom 15 had criteria for osteoporosis and five osteopenia plus either high dose prednisone and/or a history of vertebral fractures. No patients had received hormone replacement therapies. Patients with osteopenia and/or osteoporosis compared to those with normal BMD measurements at baseline were treated with bisphosphonates more frequently at the end of follow-up (40.3% vs 22.4%;  $p=0.03$ ).

### Longitudinal Changes in BMD

Table 2 shows BMD measurements at baseline and follow-up. The proportion of osteoporosis (in postmenopausal women) at lumbar spine was almost the double from the initial scan to the second scan. In premenopausal women at baseline, the proportion of low BMD ( $z$ -score  $\leq 2$ ) slightly increased over time only at the total hip. The mean

**Table 1** Characteristics of 132 patients with SLE included at the end of the follow up

Baseline characteristics	Baseline	Follow-up
Age, years, mean (SD)	42.2 ± 12.7	54.2 ± 12.3
Disease duration, years, median (IQR)	6.0 (1.0–9.7)	16.5 (11.0–20.7)
BMI, kg/m <sup>2</sup> , mean (SD)	26.9 ± 4.6	27.7 ± 4.9
Body height, m, mean (SD)	1.53 ± 0.05	1.51 ± 0.06
Smokers, %	12.8	6
Postmenopausal, %	46.9	71.6
mexSLEDAI, score, median IQR	0.8 ± 1.6	0.6 ± 1.3
SLICC/ACR DI, ≥ 1%	45.4	48.5
GCT, ever use, $n$ (%)	110 (83.3)	104 (78.9)
Prednisone dose, mg/day, mean (SD)	10.9 ± 8.8	15.5 ± 12.1
Cumulative GCT dose, g, mean (SD)	17.9 ± 16.7	39.8 ± 22.7
Calcium and vitamin D supplementation, %	85.6	77
Bisphosphonates, %	15.1	33.5
Previous self-reported vertebral fractures, %	18.9	19.6
Previous self-reported non-vertebral fractures, %	11.4	15.6
25OHvitD levels, ng/mL, mean (SD)	19.9 ± 6.9	23.5 ± 6.7
Vitamin D deficiency, %	54.3	43.3
Osteopenia, %	50.8	43
Osteoporosis, %	11.7	24.2
Low BMD, %	11.9	24.2

25OHvitD 25-hydroxyvitamin D, BMD bone mineral density, BMI body mass index, GCT glucocorticoid, IQR interquartile range, mexSLEDAI the Mexican Systemic Lupus Erythematosus Disease Activity Index, SLICC/ACR DI the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index, SD standard deviation

**Table 2** Baseline and follow-up BMD measurements

	Lumbar spine		<i>p</i> value	Total hip		<i>p</i> value
	Baseline	Follow-up		Baseline	Follow-up	
BMD (g/cm <sup>2</sup> )	1.001 ± 0.160	0.864 ± 0.141	<0.001	0.950 ± 0.134	0.796 ± 0.135	< 0.001
<i>T</i> -score	− 1.2 ± 1.2	− 1.5 ± 1.1	< 0.001	− 1.6 ± 1.4	− 0.9 ± 0.9	0.07
<i>Z</i> -score	− 0.6 ± 1.0	− 0.5 ± 1.3	0.24	1.1 ± 1.2	− 0.3 ± 0.9	0.17
Osteoporosis in postmenopausal patients (%)	11.0	20.1	0.01	11.9	15.0	0.76
Low BMD in premenopausal patients (%)	11.2	3.7	0.98	6	8	0.96
Change per year (%)	− 1.49 ± 2.15		NA	− 1.78 ± 2.25		NA

Variables were expressed as mean ± standard deviation

BMD bone mineral density

(SD) percentage changes in BMD of the participants over a median follow up of 13 years were  $-14.03 \pm 11.25\%$  ( $-1.49\%/year$ ) at the lumbar spine and  $-15.77 \pm 11.57\%$  ( $-1.78\%/year$ ) at the total hip (both comparisons  $p < 0.001$ ). A significant decrease in the *T*-score was seen at the lumbar spine ( $p < 0.001$ ) but not at the total hip ( $p = 0.07$ ; Table 2).

### Risk Factors Associated with Changes in BMD

Significant negative correlations between age and BMI at baseline and the percentage change in BMD at the total hip ( $r = -0.26$ ,  $p = 0.002$  and  $r = -0.17$ ,  $p = 0.04$ , respectively) but not for the lumbar spine ( $p = 0.69$  and  $p = 0.43$ , respectively) were found. Menstrual status at baseline was not related to percentage change in BMD either at the lumbar spine or hip (Table 3). However, SLE women with transitional menstrual status during follow-up presented significantly higher reductions in BMD at the lumbar spine but not at the total hip. Baseline accrual damage was associated with a reduction in BMD at the total hip ( $p = 0.01$ ) but not the lumbar spine ( $p = 0.39$ ). The baseline lupus activity score did not correlated with BMD changes at either site ( $p = 0.93$  and  $p = 0.43$ , respectively). New organ damage was not significantly related to BMD change either at the lumbar spine or the total hip. When baseline daily prednisone dose was correlated to BMD changes at any site, we found no significant correlations ( $p = 0.53$  and  $p = 0.96$ , respectively). Similarly, there was no significant correlation between the cumulative SLICC at the end of follow-up and BMD loss ( $p = 0.35$  and  $p = 0.82$ , respectively). 25[OH]D levels at baseline were not correlated with BMD changes at any site ( $p = 0.98$  and  $p = 0.29$ , respectively).

Patients with higher daily GCT ( $\geq 7.5$  mg for  $\geq 3$  months) at baseline tended to have a larger reduction in BMD, particularly at the lumbar spine, but this was not significant at the total hip (Table 3). No correlations were found between the cumulative dose of GCT and changes in BMD at any site ( $p = 0.06$  and  $p = 0.031$ , respectively). Antimalarials and immunosuppressants were not associated with a greater

decrease in BMD at the lumbar spine, but immunosuppressants were significantly associated with a lower BMD decrease at the total hip (Table 3). Bisphosphonate use at baseline was not significantly associated with BMD changes at any site (Table 3).

### Multivariate Analysis of Factors Associated with BMD Changes

Table 4 shows the findings of the multivariate linear regression analysis. Transitional menstrual status and daily oral GCT  $\geq 7.5$  mg for  $\geq 3$  months at the beginning of the study were independently associated with BMD loss at the lumbar spine. Only older age at baseline was independently correlated with BMD changes at the total hip.

### Discussion

To the best of our knowledge, this observational retrospective study is the longest and largest longitudinal analysis evaluating changes in BMD and potential risk factors in women with SLE. We found a significant decrease in BMD at either the lumbar spine or total hip after a median follow up of 13 years. Patients with transitional menstrual status and daily oral prednisone of  $\geq 7.5$  mg for  $\geq 3$  months had greater BMD loss at the lumbar spine. However, only older age was independently associated with BMD loss at the total hip.

Previous longitudinal reports on repeated BMD determinations in patients with SLE have shown mean annual rates of bone loss of between  $-0.08\%$  and  $-4.2\%$  at the lumbar spine and  $-0.2\%$  to  $-3.59\%$  at the total hip [8–11, 22–25]. The magnitude of annual bone loss at the lumbar spine ( $-1.49\%$ ) and total hip ( $-1.78\%$ ) in our study did not differ from previous reports from lupus cohort with different ethnic backgrounds. Studies longitudinally evaluating BMD loss in Mexican or Latin America populations are lacking; however, a Mexican study, that included persons

**Table 3** Percentage of change of BMD over follow-up by subset of clinical characteristics

Variable	Lumbar spine	<i>p</i> value	Total hip	<i>p</i> value
Menstrual status at baseline				
Postmenopausal <i>n</i> = 62	- 14.07 ± 12.19	0.90	- 17.61 ± 10.03	0.06
Premenopausal <i>n</i> = 70	- 13.83 ± 10.45		- 13.86 ± 12.44	
Premature menopause				
Yes = 25	- 16.40 ± 7.23	0.25	- 16.68 ± 8.24	0.62
No = 107	- 13.42 ± 11.89		- 15.40 ± 12.08	
Transitional menstrual status during follow-up				
Yes = 33	- 20.22 ± 8.37	<b>&lt; 0.001</b>	- 18.21 ± 11.23	0.13
No = 99	- 11.85 ± 11.84		- 14.76 ± 11.49	
Organ damage at baseline				
Yes = 60	- 14.87 ± 10.79	0.39	- 18.39 ± 11.15	<b>0.01</b>
No = 72	- 13.17 ± 11.65		- 13.32 ± 11.33	
New organ damage				
Yes = 70	- 13.25 ± 11.94	0.51	- 15.01 ± 12.09	0.59
No = 62	- 14.52 ± 10.34		- 13.57 ± 9.60	
Daily oral prednisone ≥ 7.5 mg for ≥ 3 months				
Yes = 83	- 15.24 ± 11.26	<b>0.04</b>	- 15.73 ± 12.03	0.91
No = 49	- 12.12 ± 11.34		- 15.51 ± 12.03	
Bisphosphonate therapy at baseline				
Yes = 20	- 16.48 ± 12.33	0.22	- 16.72 ± 11.03	0.40
No = 112	- 13.06 ± 11.81		- 14.63 ± 10.52	
Antimalarials at baseline				
Yes = 116	- 14.61 ± 10.89	0.09	- 15.89 ± 11.42	0.60
No = 15	- 9.43 ± 13.39		- 14.26 ± 12.32	
Immunosuppressive agents at baseline				
Yes = 66	- 12.83 ± 11.47	0.17	- 13.94 ± 12.24	<b>0.04</b>
No = 66	- 15.83 ± 12.32		- 17.86 ± 10.12	
Vitamin D deficiency at baseline				
Yes = 30	- 14.31 ± 9.48	0.97	- 18.33 ± 12.01	0.28
No = 70	- 14.41 ± 11.87		- 14.97 ± 11.87	

Bold values indicate statistical significance at the *p* < 0.05 level

*BMD* bone mineral density

aged > 50 years, reported the incidence increased by 1% per year between 2000 and 2006, similar to other countries [26].

Some traditional risk factors for osteoporosis, such as menopause and transitional menopause, have been associated with BMD loss in patients with SLE [11, 25]. We confirm that transitional menopause, which was present in 33 patients during the follow up, was associated with BMD decline at the lumbar spine. Menstrual transition is a crucial phase in the modification of bone strength in women, and determines the period for the development of osteoporosis and fracture risk at older ages [27]. Menstrual transition is accompanied by changes in oestrogens resulting in bone remodelling. It has been suggested that menstrual transition is a time-limited window of opportunity for interventions to prevent rapid bone decline and microarchitectural damage to avoid osteoporosis in later years [28]. Although bone loss at the total hip was higher in patients with transitional

menstrual status than in those without, the difference was not significant. The reasons for this finding are unclear. In the same context, the impact of premature menopause on bone loss, for which patients with SLE are at higher risk [17] has been associated with a higher 10-year probability of fracture [29], but we found that BMD changes did not differ between patients with and without premature menopause. The reasons for this finding are unclear. As expected, age correlated with bone loss, particularly at the total hip.

We also analysed disease-related factors, as have previous studies. Some cross-sectional and longitudinal studies have identified a relationship between organ damage and reduced BMD [5, 11, 30]. A recent longitudinal study found that new organ damage during follow up was associated with bone decline at the total hip and femoral neck [11]. In our study, patients with organ damage at baseline had a greater BMD reduction than those without, but this association was lost

**Table 4** Multivariate regression analysis evaluation risk factors for BMD changes (%) over time

Variable	$\beta$ (95% CI)	<i>p</i>
<b>Lumbar spine</b>		
Transitional menstrual status	- 0.317 (- 12.279 to - 3.963)	<0.001
Antimalarial use	- 0.165 (- 10.717 to 2.853)	0.97
Cumulative dose of GCT	0.190 (- 0.010 to 0.299)	0.99
Daily oral prednisone $\geq 7.5$ mg for $\geq 3$ months	- 0.172 (- 7.869 to - 0.169)	0.04
<b>Total hip</b>		
Age at baseline	- 0.295 (- 0.417 to - 0.095)	0.02
Transitional menstrual status	- 0.182 (- 10.916 to 1.433)	0.98
Menstrual status at baseline	- 0.452 (- 9.764 to 6.138)	0.06
BMI at baseline	- 0.127 (- 0.814 to 0.072)	0.13
Organ damage at baseline	- 0.132 (- 0.806 to 0.132)	0.09
Cumulative dose of GCT	- 0.100 (- 0.190 to 0.52)	0.89
Immunosuppressants	0.140 (- 0.921 to 7.318)	0.27

*BMI* body mass index, *BMD* bone mineral density, *GCT* glucocorticoid

in the multivariate regression analysis. Other factors, like older age and GCT use were potential confounders in this relationship. In cross-sectional studies, some contradictory results on the link between GCs and BMD loss in SLE have been described [31]. A systematic review and meta-analysis of cross-sectional studies found no association between GCT and reduced BMD [32]. However, more recent longitudinal analyses have consistently reported that bone loss occurs predominantly in patients with SLE treated with GCT [8, 10, 11, 24]. Our long-term follow up showed that patients treated at baseline with  $\geq 7.5$  mg of prednisone daily had greater reduction in BMD at the lumbar spine in the multivariate analysis. This may be because GCT particularly affect areas with trabecular bone such as the spine [33].

BMD loss and the risk of fractures can be prevented in patients with SLE. Guidelines for the screening and management of GCT-induced osteoporosis have been reported from different countries and/or medical societies. Many guidelines address users of long-term (3 months) oral GCT, and the daily threshold dose ranges between 5 and 7.5 mg daily of prednisone or equivalent. Some guidelines highlight the relevance of initiating protective bone treatment early in high-risk subjects (BMD *T*-score  $\leq -2.5$ , or 10 year fracture probability of  $\geq 20\%$  (major osteoporotic fracture) or  $\geq 3\%$  (hip fracture) [34, 35]. However, it has been reported that care according to quality indicators for osteoporosis in SLE is suboptimal [36, 37]. Although our study was not designed to identify optimal therapies in the prevention and treatment

of osteoporosis/osteopenia due mainly to the retrospective design and restricted sample size, we cannot rule out the possibility of suboptimal prevention/treatment in our cohort since most patients were under glucocorticoid therapy and only around one third were taking bisphosphonates at the end of follow up. Various factors that might influence the quality of care have been analysed [38].

The influence of hydroxychloroquine (HCQ) on bone mass is unclear. HCQ use has been associated with increased BMD in both the lumbar spine [39, 40] and hip [39] according to evidence from cross-sectional studies in women with SLE. However, a study (also cross-sectional) in male SLE patients described significantly lower BMD in the lumbar spine and hip in patients who had received HCQ compared with those who had not [41]. A 6-year Dutch prospective study demonstrated a significant decrease in hip BMD in patients receiving HCQ [10], but a 5-year longitudinal study in Chinese SLE patients found no impact on bone mass [11]. We found that patients receiving antimalarials (either HCQ or chloroquine) at baseline had a non-significantly higher BMD at both sites (lumbar spine and total hip) than those who did not. Although HCQ regulate the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D by inhibiting hydroxylation  $\alpha$ 1 [42], both chloroquine and HCQ prevent TRAF3 (tumour necrosis factor receptor associated factor 3) degradation in osteoclast precursors and inhibit osteoclast formation in vitro [43, 44]. Thus, the role of antimalarials on the bone balance in SLE patients need to be clarified in larger longitudinal studies.

In our study, patients receiving immunosuppressive agents at baseline had a non-significantly lower BMD reduction over time at both sites than those who did not. Immunosuppressive therapy may reduce inflammation-induced bone loss and minimize the dose and duration of GC treatment. A previous longitudinal study reported that immunosuppressive agents were associated with BMD gain at the hip [10].

Our study has several limitations. First, it was a retrospective analysis and BMD measurements were collected only at baseline and at the end of follow-up, with no annual or periodic evaluation during the follow-up, meaning a more accurate assessment of BMD changes over time was not recorded. In addition, in our study, the definition of menopause was based on only clinical criteria, without evaluation of hormone levels to confirm the menopausal status, since it was not possible to retrospectively collect these measurements in all participants.

Secondly, lupus activity may influence bone loss: in our retrospective evaluation, the total number of flares during the long follow up was incompletely recorded in many cases, making their evaluation difficult to include as a risk factor for BMD changes, even though this would have enriched the longitudinal analysis. Thirdly, most of the patients had mild SLE disease activity at study entry, and therefore our findings should

not be generalized to other SLE patients with more-severe lupus. Moreover, all participants were Mexican-Mestizo, also limiting the generalizability of the results to patients with other ethnic backgrounds. Fourthly, not all patients underwent DXA measurements at the femoral neck and the percentage of missing data were relatively high, limiting the analysis of this BMD site. Fifthly, attrition bias can not be ruled out, since patients lost during the follow up were not significantly older but had more prevalent vertebral fractures at baseline. In addition, we cannot be certain that patients with more-severe disease were not lost to follow-up, adding a higher risk of bias. Finally, it was not a prospective randomised study, so many other confounders such as vitamin D levels and modifications over time were difficult to obtain.

In conclusion, BMD changes at the lumbar spine and the total hip over a period of > 10 years was shown in women with SLE. Older age, menopausal transition and GCT use contributed independently to BMD decline. Our analysis supports the relevance of attempting to reduce GCT use in patients with SLE. In addition, screening and preventive measures according to validated guidelines should be used, particularly in patients transiting to the menopause.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00223-021-00845-0>.

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**Author Contributions** CMP, MGC, DJM and PMR contributed to the conception and design of the study and wrote and revised the manuscript. DJM, PMR and MNS, IEM contributed to data collection and analysis. CMP and DMJ made the statistical analysis. IEM, JAA and SMM revised the manuscript. All authors contributed to the critical revision and approved the final version for publication.

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## Declarations

**Conflict of interest** The authors report no conflict of interest with respect to the content of the manuscript. Outside the submitted work, Dr García-Carrasco reports royalty payments from UCB for the publication of books/chapters. The remaining authors have no conflict of interests.

**Human and Animal Rights and Informed Consent** The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee, IMSS (R-2018-2106-035).

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