Influence of Prevalent Vertebral Fractures on the Quality of Life of Patients with Systemic Lupus Erythematosus

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ABSTRACT: **Background:** The prevalence of vertebral fractures in systemic lupus erythematosus (SLE) ranges between 20% and 21.4%, and patients with these fractures have impaired walking and activities of daily living. Moreover, clinical and radiological vertebral fractures have been associated with increased mortality.

Objectives: To compare the quality of life of patients with SLE with and without vertebral fractures.

Methods: The study group comprised 140 women with SLE undergoing screening for vertebral fractures using a standardized method. SLE disease activity and organ damage were measured by the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) and the Systemic International Collaborating Clinics/American College of Rheumatology damage index (SLICC), respectively. The QUALEFFO and Center for Epidemiologic Studies Depression Scale were used to measure health-related quality of life and depression, respectively.

Results: The median age of the 140 patients was 43 years (range 18–76); disease duration was 72 months (range 6–432); 49.7% were menopausal. Thirty-four patients (24.8%) had vertebral fractures (≥ 1), mostly in the thoracic spine. Patients with vertebral fractures had a higher mean age (49.5 ± 13.4 vs. 41 ± 13.2 years, $P = 0.001$) and disease damage (57.1% vs. 34.4%, $P = 0.001$). The global QUALEFFO score was not different between the vertebral fractures group and the non-vertebral group. The only significant difference in the QUALEFFO items was in physical function ($P = 0.04$). A significant correlation was found between the severity of vertebral fractures and the QUALEFFO pain ($r = 0.27$, $P = 0.001$) and physical function ($r = 0.37$, $P = 0.02$) scores. The number of vertebral fractures correlated only with physical function ($r = 0.01$).

Conclusions: The HRQOL of women with SLE is low, regardless of whether they have vertebral fractures or not, but patients with vertebral fractures have worse physical function compared to those without. Strategies to improve the HRQOL of patients with SLE with or without vertebral fractures are necessary.

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KEY WORDS: systemic lupus erythematosus, vertebral fractures, risk factors, quality of life

SLE = systemic lupus erythematosus

Systemic lupus erythematosus is a chronic autoimmune disease with a complex clinical presentation and course [1]. The survival of patients with SLE has improved significantly [2] but has not been accompanied by a similar improvement in the quality of life. The evaluation of SLE patients today should include not only disease activity and damage but also the patient's perspective.

Vertebral fractures, the hallmark of osteoporotic fractures, associated with back pain, kyphosis, abdominal protrusion and height loss, is one item of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE [3]. Patients with ver-

tebral fractures have impaired walking and activities of daily living [4,5]. Moreover, clinical and radiological vertebral fractures have been associated with increased mortality [6]. The prevalence of vertebral fractures in SLE ranges between 20% and 21.4% [7,8], including premenopausal women, although the associated risk factors remain unclear. The aim of this study was to test the hypothesis that health-related quality of life of SLE patients with vertebral fractures is lower than that of patients without vertebral fractures.

PATIENTS AND METHODS

The study was performed between 2006 and 2008 at the Systemic Autoimmune Disease Research Unit, Hospital General Regional No. 36 IMSS, and the Osteoporosis Clinic – both in Puebla, México. All patients were covered by medical insurance provided by the government. The local ethics committee approved the study and all patients provided informed consent for their participation.

PATIENTS

The study group included women aged ≥ 18 years who met at least four American College of Rheumatology classification criteria for SLE [9,10]. Exclusion criteria were pregnancy, renal impairment (creatinine > 2 mg/dl) and untreated thyroid disease.

MEASUREMENTS

Disease activity was measured using the modified Systemic Lupus Erythematosus Disease Activity Index [12]. Cumulative disease damage was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [3]. The osteoporosis/fracture item (1 point) was excluded to obtain a modified disease index score. Information on previous and current treatment was collected, including current and past medications used to treat SLE.

EVALUATION OF VERTEBRAL FRACTURES

All patients underwent lateral radiographs of the thoracic (T8) and lumbar (L3) spine performed according to a standard protocol by an experienced radiology technician in order to detect prevalent vertebral fractures. Films were evaluated and scored by an experienced radiologist. To standardize the semi-quantitative spine radiograph score, we used the method described by Genant et al. [11]. This model assigns grades on visual inspection as follows: normal (grade 0), mildly deformed (grade 1, approximately 20-25% reduction in anterior, middle and/or posterior height, and a 10-20% reduction in area), moderately deformed (grade 2, approximately 25–40% reduction in any height and 20–40% reduction in area), and severely deformed (grade 3, approximately 40% in any height and area). To compare binary fracture versus non-fracture, a vertebral body fracture was considered only if grade 1 or higher was observed. We conducted a pilot quality assurance study to obtain technical standard parameters for lateral thoracic and lumbar spine X-rays. The kappa value for identifying any vertebral fracture was 73.

Patients with vertebral fractures were assigned to the study group and those without fractures to the control group. All participants underwent a structured interview by a rheumatologist to collect sociodemographic information (including years of formal education), traditional and potential SLE-related risk factors for fractures, and spine morphometry. Disease duration and drug use were obtained from medical records.

HRQOL was measured using the validated Quality of Life Questionnaire of the European Foundation for Osteoporosis [13], which can discriminate between patients with and without vertebral fractures. It has 41 questions organized into 5 domains: back pain, physical function, social function, general health perception, and mental function. QUALEFFO scores are expressed on a 100-point scale, with 0 corresponding to the best HRQL. Ramirez et al. [14] recently culturally adapted and validated the QUALEFFO in a Mexican population after modifications, taking local factors into account. The QUALEFFO was measured according to the instructions in its original version. The answers to each question were scored from 1 to 5, except for questions 23, 24, 25, 26 (scores 1–3) and 27 & 28 (score 1–4), which were considered not applicable and were not scored. The answer options for questions 33, 34, 35, 37, 39 and 40 were reversed in order to maintain the order from 1 (healthy) to 5 (not healthy). Parameter scores were calculated by adding the answer scores and submitting the sum to a linear transformation using a scale of 100. Symptoms of depression were measured using the Center for Epidemiologic Studies Depression Scale [15], with significant depressive symptoms defined as ≥ 16.

STATISTICAL ANALYSIS

Descriptive statistics (mean, median, SD, and proportions) of all study variables were calculated. Comparisons of continuous variables between patients with and without vertebral fractures were performed using the Student's *t*-test or the Mann-Whitney U test as indicated. The chi-square or Fisher's exact test were used to compare categorical variables. Pearson correlation coefficients were used to measure associations between continuous variables. To adjust for variables in addition to vertebral fractures that could influence HRQOL, we used five backward stepwise multivariate regression models for each of the QUALEFFO items as dependent variables. The criterion for independent variables to remain in the model was a P value ≤ 0.10. The statistical analysis was performed using the SPSS v10.0 (Chicago, IL, USA) for Windows XP program.

HRQOL = Health-Related Quality of Life
QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis

RESULTS

The final group consisted of 140 female SLE patients: 34 (24.8%) in the study group and 106 controls. The mean age was 48.7 ± 12 years in the study group and 40.5 ± 12 in the control group ($P = 0.002$).

The majority of vertebral fractures were located in the thoracic spine and most were grade 1 on the Genant scale. Twenty-five patients had only one vertebral fracture, 5 had two fractures, and 4 had three or more fractures. The patients' characteristics are shown in Table 1. There were no differences in body mass index between patients, or lifestyle factors between the two groups but patients with vertebral fractures were more likely to exercise. Patients with vertebral fractures had less formal education. A total of 84.9% of controls had more than 6 years of formal education compared with 67.6% in the study group ($P = 0.017$). These patients had a low level of disease activity at the time of the study, but most of them had disease damage and had also received corticosteroids. There were no clinical or treatment differences between the study group and controls.

HEALTH-RELATED QUALITY OF LIFE

Patients in the study and control groups are compared in Figure 1. The global QUALEFFO score was not different between the vertebral fractures group and the non-vertebral group. When each QUALEFFO item was analyzed, the only significant difference in the QUALEFFO items was in physical function ($P = 0.04$). Patients in the study group tended to have slightly higher mean ± standard error score in pain (45.8 ± 19.8 vs. 43.3 ± 24.7, $P = 0.5$), social function (54.4 ± 15.3 vs. 51.4 ± 15.2, $P = 0.3$) and general health perception (66.7 ± 20.3 vs. 62.8 ± 33.8, $P = 0.5$). In contrast, the mean mental function score was slightly lower in the study group (50 ± 16.9 vs. 52.2 ± 47.9, $P = 0.7$).

There were no bivariate correlation coefficients between the five QUALEFFO scales and the MEX-SLEDAI and SLICC/ACR damage index. With respect to disease duration and the QUALEFFO items, only physical function showed a significant positive association ($r = 0.27$, $P = 0.001$).

A significant correlation was found between the severity of vertebral fractures and the QUALEFFO pain ($r = 0.27$, $P = 0.001$) and physical function ($r = 0.37$, $P = 0.02$) scores. The number of vertebral fractures correlated only with physical function ($r = 0.01$).

DEPRESSION

Patients in the study group had slightly higher mean CESD scores, although the difference was not significant (17.4 ± 12.9 vs. 16.1 ± 12.4, $P = 0.6$). A total of 42.3% of patients in the study group and 38.8% of controls had a CESD score ≥ 16 ($P = 0.8$).

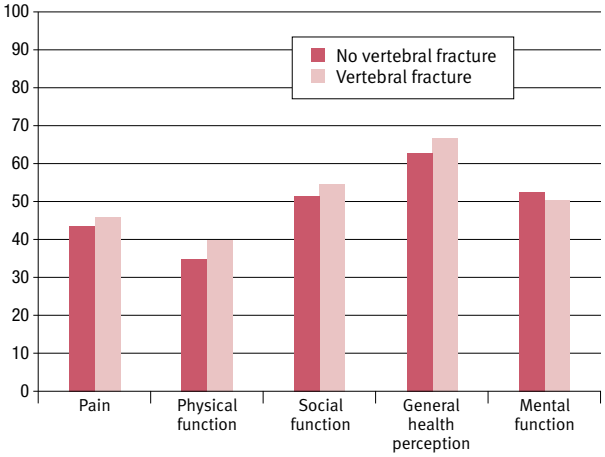
MEX-SLEDAI = modified Systemic Lupus Erythematosus Disease Activity Index
SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology
CESD = Center for Epidemiologic Studies Depression Scale

Table 1. Comparison of demographical and clinical variables in 140 women with SLE according to the presence of vertebral fractures

Subgroups of variables	Fracture group (n=34)	No fracture group (n=106)	*P* value
Demographic			
Age (yrs, mean ± SD)	48.7 ± 12	40.5 ± 12	0.002
Formal education (yrs, mean ± SD)	9.4 ± 4.2	11.2 ± 3.6	0.018
Premenopausal (%)	35.3	57.2	0.021
Body mass index (kg/m^2, mean ± SD)	28.3 ± 7.8	30 ± 33.2	0.451
Current smoker (%)	17.6	8.7	0.202
Exercise ≥ 3 times weekly (%)	5.8	21.3	0.040
Personal history of fractures (%)	11.7	20.5	0.252
Clinical			
Disease duration (mos, mean ± SD)	130.5 ± 103	106.5 ± 85.5	0.180
Disease activity (%)	26.4	28.1	0.519
MEX-SLEDAI (mean ± SD)	3.4 ± 3.4	2.7 ± 1.6	0.354
Chronic disease damage (%)	50	34.9	0.08
SLICC/ACR DI (mean ± SD)	1.1 ± .4	1.1 ± 0.5	0.681
Treatment			
Cumulative steroid dose (g, mean ± SD)	20.8 ± 20.5	18.3 ± 21.9	0.556
Ever use of other medications (%)	–	–	–
Antimalarial drugs	85.2	90.2	0.526
Hormonal replacement therapy	5.9	6.8	0.606
Bisphosphonates	11.7	11.6	0.986

SD = standard deviation, MEX-SLEDAI = Mexican Systemic Lupus Erythematosus Disease Activity Index, SLICC/ACR DI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (modified damage index excludes osteoporotic fractures as a damage item)

Figure 1. Results of the 5 domains of the QUALEFFO questionnaire in 34 SLE patients with vertebral fractures compared with 106 SLE patients without vertebral fractures. Bars show the mean score for each item. Patients with vertebral fractures scored significantly higher in the physical function scale.*$P = 0.04$



MULTIVARIATE MODELS

Demographic, clinical and treatment variables were considered possible characteristics that could influence HRQOL. Disease duration was selected as the control variable due to

the cross-sectional nature of the study. Vertebral fractures were included in all models. Depressive symptoms as a covariate were entered into the regression analysis. Five separate multivariate models were performed [Tables 2 and 3]. The regression coefficient indicates the magnitude and direction of change in each of the five QUALEFFO scales associated with each unit change in the independent variables.

Table 2. Factors associated with health-related quality of life in 140 patients with SLE

Independent variables	Pain	Physical function	Social function	General health perception	Mental function
Vertebral fractures Yes = 1, No = 0	2.5 (-6.7, 1.7)	0.04* (0.02, 0.6)	2.9 (-3, 8.9)	3.8 (-8,2, 16)	-2.1 (-18.7, 14.4)
Severity of vertebral fractures 1–3	–	9.9* (1.2, 18.6)			
Age 18–76 yrs	–	0.16 (-0.1, 1.5)	0.1 (-0.01,1.1)	–	–
Formal education 3–21 yrs	-0.8 (-1.9, 0.14)	-0.05 (-1.4, 0.2)	-0.9* (-1.6, -0.3)	–	–
SLE disease duration (mos)	–	0.14 (-1.4, 1.2)	0.09 (-0.04, 0.5)	0.004 (-0.006, 0.1)	–
MEXSLEDAI 0–20	9.5* (0.7, 18.2)	0.9 (-0.8, 6.9)	–	–	–
SLE damage 0–13	11.6 ** (3.5, 19.7)	5.2 ** (0.5, 10)	0.1 (-0.1, 4.5)	4.6 (-3.3, 17.9)	–
Adjusted R^2	0.06	0.25	0.05	0.02	0.07

*$P \leq 0.05$, **$P \leq 0.001$

Stepwise multivariate regression models were fit using each five QUALEFFO items as a dependent variable. Values shown are the regression coefficients (95% confidence interval). The independent variables, cumulative steroid dose, current use of immunosuppressive drugs, current use of antimalarials and bone mineral density measurements are not shown because they are not associated with any of the outcomes

Table 3. Factors associated with health-related quality of life in 140 patients with SLE accounting for the role of symptoms of depression

Independent variables	Pain	Physical function	Social function	General health perception	Mental function
Vertebral fractures Yes = 1, No = 0	0.06	1.029 (1.001, 1.05)	0.06	0.01	-3.4 (-25.6, 18.6)
Severity of vertebral fractures 1–3					-10.9* (-21.1, -0.7)
SLE disease duration (mos)	–	0.002 * (0.002, 0.05)	–	–	–
MEXSLEDAI 0–20	0.18 (0.08, 6.7)	–	–	–	–
SLE damage 0–13	0.18 (0.08, 7.8)	6.8 * (2, 11.7)	6.2 * (0.8. 11.7)	–	–
CESD 0–49	0.5* (0.1, 0.8)	0.4 ** (0.2, 0.6)	0.61** (0.4, 0.8)	0.8 (0.2, 1.3)	0.78** (0.48, 1.08)
Adjusted R^2	0.05	0.21	0.24	0.09	0.39

*$P \leq 0.05$, **$P \leq 0.001$

Values shown are the regression coefficients (95% confidence interval). The independent variables, age, formal education, cumulative steroid dose, current use of immunosuppressive drugs, current use of antimalarials and bone mineral density measurements are not shown because they are not associated with any of the outcomes

The factors significantly associated with HRQOL were years of formal education (they were associated with significantly improved social function scores). SLE damage was significantly associated with high (worse) pain and physical function scores [Table 2]. However, only the association with physical function remained when depressive symptoms were considered [Table 3]. Disease duration was significantly positively correlated with physical function when depressive symptoms were included [Table 3].

The cumulative steroid dose, current use of immunosuppressive drugs and antimalarials were not associated with any of the outcomes (data not shown).

DISCUSSION

The survival of patients with SLE has improved significantly and more interest is now paid to long-term complications. The evaluation of patients with SLE today should include not only disease activity and damage but also the patient's perspective since the disease is likely to have a significant impact on many physical, social and psychological aspects, irrespective of the instrument used [16]. SLE patients also have an increased risk of osteoporosis and fractures including vertebral fractures, which may affect HRQOL [17]. Therefore, we decided to investigate the impact of vertebral fractures on HRQOL.

Vertebral fractures occur in about 20% of patients with SLE, including premenopausal women [3,7,8]. Although the prevalence and risk factors of vertebral fractures in SLE patients have been studied, a major issue of the present study was the evaluation of HRQOL in SLE patients with vertebral fractures.

The overall QUALEFFO questionnaire scores confirmed the poor HRQOL of our patients. Both groups of patients had a low HRLQOL, with mean scores falling below the 25th percentile mark of reported scores for the general Latin American population in four of the five QUALEFFO domains [14]. These scores are similar to those found by Bianchi et al. [18] in patients with vertebral fractures and by Angeli et al. [19] in women receiving chronic steroid therapy. However, unlike Angeli's findings [19], there were no significant differences in the overall QUALEFFO score between patients with and without vertebral fractures.

Adjusted comparisons of the QUALEFFO instrument between the study group and controls show that the only significant association was between physical function and vertebral fractures when demographic and clinical variables were adjusted in the multivariate model. The severity of vertebral fractures was also associated with high physical function scores. Previous reports have shown that vertebral fractures are associated with reduced HRQOL and worse physical function [18,20]. Surprisingly, when the CESD was included, the association disappeared. Since depressive symptoms are firmly present in our population, it is an important reason of disability.

The QUALEFFO mental function was negatively associated with vertebral fractures when depressive symptoms were adjusted, supporting the hypothesis that the physical constraints of vertebral fractures and not mental impairment cause the reduction in physical abilities [17]. This suggests the importance of depression as a determinant of HRQOL in patients with SLE independently of whether they have fractures or not. The CESD was significantly associated with four of the five QUALEFFO components.

SLE damage measured by the SLICC damage index was significantly correlated with poor HRQOL in pain and physical function scores, but only the latter remained when depressive symptoms were adjusted for. Social function was also positively associated with chronic damage. These results differ from a previous study of SLE patients evaluated with the Medical Outcomes Study Short Form-36 [16].

In this study we demonstrated that vertebral fractures are frequent in women with SLE, HRQOL is low regardless of the presence of vertebral fractures, and patients with vertebral fractures have worse physical function. The high prevalence of vertebral fractures in young SLE women indicates the need for improved strategies for early detection and better treatment to raise the HRQOL in SLE patients.

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