Fibromyalgia prevalence and related factors in a large registry of patients with systemic lupus erythematosus

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Received on March 19, 2015; accepted in revised form on August 31, 2015.

Clin Exp Rheumatol 2016; 34 (Suppl. 96): S40-S47.

Key words: systemic lupus erythematosus, fibromyalgia, depression, disease activity

Competing interests: J.M. Pego-Reigosa is supported by grant 316265 (BIOCAPS) from the European Union 7th Framework Program (FP7/REGPOT-2012-2013.1); F.J. López-Longo has received speaker's fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, MSD, Actelion; F.J. López-Longo has received research funding from Abbvie and GSK; the RELESSER Registry was funded by several grants from GSK, Roche, UCB and Novartis; the other co-authors have declared no competing interests.

ABSTRACT

Objective. *The objective of this study is to determine the prevalence of fibromyalgia (FM) in systemic lupus erythematosus (SLE) patients and to study its relationship to depression and other SLE-related factors.*

Methods. *A cross-sectional data analysis from the RELESSER-Transversal Spanish Registry, which includes SLE patients in a national multicentre retrospective charts review, was performed. Inclusion criteria: patients who fulfilled ≥4 ACR 1997 SLE criteria. Main variables were disease duration, depression, sociodemographics, comorbidities, SLE activity symptoms, serological findings, therapies and different disease status indices. Statistical analyses included a descriptive, associative and logistic regression analyses. A literature review was performed.*

Results. *3,591 SLE patients were included, 90.1% women, 34.6 years of age at diagnosis (SD 14.6 years) and 93.1% Caucasians. FM prevalence was 6.2%. SLE patients with disease duration >5 years showed more FM than those with duration <5 years: 6.9% vs. 4.0%, respectively (p<0.05). SLE-FM patients showed higher prevalence of depression compared to non-FM-SLE patients: 53.1% vs. 14.6%, respectively (p<0.001). After adjusting by risk factors, the OR (CI) of suffering depression in FM-SLE patients was 6.779 (4.770–9.636), p<0.001. The OR of having secondary Sjögren's 2.447 (1.662–3.604), p<0.001, photosensitivity 2.184 (1.431–3.334), p<0.001, and oral ulcers 1.436 (1.005–2.051), p=0.047.*

Conclusion. *Prevalence of FM in Caucasian SLE patients was high compared to the general population, and was significantly higher in those in later stages of disease. SLE patients with depression showed a strong risk of developing FM. Photosensitivity, oral ulcers and secondary Sjögren's were the only SLE-related factors associated with FM.*

Significance and innovation

This work studies the fibromyalgia prevalence in systemic lupus erythematosus (SLE) patients. By including over 3.000 patients it helps to define this prevalence in Caucasian SLE patients.

It also suggests that the presence of depression is the strongest factor associated to the presence of fibromyalgia in SLE patients. This association grows in SLE late stages.

The presence of photosensitivity, oral ulcers and secondary Sjögren's syndrome were also associated to the presence of fibromyalgia in SLE patients.

None of the activity measures used in this work has been associated to the presence of fibromyalgia in SLE patients.

Introduction

Systemic lupus erythematosus (SLE) is one of the main autoimmune rheumatic diseases distributed worldwide, and its prevalence in Spain is estimated at 9 cases per 10.000 inhabitants (1). Due to the systemic distribution of organ involvement and the chronicity of SLE, its damage may lead to decreased life expectancy and impaired quality of life (2). Fibromyalgia (FM) is a mentally, socially and physically impairing con-

dition (3-5), of the main symptoms of which are widespread musculoskeletal pain and pain hypersensitivity. FM may also be found in SLE patients, its prevalence varying from 8–61% (4, 6, 7). This variation has been explained by the diagnostic criteria applied, the manner of assessment, patient ethnicity, and the SLE duration. As has been previously demonstrated, FM is an important predictor of poorer self-reported quality of life in SLE patients (8, 9).

One of the most intriguing points is whether FM is independently related to SLE activity, as has been classically suggested. However, most works in recent years have ruled this out (7, 10, 11). The factors that have been associated with the presence of FM in SLE patients are Caucasian ethnicity, presence of psychiatric disorders such as anxiety and depression, SLE duration (longer or shorter than five years), and lack of SLE activity (7, 8, 11).

The *RELESSER-T* Registry (SLE registry of the Spanish Society of Rheumatology-Transversal phase) is a nationwide retrospective database with an enrollment of 4,024 SLE patients from hospitals throughout Spain, and is supported by the Spanish Society of Rheumatology (SER) that maintains multiple databases on SLE and related conditions and comorbidity (12). RELESSER is the largest SLE registry in Europe to date, and it is a powerful tool for assessing the state of clinical SLE research in Southern Europe.

The aims of this study are: a) to determine the prevalence of FM in a large sample of SLE patients; b) to compare the findings between patients with short SLE disease duration and those with longer SLE disease duration; and c) to analyse the association of FM with depression, different SLE-related manifestations, laboratory markers and comorbidity conditions. We also reviewed the published literature regarding the presence of FM in SLE patients.

Material and methods

Study design and research study network

Selected data for the purposes of this study were obtained from the RELESSER-T Registry and were analysed accordingly (see *Variables*). The objectives and methodology of the RELESSER-T Registry have been already published (12). A scientific committee approved the study project.

Study population

Out of 4,024 SLE-diagnosed patients enrolled in the RELESSER-T Registry, all of those patients who fulfilled at least four American College Rheumatology (ACR) 1997 SLE diagnostic criteria (13, 14) and who fulfilled all data value selected for the purposes of this study were included. This registry was performed between 2011 and 2012 over a 10-month period. An online monitored control was used to clarify all inconsistencies, missing values, and discrepancies (12).

Variables

Sociodemographic factors: age, ethnicity, sex, age at onset, delay of diagnosis, and disease duration.

Clinical variables included: malar eruption, discoid lupus, photosensitivity, oral ulcers, secondary Sjögren syndrome (SS), arthritis, serositis, proteinuria >0.5 g/d, urine casts, seizures, and psychosis. Disease duration was defined as ≤5 and >5 years, a distribution based on results from other authors (8). FM was defined according to ACR 1990 classification criteria (15) at some stage over the course of SLE. Any medical history of depression – diagnosed by a psychiatrist and/or under specific antidepressant treatment – was also collected.

Data regarding co-morbidities included: smoking status, dyslipidaemia, diabetes, arterial hypertension, hypothyroidism, number of severe infections, number of hospitaliaations and cause(s) (12).

Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (16) at the time of the last evaluation. Cumulative damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) (17), and severity by the Katz index (18).

SLE laboratory markers included lupus anticoagulant and anti-dsDNA, ANA, anti-Ro/SS-A, anti-La/SS-B, anti-U1RNP, anti-Sm, and anti-cardiolipin antibodies. We also included the presence of haemolytic anaemia, leucopenia, lymphopenia, thrombocytopenia and hypocomplementaemia (19).

Treatment variables were previous use of oral steroids, and the mean daily maximum dosage of glucocorticoids (<10 mg, 10-29 mg, 30-59 mg, ≥60 mg), antimalarial drugs and dialysis.

All variables-related information was classified as 'present' if they occurred at any time since SLE onset (12). A specific guideline of codes and definitions for all RELESSER-T investigators was created to standardise and clarify data collection.

Literature review

A MEDLINE/PubMeD research was performed using the key words 'fibromyalgia', 'fibromyalgia-like', 'widespread pain' and 'systemic lupus erythematosus'. We selected all type of articles including an investigation of the presence of FM in SLE patients (case-series, prospective and cross-sectional studies). We excluded reviews and opinion articles.

Statistical analyses

Means and standard deviations or medians and interquartile percentiles for numeric variables based on normal distribution, as well as absolute and relative frequencies for categorical variables, were calculated. Global and segmented population-based analyses on the presence of fibromyalgia (FM) and SLE disease duration were carried out. The relation of each independent variable with the dependent variable (FM) was assessed by applying statistical tests: the Student's *t*-test for numerical variables and the Chi-squared test for comparing categorical variables among groups. Finally, in order to those factors associated with the presence of FM, an assessment calculating crude odds ratios and adjusted odds ratio with confounding factors (OR) through logistic regression was made. The multivariate model included as independent variables those that had a statistically significant result in the bivariate analysis and those deemed clinically relevant or possible confounders; how-

ever, if the included variables showed any significant correlation, they were excluded from the model. Statistically significance was assumed as $p<0,05$. All analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Sociodemographics characteristics and FM prevalence

The total number of patients who fulfilled all data value selected for the purpose of this study numbered 3,591. A total of 3,229 (89.9%) were women, with a mean age at time of diagnosis of 34.6 (SD: 14.6) years old, and median [IR] disease duration of 139 [77-224] months. A total of 2,759 (76.8%) patients had disease duration ≤5 years. A total of 3,253 (90.5%) were Caucasians, 184 (5.1%) Latin American origin, 21 (0.5%) Asiatic and 29 (0.8%) of other ethnicity. Two hundred and twenty-four patients (6.2%) were diagnosed with FM.

FM based on SLE disease duration

There was a higher prevalence of FM in patients with an SLE disease duration >5 years compared to those with a disease duration ≤5 years (6.9% *vs*. 4.0%, respectively; $p<0.05$). Additionally, depression was more prevalent in patients with longer disease duration (12.7 *vs*. 18.3%, respectively; $p<0.001$).

In the patient subgroup with a disease duration ≤5 years, SLE patients with FM (SLE-FM) were more frequently Caucasian women, older, had longer follow-up periods, and had more depression compared to those without FM (non-FM-SLE). The following SLE-related factors were associated with the absence of FM: leukopenia, low complement, ANA and dsDNA antibody positivity (Table I).

Factors associated to FM in SLE patients

When comparing SLE-FM with non-FM-SLE, SLE-FM patients were significantly older at disease onset and at time of the diagnosis. They were also more frequently women, and had longer disease duration, follow-up time and diagnosis delay. FM-SLE patients suf-

Table I. Comparisons between non-FM-SLE patients and SLE-FM patients with SLE disease durations of no longer than five years.

Variable	Total n=806	non-FM-SLE disease duration ≤5 years, n=774	SLE-FM disease duration ≤5 years, n=32	*p*-value
Age at disease onset (years)	36.4 (14.9)*	36.2 (15.0)*	40.7 (11.6)*	0.101
Age at last evaluation (years)	41.5 (14.9)*	41.3 (15.0)*	46.5 (11.2)*	0.056
Age at time of diagnosis (years)	38.9 (14.9)*	38.7 (15.0)*	43.6 (11.5)*	0.068
Disease duration (months)	48.0 [23.0-72.0]*	47.0 [23.0-71.5]*	54.0 [37.7-87.7]*	0.424
Delay in diagnosis (months)	7.0 [2.0-31.2]*	7.0 [2.0-30.7]*	9.5 [1.0-63.7]*	0.612
Follow-up time (months)	32.0 [13.0-54.0]*	31.0 [13.0-54.0]*	49.0 [26.5-73.0]*	0.027
Female (%)	708 (88.0)	676 (87.5)	32 (100.0)	0.025
Ethnicity' Caucasians (%)	682 (86.9)	650 (86.3)	32 (100.0)	0.015
Depression	101 (12.7)	86 (11.2)	15 (46.9)	<0.001
Smokers (%)	285 (39.1)	273 (38.9)	12 (44.4)	0.709
Never	443 (60.9)	428 (61.1)	15 (55.6)	
Before	145 (19.9)	140 (20.0)	5 (18.5)	0.667
Now	140 (19.2)	133 (19.0)	7 (25.9)	
Dyslipidaemia (%)	204 (26.4)	191 (25.7)	13 (41.9)	0.072
Diabetes Mellitus (%)	29 (3.6)	28 (3.7)	1 (3.1)	1.000
Arterial hypertension (%)	150 (18.8)	141 (18.4)	9 (28.1)	0.169
Autoimmune thyroiditis (%)	74 (9.5)	69 (9.2)	5 (16.7)	0.193
Malar rash (%)	366 (45.9)	347 (45.4)	19 (59.4)	0.168
Discoid rash (%)	153 (19.3)	146 (19.2)	7 (21.9)	0.887
Photosensitivity (%)	445 (56.4)	423 (55.9)	22 (68.8)	0.209
Oral ulcers (%)	329 (42.1)	316 (42.0)	13 (43.3)	1.000
Arthritis (%)	583 (73.4)	558 (73.2)	25 (78.1)	0.682
Pleuritis (%)	139 (17.6)	136 (17.9)	3 (9.7)	0.347
Pericarditis (%)	85 (10.7)	81 (10.6)	4 (12.9)	0.565
Proteinuria >0.5 g/ 24 hr. (%)	181 (22.8)	175 (22.9)	6 (20.7)	0.957
Cellular casts (%)	103 (13.2)	100 (13.4)	3 (9.7)	0.787
Convulsions (%)	28 (3.5)	28 (3.7)	0 (0.0)	0.623
Psychosis (%)	8 (1.0)	8 (1.0)	0 (0.0)	1.000
Haemolytic anaemia (%)	47 (6.0)	46 (6.1)	1 (3.4)	1.000
Leukopenia <4000/mm^3 (%)	437 (55.5)	426 (56.3)	11 (34.4)	0.023
Lymphopenia <1500/mm^3 (%)	402 (51.3)	387 (51.5)	15 (48.4)	0.879
Thrombocytopenia <100.000 mm^3 (%)	142 (18.3)	139 (18.6)	3 (10.3)	0.377
Low Complement (%)	551 (70.0)	535 (70.8)	16 (51.6)	0.037
Anti-Ro (%)	328 (41.9)	317 (42.2)	11 (34.4)	0.486
Anti-La (%)	164 (21.0)	160 (21.3)	4 (12.5)	0.327
Anti-RNP (%)	193 (24.7)	187 (24.9)	6 (19.4)	0.622
Anti-Sm (%)	183 (24.0)	177 (24.1)	6 (20.0)	0.765
Anti-dsDNA (%)	550 (69.6)	537 (70.6)	13 (44.8)	0.006
False positive Lues serology (%)	259 (34.6)	253 (35.1)	6 (20.7)	0.160
Antinuclear antibodies (%)	795 (98.9)	765 (99.1)	30 (93.8)	0.046
Amenorrhoea (%)**	1 (0.7)	0 (0.0)	1 (7.7)	0.087
Corticosteroid (%)	613 (81.7)	588 (81.6)	25 (86.2)	0.696
<10 mg daily	118 (20.0)	113 (19.9)	5 (21.7)	
10-30 mg daily	215 (36.4)	208 (36.7)	7 (30.4)	0.894
30-60 mg daily	146 (24.7)	139 (24.5)	7 (30.4)	
>60 mg daily	111 (18.8)	107 (18.9)	4 (17.4)	
Secondary Sjögren (%)	80 (11.0)	78 (11.0)	2 (8.3)	1.000
Dialysis (%)	12 (1.7)	12 (1.8)	0 (0.0)	1.000
Antimalarials (%)	559 (79.7)	540 (79.5)	19 (86.4)	0.593
No	142 (20.3)	139 (20.5)	3 (13.6)	
Past	83 (11.8)	77 (11.3)	6 (27.3)	0.070
Last evaluation	476 (67.9)	463 (68.2)	13 (59.1)	
Severe infection (%)	87 (12.1)	85 (12.2)	2 (8.7)	1.000
Number of severe infections (n=87)	1.0 [1.0-2.0]*	1.0 [1.0-2.0]*	1.0 [1.0-1.0]*	0.450
Number of SLE criteria	5.0 [4.0-6.0]*	5.0 [4.0-6.0]*	5.0 [4.0-6.0]*	0.592
SLEDAI	2.0 [0.0-4.0]*	2.0 [0.0-4.0]*	2.0 [0.0-4.0]*	0.688
SLICC/ACR DI	0.0 [0.0-1.0]*	0.0 [0.0-1.0]*	0.0 [0.0-1.0]*	0.475
KATZ	2.0 [1.0-3.0]*	2.0 [1.0-3.0]*	2.0 [1.0-3.0]*	0.740
CHARLSON	1.0 [1.0-2.0]*	1.0 [1.0-2.0]*	1.0 [1.0-2.0]*	0.136

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
*Mean (SD), **Median [P25-P75].

fered more depression, dyslipidaemia, arterial hypertension and autoimmune thyroiditis. The SLE-FM group showed more photosensitivity, secondary SS, a 10–30 mg dosage of steroid use (*i.e.* as the highest daily mean dose) and previous use of antimalarials. Non-FM-SLE patients exhibited more proteinuria, cellular casts, haemolytic anaemia, and higher SLEDAI scores. All data are shown in Table II.

Multivariate analysis was adjusted for SLE disease duration time, comorbidities, age at SLE onset, age at diagnosis, and mean highest steroids dosage. Depression was the major factor associated with the presence of FM with a 7.295 OR (CI 5.180-10.274; $p<0.001$). The presence of photosensitivity (OR 2.119, CI 1.543–2.909; $p<0.001$) and oral ulcers (OR 1.561, CI 1.101–2.214; $p<0.001$) were the other factors associated with the presence of FM (Table III). A highest mean daily steroids dosage of 10-30 mg resulted in a 1.425 OR (CI 0.873–2.326, $p=0.010$).

Table IV shows the main information regarding the principal clinical variables analysed in the twelve studies we found that matched our key words.

Table II. Comparison between non-FM-SLE patients and SLE-FM patients.

Variable	Total n=3,591	non-FM-SLE, n=3,367	SLE-FM, n=224	*p*-value
Age at disease onset (years)	32.6 (14.5)*	32.4 (14.6)*	35.5 (12.3)*	<0.001
Age at last evaluation (years)	46.3 (14.9)*	45.8 (14.9)*	52.9 (12.2)*	<0.001
Age at the time of diagnosis (years)	34.6 (14.7)*	34.4 (14.8)*	38.0 (12.4)*	<0.001
Disease duration (months)	148.0 [82.0-234.0]*	144.0 [80.0-231.0]*	199.5 [127.5-273.7]*	<0.001
Delay in diagnosis (months)	5.0 [1.0-24.0]*	5.0 [1.0-24.0]*	7.0 [1.0-34.0]*	0.252
Follow-up time (months)	102.0 [46.0-170.0]*	99.0 [44.0-166.0]*	154.5 [84.2-213.7]*	<0.001
Female (%)	3,229 (90.1)	3,006 (89.5)	223 (99.6)	<0.001
Ethnicity Caucasian (%)	3,253 (93.1)	3,042 (92.9)	211 (96.3)	0.067
Depression	604 (17.0)	485 (14.6)	119 (53.1)	<0.001
Smokers (%)	1,331 (41.0)	1,243 (40.9)	88 (43.1)	0.574
Never	1,914 (59.0)	1,798 (59.1)	116 (56.9)	
Before	787 (24.3)	741 (24.4)	46 (22.5)	0.313
Now	544 (16.8)	502 (16.5)	42 (20.6)	
Dyslipidaemia (%)	1,087 (31.5)	988 (30.5)	99 (45.2)	<0.001
Diabetes Mellitus (%)	175 (4.9)	159 (4.8)	16 (7.2)	0.153
Arterial hypertension (%)	1,051 (29.5)	960 (28.7)	91 (41.2)	<0.001
Autoimmune thyroiditis (%)	283 (8.2)	257 (8.0)	26 (12.4)	0.031
Malar rash (%)	1,949 (54.9)	1,815 (54.6)	134 (60.1)	0.126
Discoid rash (%)	736 (20.9)	681 (20.6)	55 (25.1)	0.123
Photosensitivity (%)	2,115 (60.5)	1,950 (59.5)	165 (75.7)	<0.001
Oral ulcers (%)	1,613 (46.2)	1,481 (45.2)	132 (60.8)	<0.001
Arthritis (%)	2,762 (77.9)	2,584 (77.8)	178 (80.2)	0.453
Pleuritis (%)	808 (23.0)	759 (23.0)	49 (22.3)	0.861
Pericarditis (%)	568 (16.1)	537 (16.2)	31 (14.2)	0.490
Proteinuria > 0.5 g/ 24 hr. (%)	1,101 (31.2)	1,057 (32.0)	44 (20.4)	<0.001
Cellular casts (%)	722 (21.1)	693 (21.6)	29 (13.6)	0.007
Convulsions (%)	241 (6.8)	229 (6.9)	12 (5.4)	0.452
Psychosis (%)	78 (2.2)	75 (2.2)	3 (1.4)	0.630
Haemolytic anaemia (%)	311 (8.9)	303 (9.3)	8 (3.7)	0.007
Leukopenia <4000/mm^3 (%)	2,123 (60.5)	1,992 (60.6)	131 (59.3)	0.754
Lymphopenia <1500/mm^3 (%)	1,878 (53.7)	1,757 (53.7)	121 (54.8)	0.807
Thrombocytopenia <100.000 mm^3 (%)	795 (23.1)	755 (23.4)	40 (18.5)	0.121
Low complement (%)	2,739 (77.8)	2,576 (78.1)	163 (73.8)	0.157
Anti-Ro (%)	1,374 (39.4)	1,294 (39.6)	80 (36.0)	0.326
Anti-La (%)	674 (19.3)	632 (19.4)	42 (18.9)	0.943
Anti-RNP (%)	878 (25.3)	822 (25.3)	56 (25.5)	1.000
Anti-Sm (%)	726 (21.3)	690 (21.6)	36 (16.6)	0.098
Anti-dsDNA (%)	2,567 (73.3)	2,419 (73.6)	148 (68.2)	0.097
False positive Lues serology (%)	1,283 (38.6)	1,212 (39.0)	71 (34.0)	0.174
Antinuclear antibodies (%)	3,551 (99.1)	3,332 (99.2)	219 (97.8)	0.052
Amenorrhoea (%)	90 (8.6)	85 (9.1)	5 (4.2)	0.098
Corticosteroids (%)	3,049 (89.0)	2,855 (88.9)	194 (90.2)	0.627
<10 mg daily	454 (15.7)	424 (15.7)	30 (16.7)	
10-30 mg daily	917 (31.8)	842 (31.2)	75 (41.7)	0.008
30-60 mg daily	727 (25.2)	685 (25.3)	42 (23.3)	
>60 mg daily	785 (27.2)	752 (27.8)	33 (18.3)	
Secondary Sjögren (%)	513 (14.6)	442 (13.4)	71 (31.8)	<0.001
Dialysis (%)	102 (3.0)	97 (3.1)	5 (2.3)	0.708
Antimalarials (%)	2,837 (83.2)	2,649 (82.9)	188 (87.4)	0.106
No	572 (16.8)	545 (17.1)	27 (12.6)	
Past	851 (25.0)	773 (24.2)	78 (36.3)	<0.001
Last evaluation	1,986 (58.3)	1,876 (58.7)	110 (51.2)	
Severe Infection (%)	714 (20.9)	660 (20.6)	54 (25.2)	0.124
Number of severe infections (n=714)	1.0 [1.0-2.0]*	1.0 [1.0-2.0]*	1.0 [1.0-2.0]*	0.826
Number of SLE criteria	6.0 [5.0-7.0]*	6.0 [5.0-7.0]*	6.0 [5.0-7.0]*	0.093
SLEDAI	2.0 [0.0-4.0]*	2.0 [0.0-4.0]*	2.0 [0.0-3.0]*	<0.001
SLICC/ACR DI	1.0 [0.0-2.0]*	1.0 [0.0-2.0]*	1.0 [0.0-2.0]*	0.710
KATZ	2.0 [1.0-3.0]*	2.0 [1.0-3.0]*	2.0 [1.0-3.0]	0.334
CHARLSON	2.0 [1.0-3.0]*	2.0 [1.0-3.0]*	2.0 [1.0-4.0]*	0.002

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
*Mean (SD), Median [P25-P75].

Discussion

The prevalence of FM in the SLE patients included in our study was as high as 6.9% depending on SLE disease duration, which was higher than that observed in the general Spanish population (2.4%) (1). We found FM-SLE patients were slightly younger than the general population FM subjects in a similar geographic area (38 *vs*. 40–49 (1), respectively). However, the literature shows that there is a large variability among previous studies (8–61%) (3, 6-9). This wide variability could be related to the inclusion criteria used, the ethnicity and the particular subgroups of SLE patients assessed, and other unknown factors (2, 3, 6-11). Caucasian SLE patients have been found to be at higher risk for developing FM compared to African-American and Hispanic ethnic groups (6). We could not confirm the latter, most likely due to the smaller numbers of other ethnicities included in our study. The prevalence of FM in other chronic autoimmune

diseases, such as rheumatoid arthritis, primary SS, systemic vasculitis, multiple sclerosis and systemic sclerosis is similarly greater than in the general population (20, 21).

Based on our study, the higher prevalence of FM in SLE patients seems to be directly related to longer SLE duration, as other authors have noted (8). To date, this is the first study to compare a group of relatively short SLE-duration patients (≤5 years) with a group of longer SLE-duration patients (>5 years) vis-à-vis the presence of FM. Based both on our own and on two previous studies (6, 7), the latter might suggest that the presence of FM in SLE is related to a pre-existing chronic illness, and/or to depression, rather than to SLE activity alone. On the other hand, higher SLICC/ACR DI scores have been recorded in patients with longer disease duration (22). In our own study, however, higher SLICC/ACR DI scores did not correlate with longer disease duration in the FM patient group compared to those in earlier stages. Whether such cumulative damage might also lead to depression and thence to a causative factor of FM awaits proper assessment. Further studies would be needed to address this hypothesis.

In our study, which included mostly Caucasian SLE patients, FM was associated with depression, as previous studies with smaller numbers of patients have suggested (2, 6, 7). Indeed, in the multivariate analysis, depression was the most highly weighted variable in relation to the presence of FM, as patients who suffered FM showed a 6.8-fold probability of suffering depression. In accordance with previous studies (7, 23), both the pain score and FM in SLE patients were correlated to the presence of depression and anxiety. We did not assessed anxiety symptoms per se, but we did observe the same association between depression and FM in our SLE patients.

We hypothesise that the presence of depression stems from the presence of a chronic illness rather than from neuropsychiatric SLE activity. Accordingly, we found a higher prevalence of FM and depression and lower SLE disease activity scores in the later (*vs*. earlier) stages of SLE. Whether depression in SLE is due to SLE activity remains a matter of discussion (24, 25). Nonetheless, one can reasonably argue that major depressive disorders related to neuropsychiatric SLE appear more often at disease onset or during the early stages, when other activity symptoms and higher activity indices scores are present (25).

We found that SLE patients who suffered FM were predominantly female, as well as older both at onset and diagnosis, had longer disease durations, photosensitivity and secondary SS and oral ulcers. In addition, these patients had more often used antimalarial in the past and/or had received the 10–30 mg mean daily steroids dosage (*i.e*. the highest mean dosage). The latter was found to be the only modifiable factor related to the presence of FM in Caucasian SLE patients. One possible explanation for this finding is that some physicians might have tried to relieve musculoskeletal and/or minor mucocutaneous symptoms with mild-moderate disease by administering a low-medium dose of corticosteroids. Thus, physicians should be aware of the importance of tapering steroids when possible, especially in those SLE-FM patients with mild involvement.

In a multivariate analysis that was adjusted for all these factors, the presence of photosensitivity, secondary SS and oral ulcers over the disease course were the main symptoms associated with the presence of FM, with a 2.2, 2.4 and 1.4 OR, respectively. Therefore, apart from these minor mucocutaneous manifestations described herein, SLE activity cannot be clearly linked to the presence of FM in SLE patients. Of note, *sicca* syndrome has been described in primary FM patients which may stem from the use of tricyclic antidepressants or chronic blepharitis (not specifically assessed in our study), as was suggested by Günaydin *et al*. (26). How anti-depressive treatment might impact *sicca* syndrome in our SLE patients who suffer FM remains unknown. Further studies are needed in order to determine whether SS in FM-SLE patients is a consequence of anti-depressive treatment, or, on the other hand, simply acts as a FM risk factor.

In terms of comorbidity factors also related to FM, we found that FM-SLE patients more frequently presented autoimmune thyroiditis, arterial hypertension and dyslipidaemia. To date, no clear relationship has been found between the presence of FM and dyslipidaemia in the general population. However, some studies have found an association between the presence of arterial hypertension and autoimmune thyroiditis and FM in the general population (27, 28). In contrast, no thyroid dysfunction has been found in other studies (29). Whether these comorbidity conditions may be related to the presence of FM in SLE has yet to be specifically addressed.

Table III. Logistic regression analyses of the variables associated with fibromyalgia in systemic lupus erythematosus patients.

Variable	Adjusted OR	95% CI	*p*-value
Age at disease onset	1.024	0.982-1.068	0.261
Age at diagnosis	0.980	0.939-1.023	0.359
Depression	6.779	4.770-9.636	<0.001
Malar rash	1.136	0.771-1.671	0.512
Discoid rash	0.925	0.609-1.405	0.925
Photosensitivity	2.184	1.431-3.334	<0.001
Oral ulcers	1.436	1.005-2.051	0.047
Corticosteroid use			
10-30 mg daily	1.392	0.845-2.292	0.194
Antimalarials			
Past	1.733	0.975-3.080	0.061
Last evaluation	1.179	0.663-2.098	0.575
Sjögren	2.447	1.662-3.604	<0.001
CHARLSON	0.996	0.890-1.114	0.939
SLEDAI	0.948	0.896-1.002	0.057

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table IV. Fibromyalgia in systemic lupus erythematosus patients literature review.

First author, year	Number of SLE patients	Study design	Main ethnic group	Prevalence of FM	FM diagnostic criteria used	Relation to SLE activity features (measures used)	Factors associated to FM (measures used)
Morand *et al*., 1994	87	Cross-sectional	Caucasian	25.3%	Yunus	None (SLAM, VAS)	NA
Middleton *et al*., 1994	102	Cross-sectional	Caucasian	22% (55%)	ACR 90 (FM-like)	None	Divorce; Recipient of medical disability benefits; Unemployed
Gladman *et al*., 1997	119	Cross-sectional	Caucasian	22%	ACR 90	None (SLEDAI)	Worse SF-36
Handa *et al*., 1998	158	Cross-sectional	Indian	8.2%	ACR 90	None (SLEDAI)	None (marital status, education level)
López-Osa *et al*., 1999	90	Prospective	Spanish	10%	ACR 90	None (Lower mean SLEDAI score in FM, p=NS)	None (Depression more prevalent in FM, p=NS)
Karaaslan *et al*., 1999	56	Cross-sectional	Turkish	25%	ACR 90	NA	NA
Friedman *et al*., 2003	246	Cross-sectional	Caucasian	5% (13%)	ACR 90 (FM-like)	None (SLAM)	Caucasian ethnicity; Anxiety; Depression
Valencia-Flores *et al*., 2004	106	Cross-sectional	Mexican	9.5%	ACR 90	None	Dysmenorrhoea; Sleep disturbances
Akkasilpa *et al*., 2005	173	Cross-sectional	Caucasian	17.3%	>10 FM-Tender points	NA	Lower HAQ
Wolfe *et al*., 2009	834	Survey, cross-sectional	United States population NDB)	22.1%	FM Survey Criteria (SI)	None (SLAQ, in only in 458 participants; and SLESS)	-
Torrente-Segarra *et al*., 2010	84	Cross-sectional	Caucasian	35.7%	ACR 90	None (SLEDAI, clinical and serological markers)	Anxiety Depression
Haliloglu *et al*., 2014	67	Cross-sectional	Turkish	13.4%	ACR 90	None (SLEDAI)	Women

ACR: American College of Rheumatology; FM-like: clinical symptoms of fibromyalgia without meeting ACR criteria for the presence of FM; NDB: National Data Bank for Rheumatic Diseases; HAQ: Health Assessment Questionnaire; NA: not assessed; NS: non-significant statistically; SI: Symptom Intensity scale (a combination score of Regional Pain Scale and Visual Analogue Fatigue Scale); SLAQ: Systemic Lupus Activity Questionnaire; SLAM: Systemic Lupus Activity Measure; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLESS: Systemic Lupus Erythematosus Symptom Scale.

FM in SLE patients leads to poorer self-reported health assessments, as has been previously described (6, 7, 8, 9), even in early stages of SLE. Alarcon GS *et al*. (8) demonstrated several poor quality-of-life indicators in a LUMINA cohort, a multi-ethnic group of SLE patients with an SLE duration of less than five years, FM among those reported. Hence, as SLE remains a global disease, and since the prevalence of FM might rise, physicians must be vigilant in recognising the onset of FM once depression and widespread pain coexist. Recently, high pain scores in SLE patients has been linked with deteriorating quality of life, fatigue, anxiety and depression (30).

In a search of the literature, we did not find any studies of similar design or sample size (6, 7, 10, 15, 21, 31-37). One prospective study included 90 patients, although no statistical differences were found between FM and non-FM SLE patients in terms of activity measures and other related factors (35). In the literature, the prevalence of FM in SLE patients varies from 5 to 65%, which is most likely due to the different designs and FM criteria applied in each study. We can conclude, as other authors have also found, that the most pertinent factors relating to the presence of FM in SLE patients do not derive from SLE in and of itself. Indeed, depression, anxiety, female sex and Caucasian ethnicity are the factors most frequently proposed as relevant. Moreover, some authors have suggested that various individual and societal factors – such as divorce, state welfare benefits, unemployment, and the presence of dysmenorrhoea and sleep disturbances – may play a role in the development of FM in SLE patients (each of the above was noted in separate publications).

The present study has several limitations: a) FM and depression were defined as being present at some stage over the course of SLE without knowledge of the exact onset date; b) Depression was only included as a confounding factor in those SLE cases in which the patient was receiving psychiatric

assistance or a specific treatment. Thus, its prevalence might have been underestimated, as other authors have found higher prevalence rates when using specific questionnaires and structured clinical interviews (31); c) the cross-sectional design of our study left us unable to confirm the causality of the association between FM and depression or FM and SLE minor mucocutaneous manifestations.

In conclusion, we performed a cross-sectional study based on a large group of Caucasian SLE patients from the RELESSER-T Registry in order to assess FM prevalence and related factors. We observed a prevalence of FM in Caucasian SLE patients up to 6.9%. We found depression to be, by far, the principal concomitant factor associated with FM in SLE. Of all the SLE-related manifestations, serological markers and activity indices, only the presence of photosensitivity, oral ulcers and secondary SS were related to FM. Depression might play a more important role in the pathogenesis of FM during the late stages of SLE, an effect great than that exerted by SLE activity in and of itself. Indeed, depression is more frequent during the later stages of SLE. Several comorbidities such as dyslipidaemia, arterial hypertension and autoimmune thyroiditis could also be related to the presence of FM, although further studies should be performed to clarify this point. Our observations are in accordance with previous investigations by other authors. However, this study boasts by far, the largest number of SLE patients.

Acknowledgements

The authors would like to thank Mrs Mª Jesús García de Yébenes for her work in coordinating the RELESSER-T Registry.

The authors would like to thank all of the investigators who participated in the RELESSER-T Registry patient enrolment at all the Spanish treatment centres: Ricardo Blanco, Paloma Vela-Casasempere, Rafael Melero-González, Teresa Otón-Sánchez, Eva Tornero-Muriel, Esther Uriarte-Isacelaya, Mercedes Freire-González, María Concepción Fito-Manteca, Antonio Fernández-Nebro, Javier Narváez, Antonio Zea-Mendoza, José Carlos Rosas-Gómez de Salazar, Mónica Ibáñez-Barceló, José J. Pérez-Venegas, Inmaculada de la Torre Ortega, Luis Carreño Pérez, Patricia Carreira Delgado, Esther Rodríguez-Almaraz, Esteban Salas Heredia, Gregorio Santos Soler, Carlos Santos Ramírez, José M. Senabre Gallego, Mariano Andrés Collado, José Antonio Bernal, Inmaculada Ros Vilamajó, Antonio Juan Mas, Claudia Murillo, Ivan Castellví Barranco, Emma García Melchor, Joan Calvet Fontova, María García Manrique, Carlos Galisteo Lencastre, Mireia Moreno Martínez-Losa, Raúl Menor Almagro, Miguel A. González-Gay Mantecón, Inés Pérez Martíny, M. del Carmen Bejerano, Ignacio Villa Blanco, Begoña Moreira, Elena Aurrecoechea, Teresa Ruiz Jimeno, Ángeles Aguirre Zamorano, César Magro, Enrique Raya Álvarez, Celia Erausquin Arruabarrena, M. Ángeles Acosta Mérida, Cesar A. Egües Dubuc, Jorge Cancio Fanlo, Elvira Díez Álvarez, Carlos Vitovi, Alejandra López Robles, Tomás Vázquez Rodríguez, M. Victoria Irigoyen Oyarzábal, M. Ángeles Belmonte López, Carmen M. Romero Barco, Juan Antonio Martínez López, Olga Sánchez Pernaute, Txaro García de Vicuña Pinedo, Marta Valero Expósito, Paloma García de la Peña, Silvia Rodríguez Rubio, Jorge J. González Martín, Ana Pérez Gómez, Cristina Bohórquez, Atusa Morasat Hajkhan, Ana I. Turrión Nieves, Ana J. Lois Iglesias, Aline Lucice Boteanu, M. Luz Gamir Gamir, Patricia Richi Alberti, Santiago Muñoz Fernández, María Rosario Oliva, Claudia Stoye, Íñigo Hernández Rodríguez, Coral Mouriño Rodríguez, Bruno de Aspe de la Iglesia, Ruth López González, Federico Navarro Sarabia, Francisco J. Toyos Sáenz de Miera, José Luis Marenco de la Fuente, Julia Uceda Montañés, Raquel Hernández Sánchez, Rosalía Martínez Pérez, Beatriz Rodríguez Lozano, Eduardo Úcar Angulo, M. Esther Ruiz Lucea, Luis López Domínguez, Juan J. Alegre Sancho, Isabel de La Morena Barrio, Elia Valls, Javier Manero Ruiz, Víctor E. Quevedo Vila, Sergio Machín, Javier Nóvoa, and Lucia Silva Fernández.

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