

Fibromyalgia, Systemic Lupus Erythematosus (SLE), and Evaluation of SLE Activity

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ABSTRACT. Objective. To determine if fibromyalgia (FM) or fibromyalgia-ness (the tendency to respond to illness and psychosocial stress with fatigue, widespread pain, general increase in symptoms, and similar factors) is increased in patients with compared to those without systemic lupus erythematosus (SLE); to determine whether FM or fibromyalgia-ness biases the SLE Activity Questionnaire (SLAQ); and to determine if the SLAQ is overly sensitive to FM symptoms.

Methods. We developed a 16-item SLE Symptom Scale (SLESS) modeled on the SLAQ and used that scale to investigate the relation between SLE symptoms and fibromyalgia-ness in 23,321 patients with rheumatic disease. FM was diagnosed by survey FM criteria, and fibromyalgia-ness was measured using the Symptom Intensity (SI) Scale. As comparison groups, we combined patients with rheumatoid arthritis and noninflammatory rheumatic disorders into an “arthritis” group and also utilized a physician-diagnosed group of patients with FM.

Results. FM was identified in 22.1% of SLE and 17.0% of those with arthritis. The SI scale was minimally increased in SLE. The correlation between SLAQ and SLESS was 0.738. SLESS/SLAQ scale items (Raynaud’s phenomenon, rash, fever, easy bruising, hair loss) were significantly more associated with SLE than FM, while the reverse was true for headache, abdominal pain, paresthesias/stroke, fatigue, cognitive problems, and muscle pain or weakness. There was no evidence of disproportionate symptom-reporting associated with fibromyalgia-ness. Self-reported SLE was associated with an increased prevalence of FM that was unconfirmed by physicians, compared to SLE confirmed by physicians.

Conclusion. The prevalence of FM in SLE is minimally increased compared with its prevalence in patients with arthritis. Fibromyalgia-ness does not bias the SLESS and should not bias SLE assessments, including the SLAQ. (First Release Nov 1 2008; J Rheumatol 2009;36:82–88; doi:10.3899/jrheum.080212)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

SYSTEMIC LUPUS ACTIVITY MEASURE

SYSTEMIC LUPUS ERYTHEMATOSUS ACTIVITY QUESTIONNAIRE

FIBROMYALGIA

Systemic lupus erythematosus (SLE) can be difficult to diagnose with current criteria^{1,2}, when it is necessary to rely on “soft” findings or difficult to validate signs and symptoms, and it is often the case that uncertainty lies over an SLE diagnosis in some patients. Similarly, assessing SLE activity can also be problematic. One problem relating to both diagnosis and activity is the presence of fibromyalgia

(FM), either as a separate confounding diagnosis or as a confounder of lupus activity. Uncertainty arises because fatigue, aching, and other somatic symptoms can be found in both SLE and FM.

The issue of SLE and FM has been approached by a number of investigators³⁻⁹. Two approaches to the problem have included trying to distinguish persons with FM from those with SLE, and identifying persons with SLE who also have FM. Implicit in these approaches is the assumption that FM is, or can be treated as, a separate entity. As a separate entity, FM can “cause” or be responsible for some SLE symptoms. For example, under the distinct-entity assumption a patient who has FM may experience increased fatigue because of FM.

Even though FM is a diagnostic entity recognized by the American College of Rheumatology (ACR) classification criteria¹⁰ and may have value in clinical medicine, there are sufficient clinical and epidemiological data to show that FM does not exist as a separate entity, but rather represents the end of a pain-distress spectrum¹¹⁻¹⁴. We have recently shown that the prevalence and intensity of FM-related

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symptoms — something that we call “fibromyalgia-ness” — may be thought of as a latent variable that exists as a continuum across all rheumatic diseases, and that it functions as a response to illness and illness distress¹⁵⁻¹⁷. Fibromyalgia-ness is the tendency to respond to illness and psychosocial stress with fatigue, widespread pain, general increase in symptoms, and similar factors¹⁶, and can be measured on a continuous scale using the Symptom Intensity (SI) Scale. Measurement of fibromyalgia-ness with the SI scale increases the ability to assess FM-like characteristics in SLE, and avoids the dichotomizing problem created by FM diagnosis and described by Altman and Royston¹⁸, who indicate that when dichotomizing continuous states, “Individuals close to but on opposite sides of the cut point are characterised as being very different rather than very similar”.

We examined the relation between FM diagnosis and fibromyalgia-ness and SLE in order to address 3 questions: Is FM and fibromyalgia-ness increased in SLE? To what extent are SLE diagnostic and activity symptoms influenced by FM and fibromyalgia-ness? Are SLE diagnosis and activity assessments biased by FM or fibromyalgia-ness?

MATERIALS AND METHODS

Patient population. We studied participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. NDB participants are diagnosed by United States rheumatologists and are recruited from their practices. Patients are followed prospectively with semiannual, detailed, 28-page questionnaires, as described^{19,20}. SLE patients were enrolled largely by rheumatologist referral, but also by self-referral. After enrollment of self-referred patients, we sought to obtain each patient’s consent to verify the diagnosis with the patient’s physician. SLE patients with a nonverified or pending verification of diagnosis were excluded from the main study. The physicians who referred or confirmed the diagnosis were rheumatologists in 96.3% of cases. However, we also determined the prevalence of FM in diagnosis-verified patients with SLE (N = 834) as well as in all enrolled SLE patients in a separate analysis. All patients diagnosed as having SLE completed the common set of NDB assessments in addition to specific SLE assessments. Enrollment of patients into the NDB was begun in 1998 and continues to date. When patients completed more than one semiannual survey questionnaire, we selected the last questionnaire for analysis.

We examined data from 23,231 adult patients with rheumatic disease after excluding 221 with nonverified self-reported SLE. Of the diagnoses, 834 had physician-verified SLE, 2307 had FM, 16,884 had rheumatoid arthritis (RA), and 3206 had a noninflammatory rheumatic disorder that was not FM.

To determine the prevalence of FM in SLE we used FM survey criteria^{15,16,21}. By these criteria, persons with scores ≥ 8 on the Regional Pain Scale (RPS)¹⁷ and ≥ 6 on the visual analog fatigue scale²² (VAS) are classified as having FM. The RPS is a self-report count of nonarticular regions^{17,21}. The SI scale measures fibromyalgia-ness. Derived from the fatigue and RPS scales, the SI scale combines these 2 measures in continuous form according to the following formula¹⁶: $[\text{VAS fatigue} + (\text{RPS}/2)]/2$. This yields a scale with a 0 to 9.75 range. For the comparison of SLE symptoms in SLE and FM patients, we used diagnoses of FM supplied at the time patients enrolled into the NDB. Patients with FM did not have a simultaneous diagnosis of SLE or a noninflammatory rheumatic disorder.

In addition to the SI scale, 458 patients with SLE participating in the

NDB in January 2007 completed the Systemic Lupus Activity Questionnaire (SLAQ)²³. The SLAQ is a validated²⁴ 24-item questionnaire that reduces to 17 items for scoring and has a range of 0–44. In addition, the SLAQ contains a single-item 0–10 rating scale for lupus activity and a rating scale for lupus flare (no flare, mild flare, moderate flare, severe flare). The SLAQ is a patient-reported version of the physician-reported Systemic Lupus Activity Measure (SLAM)²⁵. However, the SLAQ is a new instrument and has only been reported on twice^{23,24}.

To assess a similar lupus measure in non-SLE patients we constructed the Systemic Lupus Erythematosus Symptom Scale (SLESS) based on symptoms occurring in the previous 6 months reported by patients on the NDB semiannual questionnaire that was developed in 1998. Using scoring rules similar to those for the SLAQ, we constructed a 16-item count of symptoms. We had 16 items rather than 17 because we did not have data on adenopathy. Additionally, data for the SLESS were dichotomous rather than scaled, and the SLESS timeframe was 6 months instead of the 3 months used in the SLAQ. The range of values for the SLESS was 0–16 and items of the SLESS are shown in Table 1 and Figures 1 and 2. The specific question used to elicit responses was, “During the past 6 months have you had any of the following symptoms?” Then the checklist of 56 symptoms were listed. In this scale the following items were endorsed by patients: mouth sores; headache; chest pain; shortness of breath; loss of appetite; pain or discomfort in upper abdomen (stomach); pain or cramps in lower abdomen (colon); joint pain; joint swelling; muscle pain; weakness of muscles; depression; seizures or convulsions; tiredness (fatigue); trouble thinking or remembering; hives or welts; rash; loss of hair; red, white, and blue skin color changes in fingers on exposure to cold or with emotional upset; sun sensitivity (unusual skin reaction, not sunburn); and fluid-filled blisters. Stroke information was obtained from a specific stroke question. Mouth sores, rash, and sun sensitivity (unusual skin reaction, not sunburn) were combined into a single variable, as were chest pain and dyspnea, stroke and paresthesias, hives or welts and fluid-filled blisters, numbness/tingling/burning and stroke, depression and trouble thinking or remembering, muscle pain and weakness, joint swelling and joint pain, pain or discomfort in upper abdomen (stomach) and pain or cramps in lower abdomen (colon). The full questionnaire is available at <http://www.arthritis-research.org/documents/Ph50RAFIB.pdf> [verified Aug 21 2008].

Statistical methods. Differences in group means for diagnostic groups were tested using linear regression (Table 1). Differences between groups for SLESS items were analyzed by logistic regression and given as odds ratios and 95% confidence intervals (Figures 1 and 2). Data analysis included logistic regression in univariable and multivariable analyses. We also used fractional polynomial regression to test whether a nonlinear model of the regression of SLESS on the SI scale was superior to a linear model. We combined the RA and noninflammatory rheumatic disorders into a single group, “arthritis,” for most analyses, as results were similar in these groups. Data were analyzed using Stata (Stata, College Station, TX, USA) version 10.0. Statistical significance was set at the 0.05 level, confidence intervals were established at 95%, and all tests were 2-tailed.

RESULTS

Demographic, severity, and treatment characteristics. The mean (SD) age of the 458 SLE participants completing the SLAQ was 50.4 (12.3) years, and 95.3% were women. Current therapies included hydroxychloroquine (64.1%), prednisone (49.4%), methotrexate (12.3%), rituximab (0.8%), mycophenolate mofetil (11.8%), azathioprine (11.0%), cyclophosphamide (11.2%), and leflunomide (1.9%).

The mean composite SLAQ score and the single-item SLAQ activity score was 12.1 (7.6) and 3.8 (2.8), respectively. A mild, moderate, and severe SLE flare was reported

Table 1. Severity, SLE symptoms, and fibromyalgia-related scales.

Variables	Fibromyalgia, mean (SD)	SLE, mean (SD)	RA + NIRD (Arthritis), mean (SD)
No. of participants	2397	834	20,096
SLE Symptom Scale (SLESS) (0–16)	7.3 (3.0)	7.2 (3.7)*	4.5 (3.0)
Symptom Intensity (SI) scale (0–9.75)	5.8 (2.3)	4.0 (2.5)*†	3.6 (2.3)
Regional Pain Scale (RPS) (0–19)	10.7 (5.6)	6.8 (5.6)*†	5.6 (5.1)
Fatigue scale (0–10)	6.3 (2.7)	4.6 (3.0)†	4.5 (3.0)
Patient global (0–10)	5.0 (2.5)	3.6 (2.6)†	3.7 (2.5)

* $p < 0.05$ compared with arthritis. † $p < 0.05$ compared with fibromyalgia. NIRD: Noninflammatory rheumatic disorders.

by 34.1%, 22.0%, and 9.1% during the preceding 3 months. Alpha reliability of SLAQ score items was 82.5. The SLESS score was 7.5 (3.6), range 0–15, and its alpha reliability in the same SLE group was 83.9. The SLAQ score and SLESS were correlated at $r = 0.738$, and the strength of association was not improved by nonlinear transformations.

As the SLESS and SLAQ scores were highly correlated, we next undertook a series of analyses using the SLESS to evaluate the relation of SLE symptoms and FM in patients with SLE, arthritis, and FM. The mean age and percentage of men for the 3 diagnostic groups were as follows: SLE 50.3 (13.6) years, 6.2% male; FM 56.8 (12.9) years, 4.7% male; and arthritis 57.9 (10.3) years, 22.8% male.

SLESS levels in SLE, FM, and arthritis. As a preliminary to evaluating the relationship between SLE and FM, we first examined the level of SLE symptoms and other symptoms in SLE and arthritis patients (Table 1). Not surprisingly, as the SLESS was designed to evaluate SLE symptoms, the SLESS score was considerably greater in SLE patients compared with those with arthritis, 7.2 (3.7) versus 4.5 (3.1) ($p < 0.001$; Table 1). However, there was no difference in

SLESS scores in patients with SLE compared with FM [7.2 (3.7) vs 7.3 (3.0)].

Analysis of SLE symptoms across diagnostic groups. We examined the prevalence of SLESS items in the diagnostic groups (Table 2, Figures 1 and 2). For ease of understanding the arthritis group contribution, we show the group split into its constituent components (RA and noninflammatory rheumatic disorders) in Table 2, which provides descriptive data; Figures 1 and 2 provide odds ratios and confidence intervals. Comparing SLESS items in SLE and arthritis patients, Figure 1 and Table 2 show that all symptoms were more common in SLE than in RA and noninflammatory rheumatic disorders, but Raynaud's phenomenon (RP), rash, and fever were particularly increased.

We next compared the relative association of SLESS items with the diagnosis of SLE and FM. As shown in Figure 2, headache, abdominal pain, stroke or paresthesias, fatigue, cognitive problems, and muscle pain/weakness are more common in FM than SLE, and RP, rash, fever, easy bruising, and hair loss are more common in SLE. The horizontal lines in Table 2 separate the variables that are more or

Table 2. Percentages of patients positive for SLE Symptom Scale (SLESS) by diagnostic category.

Condition	Symptom	SLE, N = 834	FM, N = 2397	RA, N = 16,884	NIRD, N = 3206
More common in SLE than FM ($p < 0.05$)	Raynaud's	39.5	18.2	9.2	6.0
	Rash	62.6	37.9	25.4	20.0
	Fever	18.6	12.3	5.4	4.0
	Easy bruising	60.0	47.7	42.0	37.2
	Hair loss	31.7	23.8	17.4	13.0
Equally common in SLE and FM ($p > 0.05$)	Rash (other)	15.4	14.2	7.0	5.7
	Shortness of breath	39.3	38.1	24.0	24.4
	Seizures	1.4	1.4	0.6	0.6
	Anorexia	20.6	21.4	12.8	9.7
	Joint pain or swelling	79.9	81.0	74.8	76.6
More common in FM than SLE ($p < 0.05$)	Headache	53.4	62.1	29.2	28.6
	Abdominal pain	41.1	53.8	23.7	24.9
	Stroke/paresthesias	54.0	67.4	37.1	40.4
	Fatigue	77.2	86.0	59.4	55.0
	Cognitive problems	57.4	72.6	38.3	39.3
	Muscle pain or weakness	65.5	88.5	47.5	48.6

SLE: systemic lupus erythematosus, FM: fibromyalgia, RA: rheumatoid arthritis, NIRD: noninflammatory rheumatic disorders.

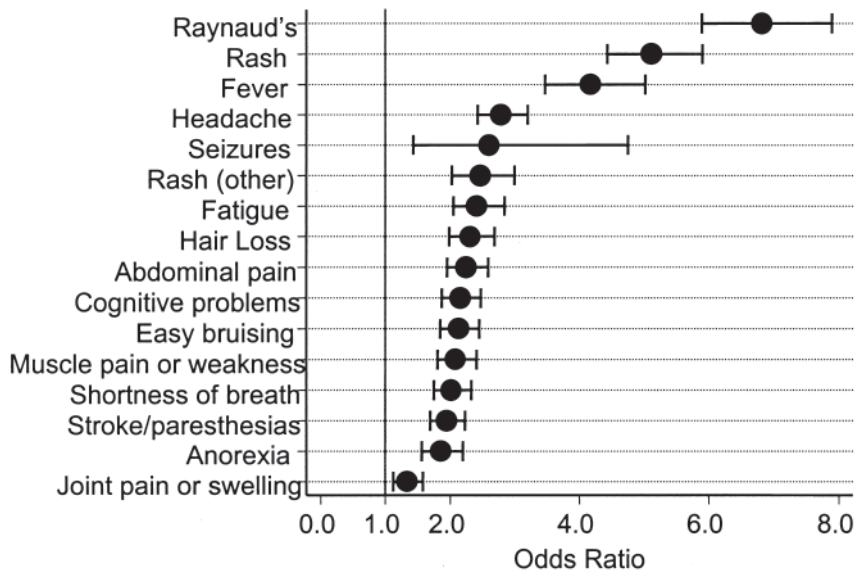


Figure 1. SLE Symptom Scale (SLESS) items in 20,141 patients with arthritis compared with 961 with SLE. Arthritis is defined as rheumatoid arthritis (N = 16,910) or noninflammatory rheumatic disorders (N = 3231). Odds ratios and 95% confidence intervals are represented by dots and their corresponding bracketed horizontal lines.

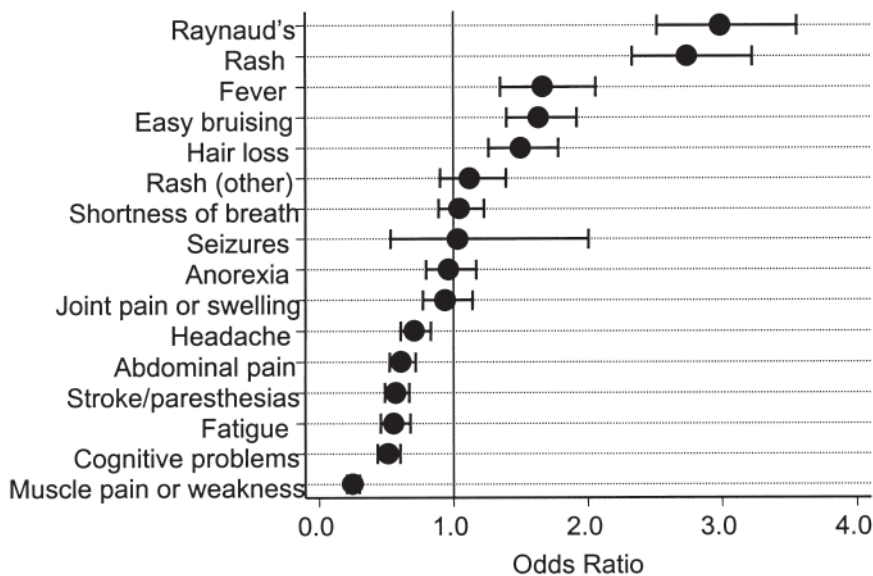


Figure 2. SLE Symptom Scale items in 2409 patients with FM compared with 961 with SLE. Odds ratios and 95% confidence intervals are represented by dots and their corresponding bracketed horizontal lines.

less common in SLE compared with FM. Overall, these analyses define sets of variables found in the SLESS and the SLAQ that are more and less associated with FM in patients with SLE.

Fibromyalgia-ness and FM in SLE. We used the SI scale to measure the extent of FM symptoms in patients in the different diagnostic groups (Table 1). The SI score was minimally, but significantly, increased (0.4 units) in SLE com-

pared with arthritis, but was substantially increased in FM (2.2 units) compared with arthritis. The distribution of fibromyalgia-ness among the 3 diagnostic groups is shown in Figure 3, where the distributions can be seen to be similar in SLE and arthritis, but shifted to the right in FM. In addition, using the suggested cutoff for diagnosis of survey FM of ≥ 8 for the RPS and ≥ 6 for VAS fatigue, 22.1% of SLE patients and 17.0% of arthritis patients would satisfy

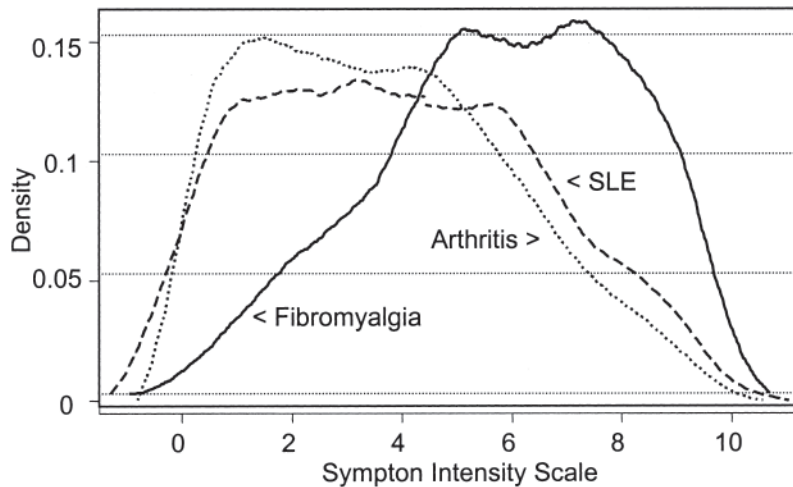


Figure 3. The distribution of Symptom Intensity Scale scores, a measure for fibromyalgia-ness, in 961 patients with SLE, 2409 with FM, and 20,141 with "arthritis." In this figure, arthritis represents rheumatoid arthritis (N = 16,910) or noninflammatory rheumatic disorders (N = 3231). Plots are kernel-density estimates.

those criteria. When data only from women were analyzed, the respective proportions were 22.0% and 18.3%. These data indicate a small increase in the prevalence of survey FM in SLE compared to arthritis and a minimal increase in fibromyalgia-ness.

Are SLE symptom scales biased by FM content? As shown above, the SLAQ and SLESS scales are mixtures of symptom items, some of which are more likely to be endorsed by patients with FM and some by patients with SLE. We studied the ratio of the FM items (headache, abdominal pain, paresthesias/stroke, fatigue, cognitive problems, muscle

pain or weakness) to the SLE items (RP, rash, fever, easy bruising, hair loss) at different levels of the SI scale to determine if the ratio was constant over different levels of fibromyalgia-ness in patients with SLE. As shown in Figure 4, the ratio was constant over the range of SI scores, and there was no evidence of a disproportionate FM symptom-reporting associated with increasing fibromyalgia-ness. In addition, we examined the relation between the SLESS and the SI scale in a fractional polynomial regression of SLESS on the SI scale. The nonlinear model was not significantly better ($p = 0.087$). These data indicate that SLE symptoms

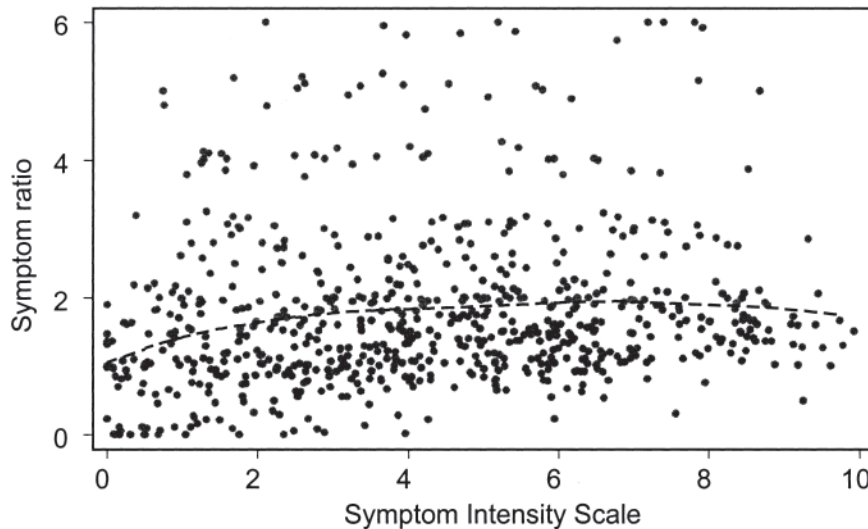


Figure 4. Ratio of the count of FM symptoms to SLE symptoms from the SLESS as a function of fibromyalgia-ness (SI scale) in SLE, displayed using Lowess regression. FM symptoms from the SLE Symptom Scale are headache, abdominal pain, paresthesias/stroke, fatigue, cognitive problems, and muscle pain or weakness; and SLE symptoms are Raynaud's phenomenon, rash, fever, easy bruising, and hair loss. The figure shows that the ratio is constant over the range of the SI scale.

scales and the SLESS scores are not biased by the degree of fibromyalgia-ness in patients with SLE.

Fibromyalgia in self-reported, but unconfirmed diagnoses of SLE. Although patients with unconfirmed SLE were excluded from the above analyses, there is a general interest in whether patients reporting to physicians that they have been diagnosed with SLE might have a high prevalence of FM. We found that self-reported SLE was associated with an increased prevalence of FM when unconfirmed by physicians, compared to confirmed SLE. Survey FM was found in 22.1% of confirmed SLE and 33.4% not confirmed or not yet confirmed.

DISCUSSION

We have shown elsewhere¹⁶ that the latent concept of fibromyalgia, here measured by the SI scale, represents a general human response to illness and stress, and, as such, is influenced by illness severity and sociodemographic characteristics. Therefore, we should expect to find a proportion of patients with high levels of fibromyalgia-ness in all rheumatic diseases. Using survey FM criteria, 22.1% of patients with SLE and 17.0% of patients with arthritis could be diagnosed as having FM.

A better sense of fibromyalgia-ness in SLE that does not rely on arbitrary cutpoints can be seen in Figure 3, in which patients with SLE differ from those with arthritis by a slight shifting of the distribution curves to the right. Based on these data it appears that arthritis and SLE are similar with respect to FM prevalence and fibromyalgia-ness; however, prevalence is increased slightly in SLE compared to arthritis. This difference could represent a real difference based on the nature of SLE or could represent diagnostic differences among physicians, a sampling effect.

The issue of FM and fibromyalgia-ness intrudes into diagnosis when SLE “soft” criteria items are used to satisfy classification criteria, and patients with FM report more symptoms than those without FM (Tables 1 and 2). The ACR SLE criteria^{1,2}, which require at least 4 positive items and which may be obtained historically, include photosensitivity, oral or nasopharyngeal ulcers, pleuritis or pericarditis, and seizures. In the presence of a positive antinuclear antibody, only 3 of the above items are required. As shown in Table 2 and described above, persons with FM report these findings more frequently than those with RA and noninflammatory rheumatic disorders. The symptom increase in FM appears to be important: we noted that survey FM prevalence in self-referred patients with SLE was 33.4% compared with 22.1% for self-referred patients with physician-confirmed diagnosis. This reinforces the need for skilled professional diagnosis in SLE. The SLE criteria are currently being revised and elimination of some of the softer items is a distinct possibility.

The evaluation of SLE activity is also complex. Of the 5 SLE-specific items we identified, only one is represented as

an ACR SLE criteria item, and only 2 are part of the SLE Disease Activity Index (SLEDAI)²⁶. Among the concerns associated with the SLAQ and SLAM is that the items of the SLAQ score, and some in the underlying SLAM, are self-reported and therefore may be distorted by the symptoms that are common in FM. However, when we examined FM from the point of view of fibromyalgia-ness (SI scores), we did not find a disproportionate increase in SLESS or SLAQ scores in patients with SLE or in the ratio of SLE to FM variables (Figure 4). Instead, we found smooth increase in both SLAQ and SI scale scores ($r = 0.676$) and between SLESS and SI scale ($r = 0.623$). Figure 3 offers further insight into this issue, for it can be seen that there is little difference between the distributions in the SI scale in patients with arthritis and patients with SLE, while the scale is shifted to the right in patients diagnosed with FM.

The prevalence of FM in SLE has been the subject of a number of investigations. Middleton, *et al*³ studied 102 patients from a public hospital SLE clinic; 22 (22%) met the ACR criteria for FM¹⁰, and another 24 (23%) had clinical FM but did not meet the classification criteria. Gladman, *et al* found a prevalence of 22% in 119 clinic patients with SLE⁴. In the John Hopkins Lupus Cohort, 17.3% of 173 SLE patients had ≥ 11 tender points⁵. In an Indian tertiary referral center cohort, Handa, *et al* found FM in 8.2% of 158 patients⁶. In a Mexican clinic, Valencia-Flores, *et al* reported 9.5% of 106 SLE patients satisfied ACR criteria⁷. In the LUMINA (Lupus in Minorities) study, Friedman, *et al* reported a prevalence of FM of 5% in 266 patients with SLE⁸. Finally, Neumann and Buskila reported that up to 65% of patients with SLE have FM⁹.

The accuracy of the ACR FM criteria depends on the pressure and technique of the examiner during the tender point examination, which in turn depends on the training of the examiner. Data from the original ACR criteria study showed considerable interexaminer variability, even with training. It seems likely that the very wide differences in prevalence among clinics is a function of the examiner rather than SLE itself. The advantage of removing the examiner from the diagnostic equation by using the SI scale and survey FM criteria is to remove such bias. In addition, this method allows large groups of patients to be studied and reduces costs. Using survey criteria, we noted that 22.1% of SLE patients satisfied these criteria. Even so, criteria are inherently flawed because the use of a cutpoint, whether in survey criteria or through the use of the tender point count in the ACR FM criteria, results in an artificial separation of patients with very similar characteristics¹⁸, for example those FM-positive patients with 11 tender points and those FM-negative patients with 10 tender points.

A better approach, we believe, is to use the SI scale as a continuous scale, as it eliminates all the problems noted above. The SI scale is the most sensitive and best correlated index available for FM-associated variables¹⁶. One would

expect, given the FM prevalence of 22.1% in SLE and 17.0% in arthritis, that the SLE patients would score slightly higher for the SI scale compared with arthritis patients, but that FM patients would have still higher scores, and that is what we found.

The SI scale also allows us to test the association between fibromyalgia-ness and SLE activity rather than dichotomizing SLE patients into FM-positive and FM-negative subjects. The correlation between fibromyalgia-ness (SI scale) and SLE activity (SLAQ) was 0.676. This finding of the association between an activity scale and the SI scale is constant across many rheumatic conditions.

Among the limitations of our study is that the SLESS and the SLAQ are not the same scale, and it is possible that study results might have been somewhat different if the SLAQ had been administered to all patients. In addition, the SLESS, unlike the SLAQ, cannot be considered an activity scale. However, within the context of FM associations both scales function similarly.

In summary, fibromyalgia and fibromyalgia-ness are slightly increased in patients with SLE compared to patients with arthritis. SLE activity scales are strongly correlated with measures of fibromyalgia-ness. However, there is no evidence that fibromyalgia or increased levels of fibromyalgia-ness disproportionately distort the SLE activity scales studied.

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