Patient phenotypes in fibromyalgia comorbid with systemic sclerosis or rheumatoid arthritis: influence of diagnostic and screening tests. Screening with the FiRST questionnaire, diagnosis with the ACR 1990 and revised ACR 2010 criteria

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ABSTRACT

Objective. *Fibromyalgia (FM) may occur with rheumatoid arthritis (RA) and systemic sclerosis (SSc), and debate remains about its diagnosis. We aimed to use three FM tools (a screening tool (FiRST), diagnostic criteria (ACR 1990 and revised 2010), to compare FM prevalence between RA and SSc patients, to describe the phenotypes of patients with comorbid FM, and to analyse links between FM and secondary Sjögren's syndrome (SS).*

Methods. *Consecutive adult patients with confirmed RA or SSc from four university hospitals were tested with the three FM tools.*

Results. *FiRST detected FM in 22.6% of the 172 RA patients, with confirmation in 22.1% (ACR1990) and 19.1% (ACR2010). ACR1990FM+ RA patients had more diffuse pain, whereas ACR2010FM+ RA patients had higher BMI and pain intensity, more diffuse pain, active disease, disability, and associated SS. FiRST detected FM in 27.8% of the 122 SSc patients, with confirmation in 30.3% (ACR1990) and 23.7% (ACR2010). ACR1990FM+ SSc patients had greater disability and pain intensity, and more diffuse pain, whereas ACR2010FM+ SSc patients had higher BMI, pain intensity, more disability and diffuse pain, and associated SS. Correlations between FM diagnostic and screening tool results were modest in both conditions. Secondary SS was associated with comorbid FM.*

Conclusion. *The prevalence of FM is high in SSc and RA, whatever the FM diagnostic tool used. Secondary SS is associated with FM in both RA and SSc. The revised ACR 2010 FM criteria and FiRST screening tool reveal specific phenotypes potentially useful for improving disease management.*

Introduction

Fibromyalgia (FM) is a frequent chronic pain condition in the general population (1, 2), and in the rheumatology setting (3). It may occur in isolation, but is also frequently associated with other pain conditions, particularly those of a rheumatic nature (4-7). Comorbid FM may affect disease activity scores, such as DAS28 in rheumatoid arthritis (RA) (8); and quality of life of other rheumatic disorders, such as systemic sclerosis (SSc) (9). Specific testing and management of FM may, therefore, be required in patients with rheumatic disease.

Most studies have used the American College of Rheumatology (ACR) 1990 criteria as a diagnostic tool for the classification of FM (10). New diagnostic criteria for FM were proposed in 2010 (the "ACR preliminary diagnostic criteria" (11). These criteria differed from the 1990 ACR criteria in three main ways: they analysed chronic widespread pain more precisely, with the Widespread Pain Index (WPI); they did not require tender point examination; and they included an assessment of fatigue, waking unrefreshed, cognitive symptoms, and somatic symptoms in general, through the Somatic Symptom Score (SSS). In 2011, a modified version of the 2010 criteria was proposed, with self-reported pain and a simplified self-reported assessment of somatic symptoms (12), for use in clinical and epidemiologic studies.

However, even the revised 2010 ACR criteria remain difficult to apply in routine practice, and a number of screening tools have been developed for the diagnosis of FM: the LFESQ (13) for screening by telephone, and the FiRST questionnaire (14) and FibroDetect (15) for clinical screening. Diagnostic and screening tools differ in their

specificity and sensitivity for detecting comorbid FM in patients with rheumatic conditions. Comorbid FM may modify the phenotype of autoimmune diseases, particularly in rheumatoid arthritis (RA) and systemic sclerosis (SSc). Secondary Sjögren's syndrome (SS) may also modify the phenotypes of RA and SSc (16, 17), and may also be associated with widespread pain. The overlap between comorbid FM and secondary SS has not been investigated in both diseases.

The aim of this study was: i) to determine the prevalence of FM in consecutive RA and SSc patients, ii) to compare the prevalence estimates obtained with the ACR 1990 and modified ACR 2010 criteria with those obtained with a screening tool, the FiRST questionnaire, iii) to define specific features of RA or SSc associated with fibromyalgia, and iv) to assess the possible overlap between secondary SS and comorbid FM.

Subjects and methods

Study overview

A population-based prevalence study was conducted during 2012, at four university hospitals. This study was cross-sectional, combining questionnaires and the clinical assessment of fibromyalgia in patients with RA and SSc.

Population

Consecutive adult patients with confirmed RA (according to ACR 2010 criteria) or SSc, according to the LeRoy and Medsger criteria for diffuse and limited subsets (18), attending four French university hospitals for routine examinations were included. Demographic and clinical characteristics were recorded: age, sex, BMI, disease duration, disease characteristics (*i.e.* diffuse or limited cutaneous SSc, disease activity *i.e.* DAS28, HAQ and SSc HAQ), pain intensity, treatment, and associated (SS). FM was diagnosed by several consecutive methods used independently: (i) physician judgment, (ii) screening for FM with the FiRST questionnaire, (iii) FM diagnosis according to ACR 1990 classification criteria and the modified ACR 2010 diagnostic criteria (with 2 sets of questions: the Widespread Pain Index and Symptom Severity Scale). All RA patients were assessed by determining painful joint counts, and performing biochemical tests and tests for specific auto-antibodies. Erosiveness was defined as erosion visible on x-rays of the hands or feet or on additional x-rays of symptomatic joints. All SSc patients underwent a physical examination (including checking for the presence of digital ulceration and skin telangiectasia in particular), laboratory testing, including routine blood tests, tests for anti-nuclear, anti-centromere, and anti-topoisomerase 1 antibodies, a chest computed tomography scan, pulmonary function tests, including measurements of forced vital capacity (FVC) and CO diffusion capacity (DLCO), and echocardiography, as part of their routine evaluation. Calcinosis was assessed by clinical examination and systematic x-rays of the hand, a common site of such damage (19). Gastro-esophageal reflux was assessed during the interview, through questions relating to the presence of clinical symptoms.

The systematic first-line clinical evaluation for secondary SS included a specific questionnaire for subjective xerophthalmia and xerostomia based on the revised American-European consensual classification criteria for SS (20) and the Schirmer-I test. The result of the Schirmer-I test was considered abnormal if no more than 5 mm of the paper was wet after five minutes. If the first-line evaluation was positive, a lip salivary gland biopsy was carried out under local anesthesia. The tissue specimens collected included at least four glands. The minor salivary glands (obtained through mucosa of normal appearance) were evaluated by an expert pathologist blind to the diagnosis, and focal lymphocytic sialoadenitis, with a focus score ≥1 (defined as the number of lymphocytic foci per 4 mm^2 of glandular tissue - Chisholm III or IV), was required for the diagnosis of Sjögren's syndrome. No salivary scintigraphy results were available for this study.

Table I. Demographic and clinical characteristics of SSc and RA patients.

	SSc n=122	RA n=172	
Age	57.5 ±12	54.4 ±15	NS
Sex ratio (% female)	82.7%	86.1%	NS
BMI (kg/m^2)	25.6 ± 5.6	25.7 ± 5.8	NS
Disease duration (years)	10.9	15.5	p=0.002
HAQ	0.89 ± 0.76	0.97 ± 0.85	NS
DAS28	Not appropriate	3.23 ± 1.46	
Pain intensity (cm VAS)	4.4 ± 2.8	4.8 ± 5.0	NS
FiRST screening tool for FM	27.8%	22.6%	NS
ACR 1990 criteria for FM	30.3%	22.1%	NS
Modified ACR 2010 criteria for FM	23.7%	19.1%	NS
Sjögren's syndrome	21.3%	20.9%	NS

Ethics approval

The study was approved by the CPP #1 Ile de France Research Ethics Committee. Written informed consent was obtained from patients before clinical examination for FM screening.

Statistical analyses

For RA and SSc patients considered separately for quantitative values, we compared patients with and without comorbid FM in two-tailed Welch's *t*-tests, in which *p*-values less than 0.05 were considered significant. For qualitative values, we used Pearson's Chi-squared test with Yates' continuity correction. Relationships between two dichotomous variables in patients with or without comorbid FM were analysed with Fisher's exact test. Agreement between the results of the diagnostic and screening tests was assessed by determining Cohen's kappa coefficient (21), a statistic measuring inter-rater agreement for qualitative (categorical) items. Statistical analyses were performed by the Biostat-TGV calculator.

Results

In total, 294 consecutive patients were recruited (Table I): 172 RA and 122 SSc patients. FM was diagnosed (ACR1990)

in 25.5% of all patients, in 30.3% of SSc patients and in 22.1% of RA patients, with no significant difference (p=0.24) between the two conditions.

Prevalence of FM in RA and SSc patients, according to diagnostic and screening FM tests (Fig. 1a and 1b)

In total, 172 patients (12.2% men, 54.4±15.11 years old) were recruited to the RA group (Fig. 1a). FM was detected by the FiRST questionnaire in 39 patients (22.6%), and confirmed with ACR 1990 criteria in 38 patients (22.1%) and with modified ACR 2010 criteria in 33 (19.1%) patients. The overlap between the criteria of the different classifications was modest (Fig. 1a): 19 participants met both the ACR 1990 and modified ACR 2010 criteria for FM, and only 13 participants met both sets of FM diagnostic criteria and the FM screening test criteria.

In total, 122 patients (13.9% men, 58.2±12.1 years old) were recruited to the SSc group: 54 with limited cutaneous SSc and 66 with diffuse cutaneous SSc. FM was detected by the FiRST questionnaire in 34 patients (27.8%), and confirmed with ACR 1990 criteria in 37 patients (30.3%) and with ACR modified 2010 criteria in 29 patients (23.7%). The overlap between the criteria of the different classifications was modest (Fig. 1b): 21 patients met both sets of diagnostic criteria for FM, and only 17 participants met both sets of diagnostic criteria for FM and the FM screening test criteria.

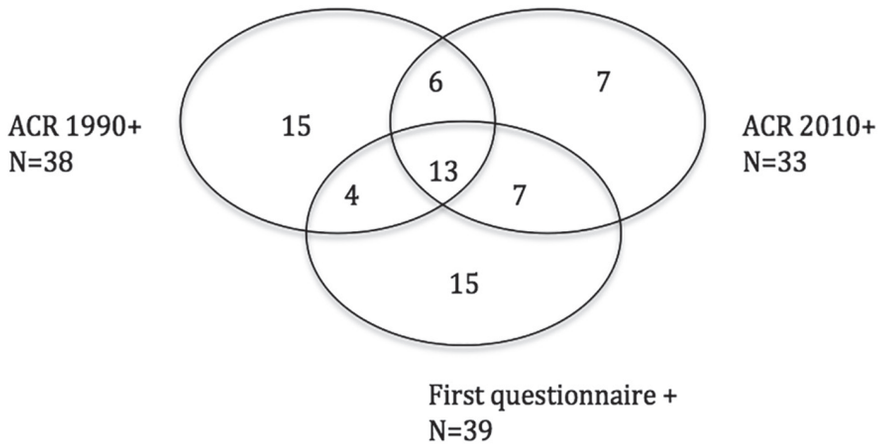

Fig. 1a. RA patients with at least one positive diagnostic or screening test result for fibromyalgia (n=67).
Overlap between the three different case definitions of fibromyalgia in the 172 RA patients: the American College of Rheumatology (ACR) 1990 criteria, the modified ACR 2010 criteria, and the FiRST questionnaire.

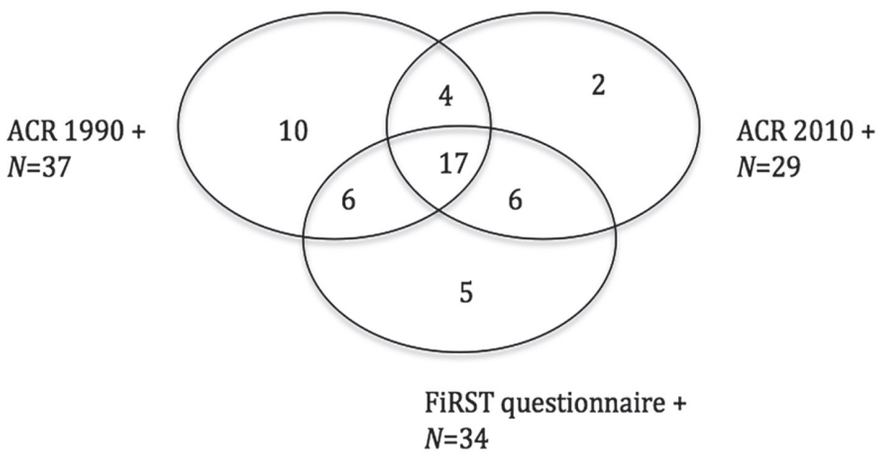

Fig. 1b. SSc patients with at least one positive diagnostic or screening test for fibromyalgia (n=50).
Overlap between the three different case definitions of fibromyalgia in the 122 SSC patients: the American College of Rheumatology (ACR) 1990 criteria, the modified ACR 2010 criteria, and the FiRST questionnaire.

Phenotype of patients with and without FM in the RA and SSc populations, according to diagnostic and screening criteria for FM

In RA patients, meeting the ACR 1990 criteria for FM (Table IIa) was not associated with any specific clinical characteristic other than the Widespread Pain Index (WPI) score. By contrast, RA patients meeting the ACR 2010 criteria for FM (ACR2010$^+$ Table IIb) had a higher BMI, greater disability (HAQ), pain intensity, disease activity, symptom severity scale score and widespread pain index values. SS was also significantly associated with FM meeting the ACR 2010 criteria. The results for the FiRST screening tool (Table IIc) showed that RA patients with positive results for this questionnaire (FiRST$^+$) had higher levels of disability (HAQ), disease activity, symptom severity scale scores and widespread pain index values. Sjögren's syndrome was also significantly associated with the detection of FM with the FiRST questionnaire.

In SSc patients, the presence of fibromyalgia, according to the ACR 1990 criteria (Table IIIa), was associated with a higher pain intensity and greater disability, more diffuse pain and more somatic symptoms. When the modified ACR 2010 criteria were used (Table IIIb), ACR2010$^+$ SSc patients were more likely to be female, and to have higher levels of disability (HAQ), higher pain intensity, symptom severity scale scores and widespread pain index values. Diffuse scleroderma and SS were significantly more frequent in SSc patients meeting the modified ACR 2010 criteria than in SSc patients not meeting these criteria.

In the FiRST screening test (Table IIIc), SSc patients considered positive for FM had higher levels of disability (HAQ) and pain intensity, higher symptom severity scale scores and widespread pain index values. SS was significantly more frequent in FiRST$^+$ SSc patients than in FiRST$^-$ SSc patients.

Table IIa. Demographic and clinical characteristics of RA patients, with and without FM, according to the ACR 1990 criteria.

	ACR1990$^+$ RA patients n=38	ACR1990$^-$ RA patients n=134	*p*
Age	55.5 ± 10	54 ± 16	NS
Sex ratio (% female)	84.2%	87.3%	NS
BMI (kg/m^2)	26.7 ± 5.9	25.5 ± 5.8	NS
Disease duration (years)	12.5 ± 9.7	16.2 ± 10.3	NS
FiRST +	17	22	p=0.005
ACR 2010	19	14	p<0.0001
WPI score [1]	4.60	2.93	p=0.03
SS scale score [2]	4.76	4.82	NS
HAQ	0.87 ± 0.7	1.0 ± 0.89	NS
DAS28	3.2 ± 1.5	3.6 ± 1.4	NS
Pain intensity (VAS)	4.7 ± 2.6	4.2 ± 2.5	NS
Sjögren's syndrome	8	28	NS
CRP	8.3 ± 16.0	8.02 ± 13	NS
AAN	2	32	NS
ACPA+	29	84	NS
RF+[3]	26	108	NS
Erosive RA	31	112	NS
Joint replacement	6	13	NS
Treatment with biological agents	30	112	NS

[1]WPI: widespread pain index; [2]SS scale score: somatic symptoms scale score; [3]RF: rheumatoid factor.

Table IIb. Demographic and clinical characteristics of 172 RA patients with and without FM, according to the modified ACR 2010 criteria.

	ACR2010$^+$ RA patients n=33	ACR2010$^-$ RA patients n=139	*p*
Age	56.3	54.0	NS
Sex ratio (% female)	90%	86.3%	NS
BMI (kg/m^2)	28.31	25.08	0.004
Disease duration (years)	17.9	15.0	NS
FiRST $^+$	20/33	19/139	p<0.0001
ACR 1990 FM$^+$	19/33	19/139	p<0.0001
WPI	10.51	1.58	p<0.0001
SS scale score	7.69	4.12	p<0.0001
HAQ	1.719	0.805	p<0.0001
DAS28	4.54	2.99	p<0.0001
Pain intensity (cm VAS)	6.2	4.5	0.003
Sjögren's syndrome	12 (36%)	24 (17.2%)	0.028
CRP	8.3 ± 16.0	8.02	NS
AAN	8	28	NS
ACPA	28	91	0.050
RF	28+ (84%)	106+ (76%)	NS
Erosive RA	27	116	NS
Joint replacement	10	25	NS
Treatment with biological agents	30	122	NS

Table IIc. Demographic and clinical characteristics of 172 RA patients with and without FM, according to the FiRST screening test.

	FIRST$^+$ RA patients n=39	FiRST$^-$ RA patients n=133	*p*
Age	55.2	54.2	NS
Sex ratio (female)	37	113	NS
BMI (kg/m^2)	26.69	25.43	NS
Disease duration (years)	17.9	14.9	NS
ACR 1990 FM$^+$	17	21	p<0.0001
ACR 2010 FM$^+$	20	13	p<0.0001
WPI	6.30	2.42	p<0.0001
SS scale score	7.56	4	p<0.0001
HAQ	1.63	0.762	p<0.0001
DAS28	4.08	3.09	p<0.0001
Pain intensity (cm VAS)	5.3	4.6	NS
Sjögren's syndrome	16	20	p<0.0001
CRP (mg/l)	9.8	7.6	NS
AAN	8	28	NS
ACPA	33	86	NS
RF	31	103	NS
Erosive RA	32	111	NS
Joint replacement	11	26	NS
Treatment with biological agents	33	109	NS

Correlations between the results of classification and diagnostic tools in RA and SSc patients

In RA patients, taking the ACR 1990 criteria as the classic diagnostic tool, the kappa coefficient for agreement between FM diagnostic and screening tool results was 0.28 with the FiRST screening questionnaire and 0.41 with the modified ACR 2010 diagnostic criteria.

In SSc patients, taking the ACR 1990 criteria as the classic diagnostic tool, the kappa coefficient for agreement between FM diagnostic and screening tools was 0.51 with the FiRST screening questionnaire and 0.50 with the modified ACR 2010 diagnostic criteria.

Accuracy of diagnostic and screening tools for FM in RA and SSc populations

Taking the ACR 1990 criteria as the gold standard, the modified ACR 2010 criteria had a sensitivity of 50% and a specificity of 90% for the detection of FM in RA patients; the corresponding values for FiRST were lower: 44% and 84%, respectively (Table IV).

Taking the ACR 1990 criteria as the gold standard, the modified ACR 2010 criteria had a sensitivity of 56% and a specificity of 90% for the detection of FM in SSc patients. Similar values were obtained for FiRST: 62% and 87%, respectively (Table IV).

Discussion

This study was the first to compare three sets of diagnostic and screening criteria for comorbid FM in two different autoimmune rheumatic conditions, RA and SSc. It confirmed the high frequency of FM in these autoimmune disorders, at 20 to 30% of cases, for both RA and SSc. It also demonstrated that autoimmune disorders are associated with a particular phenotype as a function of comorbid FM, and especially of the FM diagnostic tool used. This study reveals that FM diagnostic and screening tools have different properties relative to the rheumatic condition considered, with most tools having a high specificity but a low sensitivity. Finally, this study shows that secondary SS is associated with FM in both RA and SSc,

Table IIIa. SSc phenotypes with and without FM according to the ACR 1990 criteria.

	FM ACR 1990$^+$ SSc patients n=37	FM ACR 1990$^-$ SSc patients n=85	*p*
Age	60.7 ±12.0	57.05±15.7	NS
Sex ratio (female)	34	74	NS
BMI (kg/m^2)	28.3 ± 6.1	25.7 ± 5.8	NS
Disease duration (years)	10.2 ± 13.7	11.2 ± 10.3	NS
HAQ	1.30 ± 0.82	0.73 ± 0.85	0.001
Pain intensity (cm VAS)	5.7± 1.8	3.8 ± 5.0	0.007
FiRST+	23	11	*p*<0.0001
Diffuse SSc	14	40	NS
Pulmonary fibrosis	21	39	NS
HTAP	4	11	NS
Digital ulcers	12	45	NS
Calcinosis	18	21	NS
Telangiectasia	20	43	NS
RGO	28	65	NS
AAN	31	69	NS
Scl70	15	31	NS
Anti-centromere antibodies	15	13	NS
Antibodies against RNA polymerase III	1	2	NS
ACR 2010 FM+	19	8	*p*<0.0001
WPI	8	2,24	*p*<0.0001
SS scale score	7.48	3.87	*p*<0.0001
Sjögren's syndrome	11	14	NS

Table IIIb. Demographic and clinical characteristics of the 122 SSc patients with and without FM, according to the modified ACR 2010 criteria.

	ACR2010$^+$ SSc patients n=29	ACR2010$^-$ SSc patients n=93	*p*
Age	59	57.94	NS
Sex ratio (female)	28	73	0.049
BMI (kg/m^2)	27.39	25.11	NS
Disease duration (years)	11.30	10.75	NS
HAQ	1.399	0.7457	0.0014
Pain intensity (cm VAS)	6.4	3.8	0.0007
FiRST+	23	11	*p*<0.0001
Diffuse SSc	8	47	0.030
Pulmonary fibrosis	14	46	NS
HTAP	4	11	NS
Digital ulcers	9	43	NS
Calcinosis	8	24	NS
Telangiectasia	14	50	NS
RGO	25	71	NS
AAN	25	75	NS
Scl70	11	36	NS
Anti-centromere antibodies	14	24	0.045
Anti-RNA polymerase antibodies	1	3	NS
ACR 1990 FM$^+$	21	16	*p*<0.0001
WPI	11.862	1.580	*p*<0.0001
SS scale score	8.27	3.93	*p*<0.0001
Sjögren's syndrome	12	15	0.006

Table IIIc. Demographic and clinical characteristics of the 122 SSc patients with and without FM, according to the FiRST screening test.

	FiRST$^+$ SSc patients n=34	FiRST$^-$ SSc patients n=88	*p*
Age	58.52	58.06	NS
Sex ratio (female)	32	69	NS
BMI (kg/m^2)	27.20	25.07	NS
Disease duration (years)	10.25	9.75	NS
HAQ	1.354	0.693	*p*<0.0001
Pain intensity (mm VAS)	6.5	3.6	*p*<0.0001
Diffuse SSc	12	44	NS
Pulmonary fibrosis	16	44	NS
HTAP	12	3	NS
Digital ulcers	13	39	NS
Calcinosis	9	23	NS
Telangiectasia	17	47	NS
RGO	30	66	NS
AAN	30	70	NS
Scl70	11	36	NS
Anti-centromere antibodies	15	23	NS
Anti-RNA polymerase antibodies	1	3	NS
ACR 1990 FM$^+$	22	15	*p*<0.0001
ACR 2010 FM$^+$	22	7	*p*<0.0001
WPI	7.67	2.09	*p*<0.0001
SS scale score	8.27	3.92	*p*<0.0001
Sjögren's syndrome	14	14	0.006

consistent with a contribution of SS to FM-related symptoms.

Prevalence of comorbid fibromyalgia in patients with rheumatic disorders

Fibromyalgia (FM) has been shown to be common in patients with RA in various epidemiological studies (22). In such situations, it has been described as "secondary FM" (4), "concomitant FM" or "comorbid FM". It is also observed in several autoimmune diseases (23), including systemic lupus erythematosus (SLE) (24), SS (25) and SSc (9). It may occur in 15 to 30% of RA patients (6). These rates are much higher than the prevalence of FM in the general population (between 1.7 and 2% of the total population) based on results obtained with similar diagnostic tools (2), suggesting that the pain, inflammation and/or stress accompanying chronic rheumatic diseases may trigger FM. Our study confirms previous findings for RA, but also demonstrates that FM is highly prevalent in patients with SSc, occurring more frequently than in RA patients. It should be stressed that very few data have been published concerning SSc and the risk of FM, but the results reported here suggested that associated FM should be assessed in SSc patients, given its high prevalence.

The estimated prevalence of comorbid fibromyalgia varies with the set of diagnostic criteria used, lower estimates being obtained with the modified ACR 2010 criteria than with the 1990 criteria. Several methodological issues must be taken into account when interpreting these findings. First, clinical examination is subjective, and different examiners may draw different conclusions concerning tender points (ACR 1990 criteria). The specificity of diagnostic (revised ACR 2010 criteria) and screening (FiRST) tools, relative to the ACR 1990 criteria as the gold standard, was very good in both conditions. However, sensitivity was modest, especially in RA patients. Only half the cases of FM diagnosed according to the ACR 1990 criteria in RA patients were correctly identified with the revised ACR 2010 criteria; the frequency was slightly higher for SSc patients. The differences between the tools used begin with the

Table IV. Specificity (Sp) and sensitivity (Se) of the FiRST questionnaire and modified ACR 2010 criteria for FM in RA and SSc patients, relative to the diagnosis of FM on the basis of the ACR 1990 criteria.

		SSc	RA
FiRST	se	0.62	0.44
	sp	0.87	0.84
ACR 2010	se	0.56	0.50
	sp	0.90	0.90

Se: sensitivity; Sp: specificity.

type of data reporting: the ACR 1990 criteria are assessed by the clinician, whereas the FiRST questionnaire and modified ACR 2010 criteria rely on self-reporting. The sensitivity and specificity of the modified ACR 2010 criteria have been assessed in clinical populations. Bennett *et al*. (26) reported a specificity of 67% in patients with non-fibromyalgia chronic pain (*i.e*. 33% of people with other chronic pain conditions were incorrectly classified as having FM with the new criteria). The context may also modify the accuracy of diagnostic criteria: in patients with FM not associated with autoimmune disorders, Carrillo de la Pena *et al*. (27) found a good correlation between the results obtained with the ACR 1990 and modified 2010 criteria.

The modified ACR 2010 criteria reflect an important change in the way in which FM is viewed, with a transition from its being seen as a pain syndrome to its identification as a multi-symptomatic syndrome, and from diagnosis by the clinician to diagnosis on the basis of self-reporting. This change is reflected in the modest correlations between the results obtained with the ACR 1990 criteria and those obtained with the more recent modified ACR 2010 criteria and the FiRST screening tool. These changes led to a decrease in estimates of the prevalence of comorbid FM, even in SSc patients, in whom extra-articular symptoms are more frequent than in patients with RA.

Phenotype of patients with comorbid FM: differences between diagnostic tools

In RA, comorbid FM diagnosed with the ACR 1990 criteria was associated only with more diffuse pain, whereas comorbid FM diagnosed with the modified ACR 2010 criteria was also associated with higher levels of activity and pain intensity. We, like other authors, found that comorbid FM diagnosed with the modified ACR 2010 criteria was associated with higher disease activity; however, we did not confirm previous findings of an association between comorbid FM and the more frequent use of biological agents or a lower frequency of erosion (5, 28). However, Disease Activity Score 28 (DAS28) is not specific to disease activity and is itself increased by FM (29). Comorbid FM was also associated with a higher BMI and a higher frequency of associated SS.

Pain symptoms are common in SSc patients (9, 30). We found that comorbid FM was frequent in patients with SSc. The ACR 1990 criteria identified comorbid FMS in patients with high levels of disability and pain intensity. With the modified ACR 2010 criteria, comorbid FM was found to be more frequent in female patients, patients with diffuse SSc and patients with secondary SS. These findings are similar to those reported for SLE. In SLE (31), comorbid FM is often the most important predictor of pain and function. FM has more of an impact on quality of life than on disease activity *per se* (32), through its effects on fatigue, sleep disturbances, psychiatric disturbances, and disabilities which prevent the patient from working. The detection of FM in patients with SSc or other autoimmune diseases is, therefore, of importance, to guide patient assessment towards the evaluation of certain domains not systematically considered in patients with SSc or SLE.

Wolfe invented the term "fibromyalgianess" (FMness) to describe the strong association of FM with levels of pain and disability in all rheumatic disorders (33). Fibromyalgia (a dichotomous variable, presence or absence of this diagnosis) and fibromyalgianess (measured as a continuous variable) have a direct impact on traditional measurements of disease activity and severity, and have implications for clinical practice. FM^+ RA or SSc patients did not have a more severe primary disease phenotype in terms of joint damage in RA or organ involvement in SSc. This finding suggests that FM should not be considered a marker of primary disease severity, although it strongly contributes to disability in both conditions.

Secondary Sjögren's syndrome

Our results are consistent with those of Torrente-Segarra *et al*. (24), who also found that secondary SS was associated with FM. Pain is a major symptom in primary SS (25), and may be widespread, neuropathic or articular. SS is diagnosed on the basis of histological and biological findings, whereas FM is diagnosed solely on the basis of clinical assessment. An overlap between these two entities might therefore be anticipated. A possible association of FM features with SS has been described in several studies reporting very different prevalence values (12 to 55% of patients) and based on different classification criteria (34, 35). We found that secondary SS was associated with FM in both RA and SSc, consistent with a contribution of this condition to FM-related symptoms.

The concept of "central sensitisation" and small-nerve neuropathy

Central sensitisation is a recently developed concept that has been used to explain the occurrence of comorbid FM in patients with rheumatic conditions (36). It may account for the lack of improvement of pain in some patients with RA and comorbid FM, despite treatment with anti-inflammatory disease-modifying antirheumatic drugs (DMARDs) (37). It has been suggested that some RA patients have defects of central pain processing, including impaired descending analgesic activity. Lee *et al*. (38) showed that the relationships between inflammation, psychosocial

factors and peripheral and central pain processing are intricately entwined in RA. Areas of CNS hypoperfusion overlapping with those observed in patients with isolated FM and in patients with both SLE and FM have been reported in patients with SLE alone (39).

The recently developed concept of "small-nerve neuropathy" also highlights the links between widespread pain, FM, and autoimmune disorders. Small-nerve neuropathy has been found in patients with FM (40), and in patients with SS and widespread pain (41), potentially accounting for some of the overlap between these two entities. Autoimmune disorders have been identified as a major cause of small-nerve neuropathies (40), together with diabetes, alcohol and other metabolic conditions. Testing for small-nerve neuropathy may be proposed in cases of RA and SSc with comorbid FM.

Limitations of our study

Several studies on comorbid FM have analysed psychological variables, such as cognitive and behavioural characteristics, in rheumatologic conditions. Our study, performed during a routine rheumatology/internal medicine consultation, did not take into account anxiety, depression, fatigue and sleep disorders, or other characteristics such as catastrophising and maladaptive coping strategies. Further studies are required to determine whether comorbid FMS is significantly driven by psychological comorbid conditions in RA and SSc. We also did not systematically record concomitant drugs, especially analgesics, antiepileptics and antidepressants that may interfere with pain perception. However, they are not very frequently prescribed in rheumatological disorders and also are not really powerful; thus we may expect that their impact on the FM screening is limited.

Conclusion

We have demonstrated that the ACR 1990 and modified 2010 criteria identify RA and SSc patients with comorbid FM very differently. The results obtained with the modified ACR 2010 criteria were poorly correlated with those obtained with the ACR 1990 criteria. The modified ACR 2010 criteria defined a group of patients similar to that defined by the FiRST screening tool, but significantly different from that defined by the ACR 1990 criteria. These findings suggest that the modified ACR modified 2010 diagnostic criteria should be adopted, and the ACR 1990 classification criteria and classical tender point examination should be definitively abandoned.

The new ACR criteria and the FM screening tool are not influenced by pain alone, are self-reported and seem to be more clinically relevant for identifying the origin of pain in autoimmune disorders. Their use may prevent overtreatment, particularly in terms of DMARD and biological agent use in RA, in patients with widespread pain concomitant to autoimmune diseases. However, secondary SS is associated with FM in both RA and SSc and should be tested in comorbid FM.

The use of new diagnostic and screening tools for FM should be integrated into the assessment of widespread pain in autoimmune diseases, to make it possible to propose more effective pain management and optimal patient care.

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