Fibromyalgia in Spondyloarthritis: Effect on Disease Activity Assessment in Clinical Practice

Jean Wach, Marie-Claude Letroublon, Fabienne Coury, and Jacques Guy Tebib

ABSTRACT. ***Objective.*** Spondyloarthritis (SpA) is the second most frequent inflammatory rheumatic disease, characterized by spinal involvement, peripheral arthritis, or enthesitis with marked pain, stiffness, and fatigue. Fibromyalgia (FM) may be associated with SpA, and shares some common symptoms. We aimed to determine how FM influences assessment of SpA disease activity, which is mainly dependent on patient-based outcome measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS).

Methods. This single-center cross-sectional study included consecutive patients with SpA according to the Assessment of SpondyloArthritis International Society criteria. FM was diagnosed according to the 1990 American College of Rheumatology criteria. Patient characteristics, BASDAI, ASDAS/C-reactive protein (CRP), Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Metrology Index, and the Medical Outcomes Study Short Form-36 questionnaire were recorded and compared.

Results. The study included 103 patients with SpA; 81 with axial and 22 with peripheral forms. Eighteen patients presented with concomitant FM, of whom 12 had axial SpA and 6 peripheral SpA. Demographic characteristics did not differ except for sex, with a female predominance in the FM group that was more marked in peripheral forms. BASDAI was higher in patients with FM [median (IQR): 4.2 (4.2) vs 2.2 (3.1); p = 0.0068], whereas ASDAS-CRP was not significantly different [median (IQR): 2.7 (2) vs 2 (1.3); p = 0.1264]. Nevertheless, median ASDAS-CRP corresponded to high disease activity in patients with SpA or FM compared with moderate activity in non-FM patients.

Conclusion. FM is a frequent comorbidity in patients with SpA, especially in peripheral forms. In patients with SpA-FM, disease activity may be overestimated when measured by BASDAI and to a lesser extent by ASDAS-CRP, and this overestimation could lead to inappropriate treatment escalation. (J Rheumatol First Release ; doi:10.3899/jrheum.160104)

Key Indexing Terms:
SPONDYLOARTHRITIS FIBROMYALGIA DISEASE ACTIVITY

Spondyloarthritis (SpA) is the second most frequent inflammatory rheumatic disease after rheumatoid arthritis (RA), with an estimated prevalence of 0.5–1.9%[1]. In recent decades, the pattern of the disease has moved from the well-known male-predominant ankylosing spondylitis (AS) to descriptions of more sex-balanced forms. These include on the one hand nonradiographic axial forms and on the other, peripheral forms in which joint and enthesis involvement is predominant and still dependent on a common elementary enthesitis process[2]. This led to the need for new classification criteria, published in 2011 by the Assessment of SpondyloArthritis International Society (ASAS)[3]. These criteria focus on clinical presentation and distinguish axial SpA (axSpA), divided into radiographic forms (previously known as ankylosing spondylitis, AS) and nonradiographic forms, and peripheral SpA (pSpA), i.e., without axial involvement but with peripheral arthritis and/or enthesitis.

Although sex influence on the severity of SpA is still a matter of debate, women generally present with worse self-reported outcome and less radiographic damage in early and advanced SpA[4,5,6,7,8,9]. These studies, which postulated the potential effect of a particular behavior with regard to pain discomfort in women to explain the paradoxical discrepancy between objective and subjective presentation, unfortunately did not consider the presence of concomitant fibromyalgia (FM). Yet this frequent diffuse painful syndrome of indeterminate etiology[10], largely seen in women[11] and often associated with inflammatory diseases[12], could be one of the factors that underlie this discrepancy. In a first preliminary study comparing 18 women and 18 men with AS, Aloush and colleagues diagnosed 50% of women with concomitant FM. These patients reported higher disease activity[13]. Three further studies focused on FM in axial SpA, reporting a higher prevalence than in the general population (from 4.1% to 15.5%)[14,15,16].

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Disease activity measurement in SpA is principally based on indexes reporting the intensity of subjective discomfort. The most frequently used index, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), is calculated based on six 10-cm horizontal visual analog scales for self-measurement of subjective discomfort such as fatigue, spinal pain, peripheral joint pain and swelling, localized tenderness suggesting enthesitis, and morning stiffness[17]. The more recent Ankylosing Spondylitis Disease Activity Score (ASDAS) aims at a more objective approach by adding the erythrocyte sedimentation rate (ESR; ASDAS-ESR) or the C-reactive protein (CRP) level (ASDAS-CRP) to 3 items of the BASDAI (questions 2, 3, and 6 concerning spinal pain, peripheral joint pain, and duration of morning stiffness) and a patient global assessment of the activity of the disease[18].

The overlap between SpA and FM symptoms such as pain, fatigue, or sleep disturbance suggests that SpA disease activity assessed with these indices may be overestimated in patients with concomitant FM. This has been demonstrated for the 28-joint DAS index in RA[19,20] and it could eventually lead to an inappropriate increase in antiinflammatory treatment. Consequently, the aim of our study was to assess the effect of FM on SpA disease activity assessment measured with BASDAI and ASDAS-CRP. Functional disability and quality of life were also assessed as secondary endpoints.

MATERIALS AND METHODS

Our single-center cross-sectional study considered for inclusion consecutive patients with SpA from the department of one of the authors (JGT) between March 2010 and May 2011. Inclusion criteria were age over 18 years, fulfillment of ASAS classification criteria for axSpA[3] and of Amor[21] or European Spondylarthropathy Study Group (ESSG) classification criteria for peripheral SpA[22]. ASAS classification criteria for peripheral SpA, which were published after the beginning of our study, were assessed retrospectively, using items of the previous criteria[3]. FM was diagnosed when patients fulfilled the 1990 American College of Rheumatology (ACR) classification criteria at the time of examination or during a previous consultation[10]. To meet these criteria, patients must present widespread pain for more than 3 months with 11 or more tender points at clinical examination of 18 anatomically defined sites. A consecutive FM control population defined by the 1990 ACR criteria but without inflammatory rheumatic disease was included in our study.

A standardized case report form was completed for each patient for demographic data, current treatment, disease activity reported with BASDAI[17] and patient global assessment ("How active was your rheumatism on average during the last week?", as defined in the ASDAS-CRP index)[18], disability assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI; consisting of 10 self-reported questions about functional disability)[23], and quality of life assessed by the Medical Outcomes Study Short Form-36 questionnaire (SF-36)[24]. A single examiner (JGT) completed the form for the Bath Ankylosing Spondylitis Metrology Index (BASMI), consisting of 5 standardized measures[25], number of FM tender points, number of tender and swollen joints, sacroiliac radiographic assessment, and laboratory results.

One missing value was permitted for the BASDAI, BASMI, BASFI, and ASDAS-CRP questionnaires and 2 missing values for the SF-36; if more were missing, the patient was excluded from analysis. Missing values were replaced by the mean value of the remaining patients of each of the 2 groups (patients with SpA, and FM control patients).

Observational analysis of the effect of FM was carried out on the whole population and on axial and peripheral subgroups as defined by the ASAS classification criteria by measuring primarily the differences in BASDAI and ASDAS-CRP scores with and without this disorder. Secondary endpoints were also measured such as BASFI, BASMI scores, and the SF-36 score, to assess physical and psychological effect.

The ethical review board of the Hospice Civil de Lyon checked and approved the protocol. Because of the exclusive observational design of our study, consent of the consultative committee for the protection of persons was not required. Informed consent was obtained from all patients.

Data were analyzed using GraphPad Prism version 5.03 (GraphPad Software) and SPSS software version 17.0 (SPSS). Groups of patients were compared using the nonparametric Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables as appropriate. Continuous variables are presented as medians (interquartile range, IQR) and categorical variables as numbers (percentages). In percentage calculation for each variable, the number of missing values was excluded from the denominator. The Spearman nonparametric test was used to assess the correlation between scores. For all analyses, a p value less than 0.05 was considered statistically significant.

RESULTS

Populations. The study included 103 patients with SpA, of whom 81 presented with axSpA and 22 with pSpA. All patients diagnosed with pSpA on the basis of the Amor or ESSG criteria retrospectively fulfilled ASAS classification criteria. Eighteen patients (17.5%) had concomitant FM, including 12 patients with axSpA (14.8%) and 6 patients with pSpA (27.3%). Thirteen of the 18 patients fulfilled the ACR 1990 criteria for FM at the time of examination, whereas 5 of the 18 had fulfilled them in a previous consultation. A control group of 18 consecutive patients with FM seen during the same period agreed to complete the same form and were similarly examined.

Demographic and disease characteristics are detailed in Table 1. The proportion of women was significantly higher in the FM group than in the whole population (66.7% vs 29.4%; p = 0.0056). The sex difference was not significant in the axial subgroup (50.0% vs 26.1%; p = 0.1669), but patients with FM had less radiographic sacroiliitis. Detailed data are not presented for the subgroup with peripheral involvement but only 2 characteristics were different: women were also predominant among the patients with pSpA FM (100% vs 43.7%; p = 0.0461) and were shorter [height 159.3 cm (IQR 9.8) vs 173 cm (IQR 18); p = 0.0386]. Prescriptions did not differ between FM and non-FM patients, whether for disease-modifying antirheumatic drugs, tumor necrosis factor (TNF) inhibitors, analgesics, antidepressant agents, or hypnotics (Table 1).

Missing values. Concerning BASDAI, 3 patients had 1 missing value (item 4 for 1 patient with SpA, item 6 for 1 patient with SpA-FM, and item 4 for 1 FM control patient). Concerning ASDAS-CRP, global patient evaluation was missing in 2 patients with SpA (1 patient with SpA-FM and 1 FM control patient); CRP was missing in 4 patients with SpA and 1 FM control patient. In the axSpA subgroup, BASFI and BASMI were not analyzed in 6 and 5 patients,

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Table 1. Population characteristics. Data presented as n (%) except as otherwise indicated.

	SpA, n = 85	SpA-FM, n = 18	p*	axSpA, n = 69	axSpA-FM, n = 12	p*
Demographics						
Age, yrs, median (IQR)	41.9 (20.8)	46.4 (22.9)	0.3550	40.9 (17.7)	44.6 (23.0)	0.5995
Women	25 (29.4)	12 (66.7)	0.0056	18 (26.1)	6 (50.0)	0.1669
Weight, kg, median (IQR)	75 (23)	69.5 (23.6)	0.2323	75 (21.5)	73.2 (22.7)	0.8680
Height, cm, median (IQR)	172 (14)	163.5 (11.4)	0.0102	172 (12.5)	165.5 (13)	0.2085
BMI, kg/m^2, median (IQR)	25.6 (5.7)	25.4 (4.6)	0.8758	25.6 (5.7)	25.6 (7.1)	0.6851
Married	55 (64.7)	13 (72.2)	0.5970	45 (65.2)	8 (66.7)	1
Parent, n = 91	56/74 (75.7)	13/17 (76.5)	1	46/61 (75.4)	7/11 (63.6)	0.4651
City dweller	51 (60.0)	11 (61.1)	1	44 (63.7)	8 (66.6)	1
Active worker, n = 102	58/85 (68.2)	11/17 (64.7)	0.7820	48/69 (69.6)	9/12 (75)	1
SpA profile						
Disease duration, yrs (n = 102), median (IQR)	10.5 (13.8)	9.5 (10.8)	0.7819	11 (13)	6.5 (9)	0.3214
axSpA (ASAS)	69 (81.2)	12 (66.7)	0.2073			
Radiographic, n = 78				50/66 (75.7)	5/12 (41.7)	0.0341
Peripheral manifestations	45 (52.9)	12 (66.7)	0.3117	29 (42.0)	6 (50.0)	0.7543
Arthritis	39 (45.9)	9 (50.0)	0.7990	24 (34.8)	3 (25.0)	0.7418
Enthesitis	9 (10.6)	4 (22.2)	0.2352	7 (10.1)	3 (25.0)	0.1631
Dactylitis	6 (7.1)	2 (11.1)	0.6263	4 (5.8)	1 (8.3)	0.5614
Psoriasis	29 (34.1)	4 (22.2)	0.4119	16 (23.2)	2 (16.7)	1
IBD	3 (3.5)	1 (5.6)	0.5420	2 (2.9)	0 (0.0)	1
Uveitis	17 (20.0)	1 (5.6)	0.1864	17 (24.6)	1 (8.3)	0.2829
Prosthesis	7 (8.2)	2 (11.1)	0.6548	6 (8.69)	2 (16.7)	0.3375
HLA-B27, n = 98	53/81 (65.4)	13/17 (76.5)	0.5703	51/67 (76.1)	10/12 (83.3)	0.7237
CRP, mg/l, n = 99, median (IQR)	4 (7.0)	3.5 (8.8)	0.8646	4 (7.5)	2 (8)	0.5612
Treatment						
No. drugs, median (IQR)	2 (2)	2 (4.5)	0.9574	2 (3)	2 (2.75)	0.5041
NSAID	46 (54.1)	8 (44.4)	0.6045	39 (56.5)	12 (41.7)	0.3663
Corticosteroid	2 (2.4)	1 (5.6)	0.4415	2 (2.9)	1 (8.3)	0.3859
DMARD	29 (34.1)	3 (16.7)	0.1725	17 (24.6)	0 (0)	0.0619
Anti-TNF	26 (30.6)	3 (16.7)	0.3865	24 (34.8)	2 (16.7)	0.3201
Analgesics	23 (27.1)	7 (38.9)	0.3927	21 (30.4)	12 (33.3)	1
Hypnotic	3 (3.5)	3 (16.7)	0.0645	3 (4.3)	2 (16.7)	0.1565
Antidepressant drugs	4 (4.7)	2 (11.1)	0.2812	4 (5.8)	1 (8.3)	0.5614

* Mann-Whitney or Fisher's exact test as appropriate; $p < 0.05$ considered significant. When missing values occurred, the total number of available data for the item is indicated in brackets in column 1, and the number of missing values was then excluded from the denominator for percentage calculation for each variable concerned. SpA: spondyloarthritis; axSpA: axial SpA; FM: fibromyalgia; IQR: interquartile range; BMI: body mass index; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; analgesics: acetaminophen or morphine derivatives; ASAS: Assessment of SpondyloArthritis International Society; CRP: C-reactive protein; TNF: tumor necrosis factor.

respectively, while 2 and 5 patients had 1 missing value. Concerning SF-36, 6 patients were excluded and 1 or 2 missing values were replaced in 13 patients.

Assessment of activity. Comparisons of BASDAI according to FM status are presented in Table 2. In the whole population, total score ($p < 0.01$) and questions 2, 3, and 4 ($p < 0.05$) were higher in the SpA-FM group. In the axial subgroup, only questions 3 and 4 were significantly higher in FM patients ($p < 0.05$). In the peripheral subgroup all questions except number 6 were higher ($p < 0.05$), but interpretation should be cautious owing to the low number of patients. ASDAS-CRP was not significantly higher in SpA FM and non-FM patients. However, median ASDAS-CRP corresponded to high disease activity in patients with SpA-FM compared with moderate activity in non-FM patients.

The number of painful joints was higher in patients with SpA-FM, whereas the number of swollen joints was not (Table 2). The same results were observed in both the axial and peripheral subgroups.

In the axSpA subgroup, there was no difference according to FM status for the BASFI [median (IQR) axSpA-FM (n = 10): 1.4 (2.7); axSpA without FM (n = 65): 0.9 (2.5), p = 0.2921], and for the BASMI [median (IQR) axSpA-FM (n = 12): 1.5 (1.8); axSpA without FM (n = 64): 1.5 (3.8), p = 0.3526; Table 2]. Correlation according to Spearman's nonparametric test between BASFI and BASMI scores was found only in patients with axSpA without FM (n = 60; r = 0.5496; $p < 0.0001$) and not in patients with concomitant FM (n = 10; r = 0.2733; p = 0.4448). There was no correlation between BASDAI and BASMI in either the FM or the non-FM group (data not shown).

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Table 2. Comparison of BASDAI, ASDAS-CRP, and secondary criteria in patients with spondyloarthritis according to fibromyalgia status. Data presented as median (IQR).

Criteria	SpA, n = 85	SpA-FM, n = 18	p	axSpA, n = 69	axSpA-FM, n = 12	p	pSpA, n = 16	pSpA-FM, n = 6	p
BASDAI	2.2 (3.1)	4.2 (4.2)	0.0068	2.2 (3.2)	3.2 (5.4)	0.1587	2.2 (2.5)	4.7 (3.0)	0.0064
BASDAI 1	2.5 (4)	4.8 (5.4)	0.0861	2.5 (4.8)	3.5 (6.3)	0.7139	2 (4.5)	5.5 (4.5)	0.0105
BASDAI 2	2.5 (5)	5.5 (4.8)	0.0137	2.5 (5)	5.3 (6)	0.1534	2 (2.5)	5.5 (4.1)	0.0131
BASDAI 3	1 (3.5)	3.8 (5)	0.0018	0.5 (2.5)	3.3 (5.9)	0.0333	2.8 (3.8)	5.5 (3.1)	0.0199
BASDAI 4	1 (3.3)	4.8 (4.4)	0.0019	0.5 (2.5)	3.3 (5.3)	0.0427	2.3 (3.9)	5 (2.5)	0.0313
BASDAI 5	2 (4.5)	3.8 (4.1)	0.1450	2.5 (4.5)	2.5 (4.9)	0.5428	1.8 (2.5)	4 (2.6)	0.0459
BASDAI 6	1 (2.5)	2 (1.9)	0.9683	1 (2.5)	2.3 (2.6)	0.8500	1.8 (2.2)	1.5 (3)	0.7922
ASDAS-CRP	2 (1.3)	2.7 (2)	0.1264	2 (1.3)	2.5 (2.3)	0.5148	2 (1.2)	2.7 (1.2)	0.1307
PtGA	2.5 (4)	3.8 (4.4)	0.2146	2 (4.3)	3.6 (5.1)	0.3403	2.8 (3.3)	4.3 (3)	0.415
CRP, mg/l	4 (7)	3.5 (8.8)	0.8646	4 (7.5)	2 (8)	0.5612	4 (7)	7.5 (11)	0.5213
Tender joints, n = 102	0 (1)	2.8 (4.5)	< 0.0001	0 (0.8)	4.5 (4.5)	< 0.0001	1 (2)	4 (9.75)	0.006
Swollen joints, n = 102	0 (0)	0 (0)	0.4041	0 (0)	0 (0)	0.5812	0 (1)	0 (0.5)	0.3233
BASFI, n = 75				0.9 (2.5)	1.4 (2.7)	0.2921			
BASMI, n = 76				1.5 (3.8)	1.5 (1.8)	0.3526			

P values determined using Mann-Whitney t test; $p < 0.05$ considered significant. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score–C-reactive protein; IQR: interquartile range; SpA: spondyloarthritis; axSpA: axial SpA; pSpA: peripheral SpA; FM: fibromyalgia; PtGA: patient's global assessment; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index.

Quality of life assessed by the SF-36 did not differ between non-FM (n = 82) and FM patients (n = 15; data not shown), except for 1 of the 8 concepts, "physical health," which was lower in patients with SpA-FM [median (IQR): 70 (45) vs 85 (25); p = 0.0156].

Patients with SpA-FM were compared with 18 FM control patients (Table 3). There were no differences in demographic characteristics, total BASDAI, and ASDAS-CRP, or in the tender and swollen joint counts.

Because female predominance is a major epidemiological characteristic of FM, secondary cross-sectional analysis of the whole SPA population was performed according to sex (Table 4). Women presented significantly less axial involvement (clinical and radiographic), more peripheral manifestations, more uveitis, and were more affected by concomitant FM. BASDAI and ASDAS-CRP did not differ between men and women.

DISCUSSION

In our population of 103 patients with SpA, 18 (17.5%) were diagnosed with concomitant FM according to the ACR 1990 classification criteria. Prevalence was higher in pSpA (27.3%) than in axSpA (14.8%). Only a few previous studies have focused on FM in SpA: prevalence was 4.1% among 462 patients with AS (New York criteria) from 10 Spanish centers[14], 15.5% among 71 patients with AS (New York criteria) from 1 Brazilian center[15], and 14.9% among 402 Italian patients with axSpA [AS (New York criteria) and axial psoriatic arthritis (ASAS classification criteria for axSpA and psoriasis)][16]. For FM classification, the first 2 studies used ACR 1990 criteria while the last used ACR 2010 criteria.

It may be supposed that some primary FM may have been misclassified as SpA. Our study was not designed to compare the accuracy of different sets of criteria. However, Baraliakos, *et al* in a preliminary study compared 93 FM and 91 axSpA cases[26]. No patient with FM (median age 50.7 yrs, 93.4% women, 7.5% HLA-B27) fulfilled ASAS classification criteria for axial SpA. Doubts may remain for peripheral SpA where prevalence of FM was higher, but patients were considered as having SpA by the treating physician (JGT) even before they were considered for inclusion, and fulfilled at least 2 sets of classification criteria (either ESSG or Amor criteria and retrospectively ASAS criteria). Moreover, ASAS criteria require 1 objective symptom (arthritis, enthesitis or dactylitis) to be fulfilled[3]. Nevertheless, a lack of specificity of the new ASAS criteria has been disputed, particularly for nonradiographic axSpA and peripheral SpA[27,28]. Widespread pain and tenderness of the body in FM could be mistaken for enthesitis. Indeed, Marchesoni, *et al* found a Maastricht Ankylosing Spondylitis Enthesitis Score higher among 120 patients with FM compared to 266 patients with psoriatic arthritis, which was correlated to the number of FM tender points[29].

The frequencies of FM in our population of SpA (17.5%) and especially of axSpA (14.8%) are close to those of the Brazilian study of Azevedo, *et al* (15.5%)[15] and of the Italian study of Salaffi, *et al* (14.9%)[16]. Still, prevalence was lower in the Spanish study by Almodóvar, *et al*[14] concerning 462 AS cases from 12 centers. There may be some recruitment bias in tertiary care centers such as in our study and in the first 2 studies cited that could lead to overestimation of prevalence. Another explanation for this discrepancy may be the criteria used for SpA. Most previous studies used the New York modified criteria for AS, which represented only 55 patients

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Table 3. Comparison of demographics and disease activity assessment in spondyloarthritis patients with concomitant fibromyalgia and fibromyalgia control patients. Data presented as median (IQR) except where indicated.

	SpA-FM, n = 18	FM, n = 18	p*
Demographics			
Age, yrs	46.4 (22.9)	45.1 (24.5)	0.9621
Women, n (%)	12 (66.7)	16 (88.9)	0.2285
Weight, kg	69.5 (23.6)	66.5 (25)	0.8001
Height, cm	163.5 (11.4)	160 (10)	0.1199
BMI, kg/m^2	25.4 (4.6)	25.7 (9.2)	0.6016
Married, n (%)	13 (72.2)	9 (50.0)	0.3053
Parent, n = 34, n (%)	13/17 (76.5)	10/17 (58.8)	0.4646
City dweller, n (%)	11 (61.1)	10 (55.6)	1
Active worker, n = 33, n (%)	11/17 (64.7)	8/16 (50.0)	0.4905
Disease duration, yrs	9.5 (10.8)	9.5 (8)	0.4850
BASDAI	4.2 (4.2)	5.7 (1.1)	0.0555
BASDAI 1	4.8 (5.4)	6 (2.5)	0.2103
BASDAI 2	5.5 (4.8)	6 (2.2)	0.1713
BASDAI 3	3.8 (5)	5.5 (3.4)	0.4005
BASDAI 4	4.8 (4.4)	6 (2.1)	0.0890
BASDAI 5	3.8 (4.1)	5.5 (3.6)	0.0407
BASDAI 6	2 (1.9)	3.5 (3.1)	0.0233
ASDAS-CRP	2.7 (2)	2.8 (0.3)	0.3672
PtGA	3.8 (4.4)	5.8 (1.5)	0.0467
Joint counts			
Tender	4.5 (4.5)	11 (27)	0.1050
Swollen	0 (0)	0 (0)	0.6098
FM tender points	12 (5)	15 (5.3)	0.0231

* Mann-Whitney or Fisher's exact test as appropriate; $p < 0.05$ considered significant. In percentage calculation for each variable, the number of missing values was excluded from the denominator. IQR: interquartile range; BMI: body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score–C-reactive protein; SpA-FM: spondyloarthritis patients with concomitant fibromyalgia; FM: fibromyalgia control patients; PtGA: patient's global assessment.

in our study, with an FM prevalence of 9.1%. Still, even in the study by Almodóvar, *et al*, prevalence was higher than expected in the general population, as has been reported for other chronic inflammatory diseases[12]. Finally, this study confirms that FM prevalence is higher in SpA than in the general population.

We found a female predominance in patients with concomitant FM, as has previously been described in SpA. The sex ratio was 2 in our study, similar to the results of Almodóvar, *et al* in Spain (2.2)[14] and Salaffi, *et al* in Italy (2.3)[16], and higher than those of Azevedo, *et al* in Brazil (1.2)[15], but still lower than most estimations in the general population[10,11]. With the exception of height, female predominance was the only significant difference between FM and non-FM patients in the whole population and in the peripheral subgroup. Female predominance in patients with SpA-FM was less marked in the axial subgroup. This is in agreement with the male predominance classically observed in radiographic axSpA, whereas the sex ratio is usually more balanced in peripheral SpA[30,31,32].

However, FM prevalence in men was unexpectedly high in this clinical cohort (9.1%) compared with the frequency found in other diseases such as RA[19] or in the general population[11]. It is however consistent with the results reported by Salaffi, *et al*[16] and more generally with the increased incidence of FM in other chronic rheumatic diseases[12]. This observation may give new insight into the debate on the relationship between FM and chronic diseases such as RA or SpA: chronic inflammatory pain may induce alterations in central pain regulation mechanisms, known as central sensitization, and finally lead to chronic widespread pain and other somatic symptoms, even eventually FM, in a person who might not have developed such a condition in the absence of inflammatory disease[33,34].

BASDAI was higher in patients with FM, especially in peripheral SpA, where female predominance was the highest. In axSpA, only questions 3 and 4 relating to peripheral pain were higher in patients with FM, whereas responses to questions about fatigue and morning stiffness did not differ. Because FM is a diffuse painful syndrome, we can suppose that this difference may reflect the effect of FM rather than a more severe inflammatory process. Almodóvar, *et al* and Azevedo, *et al* reported higher BASDAI in patients with axSpA-FM[14,15], whereas Salaffi, *et al* found no significant difference in the BASDAI score between FM and non-FM patients with SpA[16]. Because BASDAI assesses symptoms, it may reflect the sum of the manifestations of both SpA and

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Table 4. Comparison of demographics, spondyloarthritis profile, and fibromyalgia status between men and women. Data presented as median (IQR) except where indicated.

	Men, n = 66	Women, n = 37	p*
Demographics			
Age, yrs	43.3 (13.3)	41.9 (20.5)	0.5895
Weight, kg	79 (20.6)	63 (15.8)	< 0.0001
Height, cm	175 (11)	161 (6)	< 0.0001
BMI, kg/m^2	26.1 (6)	24.1 (6.6)	0.0196
Married, n (%)	41 (62.1)	27 (73.0)	0.2875
Parent, n = 91, n (%)	41/56 (73.2)	28/35 (80.0)	0.6158
City dweller, n (%)	44 (66.6)	18 (48.6)	0.0940
Active worker, n = 102, n (%)	47/66 (71.2)	22/36 (61.1)	0.3764
SpA profile			
Disease duration, yrs, n = 102	11 (14)	9 (11)	0.3540
Axial SpA (ASAS), n (%)	57 (86.4)	24 (64.9)	0.0136
Radiographic, n = 78, n (%)	43/55 (78.2)	12/23 (52.2)	0.0301
Peripheral manifestations, n (%)	31 (47.0)	26 (70.3)	0.0250
Arthritis	28 (42.4)	20 (54.1)	0.3056
Enthesitis	5 (7.6)	8 (21.6)	0.0612
Dactylitis	2 (3.0)	6 (16.2)	0.0240
Psoriasis, n (%)	21 (31.8)	12 (32.4)	1
IBD, n (%)	1 (1.5)	3 (8.1)	0.1309
Uveitis, n (%)	7 (10.6)	11 (29.7)	0.0281
Prosthesis, n (%)	8 (12.1)	1 (2.7)	0.1517
HLA-B27, n = 98, n (%)	45/63 (71.4)	21/35 (60.0)	0.2684
Fibromyalgia	6 (9.1)	12 (32.4)	0.0056
BASDAI	2.2 (3.1)	2.7 (3.3)	0.4961
BASDAI 1	2.5 (4.1)	3.5 (5.5)	0.7096
BASDAI 2	2.5 (5)	3.5 (5)	0.3754
BASDAI 3	1 (4)	2 (4.25)	0.2595
BASDAI 4	1.25 (3.5)	0.5 (4.75)	0.5588
BASDAI 5	2.5 (4.5)	2.5 (4.25)	0.8412
BASDAI 6	1.5 (2)	2 (3.75)	0.5389
ASDAS-CRP	2.0 (1.6)	2.1 (1.2)	0.6086
PtGA	2.5 (4.5)	3 (4.5)	0.6343
CRP	4.5 (8)	4 (10.5)	0.9886

*P values determined by Mann-Whitney or Fisher's exact test as appropriate; $p < 0.05$ considered significant. When missing values occurred, the total number of available data for the item is indicated in bracket in column 1 and the number of missing values was then excluded from the denominator for percentage calculation for each variable concerned. IQR: interquartile range; BMI: body mass index; ASAS: Assessment of SpondyloArthritis International Society; SpA: spondyloarthritis; IBD: inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; PtGA: patient's global assessment.

FM. The high BASDAI score in our control population of FM with similar demographics underlines its lack of specificity, in accordance with previous studies reporting median BASDAI (IQR) of 6.0 (2.7) in 70 patients with FM and of 4.5 (1.6) in 248 patients with FM[16,35]. This lack of specificity in measuring SpA inflammatory disease activity in patients with concomitant FM needs to be borne in mind when anti-inflammatory therapy is discussed, with the risk of inefficacy, occurrence of adverse events, and excessive cost if TNF blockers are considered.

The ASDAS may then be of interest because it includes the ESR or CRP level as a single objective item. Salaffi, *et al* concluded that ASDAS may distinguish axSpA patients with disease activity from those with functional impairment related to FM, but values were similar in the axSpA and axSpA-FM groups and considerably overlapped with those of the FM group. We found no significant difference in ASDAS score between patients with SpA-FM and patients with SpA. However, with regard to clinical therapeutic decision making, median ASDAS-CRP in patients with SpA-FM was considered to indicate high disease activity, whereas the SpA non-FM group was considered to present with moderate activity, which may still lead to inappropriate treatment. The relative lack of specificity of ASDAS may be related to the usually low ESR and CRP levels in patients with SpA, as reported here and in other cohorts[30,31,32]. This drawback could be overcome by using high-sensitivity CRP[36] or another more pertinent marker such as calpro-

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tectin[37]. Nevertheless, in the Spanish cohort CRP was significantly lower in 19 patients with SpA-FM than in 443 patients with SpA, whereas BASDAI was higher[14]. In any case, compared with the BASDAI, ASDAS-CRP still includes 4 patient-reported outcomes (patient's global assessment and BASDAI items 2, 3, and 6), but excludes the 2 questions concerning fatigue, which are the most unspecific, and local tenderness suggestive of enthesitis, a diagnosis that may be challenging in patients who have concomitant FM.

The influence of FM on subjective assessment is also illustrated by the discrepancy observed between a high count of tender joints and a low count of swollen joints in patients with SpA-FM, as highlighted in RA[19,20], and by the lack of correlation between the BASFI and the BASMI in patients with axSpA-FM. Similarly, Almodóvar, *et al* described higher BASFI and lower Bath Ankylosing Spondylitis Radiographic Index in patients with AS-FM compared with non-FM patients[14].

Interestingly, quality of life assessed with the SF-36 questionnaire revealed little difference between patients with FM and non-FM, except for one of the 8 concepts, "physical health," which was poorer in SpA-FM, illustrating the complexity of such evaluation.

Our study has a number of limitations. The relatively small sample required the use of nonparametric tests that, although robust, limited the drawing of conclusions in some subgroup analyses, especially in the pSpA subgroup. However, the epidemiological characteristics and presentation of the SpA profile of this population, such as the more frequent axial involvement in men and the more frequent peripheral involvement in women (Table 4), were similar to the findings of larger studies, suggesting this sample was nevertheless representative[4,5,6,7,8,9]. Clinical assessment was not blinded but this did not affect our main results concerning patient-based outcome measures, and assessment by a single experienced examiner ensured accuracy[38].

FM is often associated with SpA, especially in peripheral forms and in women. This concomitant FM should be considered as an important contextual factor that may account for inaccuracy in assessing disease activity in SpA, particularly pSpA. Inflammatory disease activity may be overestimated in such patients if assessed using BASDAI, and to a lesser extent using ASDAS-CRP. When interpreting these indices, physicians should be aware of the presence of concomitant FM to avoid inappropriate escalation of anti-inflammatory treatment.

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