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Clinical science

Evaluation of the agreement between the ACR 1990 fibromyalgia tender points and an enthesitis score in patients with axial spondyloarthritis

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Abstract

Objectives: Coexistence of FM represents a challenge in the evaluation of enthesitis in patients with axial spondyloarthritis (axSpA) due to a possible overlap between the tender points (TP) due to enthesitis and those of FM. The objective was to assess the agreement between the MASES enthesitis score and the tender points of the ACR 1990 criteria in patients with axSpA.

Methods: This was a cross-sectional ancillary analysis of the Predict-SpA study (NCT03039088). Patients had a diagnosis of axSpA according to their rheumatologist and an indication to start a TNFα blocker. All patients were screened for FM according to the FiRST questionnaire. A physician was asked to assess 31 anatomically described sites in a random order without knowing to which instrument the site belonged (i.e. the 18 ACR 1990 TP and the 13 MASES sites). Agreement between the MASES and the ACR 1990 TPs by the intraclass correlation coefficient (ICC), also stratified by the presence/absence of concomitant FM according to the FiRST.

Results: Among the 526 patients, 53% were men and 202 (38%) had FM. Radiographic sacroiliitis and MRI sacroiliitis were present in 56% and 68% patients, respectively. Patients were mostly men (53.4%) with radiographic and MRI sacroiliitis in 56% and 68% patients, respectively. Mean number of ACR 1990 TP was 5.4 (S.D. 4.6) and mean MASES was 4.2 (S.D. 3.6). ICC between both scores was 0.7 [95% CI (0.6, 0.8)]. ICC between both scores was 0.6 [95% CI (0.3, 0.8)] and 0.7 [95% CI (0.6, 0.7)] for patients with and without FM, respectively.

Conclusion: These results suggest a significant overlap between both scores in patients with axSpA, including in those without concomitant FM.

Trial registration: clinicaltrials.gov, https://clinicaltrials.gov, NCT03039088

Keywords: spondyloarthritis, FM, MASES

Rheumatology key messages

- Coexistence of fibromyalgia (FM) represents a challenge in the evaluation of enthesitis in patients with axial spondyloarthritis (axSpA).
- Distinguishing between pain from enthesitis and from fibromyalgia might be difficult for both patient and physician.
- Our study suggests a significant overlap between both scores in patients with axSpA, including in those without concomitant FM.

Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by enthesis inflammation (i.e. enthesitis) either at the spine (i.e. axial involvement) or peripheral level. Peripheral enthesitis can occur in >50% of patients with axial involvement, and the most frequent sites are plantar fascia and the Achilles tendon [1–3]. Several instruments have been proposed to evaluate peripheral enthesitis in patients with SpA: the Mander/Newcastle Enthesitis Index (MEI) was the first enthesitis score, developed in 1987, and evaluates 66 entheses by local pressure, and intensity of pain is graded on a 0–3 scale (0 = no pain; 1 = mild tenderness; 2 = moderate tenderness; 3 = wince or withdraw) [4]. However, the MEI is not frequently used in routine practice and only

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scarcely in randomized controlled trials (RCTs). Under the umbrella of ASAS (Assessment of SpondyloArthritis International Society), in 2003 the Maastricht Ankylosing Spondylitis Enthesis Score (MASES) was developed [5]. This new instrument was developed based on the MEI but reducing the sites to the 13 most frequently reported enthesitis sites in a cohort of patients over time, and removing the grading. An excellent correlation between MEI and MASES was confirmed. The 13 evaluated sites include the first bilateral costochondral joints, the seventh costochondral joints, the posterior and anterior superior iliac spines, the iliac crests, the proximal insertion of the Achilles tendon and the fifth lumbar spine. The overall score is between 0 and 13 (13 being representative of the highest enthesitic involvement).

FM is a complex chronic condition of unknown aetiology and is considered as a central sensitization syndrome. Its hallmark symptoms are chronic widespread musculoskeletal pain and generalized tender points (TP) leading to significant physical disability and reduced quality of life [6, 7]. Its prevalence in the general population has been estimated around 2–7% [6], but is higher in patients with chronic rheumatic diseases such as axSpA, where it's estimated between 14–16% [8], ranging from 11.1% (6.0–16.2%) to 20.3% (6.5–34.1%) according to axSpA sub-classification [9]. This prevalence is similar when compared with other chronic rheumatic diseases [10–13].

The ACR criteria [ACR 1990 criteria and ACR 2010 and modified 2010 criteria (2011)] [14, 15] are the main classification criteria for FM. These criteria were mostly developed for research and classification purposes, and are difficult to apply in daily practice because they require some training to be implemented [16]. To be fulfilled, diffuse pain of the upper part and lower part of the body are needed for at least 3 months, along with the presence of at least 11/18 tender points. These 18 tender points were selected in 1990 by trained and blinded physicians as the most frequently reported after the examination of 558 patients including 293 with fibromyalgia and 265 control subjects.

The coexistence of FM represents a great challenge in the evaluation of enthesitis, because an overlap might exist between the MASES and the ACR criteria, regarding the evaluation of tender points. However, to our best knowledge, no study has evaluated the overlap between both indices.

These previous remarks prompted us to conduct this analysis, aiming to evaluate the agreement between the MASES and the tender points of the ACR 1990 in a population of patients with axSpA with and without concomitant FM, and to evaluate the characteristics of patients with high scores in both instruments.

Patients and methods

Study design

We conducted a cross-sectional ancillary analysis of the Predict-SpA study (clinicaltrials.gov: NCT03039088) [17]. Briefly, the Predict-SpA study was a prospective, multicentric study conducted in 2017, with the main objective to evaluate the impact of a concomitant fibromyalgia on the TNF alpha blockers (TNFb) treatment effect in axSpA. For this ancillary analysis, only cross-sectional data from the baseline visit was used.

Population

All patients from the Predict-SpA study were included. Patients were consecutive adults (>18 years old) diagnosed with axSpA according to their treating rheumatologist and in whom the decision of initiating or switching an TNFb because of an axial involvement of SpA had been made. Patients were not all TNF-naive, and in case of previous exposure to TNFb, a washout period of at least 8 weeks was required.

Collected data

Demographics: age, gender, educational level, clinical data (BMI, smoking status, disease duration); SpA classification criteria data: all items included in the Assessment in SpondyloArthritis international Society (ASAS) set of criteria for axSpA; disease activity and severity data: BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS) [18]; treatment data: ASAS-non-steroidal anti-inflammatory drugs (ASAS-NSAID) score [19], analgesics and antidepressive agents.

Definitions

For this analysis, fibromyalgia was defined as a Fibromyalgia Rapid Screening Test (FIRST) $\geq$5/6.

Briefly, the FiRST is a self-reported questionnaire, with high screening performances: a score $\geq$5/6 had a sensitivity of 90.5% and a specificity of 85.7% for the classification of FM, compared with a group of patients with chronic pain due to other rheumatic conditions (i.e. RA, SpA, OA) [20]

Assessment of the tender points (MASES entheseal sites and 1990 ACR criteria tender points)

Physical examination was carried out by a clinical investigator (e.g. a rheumatologist). The investigator was asked to perform the evaluation of 31 sites (anatomical description was provided in the case report form), asking her/him to evaluate by digital palpation with an average force of 4 kg/cm^2 (i.e. with whitening of the nail) whether the site was painful or not. These 31 sites included (in a random order, without any indication to which instrument they belonged) both the 18 tender points of the ACR 1990 criteria and the 13 enthesitic sites of the MASES. No specific training session for tender points evaluation was performed, also with the purpose to not lead rheumatologists to be able to differentiate between 1990 ACR tender points and MASES entheseal sites of evaluation (Fig. 1).

We considered that patients with >9/18 ACR 1990 tender points had a 'high number of ACR 1990 tender points', and patients with a MASES >6/13 had a 'high MASES'.

Statistical analyses

Firstly, the mean number of ACR 1990 tender points and the mean MASES per patient was calculated, and the characteristics of patients with at least one ACR 1990 tender point and a MASES >0 were described.

Secondly, the agreement between the two scores was assessed by the intraclass correlation coefficient (ICC) [21]; the ICC is a value between 0 and 1, where values below 0.5 indicate poor agreement, between 0.5 and 0.75 moderate agreement, between 0.75 and 0.9 good agreement, and any value above 0.9 indicates excellent agreement. Graphically the overlap between the two scores was represented by Venn diagrams (Fig. 2). In order to determine whether the presence of concomitant FM had an impact on such agreement, the same analyses were performed in the groups of patients with and without fibromyalgia (FM+ and FM– groups).

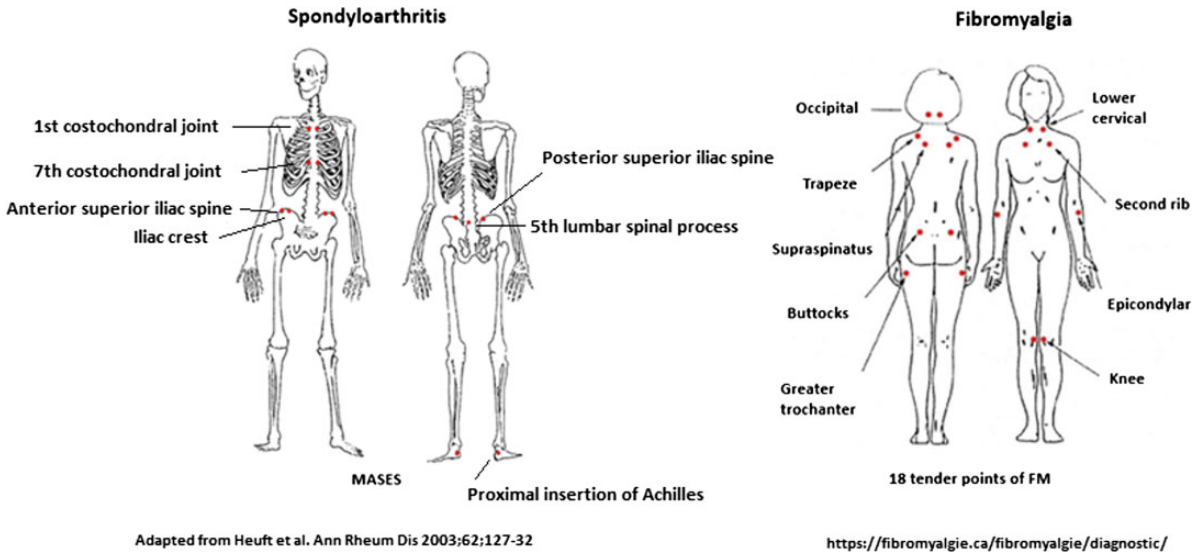

Figure 1. Points evaluated as 1990 ACR criteria tender points and MASES. Lefthand section reused with permission from [5]

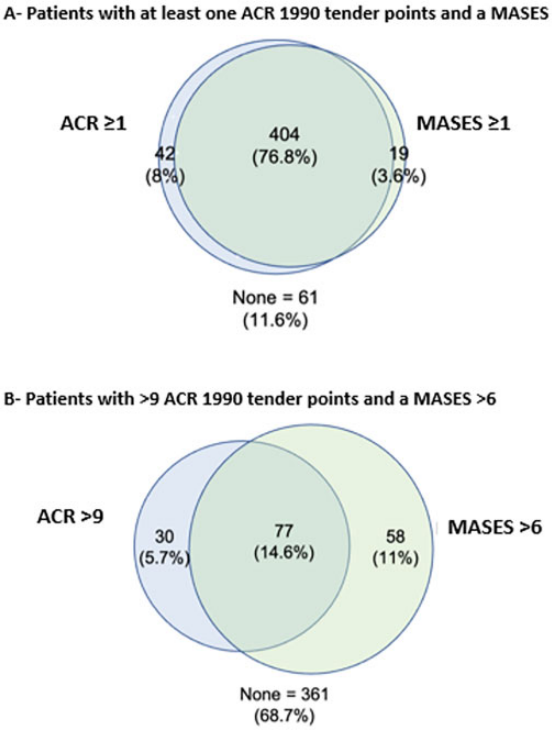

Figure 2. Venn diagrams representing ACR 1990 tender points and MASES

Thirdly, we determined the number of patients with 'high number of ACR 1990 tender points' and 'high MASES'. The overlap between these two categories was assessed by the Bennett's PABAK (prevalence-adjusted bias-adjusted kappa) statistic [22] and its 95% CI, in the whole group, but also in the subgroups of patients with and without FM.

In order to determine the factors associated with the presence of 'high number of ACR 1990 tender points' and 'high MASES', we compared patients with high scores to the rest of the population by univariate (bivariate logistic regression) and multivariate analyses (multivariate logistic regression including in the model only variables with a P-value <0.10 in the univariate analysis).

Missing data handling: patients with no data on BASDAI at baseline were excluded from the analysis in the Predict-SpA study. In multivariate analyses, missing binary variables were imputed with '0', while continuous variables were imputed by the mean. Statistical analyses were carried out on the software R (version 4.0.2) [23].

The study was approved according to national regulations by the ethics committee Comité de Protection des Personnes Ile de France III (File No. 2014-A01288-39, on 7 October 2014). All patients gave their informed written consent.

Results

Of the total 526 included axSpA patients, 441/526 (83.8%) fulfilled the ASAS classification criteria for axSpA. Patients were mostly men (53.4%), with an average age of 41.3 years (standard deviation, S.D., 11.6 years) and mean disease duration 6.3 years (S.D. 8.6 years). HLA B27 status was positive in 64.7% of patients; radiographic sacroiliitis and MRI sacroiliitis were present in 55.8% and 68.3% patients, respectively. Mean CRP was 15.3 mg/l (S.D. 25.4 mg/l), and mean BASDAI (0–10) was 5.7 (S.D. 1.8) with 83.3% of patients having a BASDAI $\geq$4 at baseline. All characteristics are summarized in Table 1. The mean number of ACR 1990 tender points was 5.4 (S.D. 4.6) and the mean MASES score was 4.2 (S.D. 3.6). Overall, 446 (84.8%), 423 (80.4%) and 404 (76.8%) patients had at least one ACR 1990 tender point, one painful MASES entheseal site and at least one painful site per instrument, respectively. Patients with at least one painful site according to both instruments were more frequently females, HLA B27 negative, with past history of heel enthesitis and antidepressants intake, with higher mean BASDAI and ASDAS scores and with concomitant fibromyalgia (see Table 1).

There was a good agreement [21] between the two scores with an ICC = 0.7 [95% CI (0.6, 0.8)]. Figure 2 represents the Venn diagrams of such overlap and Bland–Altman plots of ICC are represented on Fig. 3.

Among the 202 patients (38.4%) positively screened for fibromyalgia, scores were 7.5 (S.D. 5.0) and 5.3 (S.D. 3.8) for ACR 1990 and MASES respectively, and agreement between the two scores was moderate {ICC = 0.6 [95% CI (0.3,

Table 1. Characteristics of patients with at least one 1990 ACR tender point and a MASES >0 and comparison with the rest of the population

Variable	Total Total population $n = 526$	Patients with at least one ACR 1990 tender point and a MASES >0	
		Yes = 404	No = 122
Age, mean (S.D.), years	41.27 (11.57)	41.42 (11.69)	40.76 (11.18)
Gender (female)	**245/526 (46.58%)**	**210/404(51.98%)**	**35/122 (28.69%)**
Disease duration (years)	6.25 (8.59)	6.13 (8.29)	6.68 (9.53)
Education (university)	236/524 (45.04%)	180/402 (44.78%)	56/122 (45.90%)
BMI (2 *NA*), mean (S.D.)	25.95 (5.21)	26.21 (5.33)	25.07 (4.69)
Smoking status (ever)	331/523 (63.29%)	252/403 (62.53%)	79/120 (65.83%)
Inflammatory back pain	499/526 (94.87%)	386/404 (95.54%)	113/122 (92.62%)
History of peripheral synovitis	143/520 (27.50%)	113/399 (28.32%)	30/121 (24.79%)
History of peripheral enthesitis (heel)	**280/524 (53.64%)**	**236/401 (58.85%)**	**44/121 (36.36%)**
History of dactylitis	58/522 (11.11%)	48/400 (12.00%)	10/122 (8.19%)
History of IBD	29/523 (5.54%)	24/401 (5.98%)	5/122 (4.10%)
History of psoriasis	101/524 (19.27%)	78/402 (19.40%)	23/122 (18.85%)
History of uveitis	89/523 (17.02%)	64/403 (15.88%)	25/120 (20.83%)
Family history of SpA	211/501 (42.11%)	156/385 (40.52%)	55/116 (47.41%)
HLA-B27 negative	**165/468 (35.26%)**	**147/360 (40.83%)**	**18/108 (16.67%)**
Good NSAID response	385/510 (75.49%)	295/390 (75.64%)	90/120 (75.00%)
X-ray sacroiliitis	280/502 (55.78%)	211/390 (54.10%)	69/112 (61.61%)
MRI sacroiliitis	276/404 (68.32%)	209/314 (66.56%)	67/90 (74.44%)
History of antidepressant intake	**105/521 (20.15%)**	**95/400 (23.75%)**	**10/121 (8.26%)**
History of third ladder analgesic intake	91/515 (17.67%)	76/393 (19.34%)	15/122 (12.29%)
ASAS-NSAID score at baseline, mean (S.D.)	25.59 (40.22)	25.78 (42.31)	24.97 (32.50)
CRP (mg/L), mean (S.D.)	15.27 (25.42)	15.75 (27.06)	13.66 (19.03)
BASDAI, mean (S.D.)	**5.68 (1.82)**	**6.00 (1.69)**	**4.63 (1.85)**
ASDAS, mean (S.D.)	**3.33 (0.92)**	**3.41 (0.92)**	**3.07 (0.88)**
Fibromyalgia according to the FiRST questionnaire[a]	**202/526 (38.40%)**	**179/404 (44.31)**	**23/122 (18.85)**

Variables in bold were significantly different across groups.
[a] Fibromyalgia considered by FiRST (≥5/6).
MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

0.8)]}; only 15 of these 202 (7,4%) patients did not have any TP. Among patients without fibromyalgia, scores were lower [4.1 (S.D. 3.9) and 3.4 (S.D. 3.2] for ACR 1990 and MASES, respectively) while the agreement between the two scores was moderate to good {ICC = 0.7 [95% CI (0.6, 0.7)]} (Supplementary Table S1, available at *Rheumatology* online).

Seventy-seven patients (14.6%) fulfilled the definitions for both 'high number of ACR 1990 tender points' and 'high MASES'; the agreement between both categories was strong [PABAK = 0.7, 95% CI (0.6, 0.7)] in the total group. The proportion of such patients (i.e. fulfilling the definitions for both 'high number of ACR 1990 tender points' and 'high MASES') was strikingly higher in the comorbid FM group: 25.7% patients *vs* 7.7%, respectively. The agreement was moderate in patients with fibromyalgia [PABAK = 0.5, 95% CI (0.4, 0.6)] while it remained good in patients without fibromyalgia [PABAK = 0.7, 95% CI (0.7, 0.8)], respectively.

Patients fulfilling the definitions for both 'high number of ACR 1990 tender points' and 'high MASES' (Table 2) were significantly more frequently HLA B27 negative [OR 2.4, 95% CI (1.3, 4.4)], had a past history of talalgia [OR 1.9, 95% CI (1.0, 3.5)], a BASDAI ≥4 at inclusion [OR 4.2, 95% CI (1.2, 26.6)] and a concomitant fibromyalgia [OR 3.4, 95% CI (1.9, 6.3)].

Discussion

Our study confirms our hypothesis that a strong agreement between the MASES and the tender points of the 1990 ACR criteria of fibromyalgia exists, and interestingly, that this strong overlap exists also in the subgroup of patients without fibromyalgia. Even so, fibromyalgia was, along with the absence of HLA B27, high BASDAI scores and a history of heel pain, significantly associated with the likelihood of high scores in both instruments.

In our study, the ICC was 0.7 in the total population and also in the subgroup of patients without fibromyalgia, and 0.6 in those with concomitant fibromyalgia. Interestingly, the agreement for high scores was also good in patients without fibromyalgia, compared with those with fibromyalgia.

Roussou *et al.* had investigated the possible presence of an overlap between the FM tender points of the ACR 1990 criteria and the MEI score in patients with SpA and inflammatory spinal pain [1]. They found overlap between tender points and enthesitic sites in 75% of patients with a statistically significant correlation between the total number of enthesitic sites and the total number of tender points, with an increased frequency of enthesitis in women. Although their locations were anatomically different, 13 enthesitis sites in the MEI were clinically coincident with pain points of the ACR 1990 criteria for FM, suggesting that the examiner's discriminatory ability of palpation is limited in clinical practice by an overlap on some sites [1]. Our study differed in the use of the MEI and not the MASES, taking into account fewer enthesitic sites, the larger number of subjects and the phenotypic characteristics of SpA (526 subjects with axSpA, 95% of whom had inflammatory spinal pain, 27% and 11% of whom had a

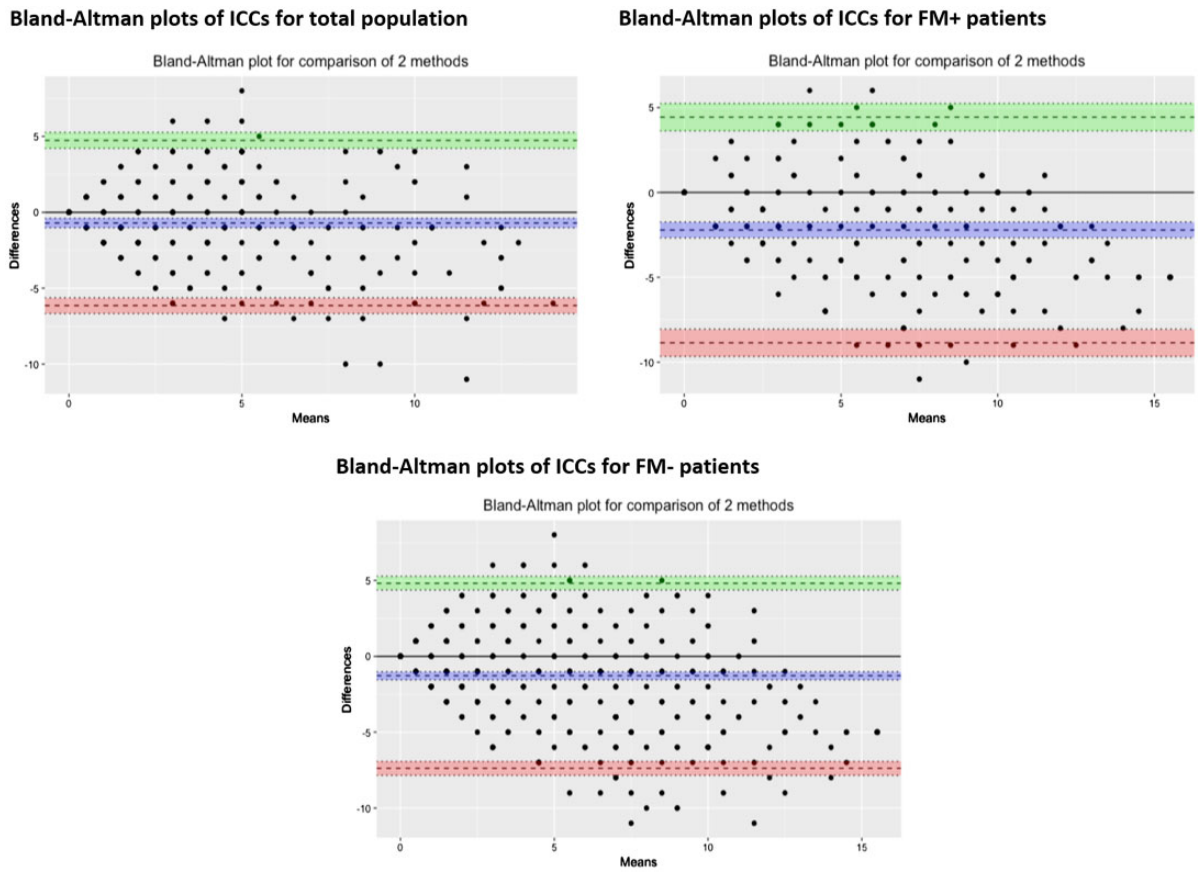

Figure 3. Bland–Altman plots of ICC. Bland–Altman plots of ICCs for total population. Bland–Altman plots of ICCs for FM+ patients. Bland–Altman plots of ICCs for FM patients

history of synovitis and dactylitis, respectively, in our study, as opposed to 60 subjects in the Roussou *et al.* study, of whom only 18.5% had isolated axial involvement and >70% had peripheral involvement).

Concomitant fibromyalgia represents a challenge for the assessment of axSpA disease activity by patient-reported outcomes, as they often find difficult to distinguish FM-related symptoms from axSpA-related symptoms [24]. However, interestingly enough, in our study, a good overlap between the two scores existed even in patients without concomitant FM, which seems even more problematic for the assessment of possible enthesitic involvement in patients with SpA, even in the absence of concomitant FM.

As expected, the prevalence of simultaneously high number of painful sites (ACR 1990 and MASES) was significantly higher in patients with FM compared with those without FM. The significant characteristics of patients with a high MASES score and a high number of tender points, compared with those without, were HLA B27-negative status, history of talalgia, high disease activity with a BASDAI ≥4 and comorbid fibromyalgia according to the FiRST. In Mease *et al.*'s study, the 121/477 (25.4%) patients with axSpA with at least one enthesitis (mean 3.9 sites) at SPARCC were more likely to be female ($P < 0.05$) with non-radiographic axSpA ($P < 0.05$), higher disease activity (higher synovial and joint index, physician global assessment, ASDAS, BASDAI and BASFI), decreased spinal mobility, and poorer QOL. Patients with enthesitis had more FM and a history of depression and greater work disability ($P < 0.05$). These patients had more often used a biologic treatment (38.8% *vs* 27.2%) or csDMARD (24.8% *vs* 13.3%) and were more frequently receiving a combination of biologics and csDMARD at the time of the study (28.6% *vs* 18.1%) compared with patients without enthesitis [2].

In contrast, in the study by Almodóvar *et al.* evaluating the characteristics of axSpA patients with or without concomitant FM (ACR 1990 criteria), patients with FM were predominantly female but the presence of enthesitis on MASES was not significantly different between the two groups [25]. In the study by Godfrin *et al.* the number of tender points among the 18 used to diagnose FM was significantly higher in patients with FM than in patients with SpA including SpA with enthesitic form, although 8 of the 11 patients with enthesitic SpA had more than the 11 tender points necessary for a diagnosis of FM according to the ACR 1990 criteria [26]. Clinical presentation was often similar in these two conditions, except that NSAIDs relieved pain in patients with enthesitic SpA but not in those with FM.

Our study has several weaknesses but also some strengths. First of all, as mentioned above, although some studies have assessed the correlation between enthesitic points of the MEI [1] or LEI [24] and FM TP, our study is, to our knowledge, the first study assessing the concordance between the MASES (a more restricted score than the MEI but also the most widely used and recommended by ASAS) and FM TP. Another strength of our study is the large number of patients studied

Table 2. Association with high number of 1990 ACR tender points (>9 tender points) and a 'high' MASES (>6)

Variable	MASES >6 and more than 9 tender points of 1990 ACR criteria		Univariate analysis		Multivariate analysis	
	Yes = 77	No = 449	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years), mean (S.D.)	42.13 (11.97)	41.12 (11.50)	1.01 (0.99, 1.03)	0.481	—	—
Gender (female)	**46/77 (59.74%)**	**199/449 (44.32)**	**1.86 (1.14 – 3.07)**	**0.013**	1.38 (0.76, 2.53)	0.286
Disease duration (years), mean (S.D.)	7.34 (8.91)	6.07 (8.53)	1.02 (0.99, 1.04)	0.231	—	—
Education (university)	32/77 (41.56%)	204/447 (45.64%)	0.85 (0.52, 1.38)	0.507	—	—
BMI (2 *NA*), mean (S.D.)	26.87 (4.90)	25.79 (5.25)	1.04 (0.99, 1.08)	0.093	1.05 (0.99, 1.10)	0.077
Smoking status (ever)	48/77 (62.34%)	283/446 (63.45%)	0.95 (0.58, 1.58)	0.851	—	—
Inflammatory back pain	75/77 (97.40%)	424/449 (94.43%)	2.21 (0.64, 13.92)	0.287	—	—
History of peripheral synovitis	**28/75 (37.33%)**	**115/445 (25.84%)**	**1.71 (1.01, 2.84)**	**0.041**	1.49 (0.77, 2.83)	0.227
History of peripheral enthesitis (heel)	**56/76 (73.68%)**	**224/446 (50.22%)**	**2.77 (1.64, 4.88)**	**<0.001**	**1.87 (1.01, 3.54)**	**0.049**
History of dactylitis	10/75 (13.33%)	48/447 (10.74%)	1.28 (0.58, 2.56)	0.509	—	—
History of IBD	5/76 (6.58%)	24/447 (5.37%)	1.24 (0.41, 3.11)	0.671	—	—
History of psoriasis	17/77 (22.08%)	84/447 (18.79%)	1.22 (0.66, 2.16)	0.500	—	—
History of uveitis	12/76 (15.79%)	77/447 (17.22%)	0.90 (0.44, 1.69)	0.758	—	—
Family history of SpA	35/74 (47.30%)	176/427 (41.22%)	1.28 (0.78, 2.10)	0.329	—	—
HLA-B27 negative	**42/69 (60.87%)**	**123/399 (30.83%)**	**3.49 (2.07, 5.97)**	**<0.001**	**2.38 (1.31, 4.37)**	**0.005**
Good NSAID response	55/76 (72.37%)	330/434 (76.04%)	0.83 (0.48, 1.45)	0.493	—	—
X-ray sacroiliitis	37/76 (48.68%)	243/426 (57.04%)	0.71 (0.44, 1.16)	0.178	—	—
MRI sacroiliitis	31/59 (52.54%)	245/345 (71.01%)	0.68 (0.40, 1.14)	0.158	—	—
Elevated CRP	44/75 (58.67%)	267/437 (61.10%)	0.90 (0.55, 1.50)	0.690	—	—
History of antidepressant intake	**25/77 (32.47%)**	**80/444 (18.02%)**	**2.19 (1.27, 3.71)**	**0.004**	**1.39 (0.69, 2.71)**	**0.346**
History of third ladder analgesic intake	**21/76 (27.63%)**	**70/439 (15.04%)**	**2.01 (1.13, 3.50)**	**0.015**	**1.64 (0.81, 3.24)**	**0.163**
ASAS-NSAID score at baseline, mean (S.D.)	18.56 (39.59)	26.80 (40.25)	0.99 (0.98, 1.00)	0.096	—	—
CRP (mg/L), mean (S.D.)	20.19 (35.47)	14.42 (23.22)	1.01 (0.99, 1.01)	0.072	1.01 (0.99, 1.02)	0.098
BASDAI ≥4	**74/77 (96.10%)**	**364/449 (81.07%)**	**5.76 (2.08, 23.90)**	**0.004**	4.18 (1.18, 26.62)	0.058
ASDAS ≥2.1	76/77 (98.70%)	418/449 (93.10%)	5.64 (1.18, 101.07)	0.091	—	—
Fibromyalgia according to the FiRST questionnaire[a]	**52/77 (67.53%)**	**150/449 (33.41%)**	**4.15 (2.50, 7.04)**	**<0.001**	**3.38 (1.87, 6.29)**	**<0.001**

Variables in bold were significantly different across groups.
[a] FM considered by FiRST (≥5/6).
MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

compared with other studies evaluating enthesitic scores and FM [1] and the small amount of missing data.

Also, one may wonder whether including only patients about to receive a TNFb (and therefore with active disease) does not constitute a limitation of the study, as we do not know whether the concordance between the tender points and the MASES would be the same in patients with less active disease and therefore less pain, particularly enthesitic pain [only 61/526 (11.6%) of the patients did not have any tender points or any painful site on the MASES].

In addition, the question may arise as to whether some patients in this trial may have been misdiagnosed as having axSpA when in fact they had isolated FM, especially given the high prevalence of FM (according to FiRST) and the fact that patients with FM were more likely to be HLA B27 negative and less likely to have radiographic or MRI sacroiliitis. However, it is important to note that all included patients were diagnosed with axSpA by a rheumatologist, who had also deemed this disease to require TNFb therapy. Besides, patients with or without FM (according to FiRST) also

fulfilled the ASAS criteria for SpA, and the other clinical signs associated with axSpA were equally distributed among the different subgroups. Moreover, patients in this study had a sufficiently high level of complaint for their treating rheumatologist to decide to initiate a TNFb, so they could be patients with severe forms of axSpA (thus more often with radiographic or magnetic sacroiliitis and HLA B27 positive) or patients with more moderate forms of axSpA but with concomitant FM. Finally, the higher frequency of positive FM criteria in patients with ankylosing spondylitis may also be related to the severity and duration of chronic pain in these patients with axSpA, according to the underlying hypothesis of the phenomenon of central sensitization to pain in rheumatic diseases [27]. Indeed, the pain associated with spondyloarthritis has a multifactorial origin, both central and peripheral, related to a currently active inflammation (on which NSAIDs are relatively effective), or to the consequences of a past inflammation (joint destruction for example). Despite NSAIDs, some patients may experience moderate pain related to altered central pain mechanisms, such as the chronic widespread pain of fibromyalgia (FM) that may be associated with SpA, so distinguishing between the two entities is often difficult. It is crucial to differentiate FM symptoms from SpA enthesitis symptoms in patients who do not respond to treatment [28] because SpA is nowadays treated with expensive drugs (biotherapy) and direct costs are higher in patients with concomitant FM than in those with only FM or isolated SpA, due to the greater frequency of combination therapy or the impact on time off work, as already explained [29].

Finally, one major limitation of our study is the absence of imaging such as MRI or ultrasound to confirm the clinical diagnosis of enthesitis detected by MASES. Indeed, the question of the need of systematic evaluation of entheses by imaging has been raised for some years already. The EULAR recommends using MRI or ultrasound to detect enthesitis [30]. MRI can provide objective evidence of enthesitic involvement in patients suspected of having enthesitic SpA, while being normal in patients with fibromyalgia [26]. In the HEEL study [31] to investigate the efficacy of etanercept in refractory calcaneal enthesitis, MRI of the heel was shown to be of high value in the evaluation of bone oedema localized to the Achilles tendon or plantar fascia, defining calcaneal enthesitis [31]. MRI has limited accessibility outside the hospital so ultrasound may be suitable in clinical practice for detecting enthesitis [32]. Doppler ultrasound evaluation of 14 peripheral entheses would make it possible to distinguish patients with PsA from patients with FM in terms of the number and distribution of enthesitic sites involved, as well as the presence of inflammatory changes, with ultrasound evidence of enthesopathy of the plantar fascia and Achilles tendon being highly specific to PsA [33]. Some have suggested that ultrasonography is a sensitive and specific method for the diagnosis of SpA [34–38], but this is not confirmed by the study of Balint *et al.* in which ultrasonographic evaluation of the heels did not differentiate between patients with SpA and controls [39], nor by that of Ebstein *et al.* in which no difference was found between SpA and RA patients with respect to enthesis abnormalities observed on ultrasound, concluding that the specificity of the ultrasound features of the entheses may be low in these inflammatory conditions involving the joints and entheses [40].

Our study, by highlighting the existence of a significant overlap between MASES and FM TP, and this despite the absence of concomitant FM (as assessed by the FiRST), raises the question of the specificity of the purely clinical assessment of peripheral enthesitis; our results suggest also the important role of imaging (namely MRI but also ultrasound) in the assessment of enthesitis, particularly in case of polyenthesitic presentations without any other objective signs of SpA and especially in order to decide treatment options. This leads to the question of whether enthesitic points should be differently evaluated only in patients with concomitant FM, especially as the presence of comorbid FM does not seem to be related to a specific phenotype of patients with axSpA. Further studies seem necessary to assess the metrological performance of MASES in patients with and without associated fibromyalgia.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are not publicly available but ancillary analysis can be performed after approval from the Predict-SpA scientific committee.

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References

1. Roussou E, Ciurtin C. Clinical overlap between fibromyalgia tender points and enthesitis sites in patients with spondyloarthritis who present with inflammatory back pain. Clin Exp Rheumatol 2012;30:24–30.
2. Mease PJ, Liu M, Rebello S *et al.* Characterization of patients with axial spondyloarthritis by enthesitis presence: data from the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. ACR Open Rheumatol 2020;2:449–56.
3. Seven S, Pedersen SJ, Østergaard M *et al.* Peripheral enthesitis detected by ultrasonography in patients with axial spondyloarthritis—anatomical distribution, morphology, and response to tumor necrosis factor-inhibitor therapy. Front Med 2020;7:341.
4. Mander M, Simpson JM, McLellan A *et al.* Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. Ann Rheum Dis 1987;46:197–202.
5. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A *et al.* Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127–32.
6. Häuser W, Perrot S, Sommer C, Shir Y, Fitzcharles MA. Diagnostic confounders of chronic widespread pain: not always fibromyalgia. Pain Rep 2017;2:e598.
7. Honda Y, Sakamoto J, Hamaue Y *et al.* Effects of physical-agent pain relief modalities for fibromyalgia patients: a systematic review and meta-analysis of randomized controlled trials. Pain Res Manag 2018;2018:1–9.
8. Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. Best Pract Res Clin. Rheumatol 2019;33:101423.

9. Jones GT, Mallawaarachchi B, Shim J, Lock J, Macfarlane GJ. The prevalence of fibromyalgia in axial spondyloarthritis. Rheumatol Int 2020;40:1581–91.
10. Blackmore MG, Gladman DD, Husted J, Long JA, Farewell VT. Measuring health status in psoriatic arthritis: the Health Assessment Questionnaire and its modification. J Rheumatol 1995; 22:886–93.
11. Hamdi W, Chelli-Bouaziz M, Ahmed MS *et al.* Correlations between clinical, radiographic, and sonographic enthesitis scores during ankylosing spondylitis [Corrélations entre les scores cliniques, radiographique et échographiques d'enthésite au cours de la spondylarthrite ankylosante]. Revue du Rhumatisme 2011;78: 251–56.
12. Mease PJ, Van den Bosch F, Sieper J *et al.* Performance of 3 enthesitis indices in patients with peripheral spondyloarthritis during treatment with adalimumab. J. Rheumatol 2017;44:599–608.
13. Bejia I, Hammouda SB, Said M, Salem KB, Touzi M, Bergaoui N. Measurement of enthesitis in ankylosing spondylitis [Mesure de l'enthésite au cours de la spondylarthrite ankylosante]. Revue du Rhumatisme 2005;601:207–323.
14. Incel NA, Erdem HR, Ozgocmen S, Catal SA, Yorgancioglu ZR. Pain pressure threshold values in ankylosing spondylitis. Rheumatol Int 2002;22:148–50.
15. Wolfe F, Smythe HA, Yunus MB *et al.* The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–72.
16. Gudu T, Gossec L. Quality of life in psoriatic arthritis. Expert Rev Clin. Immunol 2018;14:405–17.
17. Moltó A, Etcheto A, Gossec L *et al.* Evaluation of the impact of concomitant fibromyalgia on TNF alpha blockers' effectiveness in axial spondyloarthritis: results of a prospective, multicentre study. Ann Rheum Dis 2018;77:533–40.
18. Heijde D van der, Lie E, Kvien TK, Sieper J *et al.* ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.
19. Perrot S, Bouhassira D, Fermanian J; Cercle d'Etude de la Douleur en Rhumatologie. Development and validation of the Fibromyalgia Rapid Screening Tool (FiRST). Pain 2010;150:250–6.
20. Dougados M, Simon P, Braun J *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/ epidemiological studies in axial spondyloarthritis. Ann. Rheum. Dis 2011;70:249–51.
21. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J. Chiropr. Med 2016;15:155–63.
22. Mak HKF, Yau KKW, Chan BPL. Prevalence-adjusted bias-adjusted kappa values as additional indicators to measure observer agreement. Radiology 2004;232:302–3.
23. R: The R Project for Statistical Computing. https://www.r-project.org/ (3 August 2021, date last accessed).
24. Alunno A, Carubbi F, Stones S *et al.* The impact of fibromyalgia in spondyloarthritis: from classification criteria to outcome measures. Front Med 2018;5:290.
25. Almodóvar R, Carmona L, Zarco P *et al.* Fibromyalgia in patients with ankylosing spondylitis: prevalence and utility of the measures of activity, function and radiological damage. Clin Exp Rheumatol 2010;28:S33–39.
26. Godfrin B, Zabraniecki L, Lamboley V *et al.* Spondyloarthropathy with entheseal pain. A prospective study in 33 patients. Jt Bone Spine 2004;71:557–62.
27. Baraliakos X, Regel A, Kiltz U *et al.* Patients with fibromyalgia rarely fulfil classification criteria for axial spondyloarthritis. Rheumatology 2018;57:1541–7.
28. Marchesoni A, De Marco G, Merashli M *et al.* The problem in differentiation between psoriatic-related polyenthesitis and fibromyalgia. Rheumatology 2018;57:32–40.
29. Atzeni F, Boccassini L, Di Franco M *et al.* Chronic widespread pain in spondyloarthritis. Reumatismo 2014;66:28–32.
30. Ebstein E, Coustet B, Masson-Behar V *et al.* Comparaison de l'échographique des enthèses dans la polyarthrite rhumatoïde et la spondyloarthrite. Rev. Rhum 2019;86:269–74.
31. Dougados M, Combe B, Braun J *et al.* A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: the HEEL trial. Ann Rheum Dis 2010;69:1430–5.
32. Gandjbakhch F, Conaghan PG, Ejbjerg B *et al.* Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI Study of 294 patients in clinical remission or low disease activity state. J Rheumatol 2011;38:2039–44.
33. Marchesoni A, Lucia OD, Rotunno L, Marco GD, Manara M. Entheseal Power Doppler ultrasonography: a comparison of psoriatic arthritis and fibromyalgia. J Rheumatol Suppl 2012;89:29–31.
34. D'Agostino MA, Aegerter P, Bechara K *et al.* How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power Doppler ultrasonography. Ann Rheum Dis 2011;70:1433–40.
35. D'Agostino M-A, Said-Nahal R, Hacquard-Bouder C *et al.* Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. Arthritis Rheum 2003;48:523–33.
36. de Miguel E, Cobo T, Muñoz-Fernández S *et al.* Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis 2009;68:169–74.
37. Eder L, Barzilai M, Peled N, Gladman DD, Zisman D. The use of ultrasound for the assessment of enthesitis in patients with spondyloarthritis. Clin Radiol 2013;68:219–23.
38. Fujikawa K, Kawashiri SY, Endo Y *et al.* Diagnostic efficacy of ultrasound detection of enthesitis in peripheral spondyloarthritis. Mod Rheumatol 2020;30:1060–6.
39. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002;61:905–10.
40. Ablin JN, Eshed I, Berman M *et al.* Prevalence of axial spondyloarthritis among patients with fibromyalgia: a magnetic resonance imaging study with application of the assessment of spondyloarthritis international society classification criteria. Arthritis Care Res 2017; 69:724–9.