Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients

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Abstract

Objective

Fatigue is an important aspect of spondyloarthritis (SpA). However the influencing factors of fatigue in SpA are unclear. The objective of this study was to explore if fatigue is related to disease activity or to patient characteristics.

Methods

This was a retroelective observational study (Cochin COSPA study) in one tertiary-referral centre. The primary outcome was fatigue, evaluated on a 0–100mm Visual Analogue Scale (VAS). The covariates were demographic characteristics, disease subtype (axial vs. peripheral) and disease-related factors, e.g. Bath Disease Activity Index (BASDAI), patient global assessment (VAS), Bath Functional Index (BASFI). To explain fatigue, univariate then multivariate logistic regressions were conducted (with fatigue analysed as above or below 50 mm), as well as multiple linear regressions with the different covariates.

Results

Two hundred and sixty-six SpA patients were analysed. Sixty-one percent were male; mean age and disease duration were 44.5±13.5 years and 16.8±11.7 years, respectively. Mean VAS fatigue was 49.3±32.7mm; 49.6% of patients had fatigue VAS>50mm. Logistic regression showed high fatigue was associated with disease: BASDAI and BASFI ($p<0.0001$), as well as female gender ($p=0.025$) and aerobic exercise ($p=0.005$), but there was no difference in the subtypes of SpA. In multivariate analysis, the single factor explaining fatigue was patient global assessment ($p<0.001$ and odds ratio =1.35). By linear regression, demographic variables explained 2.8% of the variance, whereas disease characteristics and activity explained 44.6%.

Conclusion

Fatigue levels were high in SpA patients whatever the subtype and appeared more strongly related to the disease than to patient-related variables, thus confirming its usefulness as an outcome measure.

Key words

spondyloarthritis, fatigue, visual analogue scale

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Introduction

Fatigue is defined as a state of exhaustion and decreased strength usually accompanied by a feeling of weariness, sleepiness, and irritability with a cognitive component (1-7). The causality of fatigue has been explored in rheumatoid arthritis (RA); it is multidimensional, involving manifestations of RA (inflammation, pain, joint damage, anaemia and RA drugs), cognitive and behavioural impairment (including anxiety and depression), and personal components (social support, work, exercise and environment) (7-11).

In spondyloarthritis (SpA), fatigue is also considered as an important manifestation; this is highlighted in particular by its presence in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a widely used index (12). In a survey of 1950 ankylosing spondylitis (AS) patients (13), fatigue was considered as the third most disabling domain by patients after stiffness and pain. However, the prevalence and causality of fatigue in SpA are unclear. The prevalence of high fatigue in SpA is evaluated from 53% to 76% (4, 14, 15), but has not been assessed in the different subtypes of SpA such as predominantly axial or peripheral disease (16); most data are issued from AS cohorts (3-5, 14, 15, 17-19). Furthermore, the prevalence of fatigue may have changed over the last few years. Indeed, anti-tumour necrosis factor (anti-TNF) improves fatigue in trials (4, 20-22). We hypothesise that its use in recent years may have modified the prevalence of high fatigue in SpA, in real life.

The causes and influencing factors of fatigue in SpA are not perfectly determined. Some authors suggest fatigue is related to demographic and social elements such as female gender, depression, psychological distress, ethnicity, educational or work status (3-5, 7, 14, 15, 17, 18, 23-25). However, others have found associations between fatigue and disease activity; fatigue seems related to other questions of the BASDAI and Bath Ankylosing Spondylitis Functional Index (BASFI) (3, 14, 25). This would confirm the usefulness of assessing fatigue in the evaluation of disease activity.

The aim of this study was (a) to assess the prevalence and magnitude of fatigue in SpA and in different subtypes, in the new millennium, in a tertiary referral centre with high recourse to anti-TNF; and (b) to explore patient-related and disease-related factors explaining fatigue. This could be interesting to propose treatment of factors influencing fatigue.

Materials and methods

Study design

A retroelective observational study, COSPA (COchin SPondylArthritis), was performed between November 2009 and July 2010, in one tertiary referral centre (26-30). Its aim was to define clinical characteristics of SpA. The study was in accordance with ethical standards in France; oral informed consent was obtained from each patient.

Patients

Patients were selected from the unit database through the keywords "spondyloarthritis", "spondylarthropathy" or "psoriatic arthritis". All patients living in Paris or in the suburb of Paris and seen in our department from 2004 to 2009 were selected, if they fulfilled the Amor criteria (31), Assessment of Spondyloarthritis International Association (ASAS) axial or peripheral SpA criteria (32) or Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (33). The subtypes of SpA were identified according to the associated symptoms. This search found 1237 patients; the first 266 patients of a random selection were analysed.

Data collection and assessment of variables

All the variables were evaluated by interviewing patients or reading medical files, radiography, magnetic resonance imaging (MRI), scanner of spine and sacroiliac joints or biologic results, in particular HLAB27 and C-reactive protein (CRP).

Assessment of fatigue

The primary outcome was fatigue, evaluated on a 0–100mm visual analogue scale (VAS). The question was: "How much did unusual fatigue and weariness cause you problems in the last week?"

(34). Fatigue was analysed as a continuous variable, but also as above or below 50 mm (5, 15), considered as high and low fatigue, respectively, then with a cut-off of 70 mm.

Potential explanatory variables for fatigue

General data collected were: (a) sociodemographic elements, taht is sex, age, Body Mass Index (BMI), self-declared ethnicity, marital, educational and working status and usual aerobic exercise; (b) disease characteristics, namely all components of the Amor criteria (31), ASAS criteria (32, 35), radiographic sacroiliitis according to the modified New York criteria (36), disease duration, the predominant form of SpA (axial, peripheral, or other) according to the physician, the SpA subtype (ankylosing spondyloarthritis, psoriasis arthritis, SpA with chronic inflammatory bowel, reactive arthritis, juvenile arthritis and undifferenciated SpA (37) and HLA B27 status; (c) disease activity, taht is global health VAS, axial pain, BASDAI (12), BASFI (38) and CRP; and (d) current treatments (anti-TNF yes/no). BASDAI was analysed without the fatigue question (mean of the other questions).

Statistical analyses

Prevalence of fatigue was assessed by descriptive statistics. A histogram representing the distribution of fatigue was produced and the Kolmogorov-Smirnov's test for normality was applied (39).

To explore factors potentially explaining fatigue, several analyses were carried out:

• as a dichotomous variable:

patients with high *versus* low fatigue were compared, with a cut-off at 50mm. Univariate then multivariate stepwise logistic regressions were performed. For exploratory purposes a cut-off of 70 mm was also analysed, the results were similar. The explanatory variables analysed were sociodemographic, disease characteristics, disease activity and current treatments;

• as a continuous variable:

univariate then multiple linear regressions were performed, stepwise multivariate analysis included all the variables with $p<0.20$. To determine the variance in fatigue attributable to the different elements (calculation of R^2) (40), two separate multiple linear regressions were performed, one with patient-related explanatory variables (*i.e.* sex, age, BMI, ethnicity, marital status, educational and working status, usual aerobic exercise) and the other with disease-related variables (*i.e.* satisfaction of classification criteria, existence of radiographic sacroiliitis, disease duration, form and subtype of SpA, HLAB27, global VAS, axial pain, BASDAI (calculated without fatigue), BASFI, CRP and current biotherapy).

Analyses were performed using the SAS statistical software version 9.1. *p*-values ≤0.05 were considered as significant. Continuous variables were given as mean values (±standard deviation [SD]), whereas qualitative variables were given as absolute frequency (relative frequency).

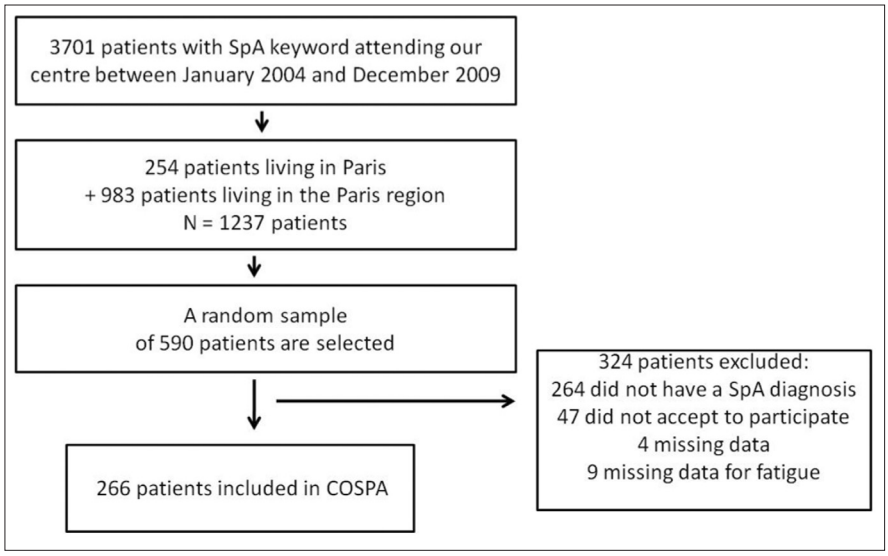

Fig. 1. Flow chart of patient's selection in the COSPA study.
The selection of patients was performed in the rheumatology unit database with SpA keywords. Only patients with the diagnosis of SpA and living around Paris were entered in COSPA and only those with available fatigue data were analysed here.
SpA: spondyloarthritis; COSPA: COchin SPondyloarthritis.

Results

Patients' characteristics

In all, 266 patients with fatigue data were analysed in the present study (Fig. 1). The population had a mean age of 44.5±13.5 years at the time of inclusion in the study, mean disease duration was 16.8±11.7 years, with mainly males (163 men, 61.3%), and 234 (88.0%) were Caucasian (Table I). The Amor criteria were fulfilled in 93.6% of the total population, and ASAS classification criteria (32, 35) in 85.7% (Table II). Among the 266 patients, 183 (68.8%) had AS, 47 (17.7%) psoriatic arthritis, 36 (13.5%) undifferentiated SpA, 22 (8.3%) SpA associated with chronic inflammatory intestinal disease, 9 (3.4%) juvenile SpA and 5 (1.9%) had reactive arthritis (some patients had more than one given diagnosis) (Supplementary Table). In all, 79.0% of patients were HLA-B27 positive (Table II) and 76.5% had a radiological or MRI sacroiliitis.

Prevalence and magnitude of fatigue

Mean fatigue VAS was 49.3±32.7mm. The median was 50.0 (inter-quartile range [IQR]=19–71) mm. This result was similar to the result obtained from the first question of the BASDAI about fatigue (data not shown). The distribution was not normal (Fig. 2). High fatigue (VAS fatigue >50mm) concerned 49.6% of patients (Table I) and 33.1% patients had a VAS fatigue >70mm (data not shown).

According to subtypes of SpA, high fatigue (with fatigue VAS >50mm) was present in 49.2% of AS, in 53.2% of psoriatic arthritis, in 68.2% in SpA with

Table I. Sociodemographic characteristics of 266 SpA patients according to the level of fatigue.

	All	Low fatigue (VAS≤50 mm)	High fatigue (VAS>50 mm)	Odds ratio ± 95%CI	*p*-value*
n (%)	266	134 (50.4)	132 (49.6)		
Sociodemographic elements:					
Females, n (%)	103 (38.7)	43 (32.1)	60 (45.4)	0.57 [0.34–0.93]	0.025
Age, years mean (SD)	44.5 (13.5)	43.8 (13.3)	45.3 (13.7)	1.01 [0.99–1.03]	0.435
Caucasian origin, n (%)	234 (88.0)	122 (91.0)	112 (84.9)	0.55 [0.26–1.18]	0.120
BMI, kg/m², mean (SD)	24.6 (4.6)	24.5 (4.8)	24.6 (4.5)	1.01 [0.96–1.06]	0.484
Married, n (%)	136 (51.1)	63 (47.0)	73 (55.3)	1.37 [0.84–2.25]	0.208
Educational status, n (%)[1 #]					
- low	51 (19.4)	18 (13.5)	33 (25.4)	0.74 [0.55–1.01]	0.043
- medium	41 (15.6)	24 (18.1)	17 (13.1)		
- high	171 (65.0)	91 (68.4)	80 (61.5)		
Aerobic exercise, n (%) [#]					
- limited by disease	45 (17.2)	13 (9.9)	32 (24.8)	0.60 [0.42–0.85]	0.005
- not regularly	117 (44.8)	62 (47.0)	55 (42.6)		
- regularly	99 (37.9)	57 (43.2)	42 (32.6)		
Professional status, n (%)[2 #]					
- active	191 (78.3)	98 (79.0)	93 (77.5)	1.14 [0.88–1.47]	0.351
- no current paid work	11 (4.5)	8 (6.5)	3 (2.5)		
- disease-related work disability	13 (5.3)	6 (4.8)	7 (5.8)		
- retired	29 (5.3)	12 (9.7)	17 (14.2)		

VAS: visual analogue scale; BMI: Body Mass Index; SD: standard deviation; SpA: spondyloarthritis; 95%CI: 95% confidence interval.
*p-value compares patients with high *vs*. low fatigue. [#]The total number of patients is different from the 266 patients because of missing data. [1]Medium: completed high school; high: university level. [2]Active: paid work or student; no current paid work: housewife or unemployment; disease disability: prolonged sick-leave or compensated work disability. (%) Calculation of percentages: number of patients of a count on total number of patients in the category of fatigue.

chronic inflammatory bowel, in 40.0% in reactive arthritis, in 55.5% in juvenile SpA and in 44.4% in undifferentiated SpA (Supplementary Table). According to forms of SpA, high fatigue was present in 48.7% of axial SpA, in 50.0% of peripheral SpA, in 54.5% of enthesiopathic forms and in 66.6% of other forms (percentage of patients of each form of SpA (Table II).

Association between fatigue and patient-related or disease-related elements.

Univariate logistic analyses explaining high fatigue:

- Sociodemographic elements (Table I): High fatigue was more frequent in females (p=0.025) and in patients with limited aerobic exercise due to disease (p=0.005). Fatigue tends to be more common in people with low educational levels (p=0.043).
- Disease related variables: There were significant differences in global health VAS, disease activity (BASDAI) and function (BASFI) according to high *versus* low fatigue (p<0.001 for the 3 outcomes), but not for axial pain (p=0.626) (Table I). The number of patients with initial elevated CRP was similar between the both groups (p=0.452).
  No statistically significant differences were found regarding different disease characteristics, and in particular between the different diagnoses or subtypes of SpA (Table I and supplementary Table).
- Treatments: One hundred and thirty-five patients (50.7%) were currently treated with anti-TNF. High fatigue was not associated with current treatments (Table II).

The results were similar with the 70 mm cut-off (data not shown).

Multivariate analysis explaining high versus low fatigue (logistic regression)

In a multivariate analysis, high fatigue was related only to high global VAS (odds ratio =1.35 [95%CI 1.24–1.47] per 5 units of global VAS, p<0.0001).

Explanation of fatigue by linear regressions

Univariate analyses largely confirmed the logistic regressions: associations were found with female gender (p=0.007), BASDAI (p=0.011) and global VAS (p<0.0001). When analysing groups of variables (either patient-related or disease-related), fatigue was explained for 46.1% by disease related variables (BASFI and global VAS, adjusted R^2=0.461) rather than by demographic characteristics, which explained only 2.8% of the variance (female gender, adjusted R^2=0.028).

Discussion

This study indicates that fatigue is an important symptom in SpA, whatever the subtype, with a mean VAS fatigue of 49.3±32.7mm and high fatigue in 49.6% of the population in this unselected real-life sample. Global VAS was the main factor associated with a higher prevalence of fatigue in SpA patients, and the variance attributable to disease activity was much higher than the variance attributable to demographic variables, suggesting that fatigue is related more strongly to disease-related variables than to demographic or patient-related characteristics.

Our study has some limitations, in particular in the selection of patients. First, it is a single centre study; however this allowed homogeneous data collection and patients were not selected on disease activity, thus leading to 'real-life' sampling. Possibly, there was a selection bias: our patients living in Paris or around Paris had a higher educational status than the general French population. However, when soliciting patients for a voluntary study, it is difficult to obtain a representative sample (41). It is to be noted that the present patients were frequently treated by anti-TNF, perhaps reflecting more severe disease. But we had a large sample of SpA patients and the patients were included consecutively. Moreover a bias of memory could exist in this cross-sectional study, but the questioning of patient was completed with a cross-check

Table II. Disease's characteristics and current treatment of 266 SpA patients according to the level of fatigue.

	All	Low fatigue (VAS≤50 mm)	High fatigue (VAS>50 mm)	Odds ratio ± 95%CI	*p*-value*
n (%)	266	134 (50.4)	132 (49.6)		
Disease related variables					
Amor's criteria, n (%)	249 (93.6)	126 (94.0)	123 (93.2)	0.87 [0.32–2.32]	0.778
ASAS criteria, n (%)	228 (85.7)	117 (87.3)	111 (84.1)	0.77 [0.39–1.53]	0.454
Disease duration, years mean (SD)	16.8 (11.7)	16.9 (12.5)	16.8 (10.8)	1.00 [0.98–1.02]	0.706
Forms of SpA, n (%)					
- Axial SpA	193 (72.6)	99 (73.9)	94 (71.2)	1.15 [0.77–1.73]	0.710
- Peripheral SpA	56 (21.0)	28 (20.9)	28 (21.2)		
- Others	17 (6.4)	7 (5.2)	10 (7.6)		
HLA B27 +, n (%) [1]	192 (79.01)	99 (80.5)	93 (77.5)	0.84 [0.45–1.55]	0.637
BASDAI (0–100mm), mean (SD)	32.4 (22.9)	22.0 (17.2)	42.9 (22.9)	1.05 [1.04–1.07]	<0.0001
BASFI (0–100mm), mean (SD)	27.6 (25.2)	18.1 (20.3)	37.1 (26.8)	1.04 [1.02–1.05]	<0.0001
Global health VAS (0–100 mm), mean (SD)	40.0 (27.3)	25.4 (19.8)	54.8 (25.8)	1.05 [1.04–1.07]	<0.0001
Current treatments: n (%)					
NSAID	133 (50.0)	61 (45.5)	72 (54.6)	1.44 [0.89–2.33]	0.141
Methotrexate	60 (22.6)	27 (20.2)	33 (25.0)	1.32 [0.74–2.35]	0.344
Sulfazalazine	8 (3.0)	2 (1.5)	6 (4.6)	3.14 [0.62–15.86]	0.171
Anti-TNF	135 (50.7)	72 (53.7)	63 (47.7)	0.81 [0.50–1.31]	0.392

VAS: visual analogue scale; SD: standard deviation; SpA: spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NSAID: nonsteroidal anti-inflammatory drugs; anti-TNF: anti-tumour necrosis factor alpha; 95%CI: 95% confidence interval.
*p-value compares patients with high *vs*. low fatigue. #The total number of patients is different of the 266 patients because of missing data. (%) Calculation of percentages: number of patients of a count on total number of patients in the category of fatigue. [1]On patients with available data for HLAB27.

Supplementary Table. Fatigue in different subtypes of SpA patients: number of patients according to the level of fatigue with a cut-off of 50 mm and mean of VAS fatigue.

Subtypes of SpA*	Total number of patients, n (%)	Low fatigue, n (%)	High fatigue, n (%)	*p*-value	Mean of VAS Fatigue ± SD (0–100mm)
Axial AS	183	93 (50.8)	90 (49.2)	0.830	50.1 (32.4)
Psoriasic arthritis	47	22 (46.8)	25 (53.2)	0.190	48.6 (33.3)
SpA with chronic inflammatory bowel	22	7 (31.8)	15 (68.2)	0.069	61.6 (36.9)
Reactive arthritis	5	3 (60.0)	2 (40.0)	1.000	42.8 (34.9)
Juvenile SpA	9	4 (44.5)	5 (55.5)	0.748	56.6 (32.6)
Undifferentiated SpA	36	20 (55.5)	16 (44.5)	0.504	44.6 (33.2)

SpA: spondyloarthritis; AS: ankylosing spondyloarthritis; VAS: visual analogue scale; SD: standard deviation. (%) Calculation of percentages: number of patients with low or high fatigue on total number of patients with a subtype of SpA . *The sum is 302 since patients could be classified as having several subtypes.

of the paper files. Another limitation is that patient's psychological status or other diseases such as hypothyroidism or diabetes mellitus, which are known to be associated with fatigue, were not assessed. Moreover, as the principal aim of this study was not explicitly fatigue, specific treatments, *e.g.* antidepressants or psychotherapy, were not noted. In the present study, fatigue was assessed by VAS (14, 34). Different scales could be used to assess fatigue in SpA: the first item of the BASDAI (12, 14) and multidimensional scores like the Multidimensional Fatigue Inventory (15), the Multidimensional Assessment of Fatigue (14) or other scores (3). However, fatigue VAS is validated in SpA (4, 22) and the Assessment of SpondyloArthritis international Society (ASAS group) has recommended this scale or the first question of BASDAI as the most appropriate measures of fatigue in daily practice (3, 7, 35). It is also easy to use and it was the most frequently used in publications at the time of conception of the study (12, 14). The 50mm cut-off in fatigue VAS chosen in this study can be discussed: however, it is widely used in publications of fatigue in SpA (4, 5, 15), and it should be noted that both analyses of fatigue as a continuous variable and the cut-off of 70mm showed the same results. Finally, although fatigue is also observed in fibromyalgia, our patients had definite SpA and most fulfilled ASAS criteria or the Amor criteria, therefore we believe our results are relevant for SpA.

In our study, the prevalence of high fatigue was high (49.6%) and was similar in different forms and sub-types of SpA, which is consistent with other authors (4, 14, 15), except for Turan *et al*. who found higher fatigue levels, *i.e*. 76% of AS patients with a first item of BASDAI ≥50/100mm (14, 15). The frequency of fatigue is similar in RA, persistent severe fatigue is present in 40% of patients (42-44). We did not find lower fatigue in patients treated by anti-TNF. This could be explained most probably by confounding by indication (patients with more severe symptoms being treated by anti-TNF). It is possible also that there was an inefficacy of anti-TNF on fatigue, however, efficacy has been indicated in randomised controlled trials (20, 21).

The only factor appearing to be linked with fatigue was global VAS. An explanation could be that patients include fatigue in the global VAS question or because high fatigue is associated with high activity disease. In term of disease characteristics, there were no statisti-

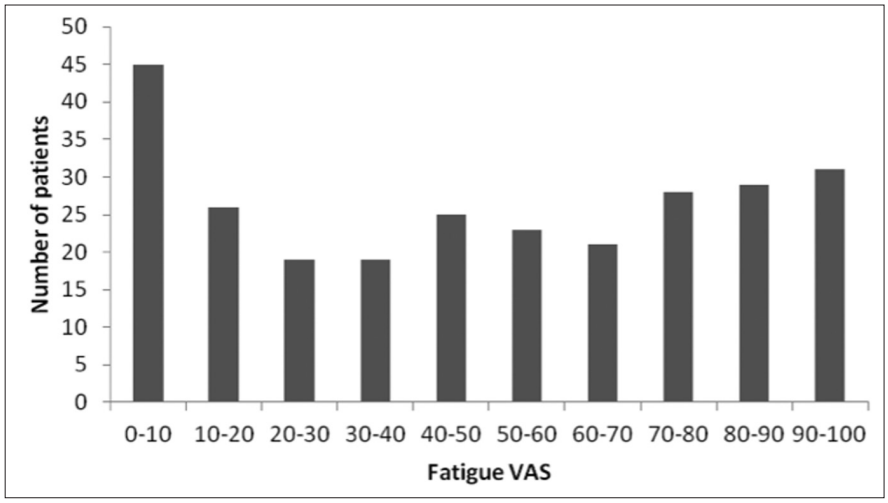

Fig. 2. Distribution of fatigue VAS (0-100mm) in 266 SpA patients.

cally significant differences between subtypes of SpA, HLA B27 or disease duration. Sociodemographic characteristics were associated with fatigue in univariate analyses (female gender and low aerobic exercise) though not in multivariate analyses; but female gender was associated with fatigue in linear regressions, which is concordant with other authors who have shown that female patients were more fatigued (14). This could be explained by a different perception of fatigue. Furthermore, limited aerobic exercise appeared to be linked with high fatigue, but we could not know if it is indirectly because of stiffness and pain; regular physical exercise may decrease fatigue (18), by reassuring patients, by improving management of fatigue and by avoiding a deconditioned state. Disease characteristics were not associated with fatigue in multivariate analyses, in particular subtypes of SpA (7, 19, 22). Some studies have shown, like us, an association between fatigue and disease activity (4, 15, 17). Thus, the study indicates that fatigue may be truly a disease manifestation, reflecting disease activity. It could be explained by the character pathological of fatigue, unlike physiological fatigue, which is improved by the rest and is linked to patient characteristics.

In the new millennium, fatigue remains an important aspect of SpA. Fatigue levels appear to be more related to the self-reported disease variables than to patient characteristics; this validates the use of fatigue as an outcome measure in trials, where fatigue is analysed in composite criteria like the BASDAI. Future studies should explore the pathophysiology of fatigue in SpA, and specifically analyse the effects of treatments including biologics on SpA-related fatigue.

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