Assessment of Fatigue in Spondyloarthritis and Its Association with Disease Activity

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ABSTRACT. ***Objective.*** To evaluate fatigue in patients with spondyloarthritis (SpA) and to define its association with disease-related factors and patients' features.

Methods. A cross-sectional multicenter study which includes 2251 patients with SpA selected from the national Spondyloarthropathies Registry (the Spanish Society of Rheumatology; REGISPONSER) Spanish cohort. The primary outcome was the assessment of fatigue performed with the first item of the Bath Ankylosing Spondyloarthritis Disease Activity Index followed by the study of its relation with different factors organized into 4 groups: sociodemographics, emotional, disease-related, and disease activity. Univariate logistic regressions, multivariate logistic regression, and multiple linear regressions were performed to relate fatigue with the studied covariates.

Results. Mean fatigue score in all patients with SpA was 4.3 ± 2.9, with statistically significant differences between different SpA types. In univariate logistic regressions, significant differences were seen for many variables included in the 4 groups. Multivariate logistic regression showed that high fatigue score was related with sex (female), emotional component, the Ankylosing Spondylitis Quality of Life score, stiffness, and high levels of 2 visual analog scale items (vertebral pain in the last week and patient's global assessment of disease activity). The multivariate linear regression showed that fatigue was mainly explained by disease-related factors and disease activity (54.1%), but sex and emotional status may also be involved in 13.5% of the variance.

Conclusion. Fatigue is associated with disease-related factors and mostly with SpA activity. However, the emotional component and sex may contribute to the onset of fatigue. (J Rheumatol First Release February 15 2016; doi:10.3899/jrheum.150832)

Key Indexing Terms:
SPONDYLOARTHROPATHY FATIGUE DISEASE ACTIVITY

Fatigue is defined as a subjective sensation of generalized weariness together with a mental component[1,2,3]. In healthy individuals it is temporary, whereas in rheumatologic patients, fatigue can be continuous and persistent in spite of appropriate daily rest[4].

Further, fatigue is one of the most important symptoms in spondyloarthritis (SpA), together with pain and stiffness[5]. However, this manifestation has not been widely studied, probably because it is a multifactorial[1], subjective symptom and it is difficult to quantify.

Causes of fatigue are not well defined yet. Some authors suggest the involvement of social components (cultural level, professional status, exercise), demographics (sex, age, or ethnicity), and psychological factors (depression, stress, cognitive impairment)[4,6,7]. However, others say that fatigue is related to disease activity and therefore is associated with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[8], the Bath Ankylosing Spondylitis Functional Index (BASFI)[9], and the patient's global assessment (PtGA) of disease activity by visual analog scale (VAS).

There are several ways to assess fatigue. One of the most common is through the use of the first question of the BASDAI[8], which measures fatigue on a 0–10 scale. Fatigue VAS[3,10] is also used to evaluate this symptom, and both have

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been validated by the Assessment of SpondyloArthritis International Society to measure fatigue in SpA[6,11]. Another scale called the Multidimensional Fatigue Inventory is used less frequently[12].

Currently, there is a lack of knowledge about fatigue, so rheumatologists are still questioning whether fatigue is an essential symptom of the disease, whether it appears as a consequence of other symptoms, or whether it is related to social, demographic, and psychological elements from each patient.

The aims of our study were to assess fatigue in Spanish patients included in the national Spondyloarthropathies Registry of the Spanish Society of Rheumatology (REGISPONSER)[13] cohort and to define the relationship of fatigue to patients and disease characteristics, as well as to confirm the findings of other studies that associate fatigue with disease activity[3].

MATERIALS AND METHODS

Study design. Our cross-sectional multicenter study aimed to (1) assess the prevalence and importance of fatigue in Spanish patients with SpA, and (2) demonstrate its association with patients' sociodemographic and emotional characteristics, as well as with disease-related factors and disease activity.

Patients. Our study included 2251 patients with different types of SpA selected from the REGISPONSER[13] Spanish cohort, which gathered 2367 patients. Our study excluded 116 patients because of missing data.

The REGISPONSER registry was launched in 2004 by the Spanish Group of Rheumatology. Twelve rheumatology departments from 8 different cities participated in the inclusion of the patients in the REGISPONSER.

The inclusion criteria in the registry were (1) to fulfill the classification criteria of the European Spondyloarthropathy Study Group (ESSG)[14]; (2) having blood tests available within 15 days of the inclusion visit and a complete radiographic study within the previous year; and (3) agreeing to complete all self-administered questionnaires. All patients gave their consent to participate in our study, which was approved centrally by the ethics committee of the University Hospital Reina Sofía.

Investigated variables. Fatigue was evaluated in each patient with the first item of the BASDAI and it was used as a dichotomous variable, considered as "high fatigue" at a score of > 5 and as "low fatigue" at a score of ≤ 5. We decided to use the cutoff of 5 because it has been used in other studies with similar characteristics[3,7,12,15]. We also used fatigue as a continuous variable when means, differences of means, and linear regressions were calculated.

Sociodemographic variables included sex, age, disease duration since first symptoms (represented in years), ethnicity, smoking, marital status, educational level, working status, and 3 exercise-related variables: work characteristics, playing a sport habitually, and the number of hours played per week.

To evaluate emotional component, we used the sixth and seventh items of the SF-12 Health Survey Scoring Demonstration (the short form of the Medical Outcomes Study Short Form-36) and the mental content component from this questionnaire, related to the emotional state of patients[16]. Patients were asked: "During the past 4 weeks, were you limited in the kind of work you do or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)? (6) Accomplished less than you would like. (7) Didn't do work or other activities as carefully as usual." Agreement with both (6) and (7) meant the presence of an emotional problem.

Different disease-related factors were included: clinical form of SpA[17] (peripheral, nonradiographic axial, and radiographic axial), HLA-B27 antigen, nonsteroidal antiinflammatory drug (NSAID) response, the Bath Ankylosing Spondylitis Radiographic Index (BASRI)[18], and the presence of inflammatory back pain according to the Calin criteria[19].

To evaluate disease activity, we used the BASFI, ankylosing spondylitis (AS) quality of life (ASQoL)[20], nocturnal vertebral pain by a 0–10 VAS, physician's global assessment (PGA) and PtGA of disease activity (also by a 0–10 VAS), and vertebral pain in the last week (0–10 VAS). In addition, we included the C-reactive protein (CRP) with a cutoff of 5 mg/dl as a dichotomous variable and the erythrocyte sedimentation rate (ESR) as a continuous variable. To assess the relation between stiffness and fatigue, we also used the fifth and sixth items of the BASDAI.

Finally, we compared fatigue with the treatment administered to the patient.

Statistical analysis. Statistical analysis was performed using G-Stat 2.0. P values ≤ 0.05 were considered significant.

Descriptive data are presented as mean ± SD when referring to quantitative variables and as absolute frequencies and percentages when referring to qualitative ones.

Prevalence of high fatigue and low fatigue in different clinical SpA entities[21] was evaluated and the differences between groups were tested using the chi-square test. Fatigue was used as a quantitative variable in the ANOVA analysis to calculate means and the difference of means for each SpA type.

Univariate logistic regressions were performed for each group of variables (sociodemographics, psychics, disease-related factors, and disease activity) and also for the treatments [methotrexate, leflunomide, sulfasalazine, and antitumor necrosis factor (anti-TNF)].

The statistically significant variables ($p < 0.05$) obtained in each univariate analysis were modeled in multivariate logistic regression, which is represented as an associative model. The presence of confounding and interaction were checked.

To determine the variance in fatigue attributable to different variables (calculated by R^2), 2 separate multiple linear regressions were performed: 1 with sociodemographics and emotional factors, and the other with disease-related and disease activity factors (all obtained from the multivariate logistic regression with $p < 0.05$).

RESULTS

There were 1546 men (68.68%) and 705 women (31.32%) enrolled in our study, with an average age of 47.73 ± 13.26 years and a mean time of disease evolution of 18.12 ± 12.83 years.

The descriptive data for the first 1379 patients included in the registry after 12 months (April 2004 to March 2005) were published previously elsewhere and are accessible[13]. Of these, 939 were men (68.1%) with a mean age of 48.0 ± 13.4 years and a mean age at onset of 29.5 ± 12.6 years. The mean of disease duration was 12.0 ± 9.9 years with a mean diagnosis delay of 6.5 ± 8.4 years. These results were similar to those obtained in the final registry used in our study.

All patients fulfilled the ESSG classification criteria, with 1282 patients (56.95%) fulfilling the New York modified criteria for AS[22]. The rest were classified as follows: 507 patients (22.52%) as arthritis and/or spondylitis associated with psoriasis, 285 (12.66%) as undifferentiated SpA (u-SpA), 100 (4.44%) as spondylitis associated with inflammatory bowel disease (a-IBD), 43 (1.91%) as reactive arthritis (ReA), and 34 (1.51%) as juvenile SpA.

The mean fatigue score for all patients was 4.29 ± 2.90, of whom 1421 (63.13%) presented a low degree of fatigue and 830 (36.87%) a high degree of fatigue.

Table 1 shows the frequency of "high fatigue" according to SpA types: PsA (38.26%), AS (37.91%), u-SpA (34.39%),

Table 1. Analysis of frequency of fatigue according to the different subtypes of SpA. P value compares patients with "low fatigue" against "high fatigue." Percentages indicate no. patients with "low fatigue" or "high fatigue" from the total no. patients with a subtype of SpA. Values are n (%) unless otherwise specified.

Subtypes	Total	Low Fatigue, ≤ 5	High Fatigue, > 5	p
Ankylosing spondylitis	1282 (56.9)	796 (62.09)	486 (37.91)	0.24
Psoriatic arthritis	507 (22.52)	313 (61.74)	194 (38.26)	0.46
Undifferentiated spondyloarthropathies	285 (12.66)	187 (65.61)	98 (34.39)	0.35
Spondylitis with IBD	100 (4.44)	66 (66)	34 (34)	0.54
Reactive arthritis	43 (1.91)	33 (76.74)	10 (23.26)	0.06
Juvenile SpA	34 (1.51)	26 (76.47)	8 (23.53)	0.10

SpA: spondyloarthritis; IBD: inflammatory bowel disease

a-IBD (34%), juvenile SpA (23.53%), and ReA (23.26%). No significant differences among the types were found. Nevertheless, when we tested fatigue as a continuous variable (Figure 1), statistically significant differences were found in fatigue between different SpA types, in particular AS versus ReA and u-Spa, respectively.

Sociodemographic variables (Table 2) showed that fatigue is more frequent in women (OR 1.62, 95% CI 1.35–1.94, p < 0.001), in married versus unmarried (OR 1.56, 95% CI 1.14–2.19, p = 0.004), and in patients who do physical work (OR 1.84, 95% CI 1.12–3.05, p = 0.017). Age and time of disease duration were significantly associated with high fatigue (OR 1.01, 95% CI 1.01–1.02, p < 0.001 in both variables). Fatigue was less frequent in patients with university studies (OR 0.30, 95% CI 0.10–0.88, p = 0.028) and in those who do physical activity (sports) habitually (OR 0.73, 95% CI 0.61–0.87, p < 0.001) with a mean of 4.8 h per week. Both advanced education and sports were considered protective factors against fatigue. No differences were encountered regarding ethnicity, smoking, or number of sports hours per week.

Concerning mental variables, Table 2 shows statistically significant differences in the sixth (OR 4.01, 95% CI 3.31–4.85, p < 0.001) and the seventh questions of the SF-12 (OR 3.61, 95% CI 2.97–4.39, p < 0.001), both belonging to the emotional component. Therefore, a positive answer to these 2 questions represented a risk factor to develop fatigue.

Table 3 presents data of disease-related factors and the univariate logistic regression for these variables. Regarding the clinical form of the disease, fatigue was more frequent in patients with radiographic axial (OR 1.47, 95% CI 1.16–1.87, p = 0.001) than in those with the peripheral form and non-radiographic axial form. Inflammatory back pain represented a risk factor (OR 1.48, 95% CI 1.18–1.87, p < 0.001) for fatigue versus another type of pain. No statistically significant differences were found regarding HLA-B27, NSAID response, and the BASRI.

Table 4 expresses the univariate logistic regressions for disease activity variables. According to high versus low fatigue, there were significant differences (p < 0.001) in the BASFI (OR 1.51, 95% CI 1.45–1.57), nocturnal vertebral pain (OR 1.48, 95% CI 1.43–1.54), vertebral pain in the last week (OR 1.58, 95% CI 1.52–1.65), PtGA (OR 1.74, 95% CI 1.65–1.82), PGA (OR 1.36, 95% CI 1.30–1.42), and ASQoL

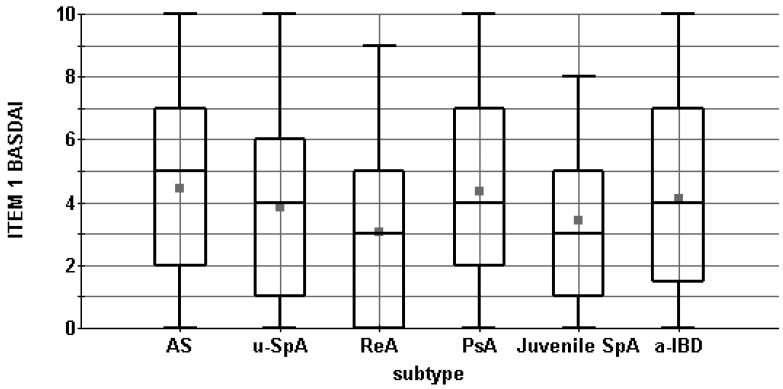

Figure 1. Differences in fatigue according to the subtype of SpA. SpA: spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; AS: ankylosing spondylitis; u-SpA: undifferentiated SpA; ReA: reactive arthritis; PsA: psoriatic arthritis; a-IBD: spondylitis associated with inflammatory bowel disease.

Table 2. Univariate logistic regression regarding sociodemographics and emotional variables. P value compares patients with "low fatigue" against "high fatigue." Percentages indicate no. patients with the covariate from the total no. patients in the category of fatigue. Values are n (%) unless specified otherwise.

Characteristics	Total	Low Fatigue, ≤ 5	High Fatigue, > 5	OR (95% CI)	p
n	2251	1421 (63.1)	830 (36.87)		
Female, ref. male	705 (31.32)	390 (27.45)	315 (37.95)	1.62 (1.35–1.94)	< 0.001
Age, yrs, mean (SD)	47.73 (13.26)	46.63 (13.76)	49.61 (12.13)	1.01 (1.01–1.02)	< 0.001
Disease duration, yrs, mean (SD)	18.12 (12.83)	17.17 (12.83)	19.73 (12.67)	1.01 (1.01–1.02)	< 0.001
Marital status					
Unmarried	240 (20.44)	172 (22.99)	68 (15.96)	Reference	
Married	884 (75.30)	546 (72.99)	338 (79.34)	1.56 (1.14–2.19)	0.004
Divorced	32 (2.73)	19 (2.54)	13 (3.05)	1.73 (0.81–3.69)	0.157
Widower	18 (1.53)	11 (1.47)	7 (1.64)	1.61 (0.60–4.32)	0.345
Educational level					
Illiterate	15 (1.28)	7 (0.94)	8 (1.88)	Reference	
Primary school	513 (43.88)	304 (40.92)	209 (49.06)	0.60 (0.21–1.68)	0.333
Secondary	207 (17.71)	138 (18.57)	69 (16.20)	0.43 (0.15–1.25)	1.124
Bachelor's	244 (20.87)	153 (20.59)	91 (21.36)	0.52 (0.18–1.48)	0.221
University	190 (16.25)	141 (18.98)	49 (11.50)	0.30 (0.10–0.88)	0.028
Work characteristics					
Sedentary	207 (31.75)	149 (34.10)	58 (26.98)	Reference	
Moderate physical activity	347 (53.22)	231 (52.86)	116 (53.95)	1.29 (0.88–1.88)	0.184
Intense physical activity	98 (15.03)	57 (13.04)	41 (19.07)	1.84 (1.12–3.05)	0.017
Sport habitually	869 (38.71)	586 (41.38)	283 (34.14)	0.73 (0.61–0.87)	< 0.001
SF-12 question 6					
Yes, ref. no	705 (32.94)	286 (21.39)	419 (52.18)	4.01 (3.31–4.85)	< 0.001
SF-12 question 7					
Yes, ref. no	619 (29.02)	253 (18.97)	366 (45.81)	3.61 (2.97–4.39)	< 0.001
SF12 MCS, mean (SD)	50.34 (5.49)	50.03 (5.50)	50.84 (5.43)	1.03 (1.01–1.04)	< 0.001

ref.: reference; SF-12: Medical Outcomes Study Short Form-36; MCS: mental component summary.

Table 3. Univariate logistic regressions regarding disease-related factors. P value compares patients with "low fatigue" against "high fatigue." Percentages indicate no. patients with the covariate from the total no. patients in the category of fatigue. Values are n (%) unless otherwise specified.

	Total	Low Fatigue, ≤ 5	High Fatigue, > 5	OR (95% CI)	p
Clinical forms					
Peripheral	382 (17.21)	268 (19.13)	114 (13.92)	Reference	
Nonradiographic axial	207 (9.32)	131 (9.35)	76 (9.28)	1.36 (0.95–1.95)	0.089
Radiographic axial	1631 (73.47)	1002 (71.5)	629 (76.80)	1.47 (1.16–1.87)	0.001
Inflammatory back pain	1840 (81.85)	1131 (79.7)	709 (85.42)	1.48 (1.18–1.87)	< 0.001
HLA-B27+	1396 (73.86)	886 (74.89)	510 (72.14)	0.87 (0.70–1.07)	0.186
NSAID response	891 (93.01)	578 (93.78)	313 (92.33)	0.85 (0.51–1.42)	0.544
BASRI, mean (DS)	5.35 (4.33)	5.28 (4.36)	5.46 (4.27)	1.01 (0.99–1.03)	0.364

NSAID: nonsteroidal antiinflammatory drugs; BASRI: Bath Ankylosing Spondylitis Radiographic Index.

(OR 1.26, 95% CI 1.23–1.28). In addition, we found statistically significant differences ($p < 0.001$) for the high values of ESR (OR 1.01, 95% CI 1.01–1.02) and CRP ≥ 5 mg/dl (OR 1.76, 95% CI 1.47–2.11), as well as for the fifth (OR 1.54, 95% CI 1.48–1.59) and sixth items of the BASDAI (OR 1.35, 95% CI 1.31–1.40), both referring to morning stiffness.

Concerning treatment, significant and protective associations were found only for anti-TNF (OR 0.63, 95% CI 0.48–0.94, $p = 0.024$).

The multivariate logistic regression (Table 5) showed that high fatigue was associated with sex (OR 1.34, 95% CI 1.03–1.74, $p = 0.031$), question 6 of the SF-12 questionnaire (OR 1.83, 95% CI 1.39–2.42, $p < 0.001$), vertebral pain in the last week (OR 1.22, 95% CI 1.15–1.29, $p < 0.001$), PtGA (OR 1.24, 95% CI 1.16–1.33, $p < 0.001$), ASQoL (OR 1.11, 95% CI 1.08–1.14, $p < 0.001$), and the fifth item of BASDAI (OR 1.26, 95% CI 1.19–1.34, $p < 0.001$). In our analysis, the sixth item of the BASDAI acted as a protective factor (OR 0.94, 95% CI 0.88–0.99, $p = 0.026$) in the appearance of fatigue.

The multivariate linear regressions showed that 13.5% of fatigue was explained by sex and the sixth question of the SF-12 ($R^2 = 0.135$), whereas disease-related factors and disease activity (vertebral pain in the last week, PtGA, ASQoL, and the fifth and sixth items of the BASDAI) explained 54.1% of the variance ($R^2 = 0.514$).

Table 4. Univariate logistic regression regarding disease activity factors. P value compares patients with "low fatigue" against "high fatigue." Percentages indicate no. patients with the covariate from the total no. patients in the category of fatigue. Values are mean (SD) unless otherwise specified.

Variables	Total, n (%)	Low Fatigue, ≤ 5	High Fatigue, > 5	OR (95% CI)	p
BASDAI	4.06 (2.38)	2.79 (1.76)	6.23 (1.62)	2.83 (2.61–3.08)	< 0.001
BASFI	3.50 (2.69)	2.53 (2.32)	5.16 (2.46)	1.51 (1.45–1.57)	< 0.001
Nocturnal vertebral pain, VAS, cm	3.61 (2.97)	2.50 (2.46)	5.51 (2.80)	1.48 (1.43–1.54)	< 0.001
Vertebral pain in the last week, VAS, cm	3.81 (2.81)	2.70 (2.37)	5.70 (2.50)	1.58 (1.52–1.65)	< 0.001
Patient's global VAS of disease activity, cm	4.42 (2.71)	3.29 (2.34)	6.36 (2.16)	1.74 (1.65–1.82)	< 0.001
Physician's global VAS of disease activity, cm	3.03 (2.11)	2.54 (1.95)	3.86 (2.10)	1.36 (1.30–1.42)	< 0.001
ASQoL	6.10 (5.12)	4.18 (4.13)	9.42 (4.97)	1.26 (1.23–1.28)	< 0.001
CRP ≥ 5 mg/dl, %	953 (45.49)	534 (40.33)	419 (54.35)	1.76 (1.47–2.11)	< 0.001
ESR, mm/h	18.02 (15.82)	16.87 (14.58)	19.99 (17.56)	1.01 (1.01–1.02)	< 0.001
Item 5 BASDAI	4.43 (3.15)	3.16 (2.73)	6.61 (2.57)	1.54 (1.48–1.59)	< 0.001
Item 6 BASDAI	3.54 (2.97)	2.62 (2.68)	5.10 (2.87)	1.35 (1.31–1.40)	< 0.001

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analog scale; ASQoL: ankylosing spondylitis quality of life; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 5. Multivariate logistic regression regarding the statistically significant covariates obtained in the univariate logistic regressions. Chi-square: 938.35 p < 0.001. P value compares patients with "low fatigue" against "high fatigue."

Variables	OR (95% CI)	p
Female, ref. male	1.34 (1.03–1.74)	0.031
SF-12 question 6	1.83 (1.39–2.42)	< 0.001
Vertebral pain in the last week, VAS, cm	1.22 (1.15–1.29)	< 0.001
Patient's global VAS of disease activity, cm	1.24 (1.16–1.33)	< 0.001
ASQoL	1.11 (1.08–1.14)	< 0.001
Item 5 BASDAI	1.26 (1.19–1.34)	< 0.001
Item 6 BASDAI	0.94 (0.88–0.99)	0.026

ref.: reference; SF-12: Medical Outcomes Study Short Form-36; VAS: visual analog scale; ASQoL: ankylosing spondylitis quality of life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

DISCUSSION

Our study shows that fatigue is an important symptom in patients with SpA, having a prevalence of 36.87%. Our results are different from those of studies from other countries[1,3], in which the prevalence of fatigue is around 50%, perhaps because sociodemographics and ambient characteristics are not the same.

Our study has some limitations. One of them is the data collection, which was performed by different rheumatologists. Another is the use of a diverse range of laboratories to quantify the blood tests. However, this provides a greater external validity to our results. Another limitation is that we did not assess the presence of other diseases that produce fatigue, such as hypothyroidism, diabetes, and obstructive sleep apnea syndrome.

Our study shows the involvement of sociodemographic factors, especially sex, in the appearance of fatigue. The appearance of fatigue in women may be explained by the effect of cortisol and the female hypothalamic-pituitary-gonadal axis theory suggested by some authors for other musculoskeletal diseases[23,24].

We showed that patients who do physical work have high levels of fatigue; nevertheless, doing aerobic exercise habitually represents a protective factor against developing this symptom. Therefore, aerobic exercise of moderate intensity, which includes walking, postural correction therapy, and swimming, is recommended to prevent fatigue in patients with SpA[25,26,27].

Our results suggest that fatigue is related to the emotional status, which confirms the influence of a psychological component in the development of this symptom[28] and emphasizes the importance of a multidisciplinary treatment for patients with SpA.

Regarding disease-related factors, we showed that fatigue is associated with the radiographic axial form and inflammatory back pain. Both can be related to nocturnal pain, and as a consequence can lead to frequent awakening during the night[26,29], causing high fatigue during the day.

Fatigue was less frequent in patients who received anti-TNF. This result is unexpected because patients who are treated with biologic drugs often have more severe disease or resistance to other treatments. However, our results are similar to other studies that demonstrated a reduction in fatigue of > 50% after 3 years of treatment with anti-TNF[30]. This can be explained by the improvement in other variables associated with fatigue, such as the BASFI, pain in the last week, and the ASQoL.

Our study confirms the relationship between high fatigue and the high disease activity measured with PtGA of disease activity[3], the BASFI, pain in the last week, and ASQoL.

Our analysis shows that the fifth item of the BASDAI (referring to stiffness intensity) acts as a risk factor for developing fatigue while the sixth item of the BASDAI (referring

to stiffness duration) is a protective factor. One possible explanation could be that patients with longer stiffness duration may have a high level of vertebral ankylosis and longer disease duration, so they could have a "normalization" phenomenon or "familiarization" to fatigue[29]. Therefore, the importance of stiffness lies in its intensity and not in its duration.

Our study shows that 54.1% of fatigue is explained by disease-related factors and disease activity, whereas sex and mental component explain it in 13.5% (a significant percentage considering the multifactorial characteristic of this symptom). These results point to the emotional component and sex as contributory causes in the appearance of fatigue. Therefore, we recommend a multidisciplinary approach for the treatment of fatigue in clinical practice in patients with SpA. Fatigue assessment is necessary in daily practice, and fatigue should be considered an SpA symptom with an importance comparable to pain and stiffness.

Future studies will need to assess fatigue at several timepoints to obtain a better understanding of this symptom. Studies could focus on its physiopathology and its use as a principal outcome in clinical trials.

APPENDIX 1.

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