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Artículo original

Fatiga en pacientes con espondiloartritis: datos en un centro de atención terciaria en Brasil

Fatigue in patients with spondyloarthritis: data from a tertiary care center in Brazil

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Palabras clave: fatiga; espondiloartritis; actividad de la enfermedad.

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RESUMEN

Introducción: la fatiga es frecuente en los pacientes con espondiloartritis axial (SpA), afectando la calidad de vida y su causa no es completamente comprendida.

Objetivos: estudiar factores asociados a la fatiga en pacientes con SpA.

Materiales y métodos: se incluyeron pacientes con SpA. La actividad de la enfermedad se constató mediante BASDAI (*Bath Disease Activity Index*), ASDAS-ESR (Ankylosing Spondylitis Disease Activity Score-globular sedimentation rate) y ASDAS-CRP (proteína C reactiva). La depresión se midió por CES-D (*Center for Epidemiological Scale–Depression*), la función por BASFI (*Bath Ankylosing Spondylitis Functional Index*) y la calidad de vida por el SF-12. El FACIT (*Functional Assessment of Chronic Illness Therapy-fatigue*) se utilizó para medir la fatiga.

Resultados: Se incluyeron 74 pacientes con SpA. La fatiga se correlacionó con BASDAI (rho=-0,74); BASFI (rho=-0,74); ASDAS-ESR (rho=-0,55); ASDAS-CRP (rho=-0,54); y CES-D (rho=-0,73). El modelo de regresión múltiple mostró que BASFI (coef β -2,60; 95%IC -3,65 a 1,55; p<0,0001) y CES-D (coef β -0,44; 95%IC 0,09 -0,63 a 0,24; p<0,0001) se correlacionaron con FACIT-fatiga, ajustado por ASDAS, artritis periférica, lesiones cutáneas, edad, sexo y años de la enfermedad.

Conclusiones: en esta serie, la fatiga en pacientes con SpA se asoció con la capacidad funcional y la depresión.

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Key words: *fatigue; spondyloarthritis; disease activity.*

ABSTRACT

Introduction: fatigue is common in patients with axial spondyloarthritis (SpA), affecting quality of life, and its cause is not fully understood.

Objectives: to estimate variables associated with fatigue in patients with SpA.

Materials and methods: patients with SpA were included. Disease activity was assessed using BASDAI (Bath Disease Activity Index), ASDAS-ESR (Ankylosing Spondylitis Disease Activity Score-globular sedimentation rate), and ASDAS-CRP (C-reactive protein). Depression was measured by CES-D (Center for Epidemiological Scale–Depression), function by BASFI (Bath Ankylosing Spondylitis Functional Index), and quality of life by SF-12. FACIT (Functional Assessment of Chronic Illness Therapy-fatigue) was used to measure fatigue.

Results: 74 patients with SpA were included. Fatigue was correlated with BASDAI (rho=-0.74); BASFI (rho=-0.74); ASDAS-ESR (rho=-0.55); ASDAS-CRP (rho=-0.54); and CES-D (rho=-0.73). The multiple regression model showed that BASFI (coef β -2.60; 95%CI -3.65 to 1.55; p<0.0001) and CES-D (coef β -0.44; 95%CI 0.09 -0.63 to 0.24; p<0.0001) were correlated with FACIT-fatigue, adjusted for ASDAS, peripheral arthritis, skin lesions, age, sex, and years of disease.

Conclusions: in this series, fatigue in patients with SpA was associated with functional capacity and depression.

INTRODUCTION

Fatigue is frequent in patients with rheumatic diseases[1]. Despite this, its cause is not completely understood and seems multifactorial. In the case of rheumatoid arthritis (RA), it is considered an extra-articular manifestation of the disease[2] and is linked to pain, disease activity, sleep disturbance, and depression[3]. A systematic review by Nikolaus et al.[4] found pain, disability, and depression as the most important variables related to fatigue in RA; also, conflicting evidence was observed of its association with inflammatory indicators. In spondyloarthritis (SpA), this problem has been studied less than in RA. In these diseases, fatigue was found to be equal in all SpA subtypes and associated with disease activity measured by the Bath Ankylosing Spondylitis disease activity index (BASDAI)[5]. Others have found that in addition to high disease activity, functional disability and worse mental health were significant associations[6].

The Outcome Measures in Rheumatology (OMERACT) considered fatigue to be one of the primary outcomes in the quality of life of rheumatic patients, and it recommended that it be measured and treated whenever possible[7].

In Brazil, a study of fatigue in SpA patients has shown that fatigue levels did not differ according to diverse SpA subtypes. However, this symptom was more common in females, sedentary patients, and those with worse functionality and quality of life[8]. This data was analyzed ten years ago, and no new reports were published. In addition, there is no evidence of this in our population. Our objective was to estimate the fatigue in patients with axial SpA and its possible associations with epidemiological data, disease activity, depression, functional status, quality of life, and treatments.

MATERIALS AND METHODS

This is an observational cross-sectional study approved by the Local Committee of Ethics in Research under protocol number 3.003.040. To be included, patients fulfilled the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial SpA[9] and were ≥18 years of age. Pregnant women, patients with associated chronic diseases, and those with untreated hypothyroidism were excluded. The studied group is a convenience sample that includes all SpA patients who have had regular consultations for one year in a single tertiary center.

Patients were invited to participate in the study according to the appointment order. Clinical profile (type of SpA, articular and extra-articular manifestations), epidemiological data (age,

sex, age at disease onset, auto-declared ethnic background, tobacco exposure), laboratory data (ESR or erythrocyte sedimentation rate; CRP or C reactive protein and presence of HLA B27) as well as data on used treatment were collected from the medical records. The Bath Ankylosing Spondylitis Functional Index (BASFI)[10], Center for Epidemiological Scale-Depression (CES-D)[11], 12-Item Short-Form Health Survey (SF-12)[12] and the Functional Assessment of Chronic Illness Therapy-version 4 (FACIT-F) were recorded[13]. Disease activity was performed by Bath Ankylosing Spondylitis disease activity index (BASDAI)10, Ankylosing Spondylitis Disease Activity Score (ASDAS)-ESR and ASDAS-CRP[14].

The BASFI is a ten-item questionnaire that analyzes a SpA patient's ability to perform daily activities. Its scores range from 0 (best scenario) to 10 (severe disability)[10]. The CES-D is a self-reported questionnaire that evaluates depression. Its twenty questions range from 0 to 60, with higher scores indicating more symptomatology. Values between 15 and 21 indicate mild to moderate depression, and over 21 indicate major depression[11].

The BASDAI is an activity index considering fatigue, axial and peripheral pain, enthesitis, and duration and intensity of morning stiffness). Values ≥4 are classified as high activity[10]. ASDAS-ESR and ASDAS-CRP are activities indexes that value axial and peripheral pain, the degree of morning stiffness, a VAS (visual analogic scale) on general health and ESR or CRP values. Patients with ASDAS-ESR and ASDAS-CRP ≤1.3 considered to have inactive disease. Values between ≥1.3 and <2.1; between ≥2.1 and <3.5; and ≥3.5 were considered as with low, high and very high disease activity respectively[14].

The FACIT-total (Functional Assessment of Chronic Illness Therapy – version 4) is an instrument that ranges from 0-160 and has the result obtained through 40 questions, each of them scoring from 0 to 4. The subscale FACIT--fatigue (a thirteen-item questionnaire ranging from 0-52) was used to estimate fatigue. The FACIT-fatigue takes into account symptoms from the last seven days. Lower results mean a higher degree of fatigue[13].

All these instruments were translated into Portuguese and validated in the Brazilian population[15-18].

Data distribution was analyzed by the Shapiro Wilk test. Nominal variables were expressed in percentages. Continuous variables were presented through central tendency and respective measures of dispersion: mean and standard deviation if the sample had a normal distribution and median and interquartile range if the distribution was non-normal. A comparison of two continuous data was done using the Mann-Whitney test. More than two continuous variables were compared using the Kruskall-Wallis test, followed by Dunn's multiple comparison tests for adjusted p values. Correlations between FACIT-fatigue with BASDAI, ASDAS, ESR, CRP, SF-12, and CES-D were performed using the Spearman test. A multiple regression model was used to evaluate the values of FACIT-fatigue according to variables that were associated with $p<0.1$. The adopted significance was 5%. The statistical analysis was performed with the MedCalc® Statistical Software version 22.001 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

RESULTS

A sample of 74 patients with radiographic axial SpA was included. Its main characteristics are shown in table 1. In this sample, the median BASDAI was 3.0 (IQR = 1.6-5.2); the mean ASDAS-ESR was 2.7±0.96, and the mean ASDAS-CRP was 2.5±1.00. According to the BASDAI, 39.1% of the patients had active disease. Regarding ASDAS CRP, 18.9% had low activity, 51.34% had high activity, and 18.9 had very high activity. In the case of ASDAS ESR, 21.6% had low activity, 47.2% had high activity, and 27% had very high activity.

The median BASFI was 2.8 (IQR=0.67-5.32); the median SF-12 physical domain was 40.9 (IQR=30.7-50.0); the median SF-12 mental domain was 47.2 (IQR=34.3-49.2). The median CES-D was 9.0 (IQR=1.0-23.0); seven (9.4%) patients showed CES-D scored between 15-21 (mild to moderate depression) and in 21 (28.3%) it was over 21 (major depression). The median value of FACIT-total was 129.7 (IQR=95.7-149.2), and of FACIT-fatigue was 45.9 (IQR=25.7-50.0).

Table 2 shows the correlations between fatigue measured by FACIT-fatigue and the studied variables. This table demonstrated that activity indexes (ASDAS-ESR and ASDAS-CRP) correlated well with fatigue but not the isolated values of ESR and CPR. Quality of life (both physical and mental), depression, and

functionality are also correlated with fatigue values.

Table 3 shows the values of FACIT-fatigue according to the activity indexes when the disease was classified according to the activity level, confirming the results in Table 2.

Table 4 shows the associated clinical variables and the main medications used to treat axial and extra-axial manifestations of these patients at the time of data collection. It shows that patients with associated peripheral arthritis and those using nonsteroidal anti-inflammatory drugs (NSAIDs) had lower values in FACIT-fatigue.

The comparison of FACIT-fatigue according to sex showed that females had median values of 45.0 (IQR=18.5-50.0) and men 44.5 (IQR=30.0-50.0) without statistically significant (p=0.61). Patients with work incapacity (total or partial) had median FACIT-fatigue of 34.0 (IQR=18.0-50.0) and those without it of 46.0 (IQR=32.0-50.5) being statistically significant (p=0.03).

The multiple regression model showed that BASFI (coef β -2.60; 95%IC -3.65 to 1.55; p<0.0001) and CES-D (coef β-0.44; 95%IC 0.09 -0.63 to 0.24; p<0.0001) correlated with FACIT-fatigue, adjusting by ASDAS CRP, ASDAS ESR, peripheral arthritis, cutaneous lesions, age, gender, and disease duration (table 5).

Table 1: Clinical and demographical data of studied sample of spondyloarthritis patients (n=74).

Females, n (%)		34 (45.9%)
Males, n (%)		40 (54%)
Ethnic background, n (%)		
Caucasians		69 (93.2%)
Afro descendants		4 (5.4%)
Asiatic		1 (1.3%)
Age in years, mean (SD)		50.6±12.4
Disease duration in years, median (IQR)		9.5 (5.0-12.2)
Exposed to tabaco (current and ex-smokers), n (%)		40 (54%)
Spondyloarthritis manifestations, n (%)		
Peripheral arthritis		42 (56.7%)
Uveitis		26 (35.1%)
Psoriasis		27 (36.4%)
Inflammatory bowel disease		4 (5.4%)
HLA B27 positivity, n (%)		33/60 (55%)
Working status, n (%)		
	With labor incapacity (total or partial)	25 (33.7%)
	Without labor incapacity	49 (66.2%)
Erythrocyte sedimentation rate - mm, median (IQR)		24.0 (13.7-43.5)
C reactive protein - mg/dL, median (IQR)		3.7 (1.5-10.8)
Used medications, n (%)		
NSAID		22 (29.7%)
Methotrexate		17 (22.9%)
Sulfasalazine		8 (10.8%)
Leflunomide		7 (9.4%)
Anti TNF alpha drugs		34 (45.9%)
Secuquinumab		4 (5.4%)
Glucocorticoid		2 (2.7%)

NSAID = non-steroidal anti-inflammatory drugs; IQR= interquartile range; SD= standard deviation; n= number; IBD= inflammatory bowel disease.

Table 2: Correlation of FACIT-fatigue with disease activivity, function, depression and quality of life.

	Spearman Rho	95%CI	P
BASFI	-0.74	-0.83 to -0.61	<0.0001
ASDAS-CRP	-0.54	-0.68 to -0.34	<0.0001
ASDAS-ESR	-0.55	-0.69 to -0.36	<0.0001
SF-12 (mental domain)	0.60	0.42 to 0.73	<0.0001
SF-12 (physical domain)	0.73	0.60 to 0.82	<0.0001
CES-D	-0.73	-0.82 to -0.60	<0.0001
Erythrocyte sedimentation rate	-0.07	-0.30 to +0.16	0.54
C reactive protein	0.04	-0.20 to +0.28	0.72

BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS= Ankylosing Spondylitis Disease Activity Score; ESR= Erythrocyte sedimentation rate; CRP= C reactive protein; SF-12=12-Item Short-Form Health Survey); CES-D=Center for Epidemiological Scale – Depression; FACIT= Functional Assessment of Chronic Illness Therapy.

Table 3: FACIT-fatigue values according to degree of disease activity.

Instrument		FACIT-fatigue - Median (IQR)	P
ASDAS CRP			
	Inactive	50 (45.2-51.5)	0.001*
	Low activity	50.0 (37.7-52.0)	
	High activity	45.0 (29.0-52.0)	
	Very high activity	13.5 (9.7-35.2)	
ASDAS ESR			
	Inactive	52.0 (46.0-52.0)	0.0001**
	Low activity	50.0 (44.2-51.7)	
	High activity	45.0 (30.0-52.0)	
	Very high activity	21.5 (9.2-38.5)	

** Differences between inactive vs very high activity (adjusted p = 0.009) and low activity vs very high activity (adjusted p= 0.002).*
*** Differences between inactive disease vs very high activity (adjusted p=0.01); low activity vs very high activity (adjusted p=0.0005) and high activity vs very high activity (adjusted p=0.006).*
IQR= interquartile range.

Table 4: Values of fatigue measured by FACIT-fatigue according to extra axial manifestations, presence pf B27 and used medications.

	With the variable Median (IQR)	Without the variable Median (IQR)	P
Peripheral arthritis	39.5 (19.0-49.2)	48.5 (36.2-51.0)	0.01
Psoriasis	33.5 (18.5-49.2)	45.0 (32.5-50.0)	0.09
Uveitis	43.5 (29.7-50.0)	45.0 (24.2-50.0)	0.99
Inflammatory bowel disease	45.0 (44.0-51.0)	43.0 (25.0-50.0)	0.21
Presence of HLA B27 (n=60)	45.0 (31.0-50.0)	45.0 (25.0-51.0)	0.68
Used medications			
Methotrexate	45.0 (27.0-50.0)	44.0 (25.5-50.0)	0.70
Sulfasalazine	43.5 (35.2-48.7)	45.0 (25.0-50.0)	0.92
Leflunomide	49.0 (34.0-52.0)	45.0 (25.0-50.0)	0.49
Anti TNF-alpha drugs	39.5 (28.0-50.0)	45.0 (24.5-50.0)	0.75
NSAIDs	29.9 (13.7-49.2)	45.5 (34.5-50.0)	0.01

NSAIDs = non-steroidal anti-inflammatory drugs; IQR= interquartile range.

Table 5: Multiple regression model using FACIT-Fatigue as dependent variable.

	β	SE	95%CI	P
ASDAS CRP	-0,83	2.23	-5.47 to -3.44	0.61
ASDAS ESR	-1,48	1.64	-4.12 to 2.45	0.37
BASFI	-2.60	0.52	-3.65 to 1.55	<0.0001
CES-D	-0.44	0.09	-0.63 to 0.24	<0.0001
Peripheral arthritis	-2.23	2.05	-6.33 to 1.86	0.27
Cutaneous lesions	2,97	2.38	-1,78 to 7,73	0.21
Age	0,07	0.09	-0.10 to 0.26	0.10
Disease duration	0.12	0.14	-0.16 to 0.41	0.39
Sex	-0.44	1,91	-4,28 to 3,39	0.81
R2 = 0.77; R2 adjusted=0.73				

BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS= Ankylosing Spondylitis Disease Activity Score; ESR= Erythrocyte sedimentation rate; CRP= C reactive protein;
CES-D=Center for Epidemiological Scale – Depression; FACIT= Functional Assessment of Chronic Illness Therapy .

DISCUSSION

These study results indicated that fatigue in patients with SpA was linked to disease activity, functional index, mood disorders, peripheral arthritis, and NSAID use, but not among anti-TNF-alpha users. Additionally, fatigue negatively impacted the physical and mental quality of life and employability.

Fatigue has been described as a state of tiredness and reduced strength, frequently associated with lethargy, irritability, and cognitive dysfunction[19,20]. Its importance has been recognized for many years, as shown in a survey done in 1950 among ankylosing spondylitis patients. This survey showed that fatigue has been pointed out as the third most crucial incapacitating symptom after stiffness and pain[21]. In recent years, despite the important progress in the pathophysiology and treatment of SpA, fatigue remains poorly managed, and many patients feel this symptom is ignored by their clinicians[22]. Part of this issue results from difficulties in understanding the underlying mechanisms, including inflammatory process/pro-inflammatory cytokines and/or psychological distress[23].

The present study found a negative correlation between the FACIT-fatigue scale and ASDAS-CRP and ASDAS-ESR but not with ESR and CRP. This inconsistency may be because ASDAS CRP or ESR takes into account other variables, such as pain, stiffness, and a feeling of general health, that are not necessarily associated with inflammation. On the other hand, ESR and CRP are unspecific inflammatory markers that any other concomitant inflammatory process may influence.

Other authors have found an association of fatigue with BASDAI and ASDAS. Bedaiwi et al.[24] found fatigue associated with disease activity in a sample that also included patients with non-radiographical SpA. Dagfinrud et al.[25] found an association of fatigue with self-reported measures of disease activity but not with clinical measures of inflammation. López-Medina et al.[26] found an association of fatigue not only with disease activity but also with female sex and with emotional components. We did not associate fatigue with females but found a correlation with the values of CES-D. Schneeberger et al.[6] stated that depression was the main determinant of fatigue in their ankylosing spondylitis cohort; Aissaoui et al.[27] also linked fatigue to mood disorder and sleep disturbance but found that disease activity seems to be the major determinant. The preponderance of disease activity over other variables was also noted by Günaydin et al.[28]. Although this study found a correlation between fatigue and disease activity, the multiple variable analysis did not show this association. The same was observed with the presence of peripheral arthritis.

Like our series, another Brazilian cohort[8] observed that functionality and quality of life were associated with fatigue. However, unlike in our study, females were also associated with fatigue. Perhaps the small sample in our series did not have enough power to evidence this association.

A Canadian study with 681 individuals with SpA has shown that the use of anti-TNF-alpha

drugs, although producing some decrease in fatigue, did not benefit the majority of patients[24]. We could not prove any beneficial effect of anti-TNF-alpha drugs. However, we found that patients using NSAIDs had lower scores on the FACIT-fatigue scale. The inhibition of prostaglandin has shown to be helpful in the treatment of chronic fatigue stress-induced behavioral alterations in mice[29]. In addition, some authors have found positive correlations between COX-2 production by human peripheral blood lymphocytes and the severity of chronic fatigue syndrome, proposing that these patients should be treated with prostaglandin inhibitors[30]. Dernis-Labous et al.[31] showed that NSAIDs strongly reduced pain and improved functional impairment but that changes in fatigue were of low magnitude. The association of prostaglandin levels in fatigue of SpA is unclear and deserves further studies.

The present study also showed that fatigue negatively influenced patients' quality of life and working capacity. Espahbodi et al.[32], studying axial spondylarthritis patients from the UK, found that work productivity and impairment were associated with fatigue and suggested that improving this symptom is important to enhance work status. Early interventions that combine pharmacological treatment controlling pain, inflammation, and depression with nonpharmacological interventions such as energy management education, cognitive behavioral therapy, and exercise may help to improve the patient's quality of life[33].

This work has some limitations: the small number of subjects, its cross-sectional design, the lack of patients treated with glucocorticoids and secukinumab, and its lack of data on BASMI (Bath Ankylosing Spondylitis Metrology Index). In addition, considering the epidemiology of radiographic axial SpA, the male sample was underrepresented. The authors believed this is because females are more cooperative with data collection. Moreover, the sample did not have patients with non-radiographic SpA. Despite this, it highlights the strong association of fatigue with functional index, and depression. Moreover, it brings to attention the need to study the role of NSAID in this context.

CONCLUSIONS

In conclusion, in this sample, similar to other series, fatigue in SpA patients was associated with functional index and depression.

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