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Measuring Fatigue in Rheumatoid Arthritis' Patients with the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS): A Cross-Sectional Study

Romatoid Artrit Hastalarında Bristol Romatoid Artrit Yorgunluk Çok Boyutlu Anketi (BRAF-MDQ) ve Bristol Romatoid Artrit Yorgunluk Sayısal Derecelendirme Ölçeği (BRAF-NRS) ile Yorgunluğun Ölçülmesi: Kesitsel Bir Çalışma

Suade Ozlem Badak

Adana City Training and Research Hospital, Internal Medicine and Rheumatology, Department of Internal Medicine, Division of Rheumatology, Adana, Turkey

Abstract

Fatigue is a common problem in Rheumatoid Arthritis (RA) and many factors are responsible for its etiology. The aim of this cross-sectional study was to investigate the current status of fatigue and to evaluate the factors related to fatigue by using the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS) developed specifically for RA in patients with RA. 64 patients with RA were included in the study. The Disease Activity Score (DAS28-CRP) of 28 joints was used to assess disease activity, and the Health Assessment Questionnaire (HAQ) was used to assess functional status. In addition, BRAF-MDQ and BRAF-NRS scales were used to assess fatigue, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to screen for psychiatric symptoms. All correlations between BRAF-MDQ, BRAF-NRS scales and DAS28-CRP, BAI, BDI were statistically significant ($p<0.05$, each other). BRAF-MDQ, BRAF-NRS scales were found to be unrelated to age, seropositivity, and drugs used. Considering the effect of disease activity, HAQ, anxiety and depressive symptoms on the BRAF-MDQ total, it was associated only with BAI ($p<0.001$, 95% CI 0.593-1.768). In this study, we showed the contribution of anxiety and depressive symptoms to fatigue as well as disease activity. We consider that effective interventions focusing on these symptoms can improve fatigue and reduce the burden of chronic disease.

Keywords: Anxiety; bristol rheumatoid arthritis fatigue multidimensional questionnaire; bristol rheumatoid arthritis fatigue numerical rating scale; depression; rheumatology; rheumatoid arthritis

Özet

Yorgunluk Romatoid Artrit'te (RA) sık görülen bir sorundur ve etiyolojisinden birçok faktör sorumludur. Bu kesitsel çalışmanın amacı, RA'lı hastalarda RA için özel olarak geliştirilen Bristol Romatoid Artrit Yorgunluk Çok Boyutlu Anketi (BRAF-MDQ) ve Bristol Romatoid Artrit Yorgunluk Sayısal Derecelendirme Ölçeği (BRAF-NRS) kullanılarak yorgunluğun mevcut durumunu araştırmak ve yorgunluk ile ilgili faktörleri değerlendirmektir. RA'lı 64 hasta çalışmaya dahil edildi. Hastalık aktivitesini değerlendirmek için 28 eklemin Hastalık Aktivite Skoru (DAS28-CRP), yorgunluğu değerlendirmek için BRAF-MDQ, BRAF-NRS ölçekleri, psikiyatrik semptomları taramak için Beck's Depresyon Envanteri (BDI), Beck's Anksiyete Envanteri (BAI), fonksiyonel durumu Değerlendirmek için Sağlık Değerlendirme Anketi (HAQ) kullanıldı. BRAF-MDQ, BRAF-NRS ölçekleri ile DAS28-CRP, BAI, BDI arasındaki tüm korelasyonlar istatistiksel olarak anlamlıydı ($p<0.05$, birbirİ). BRAF-MDQ, BRAF-NRS ölçeklerinin yaş, seropozitiflik ve kullanılan ilaçlarla ilişkisiz olduğu bulundu. Hastalık aktivitesi, HAQ, anksiyete ve depresif semptomların BRAF-MDQ toplamına etkisi dikkate alındığında sadece BAI ile ilişkili idi ($p<0,001$, %95 CI 0,593-1.768). Bu çalışmada, anksiyete ve depresif belirtilerin hastalık aktivitesinin yanı sıra yorgunluğa katkısını gösterdik. Bu semptomlara odaklanan etkili müdahalelerin yorgunluğu iyileştirebileceğini ve kronik hastalık yükünü azaltabileceğini düşünüyoruz.

Anahtar Kelimeler: Anksiyete; bristol romatoid artrit yorgunluk çok boyutlu anketi; bristol romatoid artrit yorgunluk sayısal derecelendirme ölçeği; depresyon; romatoloji; romatoid artrit

Correspondence:
Suade Ozlem BADAK
Adana City Training and Research Hospital,Internal Medicine and Rheumatology, Department of Internal Medicine, Division of Rheumatology, Adana, Turkey
e-mail: suadeozlembadak@gmail.com

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1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune, chronic inflammatory disease characterized by joint swelling, tenderness and destruction of synovial joints, which can lead to severe disability.

A total of 40-70% of people with rheumatoid arthritis report severe fatigue, a very important symptom of RA, as in other chronic diseases (1,2).

It has been previously stated that RA fatigue is a multifactorial experience likely to differ from that in other chronic conditions (3). It is thought that fatigue may be a result of the systemic effects of the disease, pain and joint symptoms, or the drugs used in the treatment, as well as due to conditions such as sleep disorders and bad mood (4,5).

RA-specific questionnaires have been developed to evaluate several dimensions of fatigue experienced by RA patients (6). The aim of the study was to investigate the current state of fatigue and factors related to it in patients with RA using the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS) developed specifically for RA.

2. Materials and Methods

In this cross-sectional study, 64 patients diagnosed with RA according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 EULAR/ACR (19) criteria, followed in the rheumatology outpatient clinic between April 2021 and October 2021, were randomly included.

Patients who were pregnant, diagnosed with comorbid diseases such as overlap syndrome, diabetes, congestive heart failure, kidney failure, cancer, fibromyalgia, chronic fatigue syndrome, severe psychological disorder, using antidepressant or anxiolytic group drugs, and could not speak and/or understand Turkish were excluded from the study.

All participants gave written full consent in accordance with the Declaration of Helsinki. The Ethics Committee of the University of Cukurova approved the study (April 2021, approval number = 110).

The demographic data of the patients and the drugs used were recorded. The number of tender and swollen joints was determined by physical examination. C-reactive protein (CRP, mg/L), rheumatoid factor (RF, nephelometric) and anti-cyclic citrulline peptide (anti-CCP, U/ml) values were noted in laboratory findings. Disease activity was calculated with the Disease Activity Score of 28 joints, CRP (DAS28-CRP) (7).

BRAF-MDQ and BRAF-NRS scales were used to evaluate fatigue, Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI) were used to screen for psychiatric symptoms, and Health Assessment Questionnaire (HAQ) was used to evaluate functional status.

The BRAF-MDQ consists of 20 items on the effect of fatigue symptoms in the last 7 days. There are four sub-dimensions: physical fatigue (4 items), living with fatigue (7 items), cognitive fatigue (5 items), and emotional fatigue (4 items). Except for item 1 (0-10 points), 2 (0-7 points), and 3 (0-2 points), the others receive 0-3 points. A total fatigue score is obtained by summing 20 item scores. The BRAF-MDQ total fatigue score ranges from 0 to 70. Physical fatigue, living with fatigue, cognitive fatigue and emotional fatigue scores are obtained by summing the subscale items.

The BRAF-NRS has three subgroups to assess the severity and impact of fatigue and coping with fatigue over the past 7 days. Each item scores between 0 and 10 (2) (Question 1: 0; I did not feel tired - 10; I felt completely exhausted, Question 2: 0; had no effect-10; had a great effect, Question 3: 0; very good–10, not good at all) (8,9,10).

HAQ is a total of 20 questions consisting of 8 subtitles. It consists of dressing, getting up, eating, walking, hygiene, lying, grasping and external activities (11,12).

BAI is used to determine the frequency of anxiety symptoms experienced by individuals. It is a Likert-type self-assessment tool consisting of 21 items, each scored between 0 and 3. Anxiety level is measured according to the total score on this scale (0-7 points = minimum, 8-15 points = mild anxiety, 16-25 points = moderate anxiety, 26-63 points = severe anxiety) (13,14)

BDI: Behaviors and symptoms specific to depression are described in sentences. Each sentence is given a score between 0-3. It consists of twenty-one items, which are listed from mild to severe form. Patients are asked to choose the statement that best describes their current situation, and the result is obtained by summing up the items (15,16)

Statistical Analysis

Statistical analyzes were performed using SPSS 23.0 (SPSS Inc, Chicago, IL, USA). The conformity of the data to the normal distribution was analyzed with the Kolmogorov-Smirnov test. The analysis of normally distributed continuous variables was done with Student's t-test, and the analysis of non-normally distributed continuous variables was done with Mann Whitney U test. Spearman correlation test was used to analyze the relationships between continuous variables. Those with a P value below 0.05 were considered statistically significant. A linear regression model was created to determine the effect of DAS28-CRP, HAQ,BAI, and BDI on BRAF-MDQ total. The impact of each variable was expressed with the regression coefficient of the linear regression model, with 95% confidence intervals. Those with a P value below 0.05 were considered statistically significant.

3. Results

The average age of 64 patients, 38 (59.4%) of whom were women, was 47 and the average disease duration was 45 months. The median DAS28-CRP score was 1.66. 37 (57.8%) of the patients were in remission. 49 (76.9%) were receiving cDMARD and 15 (23.4%) were receiving bDMARD treatment (Table 1). All scores of the instruments used in the study are shown in Table 1.

Table 1. Demographic, clinic characteristics and scores of questionnaires of the study group

		Median(IQR)
Age		47 (6)
Gender, Female/Male, n		38/26
Disease duration (months)		45(84)
Seropositive, n(%)		51(70.9)
Drugs used	cDMARD. n(%)	49(76.6)
	bDMARD. n(%)	15(23.4)
DAS28-CRP		1.66 (1.98)
HAQ		0.825 (0.6)
BRAF-MDQ	Physical	29 ±19.73[a]
	Living	9.5 (11)
	Cognitive	7.5 (11)
	Emotiona	6 (8)
	Physical	4(6)
BRAF-NRS	Fatigue severity	3(2)
	Effect of fatigue	3(2)
	Coping with fatigue	3(2)
BAI		21.66 ±16.50[a]
BDI		16.23± 12.90[a]

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, bDMARD; biological disease-modifying antirheumatic drug, cDMARD; conventional disease-modifying antirheumatic drug, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints,HAQ; Health Assessment Questionnaire [a]: mean±std şeklinde verilmiştir.

While no statistically significant correlation was found between age and BRAF-MDQ and BRAF-NRS subgroups (p> 0.05), there was a weak correlation with disease duration (r=0.251, p<0.05).

BRAF-MDQ total was significantly higher in females (p<0.05) (Table 2). While HAQ showed weak correlation with BRAF-MDQ total (r=0.25, p<0.05), no statistically significant correlation was observed between BRAF-NRS subgroups (p> 0.05).

Table 2. Relationship between BRAF-MDQ, BRAF-NRS and gender, seropositive and drugs used

		BRAF-MDQ	p	BRAF-NRS-Fatigue severity[b]	p	BRAF-NRS Effect of fatigue[b]	p	BRAF-NRS Coping with fatigue[b]	p
Gender	Female	34.121±17.46	**<0.05**	3(0-10)	**<0.05**	3(0-7)	>0.05	3(0-7)	>0.05
	Male	20.154±20.251		3(0-10)		3(0-8)		3(0-8)	
Seropositive	Negative	24.154±23.00	>0.05	3(0-10)	>0.05	3(0-8)	>0.05	2(0-8)	>0.05
	Positive	29.54±18.91		3(0-10)		3(0-7)		3(0-7)	
Drugs used	cDMARD	26.25±19.52	>0.05	3(0-10)	>0.05	3(0-7)	>0.05	3(0-7)	>0.05
	bDMARD	32.62±19.91		3(0-10)		3(0-8)		3(0-8)	

BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, [b]: given as median (minimum-maximum).

All correlations between BRAF-MDQ, BRAF-NRS scales and DAS28-CRP, BAI, BDI were statistically significant. Relationships between fatigue questionnaires and DAS28-CRP, HAQ, BAI and BDI scores are presented in Table 3. Considering the effect of disease activity, HAQ, anxiety and depressive symptoms on the BRAF-MDQ total, it was associated only with BAI (p<0.001, 95% CI 0.593-1.768). (Table 4).

Table 3.Spearman's (ρ) correlation coefficients between fatigue DAS28-CRP, HAQ. anxiety and depressive symptoms

		DAS28-CRP		HAQ		BAI		BDI	
		r	p	r	p	r	p	r	p
BRAF-MDQ	Total	0.990	< 0.001	0.254	<0.05	0.993	< 0.001	0.993	< 0.001
	Physical	0.972	< 0.001	0.251	<0.05	0.976	< 0.001	0.976	< 0.001
	Living	0.985	< 0.001	0.289	<0.05	0.986	< 0.001	0.978	< 0.001
	Cognitive	0.959	< 0.001	0.195	<0.05	0.964	< 0.001	0.961	< 0.001
	Emotional	0.944	< 0.001	0.172	<0.05	0.949	< 0.001	0.949	< 0.001
BRAF-NRS	Fatigue severity	0.869	< 0.001	0.199	>0.05	0.876	< 0.001	0.995	< 0.001
	Effect of fatigue	0.805	< 0.001	0.128	>0.05	0.813	< 0.001	0.810	< 0.001
	Coping with fatigue fatigue	0.746	< 0.001	0.146	>0.05	0.758	< 0.001	0.760	< 0.001

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints, HAQ; Health Assessment Questionnaire

Table 4. Linear regression analyses with BRAF-MDQ

Variable	β	95% CI	p value
DAS28-CRP	.054	-2.943, 4.836	0.628
HAQ	-.042	-3.318, 0.478	0.140
BAI	**.987**	**0.593, 1.768**	**0.000**
BDI	-.046	-.592, 0.450	0.786

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, bDMARD; biological disease-modifying antirheumatic drug, cDMARD; conventional disease-modifying antirheumatic drug, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints, HAQ; Health Assessment Questionnaire

4. Discussion

As a result of this study, it was observed that fatigue in RA patients was correlated with disease activity, anxiety and depression symptoms, while it was not associated with age, seropositivity, and drugs used.

There are few studies in the literature investigating the relationship of fatigue with disease activity and psychiatric symptoms using BRAF-MDQ, BRAF-NRS questionnaires in RA patients. Fatigue, a common and persistent problem in RA, has many adverse effects on patients' ability to perform daily self-care and socially relevant tasks, to the detriment of their physical, mental or emotional well-being (17). Fatigue in RA was found to be responsible for 52-57% of physical and social functioning problems, 64% of mental health symptoms, and 51% of perceived worsening in general health (18). However, unlike pain or disability, fatigue is rarely seen as a therapeutic target in its own right (19).

Colak S. et al., in their study of 180 patients, more than half of whom were in remission, showed that fatigue and disease activity were associated. Olsen CL. et al. showed in their longitudinal, prospective studies that fatigue persisted in patients who achieved remission after 6 months of DMARD therapy (20). Our sample was also predominantly in remission or low disease activity, and a significant correlation was observed between DAS28-CRP and fatigue ($p<0.05$).

Many of the inflammatory biomarkers that are elevated in RA, especially tumor necrosis factor (TNF)-α and interleukin (IL-6) have been associated with fatigue (4). There are studies showing that fatigue continues even though disease activities are in remission (21). This may indicate that fatigue is not only associated with disease activity or systemic inflammation, but also with other factors such as anxiety, depression, and physical disability.

Progressive joint damage can cause increased fatigue. However, thanks to evolving treatment options, the role of disability are complex to interpret, as joint damage and disability that once determined the course of RA are less common (21). While there was a significant but weak correlation between our patients' HAQ scores and BRAF-MDQ total and subgroups, we did not detect a correlation between BRAF-NRS subgroups. In the linear regression analysis, HAQ was not found to be a predictive factor for fatigue ($p>0.05$, 95% CI:-3.318, 0.478). Stebbings S. et al. investigated fatigue-related factors in RA patients using the Multidimensional Assessment of Fatigue-Global Fatigue Index (MAF-GFI). They found that the strongest fatigue correlates in the RA cohort were depression ($P < 0.001$) and anxiety ($P < 0.001$). They found no significant association with HAQ ($P = 0.10$), pain ($P = 0.43$), and DAS-28 ($P = 0.07$) (22).

There are different results in the literature about the relationship between disease duration and fatigue. While there are studies stating that long illness/symptom duration is significantly associated with fatigue, there are also studies that do not support the relationship between fatigue and duration of illness (23,24). In this study, no correlation was found between disease duration and fatigue ($p>0.05$).

Belza et al. showed that female gender was among the variables responsible for fatigue in RA patients (23). Similarly, BRAF-MDQ

total and BRAF-NRS fatigue severity scores were significantly higher in females in our study (p<005). Nikolaus et al. reported that younger women were more susceptible to fatigue than men and older people (25). In our study, no relationship was found between age and fatigue (p>0.05).

The prevalence of psychiatric comorbidity is also high in patients with RA. The reported lifetime prevalence of depression ranges from 16 to 48%, while estimates of the prevalence of anxiety vary between 13 and 70% (26,27,28). The relationship between psychological symptoms and fatigue has been previously evaluated with fatigue scales other than BRAF-MDQ and BRAF-NRS, and it is shown that there is a strong relationship between fatigue and depression and anxiety (23,29,30,31,32).

Patients with RA describe not only physical, but also cognitive fatigue, such as emotional one and lack of motivation and inability to concentrate. In this study, fatigue was evaluated by disease-specific BRAF-MDQ and BRAF-NRS questionnaires, and its relationship with anxiety and depression was examined. A strong correlation was found with physical, living, cognitive and emotional fatigue (P<0.05, each other). When the effect of disease activity, HAQ, anxiety and depressive symptoms on BRAF-MDQ total was examined, it was observed that it could be accounted for only by BAI (p<0.001, 95% CI 0.593-1.768).

There are some limitations in this study. First, the number of patients is small. Therefore, it is not representative of the entire RA population. Secondly, it is not possible to determine from our data whether anxiety and depression affect BRAF-MDQ and BRAF-NRS or whether fatigue causes anxiety and depression. Longitudinal studies with larger samples may provide stronger evidence for the cause/effect relationship between variables. Another is that other factors such as fatigue-related sleep disturbance, social support status were not evaluated, and evaluating them could provide additional information. The patients in this study had a relatively low to moderate HAQ score, so it may not be possible to know whether high disability may contribute differently to fatigue. However, this study may contribute to the literature in terms of demonstrating the level of fatigue and related factors even in patients with little or no functional limitation. In addition, to the best of our knowledge, it is one of the rare studies in the literature evaluating BRAF-MDQ, BRAF-NRS, and psychological symptoms.

5. Conclusion

Many factors are blamed for the etiology of fatigue in RA patients. This study showed the contribution of disease activity, anxiety, and depressive symptoms to fatigue. We think that more extensive studies on related factors are needed to make effective interventions against fatigue in RA patients.

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