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Evaluation of Fatigue in Patients with Rheumatoid Arthritis and Determination of Related Factors: A Cross-Sectional Study

Romatoid Artritli Hastalarda Yorgunluğun Değerlendirilmesi ve İlişkili Faktörlerin Belirlenmesi: Kesitsel Bir Çalışma

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ABSTRACT Objective: People with rheumatoid arthritis (RA) often experience fatigue. However, most of these individuals are not assessed for fatigue. The purpose of this study was to examine the relationship between functional status, pain, disease activity, and fatigue in people with RA. **Material and Methods:** 141 individuals with RA participated in this study. Patients' pain intensity was assessed using the visual analog scale (VAS). The Health Assessment Questionnaire (HAQ) was used to determine functional status. The scale for assessing the disease activity of the participants was the Disease Activity Score-28 (DAS-28). To assess fatigue, the Fatigue Symptom Inventory (FSI) was used. **Results:** Duration scores (amount of time felt tired, number of days felt tired), interference score and severity scores (current, mean, minimum, maximum) of FSI had statistically significant relationships with the number of tender and swollen joints, HAQ, DAS-28, VAS motion and rest scores ($p<0.05$). FSI scores were not associated with duration or age. The HAQ score was a statistically significant predictor of high clinical fatigue in logistic regression analysis. **Conclusion:** Fatigue was found to affect patients with RA independently of disease duration. Fatigue was associated with functional status, pain, and disease activity. The findings suggest that functional status independently associated with clinical fatigue. Fatigue should be considered as a considerable symptom in the clinical assessment of patients and associated factors should be addressed.

Keywords: Fatigue; rheumatoid arthritis; pain

ÖZET Amaç: Romatoid artritli (RA) hastalarda yorgunluk yaygın olarak görülen bir semptomdur ancak bu hastaların çoğu yorgunluk açısından değerlendirilmemektedir. Bu çalışmada, RA'lı hastalarda yorgunluk ile fonksiyonel durum, hastalık aktivitesi ve ağrı arasındaki ilişkiyi belirlemek amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya toplam 141 RA'lı hasta dâhil edilmiştir. Hastalarda görsel analog skala [visual analog scale (VAS)] kullanılarak ağrının şiddeti değerlendirilmiştir. Katılımcıların fonksiyonel durumları Sağlık Değerlendirme Anketi [Health Assessment Questionnaire (HAQ)], hastalık aktiviteleri ise Hastalık Aktivite Skoru-28 [Disease Activity Score-28 (DAS-28)] ile belirlenmiştir. Yorgunluğu değerlendirmek için Yorgunluk Semptom Envanteri [Fatigue Symptom Inventory (FSI)] kullanılmıştır. **Bulgular:** İstatistiksel olarak FSI süre skorları (yorgun hissedilen süre, yorgun hissedilen gün sayısı), interferans skoru, şiddet skorları (mevcut, ortalama, minimum, maksimum) ile şiş ve hassas eklem sayısı, HAQ, DAS-28, VAS skorları arasında bir ilişki mevcuttu ($p<0,05$). Hastalık süresi ve yaş ile FSI skorları arasında istatistiksel olarak bir ilişki görülmemiştir. Lojistik regresyon analizi, HAQ skorunun yüksek klinik yorgunluğun istatistiksel olarak anlamlı bir belirleyicisi olduğunu göstermiştir. **Sonuç:** Hastalık süresinden bağımsız olarak RA'lı hastalarda yorgunluk hastaları etkilemektedir. Yorgunluk RA'lı hastalarda ağrı, fonksiyonel durum ve hastalık aktivitesi ile ilişkilidir. Bulgular RA'lı hastalarda fonksiyonel durum ile klinik yorgunluğun bağımsız olarak ilişkili olduğunu göstermektedir. Yorgunluk RA'lı hastaların klinik değerlendirmesinde önemli bir semptom olarak göz önünde bulundurulmalı ve ilişkili faktörler ele alınmalıdır.

Anahtar Kelimeler: Yorgunluk; romatoid artrit; ağrı

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Rheumatoid arthritis (RA) is an autoimmune systemic disease with polyarthritis involvement. RA, especially affecting symmetrically the joints of the hands. It is also characterized by limitation of movement, pain, swelling of joints and extra-articular symptoms such as fatigue, weakness, fever and muscle pain.[1]

Fatigue is defined as a feeling of extreme tiredness and a constant state of exhaustion. The prevalence of fatigue is reported to be 14-15% in adults.[2] People with RA often experience fatigue, but it is often overshadowed by symptoms such as limitation of movement and pain. 40-80% of patients with RA experience fatigue. Although the etiology of fatigue has not been completely explained, it has multidimensional features such as pain, inflammation, sleep disturbance, psychosocial factors, and disability.[3] Fatigue affects physical, mental and social functions in patients with RA, disrupts daily activities and causes a deterioration in quality of life.[4]

Several studies have been conducted to identify factors associated with RA and fatigue. Fatigue has been shown to be associated with several factors, including sleep disturbance, disease activity, gender, physical function, and pain in RA.[5-7] The primary objective of this study was to determine the relationship between fatigue and functional status, pain, and disease activity in RA. The demonstration of an association between age, gender, disease duration, and fatigue are a secondary objective.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

A total of 153 patients who were admitted to the training and research hospital, were evaluated for the study. Twelve participants who were following the exclusion criteria were excluded from the study. Finally, 141 participants (38 males, 103 females) were included in the evaluation. Study participants were identified using the American College of Rheumatology (ACR)/European League Against Rheumatism 2010 RA classification criteria. Patients with neurological disease, malignancy, major psychiatric disorders, thyroid diseases, hypovitaminosis, and anemia were excluded.

Ankara Physical Therapy and Rehabilitation Training and Research Hospital Ethics Committee approval was obtained for the study (date: December 20, 2013, no: B.10.1TKH.5.06.0.02.Z.F1.08-6105). Informed written consent signature was obtained from all participants and then included in the study. The principles of the Declaration of Helsinki were followed in this study.

DEMOGRAPHIC AND CLINICAL ASSESSMENT

Clinical and sociodemographic characteristics, medications and comorbidities of all patients were recorded. RA-related symptoms (such as pain, morning stiffness, joint swelling, increased temperature) and duration of the disease were noted. Locomotor system examination and general physical examination were performed. The number of swollen and tender joints was determined and recorded during the examination.

Pain was determined by visual analog scale (VAS) during movement and at rest. Patients were asked to place a single line on a 10 cm line at the point corresponding to their pain intensity during movement and at rest. On the line 0: no pain, 10 cm: unbearable pain was marked. The patients were explained in detail that progression from 0 to 10 on the scale indicated an increase in pain intensity.[8]

The scale for assessing the disease activity of the participants was the Disease Activity Score-28 (DAS-28). Since the signs and symptoms of RA are diverse, disease activity cannot be determined on a single variable. For this reason, the DAS-28 scale, which evaluates several parameters together and has high validity, was developed. The number of swollen and tender joints in DAS-28 was evaluated over twenty-eight joints. C-reaktive protein (CRP) or erythrocyte sedimentation rate (ESR) value and VAS are required in the calculation, and the DAS-28 score is obtained by entering all these parameters into the calculation program. According to ACR criteria, a DAS-28 score below 2.6 is considered remission.[9]

The functional status of the patients was evaluated with Health Assessment Quastionnaire (HAQ). HAQ is a comprehensive, widely used, patient-oriented and validated outcome assessment scale. It has been approved by the ACR the assessment of RA pa-

tients. A total of twenty activities from eight fields are queried. In the HAQ assessment, if the person cannot do the activities asked to the person at all, it is considered 3 points, if he/she has a lot of difficulty, 2 points, if he/she has some difficulty, 1 point and if he/she can do them without any difficulty, 0 points. The worst (highest) score for each domain is considered as the score for that domain. The HAQ score is obtained by summing the scores of the domains and dividing by eight.[10]

Fatigue levels of the patients were determined using the Fatigue Symptom Inventory (FSI). The FSI was first published in 1988 and consists of a total of fourteen questions. Four of these questions assess fatigue severity, two assess fatigue frequency, seven assess fatigue-related perceived interference and one assesses the daily pattern of fatigue. FSI assess the severity of fatigue with the 11-point scale (0: not at all tired, 10: overly tired) at the maximum, minimum, average, and current fatigue levels within the past week. If the mean score of the items assessing fatigue severity in the past week or the score of the average fatigue severity item is three or greater, the patient is considered to have clinically significant fatigue. The effect of fatigue on the quality of life is determined by questions about the general activity level of the person, ability to dress and bathe, ability to concentrate, work activity, relationships with other people, enjoying life and how much it affects mood. There are seven questions on this topic and these questions are evaluated on the 11-point scale. The interference score is calculated by averaging the scores of these seven items. The number of days felt tired last week, and the duration felt tired are questioned to assess the duration of fatigue. While the number of days felt tired is determined as 0-7 days, the duration felt tired is assessed with 11-point scale (0: never during the day, 10: all day).[11]

STATISTICAL ANALYSIS

Data analysis was performed with SPSS 23.0 (IBM, USA) on Windows. Statistical normality was evaluated by Shapiro-Wilk tests and Kolmogorov-Smirnov. Continuous variables were expressed as mean±standard deviation and median (minimum-maximum). Categorical variables were reported as numbers and frequencies. Pearson's chi-square test was used to compare gender rate between the clinical fatigue and clinical not fatigue groups.

For comparison of means of two continuous variables, since the data did not have a normal distribution, Mann-Whitney U test was used. Correlation tests were performed using Pearson's correlation test when parametric conditions were met and Spearman correlation test when the data was nonparametric.

The independent determinants of fatigue were examined using logistic regression analysis in multivariate analysis. Model fit was assessed using Hosmer-Lemeshow goodness-of-fit statistics. Statistical significance was accepted as $p<0.05$.

RESULTS

Clinical and demographic information of the participants is presented in Table 1. Clinically significant fatigue was presented in 96 (68.1%) of the study participants. Clinically significant fatigue was presented in 77% of female patients and 42.1% of male patients. The proportion of those with clinically significant fatigue was statistically lower in male patients than female patients ($p<0.001$).

There were forty-five patients (31.9%) whose fatigue was worse in the evening, 4 (2.8%) worse in the

TABLE 1: Demographic and clinical data of patients.

	Total (n=141)	
Feature	**Number**	**%**
Female	103	73
Male	38	27
Age (year)		
X±SD	54.67±10.70	
Duration of illness (years)		
X±SD	14.31±10.89	
Presence of comorbidities	82	58.2
Comorbidities		
Diabetes mellitus	24	17.0
Hypertension	54	38.3
Respiratory system diseases	11	7.8
Osteoarthritis	41	29.1

Data were presented as X±SD for continuous variables and as number (percentage) for categorical variables; SD: Standard deviation.

afternoon, 61 (43.3%) worse in the morning, and 27 (9.1%) without a daily pattern of fatigue. There were four people (2.8%) who never felt tired.

The Relationship between FSI Severity Scores and Other Parameters is shown in Table 2.

The Relationship between FSI Duration Scores, Interaction Score and Other Parameters is presented in Table 3.

Comparison of patients with clinical fatigue and clinical not fatigue shown in Table 4. For all

TABLE 2: Correlation between Fatigue Symptom Inventory severity scores and other parameters.

		Maximum fatigue	Minimum fatigue	Average fatigue	Current fatigue
HAQ	r value	0.499**	0.432**	0.541**	0.455**
	p value	<0.001	<0.001	<0.001	<0.001
Number of swollen joints	r value	0.308**	0.306**	0.325**	0.232**
	p value	<0.001	<0.001	<0.001	0.006
Number of sensitive joints	r value	0.268**	0.300**	0.293**	0.297**
	p value	0.001	<0.001	<0.001	<0.001
VAS resting score	r value	0.491**	0.373**	0.470**	0.384**
	p value	<0.001	<0.001	<0.001	<0.001
VAS motion score	r value	0.468**	0.474**	0.496**	0.521**
	p value	<0.001	<0.001	<0.001	<0.001
DAS-28	r value	0.348**	0.330**	0.350**	0.282**
	p value	<0.001	<0.001	<0.001	0.001
Age	r value	0.110	0.091	0.080	0.105
	p value	0.193	0.283	0.348	0.216
Disease duration	r value	0.009	0.120	0.099	0.064
	p value	0.913	0.158	0.243	0.449

**p<0.01 significant correlation; HAQ: Health Assessment Quastionnaire; VAS: Visual analogue scale; DAS-28: Disease Activity Score-28.

TABLE 3: Correlation between Fatigue Symptom Inventory duration scores, interference score and other parameters.

		Day felt tired	Time felt tired	Interference score
HAQ	r value	0.450**	0.541**	0.625**
	p value	<0.001	<0.001	<0.001
Number of swollen joints	r value	0.235**	0.336**	0.338**
	p value	0.005	<0.001	<0.001
Number of sensitive joints	r value	0.257**	0.363**	0.404**
	p value	0.002	<0.001	<0.001
VAS resting score	r value	0.392**	0.524**	0.462**
	p value	<0.001	<0.001	<0.001
VAS motion score	r value	0.454**	0.518**	0.542**
	p value	<0.001	<0.001	<0.001
DAS-28	r value	0.162	0.253**	0.423**
	p value	0.056	0.003	<0.001
Age	r value	0.140	0.128	0.131
	p value	0.098	0.131	0.122
Disease duration	r value	0.192*	0.132	0.159
	p value	0.023	0.120	0.59

**p<0.01 significant correlation; HAQ: Health Assessment Quastionnaire; VAS: Visual Analogue Scale; DAS28: Disease Activity Score-28.

TABLE 4: Comparison of patients' clinical fatigue and clinical not fatigue.

Clinical situation	Fatigue (n=96) X̄±SD (minimum-maximum)	Not fatigue (n=45) X̄±SD (minimum-maximum)	Total (n=141) X̄±SD (minimum-maximum)	p value
HAQ	1.02±0.80 (0-3)	0.28±0.48 (0-2.4)	0.79±0.70 (0-3)	<0.001*
Number of swollen joints	1.6±2.40 (0-10)	0.6±1.43 (0-6)	1.3±2.19 (0-10)	0.001*
Number of sensitive joint	3.65±4.45 (0-20)	1.8±2.95 (0-15)	3.1±4.11 (0-20)	0.006*
VAS resting score	5.04±2.79 (0-10)	2.95±2.25 (0-8)	4.37±2.79 (0-10)	<0.001*
VAS motion score	4.86±2.98 (0-10)	2.55±2.46 (0-10)	4.12±3.02 (0-10)	<0.001*
DAS-28	3.36±1.20 (1.13-6.52)	2.65±1.04 (1.42-6.10)	3.02±1.61 (1.13-6.52)	<0.001*

*p<0.05 significant correlation; p: Mann-Whitney U test; HAQ: Health Assessment Quastionnaire; VAS: Visual analogue scale; DAS-28: Disease Activity Score-28; SD: Standard deviation.

parameters, there was a significant difference between the group with clinical fatigue and the group without.

Logistic regression analysis of clinical fatigue is available in Table 5. Logistic regression analysis showed that the increase in HAQ score independently contributed to the increase in clinical fatigue.

DISCUSSION

The main objective of the study was to evaluate the association of fatigue with disease activity, functional status, and pain severity in RA. The results showed that higher levels of fatigue in these patients were associated with higher disease activity and pain severity. It was also found that functional status was independently associated with clinical fatigue in RA.

It was determined that a high proportion of patients (68.1%) had clinically significant fatigue and it was higher in female patients. Studies in the literature show that 40-80% of RA patients experience clinically significant fatigue.[3,12] Some studies find no relationship with fatigue and gender, whereas others find a close relationship with female gender.[5,6]

The relationship was found between pain scores and fatigue values. Similarly, in many studies, pain was shown as a factor affecting fatigue.[3,7,13] Pollard et al. stated that fatigue is associated with depression and pain. It has been reported that the relationship between disease activity and fatigue is much less than the relationship between fatigue and pain in patients with RA.[3] It is important to treat inflammation to reduce fatigue, but it has been proposed that pain

TABLE 5: Logistic regression analysis of clinical fatigue.

Odds ratio		95.0% CI Lower	Upper	p value
HAQ	4.595	1.554	13.58792	0.006*
Number of swollen joints	1.393	885	2.190	0.152
Number of sensitive joint	878	657	1.158	0.355
VAS resting score	1.154	939	1.419	0.154
VAS motion score	1.171	950	1.443	0.139
DAS-28	821	373	1.505	0.624

*p<0.05 significant correlation; CI: Confidence intervals; HAQ: Health Assessment Quastionnaire; VAS: Visual analogue scale; DAS-28: Disease Activity Score-28.

should also be tackled.[13] Even if the disease is in remission, excessive pain may be associated with high fatigue scores. This suggests that it may be due to a common etiology such as central sensitization rather than cause and effect relationship between the two parameters.[14] Pain is a symptom that should not be ignored in combating fatigue. Further studies are needed to elucidate this complex relationship between pain and fatigue.

There was a meaningful relationship between functional status and fatigue level. Worsening of functional status was found to contribute independently to the increase in clinical fatigue. In a study that examines the relationship between fatigue and physical activity, similarly, it was shown that the level of fatigue decreases as patients' functional status improves.[15] In a systematic review, it is stated that pain, functional status, and depression are the 3 main components that affect the mechanism of fatigue formation. Some variables are mentioned that fatigue can be both a cause and a consequence. These variables are physical, cognitive, and emotional functions.[7] For this reason, it is difficult to determine whether physical function decreases as fatigue increases or fatigue increases as physical function decreases. Like our study, there are studies showing that fatigue is associated with functional status in RA, as well as studies showing that pain is an independent determinant of fatigue in patients with RA.[16,17] It has been reported that RA may negatively affect the functional status of patients after joint damage by limiting their ability to perform basic activities of daily living such as walking, dressing, and this may affect fatigue status.[16] Gouda et al. reported that pain and functional status significantly predict the risk of sleep disturbance in patients with RA.[18]

A positive correlation was found between fatigue parameters and the number of tender and swollen joints. As the number of swollen and tender joints are clinical indicators of inflammation, it is expected to be associated with fatigue. In an 8-year study that examined fatigue in RA, it is found that more severe fatigue levels were accompanied by increased inflammatory indicators (sensitive and swollen joints, CRP level, etc.).[12] On the other hand, Madsen et al. stated that there was no relationship between the number of swollen and tender joints and fatigue. Although the number of swollen and sensitive joints is an indicator of inflammation, it wasn't found to be related to fatigue and this finding was attributed to the lack of a sufficiently sensitive scale.[13]

In this study, a weak relationship was found between fatigue scores and DAS-28 scores. Similarly, Pollard et al. stated that disease activity affects fatigue, but pain and depression were the most affecting factors to fatigue.[3] In a study by Madsen et al. in which disease activity was determined by ESR, CRP and DAS-28 score, no positive correlation was found between ESR and fatigue, whereas a positive correlation was reported between CRP and fatigue. Also, a positive correlation was found between DAS-28 and fatigue, but not as strong as the relationship between CRP and fatigue. Because DAS-28 is a scale with various components, this finding was attributed to the possibility of weakness in the measurement of inflammation compared to parameters that directly measure inflammation.[13] Inflammation is involved in the pathophysiology of fatigue. This indeterminate relationship between direct or indirect indicators of inflammation and fatigue may be due to the confounding factors such as whether the disease is under control, duration of the disease, current treatments of the patients and the strength of the indicators to reflect the severity of inflammation. It has been reported that there is a relationship, albeit weak, between fatigue and disease activity in RA.[19]

There are studies showing that increased levels of fatigue negatively affect quality of life by reducing the patient's activity level and motivation. For this reason, fatigue is an issue to be tackled in RA patients.[20]

There are studies showing negative correlation between fatigue and age in RA. In other words, higher levels of fatigue were associated with younger ages.[3,21] Similarly, there are studies showing that there is no relationship between fatigue and age.[6,7] Compatible with the literature, in this study, no relationship was found between fatigue and disease duration. Madsen et al. reported that the duration of the disease did not affect fatigue. However, they stated that this was an unexpected situation. They stated that

long disease duration leads to erosion and long years with these joints may cause a higher degree of fatigue.[13] Further studies are needed to reveal the relationship between disease duration and fatigue in RA.

Since fatigue is multifactorial, conditions that have been associated with fatigue in previous studies, such as functional status, sleep disturbances, and pain should be identified. Effective interventions in these areas can lead to significant reductions in fatigue levels.[22]

Fatigue, sleep disorders, depression, anxiety, fibromyalgia, frailty, sarcopenia, and cachexia are disorders that should be evaluated in RA patients. Parameters such as depression, sleep quality and social life have been shown to play a key role on fatigue in RA patients.[3,6,12,15] Early detection of these disorders in RA affects the prognosis of the disease. RA and fibromyalgia syndrome (FMS) may coexist at a rate of 20% or more. The association of FMS and RA may negatively affect disease activity scores. Fibromyalgianess can be seen in more than one third of patients with RA, with inadequate response to RA treatment and higher disability scores.[23] In FMS patients, 16% to 80% have chronic fatigue syndrome, while 78% to 94% experience fatigue.[24] The coexistence of FMS with other rheumatologic diseases seems to increase fatigue.[25] Therefore, in our study, fatigue in RA patients may be affected by concomitant FMS.

In patients with RA, the quality of life of patients with extra-articular symptoms is negatively affected in the psychological domain, more so in the physical domain. Therefore, comprehensive, and multidisciplinary evaluation is important in these patients.[26] Psychosocial interventions and physical activity and may have beneficial effects on fatigue in RA.[27] There are studies indicating that healthcare professionals do not adequately address patients with RA-related fatigue. It has also shown that healthcare professionals do not have competencies in informing patients about managing their fatigue. Therefore, there is a need for training for healthcare professionals in identifying fatigue and managing associated factors. There is also a need for more data on effective interventions to help reduce RA-related fatigue.[28]

The relationship between fatigue and parameters such as pain, disease activity, functional status, disease duration, gender, and age were examined. It is an important study to identify the factors associated with RA and to demonstrate that functional status is a factor that independently influences clinical fatigue. The limitation of this study is that factors that may affect fatigue such as fibromyalgia, depression, and sleep quality were not evaluated.

CONCLUSION

Fatigue has a significant impact on quality of life in the RA population. However, in clinical evaluation of RA patients, it is often overlooked in daily practice. Fatigue status of all RA patients should be questioned carefully. It is particularly important to identify and fight the factors that may affect fatigue in terms of the social participation of the patient in the treatment. Therefore, fatigue should be considered when determining treatment strategies for RA and a fatigue management plan should be developed.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gizem Kılınç Kamacı, Sumru Özel, Hatice Bodur;* ***Design:*** *Gizem Kılınç Kamacı, Sumru Özel;* ***Control/Supervision:*** *Sumru Özel, Sibel Ünsal Delialioğlu, Hatice Bodur;* ***Data Collection and/or Processing:*** *Gizem Kılınç Kamacı, Fatma Gül Yurdakul;* ***Analysis and/or Interpretation:*** *Sibel Ünsal Delialioğlu, Fatma Gül Yurdakul, Gizem Kılınç Kamacı;* ***Literature Review:*** *Gizem Kılınç Kamacı, Sibel Ünsal Delialioğlu;* ***Writing the Article:*** *Gizem Kılınç Kamacı, Sibel Ünsal Delialioğlu;* ***Critical Review:*** *Sibel Ünsal Delialioğlu, Sumru Özel, Hatice Bodur.*

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