FATIGUE IN RHEUMATOID ARTHRITIS: ASSOCIATION WITH SEVERITY OF PAIN, DISEASE ACTIVITY AND FUNCTIONAL STATUS.

Yesim Garip*, Filiz Eser*, Lale Akbulut Aktekin*, Hatice Bodur*

Abstract

Objective: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic symmetric polyarthritis causing progressive joint destruction and disability. Major patient complaints are pain, disability and fatigue. The aim of this study is to assess fatigue and its association with disease-specific variables (severity of pain, disease activity, and functional status) in patients with RA.

Patients and Methods: A total of 160 RA patients were included in the study. Fatigue was measured by using Fatigue Symptom Inventory (FSI). The quadrivariate Disease Activity Score-28 (DAS28) was used for evaluating disease activity and Health Assessment Questionnaire (HAQ) for determining functional status. Severity of pain was measured by using 10 cm Visual Analog Scale-Pain (VAS-pain).

Results: Intensity items of FSI (most fatigue, least fatigue, average fatigue, current fatigue) were strongly correlated with DAS28, HAQ, and VAS pain (p=0.000). When the correlation coefficients were analyzed, current fatigue showed the highest correlation with VAS-pain (r: 0.96). This was followed by DAS28 and HAQ, respectively (r: 0.77 and 0.70) (p=0.000). Duration items of FSI (number of days fatigued, amount of time fatigued) were significantly correlated with DAS28, HAQ, and VAS pain (p=0.000). Also there were significant positive correlations between interference scale of FSI and DAS28, HAQ, and VAS-pain (r: 0.68, 0.61 and 0.67, respectively) (p=0.000). None of FSI subgroups showed statistically significant correlation with disease duration.

Conclusions: Fatigue is strongly associated with severity of pain, disease activity and functional status. Fatigue should be included in clinical practice and clinical trials as a RA outcome measure.

*Numune Training and Research Hospital, Physical Medicine and Rehabilitation Department, Samanpazari, Ankara, Turkey

Keywords: Rheumatoid Arthritis; Fatigue; Disease Activity; Functional Status.

Introduction

Fatigue is generally defined as a sense of persistent tiredness or exhaustion that is often distressing to the individual. It is one of the common complaints of Rheumatoid Arthritis (RA)[1]. Fatigue can be described as 'enduring, subjective sensation of generalized tiredness or exhaustion'. It is generally subscribed to disease-related factors such as inflammation, anemia and pain[2,3].

Fatigue is a subjective phenomenon and assessed by individual self-report. Various self-report measures have been developed to evaluate fatigue in chronic diseases. These measures range from one-item scales of intensity (i.e., visual analog scales) to multidimensional measures such as Multidimensional Fatigue Symptom Inventory (MFSI)[1].

The aim of this study is to evaluate correlation between fatigue and disease-specific variables (severity of pain, disease activity, and functional status) in patients with RA.

Patients and Methods

The study included a total of 160 RA patients, who were followed at the outpatient rheumatology clinic of physical medicine and rehabilitation department of Numune Training and Research Hospital which is a major referral center under Ministry of Health, located in Ankara, capital city of Turkey. All of the patients fulfilled the diagnostic criteria of the American College of Rheumatology (ACR)[4]. Patients' age, gender, number of swollen and tender joints, erythrocyte sedimentation rate (ESR) were recorded. The quadrivariate Disease Activity Score-28 (DAS28) was used for evaluating disease activity[5] and Health Assessment Questionnaire (HAQ)

for determining functional status[6]. 10 cm Visual Analog Scale-Pain (VAS-pain) was used to evaluate the level of pain[7]. Fatigue was assessed by using Turkish version of Fatigue Symptom Inventory (FSI) [Oksuz E., Malhan S., Tulunay F.C. Reliability and Validity of the Fatigue Symptom Inventory. In: Value in Health; Greece 2008 Nov; 11 (6), A426 – – SCI- (meeting abstract)]

FSI, first published in 1998, is a 14-item self-report measure designed to assess fatigue intensity (four items), duration (two items), its interference with quality of life (7 items), and the daily pattern of fatigue. Intensity is measured on separate 11--point scales (0=not at all fatigued; 10=extreme fatigue) that assess most, least, current fatigue and average fatigue in the previous week. Each of these is scored as an individual item. The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the previous week using an 11 point rating scale (0 = no interference and 10 = extreme interference). These 7 items are averaged to obtain an interference scale score. Duration items (number of days fatigued, amount of time fatigued) assess fatigue frequency. It is measured as the number of the days (from 0 to 7 days) in the past week that respondents felt fatigued and the amount of each day on average respondents felt fatigued (0=none of the day, 10= the entire day). Each of these is scored as an individual item. The final item asks respondents to indicate their daily pattern of fatigue and so provides descriptive information about possible diurnal variation in the daily experience of fatigue (0=not at all fatigued, 1=worse in the morning, 2=worse in the afternoon, 3= worse in the evening, 4=no consistent daily pattern of fatigue). Final item provides information only and is not intended to be used as a quantitative scale [1, 8]. The items included in the FSI are shown in appendix I[8,9].

Statistical Analysis

Descriptive statistics [mean, median, SD (standard deviation), minimum, maximum and frequencies] were used for assessing the demographics and clinical parameters. Correlations between fatigue items and pain, disease activity, and functional status were evaluated with correlation analysis. The presence of correlation was examined with Pearson's correlation coefficient. A value of $P<0.05$ was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences-13.0 (SPSS-13.0) software.

Results

A total of 160 RA patients (132 females, 28 males) were included in the study. Mean age of patients was 53.16 ± 11.98 (24-79) years. Mean disease duration was 142.3 ± 98.88 (4-480) months. Of the patients 57.5% (92 patients) were fatigued in the morning, 20% (32 patients) were not at all fatigued, 6.25% (2 patients) were fatigued in the afternoon, and 1.25% (10 patients) were fatigued in the evening. 15% of them (24 patients) did not declare any consistency in the daily pattern of fatigue. Mean scores of DAS-28, HAQ, VAS-pain and FSI subgroups (intensity items, duration items, and interference scale), demographics and clinical data are summarized in Table I.

Intensity items (most fatigue, least fatigue, average fatigue, current fatigue) were strongly correlated with DAS28, HAQ, and VAS-pain (p=0.000). When the correlation coefficients were analyzed, current fatigue showed the highest correlation with VAS-pain (r: 0.96). DAS28 and HAQ followed it, respectively (r: 0.77, 0.70) (p=0.000) (Table II).

Duration items (number of days fatigued, amount of time fatigued) were strongly correlated with DAS28, HAQ, and VAS-pain (p=0.000) (Table II).

Also there were significant positive correlations between interference scale and DAS28, HAQ, and VAS-pain (r: 0.68, 0.61 and 0.67 respectively) (p=0.000) (Table II).

None of FSI subgroups showed statistically significant correlation with disease duration (Table II).

Discussion and Conclusions

To our knowledge this is the first study to demonstrate that fatigue levels are strongly correlated with three important items: severity of pain, functional status and disease activity. The strongest correlation was showed for current fatigue and VAS-pain. This association had been previously found in the study of Huyser et al., where fatigue was measured by using Piper Fatigue Self-Report Scale (PFS), however they did not find a strong association between fatigue and disease activity[10]. On the other

Table I. Demographic and Clinic Patient Data

	Minimum	Maximum	Mean	SD	Median
Age (year)	24.0	79.0	53.16	11.98	54.00
Disease duration (months)	4	480	142.3	98.88	120
Swollen joints	0	10	0.63	1.44	0
Tender joints	0	26	2.92	4.61	1
ESR	2	80	22.4	15.79	18
DAS28	0.49	7.58	3.37	1.37	3.08
HAQ	0	3.0	0.84	0.75	0.75
VAS-pain	0	10.0	4.16	2.66	4
Most fatigue	0	10	5.89	2.93	6
Least fatigue	0	10	2.2	2.55	1
Average fatigue	0	10	3.99	2.75	4
Current fatigue	0	10	4.3	2.72	4
Number of days fatigued	0	7	3.46	2.32	3
Amount of time fatigued	0	10	4.23	2.87	5
Interference scale	0	10	3.44	2.95	3.28

Most fatigue, least fatigue, average fatigue, current fatigue: FSI intensity items; Number of days fatigued, amount of time fatigued: FSI duration items; Interference scale: FSI Interference item; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score; HAQ (Health Assessment Questionnaire): Functional Status Health Assessment Questionnaire;VAS pain:Visual Analog Scale-pain

Table II. The relation between FSI Scales and Other Parameters

		DAS28	HAQ	VAS-pain	Disease Duration
Most fatigue	r	0.62**	0.59**	0.66**	0.01
	p	0.000	0.000	0.000	0.9
Least fatigue	r	0.65**	0.64**	0.65**	0.04
	p	0.000	0.000	0.000	0.55
Average fatigue	r	0.69**	0.67**	0.71**	0.08
	p	0.000	0.000	0.000	0.92
Current fatigue	r	0.77**	0.70**	0.96**	-0.01
	p	0.000	0.000	0.000	0.86
Number of days fatigued	r	0.59**	0.60**	0.62**	-0.01
	p	0.000	0.000	0.000	0.93
Amount of time fatigued	r	0.72**	0.68**	0.72**	-0.2
	p	0.000	0.000	0.000	0.86
Interference scale	r	0.68**	0.61**	0.67**	0.01
	p	0.000	0.000	0.000	0.93

Most fatigue, least fatigue, average fatigue, current fatigue: FSI intensity items; Number of days fatigued, amount of time fatigued: FSI duration items; Interference scale: FSI Interference item; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score; HAQ (Health Assessment Questionnaire): Functional Status Health Assessment Questionnaire;VAS pain:Visual Analog Scale-pain

hand, Raterman and Pollard reported strong associations between fatigue and disease activity, confirming our data. Raterman used two questionnaires [Checklist Individual Strength (CIS) and the Need for Recovery Scale (NFR)] for the measurement of several aspects of fatigue severity[11]. Nevertheless, in Pollard's study, the relationship between fatigue and pain was less significant and fatigue was accessed simply by using 100 mm VAS--fatigue, which did not permit to access the different aspects of fatigue in detail[12].

Fatigue is a multifactorial and a complex symptom and its assessment requires a multidimensional questionnaire that identifies more detailed

profile of fatigue. We evaluated fatigue by using FSI. FSI deals with various characteristics of fatigue including severity and frequency of fatigue and its perceived interference with quality of life in terms of general and normal work activities, ability to concentrate, enjoyment of life and mood. Furthermore, it states daily patterns of fatigue[8]. FSI is sensitive enough to detect changes over time, therefore it can be used as an outcome measure[13]. It was suggested as a useful instrument for assessment of fatigue[14].

In our study, pain was the first in rank among the variables that influenced fatigue. Similar relationships between fatigue and pain intensity were also reported by Riemsma, Tack and Hoogmoed[15,16,2].

We found that fatigue was significantly correlated with functional status. This result concords with the findings of Hoogmoed et al., and other studies which confirmed that fatigue has a negative impact on functional status in RA. Hoogmoed et al., evaluated fatigue by using CIS. They concluded that fatigue in RA was primarily related to pain and functional status[2]. It was found a similar correlation between fatigue and physical function in the study of Riemsma et al., where physical function was measured by using Arthritis Impact Measurement Scale-2 (AIMS-2)[15]. Likewise, Belza and Fifield noted that fatigue was associated with functional disability[17,18].

In the present study, no association was found between fatigue and disease duration. Pollard and Treharne found similar results, with no significant relationship between fatigue and disease duration[12,19]. Studies investigating the relationship between fatigue and disease duration in RA have contradictory results. Riemsma found that, among RA patients, fatigue positively correlated with disease duration[15]. Contrarily, Belza suggested that greater fatigue was associated with shorter disease duration[17].

Wolfe et al., found fatigue as correlated with almost all demographic and clinical variables, but in multivariate analyses the strongest independent predictors of fatigue were pain, sleep disturbance, depression, number of tender joints and functional disability[20].

To our knowledge, this study is the first to demonstrate daytime patterning of fatigue in RA patients. We found that fatigue was greater in the morning. More than half of the patients indicated that they felt fatigued in 3-4 hours after awakening and level of fatigue decreased during the day. This may be due to dysregulation of hormones. Sternberg et al., suggested that both inflammation and fatigue in RA might derive from dysregulation of the hypothalamic-pituitary- adrenal axis[21].

In all of these studies, fatigue was found as strongly associated with severity of pain. It was concluded that the pain was the strongest predictor of fatigue. The association between pain and fatigue in RA has not just been exactly known. It needs more studies for explaining this relationship.

It was reported a statistically significant correlation between fatigue and disease activity in most of the studies. Fatigue is a common symptom of RA, but it is not included in the disease activity core set measures and indices in RA. It should take place in clinical practice and trials as a RA outcome measure.

Correspondence to
Yesim Garip
Numune Training and Research Hospital,
Physical Medicine and Rehabilitation Department,
Samanpazari, Ankara, Turkey
E-mail: dryesimgarip@gmail.com

References

1. Donovan KA, Jacobsen PB. The Fatigue Symptom Inventory: a systematic review of its psychometric properties. Support Care Cancer 2010;19:169-185
2. van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology (Oxford): 2010; 49: 1294-1302
3. Belza B. The impact of fatigue on exercise performance. Arthritis Care Res 1994; 7: 176-180.
4. Arnett FC, Edworthy SM, Block DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of Rheumatoid Arthritis. Arthritis Rheum 1988; 31: 315-324
5. Prevoo MLL, van't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Arthritis Rheum 1995; 38:44–48
6. Kucukdeveci AA, Sahin H, Ataman S, Griffiths B, Tennant A. Issues in Cross- Cultural Validity: Example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. Arthritis Rheum 2004; 51:14–19
7. Price DD, McGrath P, Rafii A. Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17:45– 56
8. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. Qual Life Res 2000; 9: 847-854.
9. Hann DM, Jacobsen PB, Azzarello LM et al. Measure-

ment of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual Life Res 1998; 7: 301-310.
10. Huyser BA, Parker JC, Thoreson R, Smarr KL, Johnson JC, Hoffman R. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998; 41: 2230-2237
11. Raterman HG, Hoving JL, Nurmohamed MT, et al. Work ability: a new outcome measure in rheumatoid arthritis? Scand J Rheumatol 2010; 39:127-131
12. Pollard LC, Choy EH, Gonzalez J, Khoshaba B and Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology 2006; 45: 885–889
13. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage 2009; 37:107-128
14. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res 2004;56: 157–170
15. Riemsma RP, Rasker JJ, Taal E, Griep EN, Wouters JM, Wiegman O. Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. Br J Rheumatol 1998; 37: 1042-1046
16. Tack BB. Self-reported fatigue in rheumatoid arthritis. A pilot study. Arthritis Care Res 1990; 3: 154-157
17. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. Journal of Rheumatol 1995; 22: 639-643
18. Fifield J, Tennen H, Reisine S, McQuillan J. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. Arthritis Rheum1998; 41: 1851-1857.
19. Treharne GJ, Lyons AC, Hale ED, Goodchild CE, Booth DA, Kitas GD. Predictors of fatigue over 1 year among people with rheumatoid arthritis. Psychol Health Med 2008; 13: 494-504.
20. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996; 23(8): 1407-1417.
21. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease: Ann Intern Med 1992; 117 (10): 854-866

APPENDIX I

The Fatigue Symptom Inventory (FSI)

1. Rate your level of fatigue on the day you felt **most** fatigued during the past week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

2. Rate your level of fatigue on the day you felt **least** fatigued during the past week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

3. Rate your level of fatigue on the **average** during the last week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

4. Rate your level of fatigue **right now**.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

5. Rate how much in the past week, fatigue interfered with your **level of activity**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

6. Rate how much, in the past week fatigue interfered with your **ability to bathe and dress yourself**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

7. Rate how much, in the past week fatigue interfered with your **normal activity (includes both work outside the home and housework)**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

8. Rate how much, in the past week fatigue interfered with your **ability to concentrate**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

9. Rate how much, in the past week fatigue interfered with your **relations with other people**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

10. Rate how much, in the past week fatigue interfered with your **enjoyment of life**.
    0 1 2 3 4 5 6 7 8 9 10
    No interference *Extreme interference*

11. Rate how much, in the past week fatigue interfered with your **mood**.
    0 1 2 3 4 5 6 7 8 9 10
    No interference *Extreme interference*

12. Indicate **how many days**, in the past week, you felt fatigued for any part of the day.
    0 1 2 3 4 5 6 7 *days*

13. Rate **how much of the day**, on average, you felt fatigued in the past week.
    0 1 2 3 4 5 6 7 8 9 10
    None of the day *The entire day*

14. Indicate which of the following best describes the **daily pattern** of your fatigue in the past week
    0 1 2 3 4 5 6 7 8 9 10

0=not at all fatigued, 1=worse in the morning, 2=worse in the afternoon, 3= worse in the evening, 4=no consistent daily pattern of fatigue.