Assessment of fatigue in rheumatoid arthritis and its relation to pain and disease activity measures

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Background
Fatigue is a serious outcome of rheumatoid arthritis (RA). Inflammatory synovitis is potentially an important causal factor for RA fatigue. Other factors include psychosocial factors, health beliefs, illness perceptions, and poor social support. Fatigue also has strong relationships to pain and depression.

Objective
The aim of the study was to define the amount of fatigue experienced by RA patients, and determine the relative contribution of RA disease activity to fatigue in comparison with factors such as pain and treatment in established RA cases using different instruments to assess fatigue [visual analog scale (VAS) fatigue and the vitality subscale of the Medical Outcomes Study Short Form 36 (SF-36) questionnaire].

Patients and methods
A total of 50 adult patients diagnosed with RA according to the 1987 Revised American College of Rheumatology – 42 of them being female and the remaining eight being male, with a mean age of 45.36 ± 9.6 years and a mean disease duration of 7.78 ± 4.1 years – were included in the study. Fatigue was measured using a 100 mm VAS and the SF-36 vitality scores. We measured pain using 100 mm VAS, Disease Activity Score for 28 joint counts (DAS28), early morning stiffness, the modified Health Assessment Questionnaire score, and the physician global assessment score.

Results
Fatigue was common in RA patients. Out of 50 patients, 42 patients had fatigue (VAS ≥ 20 mm), and at the same time 26 had high fatigue scores (VAS³50 mm). The mean SF-36 energy and vitality score was 60.5 ± 23.1. The VAS fatigue scores and the SF-36 vitality scores were significantly correlated with disease activity measures, including duration of morning stiffness (P = 0.001), articular index (P < 0.0001), VAS pain (P < 0.0001), DAS28 (P < 0.0001), C reactive protein (CRP) (P = 0.04 and 0.001, respectively), erythrocyte sedimentation rate (ESR) (P = 0.04), and rheumatoid factor positivity (P = 0.04 and 0.01, respectively). Pain had the strongest association with fatigue, followed by articular index, duration of morning stiffness, ESR, DAS28, and finally CRP in that order.

Conclusion
High fatigue levels are common in RA and are mainly linked to pain. VAS fatigue scores are simple measurements that can be used for assessment of fatigue in patients with RA.

Keywords:
fatigue, Medical Outcomes Study Short Form 36 vitality scores, rheumatoid arthritis, visual analog scale fatigue

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Introduction

Rheumatoid arthritis (RA) is an autoimmune, systemic, inflammatory disease causing pain and disability [1]. RA primarily affects joints, which leads to pain, deformities, joint destruction, and disability, but it also produces such extra-articular symptoms as fatigue [2].

Fatigue is a subjective symptom just like pain, and is associated with many diseases and thereby also with RA. A generally accepted definition of fatigue in RA does not exist; also a consensus definition for fatigue is not present in the literature [3]. However, most authors define fatigue as 'an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work' [4]. For chronic fatigue, Piper's definition is widely used in international studies and is as follows: 'chronic fatigue is perceived as unpleasant, unusual, abnormal or excessive whole-body tiredness, disproportionate to or unrelated to activity or exertion and present for more than 1 month. Chronic fatigue is constant or recurrent, it is not dispelled easily by sleep or rest and it can have a profound negative impact on the person's quality of life' [4].

Fatigue is experienced by up to 90% of patients with RA and its causality is likely to be multidimensional [5–7]. Fatigue has far-ranging consequences on patients' lives and is a serious outcome for many patients [8–11]. Fatigue is common in RA and its absence characterizes disease remission [12]. Qualitative studies highlight the importance that people with RA attribute to fatigue [13,14]. Between 40 and 80% of RA patients attending specialist clinics have clinically relevant fatigue, which is a feature of active disease [7,12]. By contrast, few cases (under 5%) are in remission [15], in which there is no fatigue. These suggest that disease activity is one underlying factor in the pathogenesis of fatigue in RA [12].

The improvement in fatigue was associated with falls in disease activity, providing the best evidence yet that inflammatory synovitis is potentially an important causal factor for RA fatigue [12].

Several other factors influence RA fatigue, including psychosocial factors, health beliefs, illness perceptions, and poor social support [16,17]. Fatigue also has strong relationships with pain and depression [2,18–21].

Our aim was to define the contribution of RA disease activity to fatigue in comparison with factors such as pain and treatment in established RA cases using different instruments to assess fatigue.

Patients and methods

Patients

Fifty adult patients, older than 16 years, suffering from RA, according to the 1987 Revised American College of Rheumatology (formerly American Rheumatism Association) criteria for RA [22], were included in the study.

Patients' assessments

The following information was collected for the current study: demographic data (age, sex, and disease duration), information on treatment (current nonsteroidal, steroidal, DMARDs), pain levels [100 mm visual analog scale (VAS)], Disease Activity Score for 28 joint counts (DAS28) and its constituent components (28 tender joint count, 28 swollen joint count, patient global assessment, and ESR), early morning stiffness in minutes, the modified Health Assessment Questionnaire (HAQ) [23] score, and the physician global assessment score.

Assessment of fatigue

For a global assessment of fatigue severity, fatigue was measured using a 100 mm VAS, ranging from 0 (no fatigue) to 100 (fatigue as bad as it could be), and also using the vitality subscale of the Medical Outcomes Study Short Form 36 (SF-36) questionnaire [24].

The vitality subscale of the SF-36 questionnaire involves four questions (number 23: Pep/life; number 27: energy; number 29: worn out; and number 31: tired). Questions 23 and 27 are scaled from 1 to 6 as the original response and the recorded value is scored from 100 to 0. Questions 29 and 31 are scaled from 1 to 6 as the original response and the recorded value is scored from 0 to 100.

The recorded scores for the answered questions out of these four questions were summed up and divided by the number of questions answered. A score of 100 represented high energy with no fatigue, and a lower score suggested a loss of energy and fatigue.

Results

Among 50 patients studied, 42 (84%) were female and eight (16%) were male. The mean age of the patients was 45.36 ± 9.6 years (range 23–61 years), and the mean disease duration was 7.78 ± 4.1 years (range 2–19 years) (Table 1).

Forty-two out of our 50 patients had fatigue; 42 (84%) patients had VAS score at least 20 mm, indicating fatigue, and at the same time 26 (52%) patients had VAS score at least 50 mm, indicating high fatigue. We also assessed fatigue using the SF-36 energy and vitality score (range 0–100). The lower the score, the more severe the fatigue. The mean SF-36 energy and vitality score in our study was 60.5 ± 23.1 (range 15–95) (Table 1).

Table 1 Demographic and clinical data of rheumatoid arthritis patients

Item	Range	Mean ± SD
Age (years)	23–61	45.36 ± 9.6
Duration of illness (years)	2–19	7.78 ± 4.1
VAS (pain)	1–8	4.4 ± 2.1
Articular index	4–30	12 ± 5.1
DAS28	2.1–6.8	4.7 ± 1
HAQ index	1.2–2.8	2.1 ± 0.4
VAS (fatigue)	10–80	44.3 ± 20.8
SF-36	15–95	60.5 ± 23.1
Sex [*n* (%)]		
Male	42 (84)	
Female	8 (16)	
VAS (fatigue) ≥ 20 mm [*n* (%)]	42 (84)	
VAS (fatigue) ≥ 50 mm [*n* (%)]	26 (52)	

DAS28, Disease Activity Score for 28 joint counts; HAQ, Health Assessment Questionnaire; SF-36, Medical Outcomes Study Short Form 36; VAS, visual analog scale

The VAS fatigue scores were significantly correlated with disease activity measures, including duration of morning stiffness (r = 0.47, P = 0.001), articular index (r = 0.57, P < 0.0001), VAS pain (r = 0.90, P < 0.0001) (Fig. 1), DAS28 (r = 0.55, P < 0.0001) (Fig. 2), CRP (r = 0.30, P = 0.04), ESR (r = 0.33, P = 0.04), and rheumatoid factor positivity (r = 0.36, P = 0.04) (Table 2).

Fatigue was not associated with the DMARDs used by our patients (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), nor with steroids or NSIADs. It was also unrelated to age, disease duration, sex, rheumatoid nodules, and anemia. However, a very strong association was found between the SF-36 score and VAS fatigue (r = 0.74, P < 0.0001).

Table 2 Correlation between visual analog scale fatigue scores, Medical Outcomes Study Short Form 36, and the disease activity measures

Item	VAS (fatigue)	SF-36
Duration of morning stiffness		
r	0.47	0.44
P	0.001	0.001
Articular index		
r	0.57	0.56
P	<0.0001	<0.0001
VAS (pain)		
r	0.90	0.82
P	<0.0001	<0.0001
DAS28		
r	0.55	0.48
P	<0.0001	<0.0001
CRP		
r	0.30	0.38
P	0.04	0.001
ESR first hour		
r	0.33	0.36
P	0.04	0.04
Rheumatoid factor (RF)		
r	0.36	0.39
P	0.04	0.01

DAS28, Disease Activity Score for 28 joint counts; SF-36, Medical Outcomes Study Short Form 36; VAS, visual analog scale.

The parameters that correlated with VAS fatigue were also significantly correlated with SF-36 (morning stiffness, r = 0.44, P = 0.001), articular index (r = 0.56, P < 0.0001), VAS pain (r = 0.82, P < 0.0001), DAS28 (r = 0.48, P < 0.0001), CRP (r = 0.38, P = 0.001), ESR (r = 0.36, P = 0.04), and rheumatoid factor positivity (r = 0.39, P = 0.01) (Table 2).

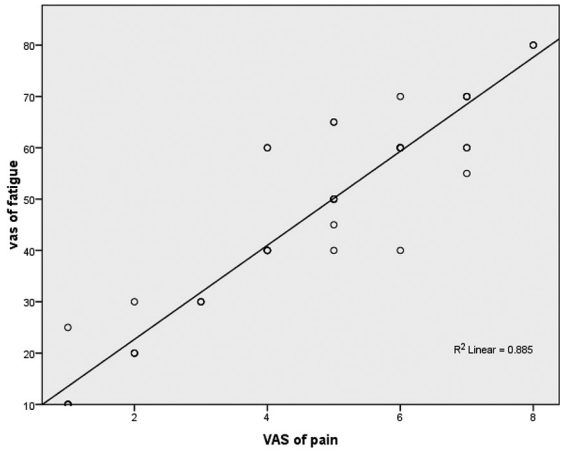
Multiple linear regression in the initial clinical association study showed that seven variables explained 64% of the variation in VAS fatigue scores. Pain had the strongest association (P = 0.001), followed by articular index, duration of morning stiffness, ESR, DAS28, and finally CRP in that order.

Discussion

Fatigue is a common and dominant complaint among patients with RA, and is regarded as an extra-articular symptom of the disease. Unlike normal tiredness, fatigue is chronic, not related to overexertion, and poorly relieved by rest. The prevalence is high, and several RA-related components have been reported as predictors of fatigue [25]. Fatigue contributes to work disability, personal injury, inability to participate in a rehabilitation program, and strained relationships [26].

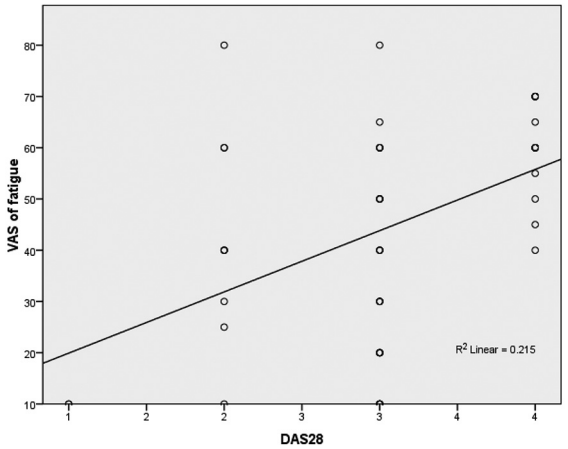
Our study found that patients with active RA had high levels of fatigue. Several factors were significantly associated and correlated with fatigue, mainly with

Figure 1



Relation between visual analog scale (VAS) for pain and VAS for fatigue.

Figure 2



The relationship between visual analog scale (VAS) for fatigue and Disease Activity Score for 28 joint counts (DAS28).

some disease activity indicators, including duration of morning stiffness, articular index, DAS28, CRP, and ESR, and also with rheumatoid factor positivity.

Multiple regression analyses show that pain is the single most important factor.

Pollard *et al.* [12] found that RA patients had high fatigue levels; 80% of patients had clinically relevant fatigue (VAS score ≥20 mm) and over 50% had high fatigue scores (VAS score ≥50 mm). However, in their study the mean SF-36 energy and vitality score was 51, which is substantially lower than that of normal UK populations, who have reported mean scores of 61–65, but this score is in agreement with our results.

Further, they found that VAS fatigue scores were significantly correlated with disease activity measures, including early morning stiffness ($r = 0.46$, $P < 0.001$), DAS28, VAS pain, and HAQ ($r = 0.51$, $P < 0.001$). Correlations with measures of disease activity were similar whether fatigue was measured using the VAS or the SF-36 energy and vitality score (SF-36 energy and vitality score: DAS28: $r = 0.41$, $P < 0.001$, HAQ: $r = 0.46$, $P < 0.001$; VAS fatigue: DAS28: $r = 0.47$, $P < 0.001$, HAQ: $r = 0.46$, $P < 0.001$).

They also found that fatigue was not associated with other DMARDs (sulfasalazine, hydroxychloroquine, leflunomide, gold, azathioprine, cyclosporin, d-penicillamine), anti-TNF therapy (etanercept, adalimumab, infliximab), and steroids.

Also, in multiple linear regression pain had the strongest association with VAS fatigue scores, followed by HAQ.

Therefore, they concluded that high fatigue levels characterize RA patients and that it is mainly linked to pain. They suggested that fatigue is centrally mediated in established RA.

Similar to our findings, Belza *et al.* [6], Lorish *et al.* [27], and Wolfe *et al.* [7] had also found a strong correlation with pain in their regression model and reported it to be the most important factor.

Fatigue can be used as an RA outcome measure, and thus it is crucial to identify its best assessment instrument. VAS fatigue scores are simple and reproducible. When using VAS scores and SF-36 energy and vitality scores in our study and in the study by Pollard *et al.* [12], and also when Wolfe [28] compared VAS scores with three multidimensional fatigue scales, it was found that the VAS fatigue scale performed favorably compared with more detailed scales.

Conclusion

High fatigue levels are common in RA and are mainly linked to pain. VAS fatigue scores are simple and reproducible, and can be used for the assessment of fatigue in patients with RA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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