



# The Enigma of Fatigue

Fatigue is an enigma: Everyone seems to know what it is, but a detailed definition is hard to provide. Like water, it slips away and cannot be grasped. There are no laboratory tests, no magnetic resonance image can quantify it objectively, and no specific treatment is available.

Fatigue is a common and often severe complaint. In the adult US population, 9.4% have fatigue during at least one month<sup>1</sup>, and as many as 22% of working adults were fatigued in The Netherlands<sup>2</sup>, as summarized in the article by Bergman, *et al* in this issue of *The Journal*<sup>3</sup>.

When a patient with rheumatoid arthritis (RA) starts talking about fatigue, the doctor will look for anemia, hypothyroidism, and other treatable explanations first. But when fatigue persists, the doctor does not know what to say: as a patient with RA recently told me, “Doctors do not seem able to understand or to handle fatigue, so despite the fact it is one of my main problems, I stopped talking about it in the clinic.” This fits in with the findings of a postal questionnaire among Dutch rheumatologists<sup>4</sup>, and with in-depth studies in UK patients, most of whom did not discuss fatigue with their clinicians, but when they did they felt it was dismissed<sup>5</sup>.

Fatigue is a significant problem for people with rheumatic diseases as it contributes to many aspects of life. Studies have found the prevalence of fatigue in RA patients to be 88%–98%<sup>6</sup>. Patients with osteoarthritis (OA) experience notable amounts of fatigue and indicate it has substantial impact on their lives<sup>7</sup>.

Fatigue can be both physical and cognitive, manifesting as inability to think clearly, concentrate, or be motivated to do anything<sup>5</sup>. Patients perceive their fatigue as unmanageable and unresolving, and professional support is rare<sup>8</sup>.

A distinction is drawn between fatigue and tiredness: a person may be tired after exercise or straining work but fatigue is more like exhaustion. Hewlett, *et al* use the description by RA patients of overwhelming and uncontrollable<sup>5</sup>, but a number of US dictionaries list fatigue and tired-

ness as synonyms. In the study from Bergman, *et al*<sup>3</sup>, the measurement tool, a visual analog scale (VAS), includes both words, which may cause some difficulties with interpretation.

## FATIGUE AS OUTCOME MEASURE?

Fatigue is recommended by OMERACT, by the European League Against Rheumatism, and the American College of Rheumatology as a patient centered outcome measure, and it was proposed to add fatigue to the “core set” of outcome measures of RA<sup>9,10</sup>. But can we really measure an enigma?

Large questionnaires have been developed to make sure every aspect of the complaint is reflected, but a simple fatigue VAS correlated with the Multidimensional Assessment of Fatigue scale (alpha  $r = 0.80$ ) and with the FACIT (Functional Assessment of Chronic Illness Therapy) fatigue scale (alpha  $r = 0.78$ )<sup>11,12</sup>.

The simple VAS appears to be a good method to measure fatigue, but what is one measuring? In the study from Bergman and colleagues the question was arbitrarily chosen as, “How much of a problem has fatigue or tiredness been for you in the past week?”. Presumably the dual terminology was chosen since in the USA the terms fatigue and tiredness are often seen as synonyms, and most patients do not know the difference.

## FATIGUE DOES NOT CORRELATE WITH INFLAMMATION

Bergman, *et al* prove that levels of fatigue in the inflammatory disorder RA are not significantly different from those in the noninflammatory disorder OA, as measured with a VAS. They do not differ in a clinical or in a research setting. In fibromyalgia (FM) the values were substantially higher<sup>3</sup>. Pain scores did not differ in RA versus OA but were higher in FM. This very important finding adds to the enigma of fatigue. The current study does not answer the question whether fatigue in OA and RA can be explained by the same

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factors and whether fatigue has the same meaning for both groups.

It has been known for a long time that fatigue does not correlate with erythrocyte sedimentation rate<sup>13</sup>, but Bergman and colleagues show that fatigue is not an inflammatory variable and has virtually no relationship with number of swollen or tender joints. Regarding a moderate association of fatigue with the Disease Activity Scale 28 (DAS28) score, 79% could be explained by the patient global assessment. Fatigue is not an inflammatory variable and has no unique association with RA or RA therapy<sup>3</sup>.

## PAIN AND FATIGUE

It has also been known for a long time that pain correlates with fatigue, but it is interesting to learn that the patient global, a question in the DAS28, correlates strongly with fatigue and is probably to a large extent explained by pain<sup>3</sup>. Fatigue correlates even more with pain than with patient global<sup>3</sup>.

In recent clinical trials fatigue improved after treatment, for example, in RA patients an improvement was seen after 24 weeks of 9.1 on a FACIT scale of 0–52, almost the same as the 23.4 improvement in pain (VAS)<sup>14</sup>. Pollard, *et al* state that fatigue in RA reflects pain and not disease activity<sup>15</sup>. In a longitudinal study over a period of one year, fatigue was associated with social stress in both patients and controls; and in patients with RA fatigue was associated with anxiety, less help at home, and more disability; in the multivariate model, more bodily pain was no longer associated<sup>16</sup>. Some patients stated during in-depth interviews that fatigue is their worst RA symptom, whereas others experience pain as the worst symptom<sup>5</sup>. These findings add to the enigma: What is the relationship of pain and fatigue as perceived by patients with RA?

## WHAT EXPLAINS FATIGUE?

### THE COMPOSITION OF FATIGUE

Bergman, *et al*<sup>3</sup> showed that fatigue scores in OA and RA are very similar; but the way they are composed might differ, and psychosocial factors may play a more important role in RA than in OA. It is important to study the contribution to fatigue of different factors in OA and RA and in other rheumatic diseases, like Sjögren's syndrome and systemic lupus erythematosus, but it is likely that because of different patient experiences and the use of language, different measuring instruments may be needed for each disease.

Most studies find that fatigue in RA is explained to a large extent by pain, but other factors play a role, including learned helplessness, depression, and anxiety<sup>17,18</sup>. Wolfe, *et al* showed that depression together with pain and sleep disturbance are the strongest independent predictors of fatigue<sup>6</sup>; Huyser, *et al* found that the best predictors of increased fatigue were higher levels of pain, more depressive symptoms, and female sex<sup>19</sup>. The level of fatigue is also

determined by self-efficacy towards coping with RA and towards asking for help, and problematic social support, which expresses itself in lack of sympathy or understanding from the social network<sup>13</sup>. Sex, disease duration, functional status, and affect appear not to be significant predictors<sup>13</sup>. Fatigue is associated with illness severity and reduced quality of life, as found by Repping-Wuts, *et al*<sup>20</sup>.

## WHAT DOES FATIGUE MEAN FOR THE INDIVIDUAL PATIENT?

The perception of fatigue differs between men and women. An in-depth interview study among 31 patients with RA showed different patterns in emotions, consequences, and management of fatigue between men and women. Mainly women with multiple roles in daily life reported negative consequences of fatigue, for example regarding mobility and activity, social contacts, work, and stress. Men reported fewer negative consequences than women, and none at all for social contacts, work, or stress. These differences could be related to the number of daily roles patients had to fulfil (e.g., spouse, housekeeping, care for children, work). With regard to coping with fatigue, a similar pattern was found: women reported that they have to find a balance to be able to cope with their fatigue while no men mentioned the need for this strategy. Men reported no gender-specific coping strategies<sup>21</sup>.

Some patients have no problem with fatigue. It is a challenge to look for the differences between these patients and others who have difficulty in coping.

Patient perspective is very important regarding fatigue. During the recent OMERACT meeting it was recommended as a measure in all studies and work is under way, for example, on the assessment of sleep<sup>22</sup>, but the study of Bergman and colleagues again calls into question the usefulness of fatigue as an outcome measure in clinical trials of medical therapy.

There are many definitions of fatigue, but, as with pain, the definition is not the most important issue in clinical practice. Rather, the issue is the way fatigue can and should be assessed, because quantifying fatigue enables us to study fatigue<sup>20</sup>. It is important to develop a valid multidimensional fatigue questionnaire that is sensitive to change and discriminates fatigue from pain and depression; such an instrument would add to our insight into the causes and treatment of fatigue.

## THE ENIGMA UNVEILED?

Fatigue is an important problem for most patients with rheumatic conditions. Measuring fatigue adds to the clinician's understanding and to clinical care. It seems likely that fatigue has a multicausal pathway, with various components contributing different amounts in different patients at different times<sup>22</sup>. Awareness of gender differences and patient's daily roles is also important in patient care and research<sup>21</sup>.

Studies are needed to unveil the causes of this enigma and to find solutions to help our patients.

**JOHANNES J. RASKER, MD,**  
Rheumatologist,  
Department of Behavioral Sciences,  
University Twente, PO Box 217 Cubicus B 216,  
Enschede, 7500 AE, The Netherlands

*Address reprint requests to Prof. Rasker. E-mail: J.J.Rasker@utwente.nl*  
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