

ANEMIA VERSUS DISEASE ACTIVITY AS CAUSE OF FATIGUE IN RHEUMATOID ARTHRITIS

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Abstract

Background: Fatigue is a common complaint in rheumatoid arthritis patients and contributes to loss of quality of life.

Objective: To study the influence of hemoglobin levels and disease activity index upon fatigue in patients with rheumatoid arthritis (RA).

Methods: We studied 130 RA patients for DAS 28, hemoglobin levels and fatigue as measured by FACIT F.

Results: No association between fatigue with hemoglobin levels was observed. A positive association with DAS-28 was found. Decomposing DAS-28, no association could be detected with sedimentation rate but a positive correlation with analogical scale for general health, number of swollen and painful joints was found.

Conclusion: Although a positive association of fatigue with DAS-28 is found it appears that the most important items in connection with fatigue are swollen and tender joints as well as general health status. Hemoglobin levels were not related to fatigue in our patients.

Keywords: Rheumatoid Arthritis; Hemoglobin; Fatigue; DAS-28; Pain.

Introduction

Rheumatoid arthritis (RA) is a chronic disease that affects mainly diarthrodial joints but also causes systemic symptoms such as weakness, loss of weight and fatigue¹.

Fatigue is a symptom described as chronic prostration not relieved by appropriate sleep that causes incapacity to participate in social and professional activities as well in rehabilitation programs². It generates a feeling of uselessness that contribu-

tes to depression and loss of quality of life³.

The etiology of fatigue in patients with RA is not well clarified and may be multifactorial. Anemia, high levels of inflammatory cytokines (such as TNF- α and interleukin-6), chronic pain, sleep disturbances and depression are pointed out as explanations for this symptom^{2,4-7}. In the VI Meeting of OMERAC (*Outcome Measures in Rheumatology Clinical Trials*) a large number of RA patients indicated that fatigue should be a priority for new research³. Nevertheless in daily practice most of RA patients do not complain of fatigue either because they have accepted it as an inevitable part of the disease or because they believe that such complaints are not to be valued.

In this study we searched for possible associations of anemia, disease activity and degree of pain with fatigue experienced by RA patients.

Methods

We included 130 RA patients from our Rheumatology Unit that were seen from January 2009 to January 2010. To participate in this study, patients should fulfill at least four (classification) criteria for RA from the American College of Rheumatology⁸, be older than 18 years and have mental capacity to understand the study. This study was approved by the local Committee of Ethics in Research and all participants signed an informed consent. Of these 130 patients, 15 (11.5%) were male and 115 (88.5%) female with a mean age of 52.14 \pm 12.06 years (18 to 84).

After recording patient's demographic data, the *Functional Assessment of Chronic Illness Therapy-Fatigue*, FACIT F (version 4) was applied for fatigue measurement. FACIT-F is a questionnaire initially designed to measure fatigue in cancer patients that later was validated for RA patients^{9,10}. The entire set of 40 questions is divided in five subsets: physical, social, emotional and functional well being and additional concerns. Each of these subsets

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consists of a few questions with responses ranging from zero to four meaning - "not at all" to "very much" (Appendix 1). Response score to negatively phrased questions must be reversed and the score is then summed. A high score represented a low level of fatigue.

Rheumatoid arthritis activity was calculated by DAS-28 4v^{11,12} and all patients had blood drawn for measurement of ESR (erythrocyte sedimentation rate) and hemoglobin level. The first was measured by Westergreen method and the second through an automatic analyzer (Advia 12®, Bayer).

Obtained data were grouped in frequency and contingency tables. The Fisher, and Mann-Whitney were used for association studies (the first for nominal and the later for numerical data). Correlation studies were done with Spearman and Pearson tests used for non parametric and parametric data respectively, with help of the software Graph Pad Prism, 4.0. Adopted significance was 5%.

Results

In the studied population, the obtained DAS-28 varied from 0.49 to 7.62 (mean 3.68 ± 1.56); ESR values from 2 to 104 mm (mean 21.40 ± 21.69) and hemoglobin levels from 9.1 to 16.5g/dl (mean 13.41 ± 1.31 g/dl). FACIT-F scored from 38 to 156 (mean 98.54 ± 28.30).

Studying DAS-28 associations with patient's age and gender we found no association with age ($p=0.188$) nor with gender ($p=0.40$). An association could be found between DAS-28 and hemoglobin levels ($p>0.0001$).

FACIT-F showed correlation with the levels of DAS-28 ($p=0.007$; $r=-0.31$; 95%CI = -0.47 to -0.12) but no correlation with hemoglobin levels ($p=0.22$;

$r=-0.11$), patients age ($p=0.55$) or any association with gender ($p=0.28$).

As DAS-28 is a composite measurement where the number of swollen and painful joints is computed, as well as VAS (visual analogic scale from zero to 10) of general health and ESR, we studied the association of each isolated item with FACIT-F. We found that it had no association with ESR ($p=0.28$). A positive association was found with number of swollen joints ($p=0.01$; $r=-0.22$; 95% CI = -0.39 to -0.043) and painful joints ($p<0.001$; $r=-0.34$; 95%CI = -0.50 to -0.17) and general health VAS ($p=0.002$; $r=-0.32$; 95% IC = -0.47 to -0.15) (Figure 1).

Discussion

Fatigue has been previously reported to occur in 40 to 80% of RA patients and diminishes in remission of disease^{1,2}. The use of DMARDs or anti TNF- α drugs results in relief of this symptom which suggests a relationship with disease activity^{1,6}. Interestingly it has been found that inflammatory markers do not reflect fatigue⁵ but that the measurement of DAS-28 does¹, as in this study.

There are several theories to explain the appearance of fatigue in RA patients. One of them is that the fatigue is due to high levels of pro-inflammatory cytokines such as IL-6 or TNF- α ⁵. Receptors to TNF- α have been demonstrated in neurons suggesting that this cytokine also modulates pain pathways. Chronic pain situations are associated with high TNF- α levels⁵. On the other side, Wolfe et al⁶ found that anti TNF therapy in RA patients is no better than traditional DMARDs in relieving fatigue, showing that fatigue relief is not restricted to TNF- α modulation

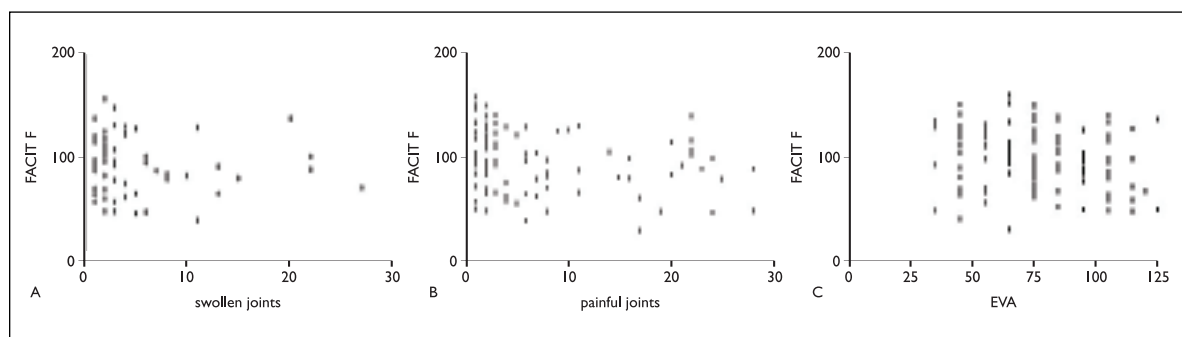


Figure 1. Correlation of FACIT-F with swollen joints (A), painful joints (B) and general visual analogic scale (VAS) (C) in 130 patients with rheumatoid arthritis.

Another explanation could be chronic disease anemia found in RA patients with high levels of activity¹⁴⁻¹⁶. Anemia is the most common hematological problem in patients with RA, occurring in about 50% of the patients¹⁶. According to Han et al¹⁶ presence of anemia has the capacity to predict decrease in physical and cognitive function, in a four year period. Also known as anemia of inflammation¹⁵, it is associated with increased iron absorption and retention within cells of the reticulo-endothelial system leading to low circulating iron levels, low serum binding capacity despite adequate iron storage. Given that iron is essential for microbial growth, this iron sequestration is thought to be a part of the host defense¹⁵. IL-6 plays important role in this context as it regulates hepcidin production known as the gate keeper of iron stores¹⁵. In cancer patients there is a positive relationship between IL-6 levels and fatigue; in AR patients anemia is one of the factors associated with poor physical function¹⁶. Regardless of this, no association could be proven between fatigue and anemia by Pollard et al¹ as in our study. This suggests that fatigue in RA is not simply explained by muscle fatigue but is a more complex phenomenon. As a third explanation, pain that is caused by joint inflammation could be responsible for fatigue. This statement matches the observations of Pollard et al¹ that believe that the association with disease activity is secondary and that joint pain is the most important causal factor. This is supported by another study⁵ that found that fatigue in RA patients was almost equal to that referred by osteoarthritis patients. Wolfe et al⁶ coined the term fibromyalgic RA to describe a subset of patients with high levels of fatigue, pain and depression.

In the present study we have found an association of fatigue with disease activity measured by DAS-28. However, analyzing in depth the instrument we found that only the number of painful and swollen joints and general health VAS maintains this relationship. Moreover, no association could be found with hemoglobin levels. These findings suggest that in patients with predominantly fatigue complaints all the efforts should be directed to achieve better inflammatory control.

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FACIT F (V.4) BRAZILIAN PORTUGUESE VERSION (*)

Abaixo você encontrará uma lista de afirmações que outras pessoas com a sua doença disseram ser importantes. Por favor, faça um círculo em torno do número que melhor corresponda ao seu estado durante os últimos 7 dias.

	Nem um pouco	Um pouco	Mais ou menos	Muito	Muitíssimo
BEM ESTAR FÍSICO					
Estou sem anergia	0	1	2	3	4
Fico enjoado (a)	0	1	2	3	4
Por causa do meu estado físico tenho mais dificuldade em atender as necessidades da família	0	1	2	3	4
Sinto-me doente	0	1	2	3	4
Tenho que me deitar durante o dia	0	1	2	3	4
BEM ESTAR SOCIAL-FAMILIAR					
Sinto que tenho uma boa relação com os meus amigos	0	1	2	3	4
Recebo apoio emocional da minha família	0	1	2	3	4
Recebo apoio dos meus amigos	0	1	2	3	4
Estou satisfeito com a maneira como minha família fala sobre a minha doença	0	1	2	3	4
Sinto-me próximo do meu parceiro (ou da pessoa que me dá apoio)	0	1	2	3	4
Independente do seu nível atual de atividade sexual, favor de responder a pergunta a seguir: Se preferir não responder assinale o quadrículo <input type="checkbox"/> e passe para a próxima seção.					
Estou satisfeito com a minha vida sexual.	0	1	2	3	4
BEM ESTAR EMOCIONAL					
Sinto-me triste	0	1	2	3	4
Estou satisfeito com a maneira como enfrento a minha doença	0	1	2	3	4
Estou perdendo a esperança na luta contra a minha doença	0	1	2	3	4
Sinto-me nervoso	0	1	2	3	4
Estou preocupado com a ideia de morrer	0	1	2	3	4
Estou preocupado que o meu estado venha a piorar	0	1	2	3	4
BEM ESTAR FUNCIONAL					
Sou capaz de trabalhar (inclusive em casa)	0	1	2	3	4
Sinto-me realizado com o meu trabalho (inclusive o de casa)	0	1	2	3	4
Sou capaz de sentir prazer em viver	0	1	2	3	4
Aceito a minha doença	0	1	2	3	4
Durmo bem	0	1	2	3	4
Gosto das coisas que normalmente faço para me divertir	0	1	2	3	4
Estou satisfeito com a qualidade da minha vida neste momento	0	1	2	3	4
PREOCUPAÇÕES ADICIONAIS					
Sinto-me fatigado	0	1	2	3	4
Sinto fraqueza generalizada	0	1	2	3	4
Sinto-me sem forças	0	1	2	3	4
Sinto-me cansado	0	1	2	3	4
Tenho dificuldade em começar as coisas porque estou cansado	0	1	2	3	4

continua na página seguinte

<i>continuação</i>					
	Nem um pouco	Um pouco	Mais ou menos	Muito	Muitíssimo
Tenho dificuldade em acabar as coisas porque estou cansado	0	1	2	3	4
Tenho energia	0	1	2	3	4
Sou capaz de fazer as minhas atividades normais	0	1	2	3	4
Preciso dormir durante o dia	0	1	2	3	4
Estou cansado demais para comer	0	1	2	3	4
Preciso de ajuda para fazer as minhas atividades habituais	0	1	2	3	4
Estou frustrado por estar cansado demais para fazer as coisas que eu quero	0	1	2	3	4
Tenho que limitar as minhas atividades sociais por estar cansada	0	1	2	3	4

(*) Brazilian Portuguese validation – Ishikawa NM. Validação do FACIT- F no Brasil e avaliação da fadiga e qualidade de vida em mulheres com câncer de mama. Tese de doutorado. Campinas, SP, UNICAMP, 2009.

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