Exercise and Fatigue in Rheumatoid Arthritis

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ABSTRACT: Fatigue, the enduring sensation of weakness, lack of energy, tiredness or exhaustion, is described by 40%–80% of patients with rheumatoid arthritis as their most disabling symptom with wide-ranging consequences for quality of life. Little attention has been paid to its multidimensional nature or to its reliability as a measure to evaluate progression of the disease. Low impact aerobic exercise affects the level of fatigue, and this same level of fatigue influences the exercise itself. We searched Medline, Cochrane Collaboration Register of Controlled Trials (CCRCT), Lilacs, PubMed and Scopus databases for randomized controlled trials (with appropriate description of methods, materials and results) on the assessment of fatigue and exercise. Review articles, case reports, letters to the editor and editorials were excluded. Of 121 references initially identified, 4 randomized controlled trials met the inclusion criteria. Two studies used the MAF scale (Multidimensional Assessment of Fatigue), one used the MAC (Mental Adjustment to Cancer) fatigue scale, and all trials used POMS (Profile of Mood States) to assess fatigue. All four trials conducted a 12 week program of two to three times/week and different periods of follow-up. Two studies used low impact aerobic exercise, one used dance-based exercise, and another study followed a home cardiopulmonary conditioning program using a stationary bicycle. While fatigue appears to be a reliable outcome measure in the clinical management of RA, especially when related to exercise prescription, further research is needed to evaluate the correlation between exercise, fatigue and quality of life, using fatigue scales validated to explore the different components of fatigue and its wide-ranging consequences.

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KEY WORDS: rheumatoid arthritis, fatigue, exercises, fitness, quality of life

Fatigue is the enduring sensation of weakness, lack of energy, tiredness or exhaustion, reported by 40%–80% of rheumatoid arthritis patients as their most disabling symptom [1-3]. Unlike normal tiredness, fatigue is chronic, typically not related to overexertion and poorly relieved by rest. It is often multifactorial and could be worsened by disease-related components, including comorbid conditions, disease duration, functional status, disease activity, lifestyle factors, level of activity, and inadequate social support [1-3].

Because it is regarded as an extra-articular symptom, little attention has been paid to its multidimensional nature and its wide-ranging effects on quality of life. Until recently, the significance of fatigue for patients failed to capture the attention of many clinicians, with patients reporting a lack of support from health professionals who relate mainly to physical problems and disease activity. Moreover, patients sometimes believe nothing can be done and do not talk to their physician about fatigue [4,5].

Unlike pain and disability, fatigue is rarely addressed as a treatment target in its own right and is seldom recommended as a main outcome for clinical trials. The OMERACT (Outcome Measures in Rheumatology) network of international researchers highlighted fatigue as a main outcome and recommended that it be measured whenever possible [4].

Fatigue was identified as a reliable distinguisher of quality of life between RA patients who are doing well and those who are doing less well. According to Minnock et al. [6], fatigue is a valid and reliable outcome measure in RA, ranking third for relative sensitivity to change after pain and tender-joint count. They also found fatigue to be an independent measure of outcome and recommended that it be considered for inclusion as a main outcome measure in RA [4,6].

There are several scales to assess fatigue but only a few are validated as reliable tools. Hewlett and colleagues [7] conducted a systematic review of the scales used to measure fatigue in RA and the evidence for their validation. They found 23 fatigue scales of which 17 had no data on validation or limited evidence. Six scales showed reasonable evidence of validation: two are generic, namely POMS (Profile of Mood States) and SF-36 (Medical Outcomes Study 36-item Form Health Survey), and four are specific, MAF (Multidimensional Assessment of Fatigue), Ordinal Scales, VAS (Visual Analogue Scale) and FACIT-F (Functional Assessment of Chronic Illness Therapy Fatigue) [7].

RA = rheumatoid arthritis

Figure 1. Flow chart of reference selection

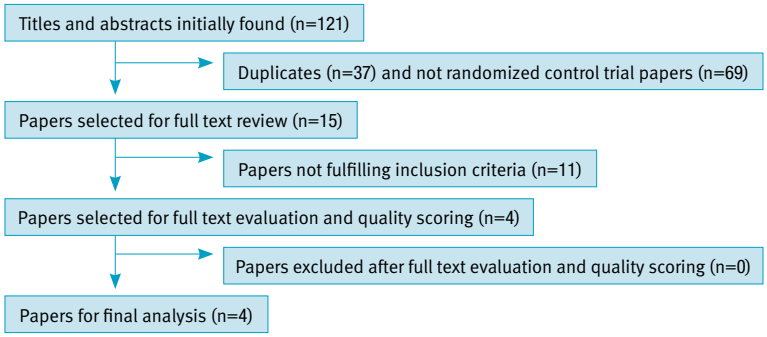

Table 1. Description of patients, by trial

	Neuberger et al. [13]	Neuberger et al. [10]	Noreau et al. [12]	Daltroy et al. [15]	Total
Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Sample size	220	25	29	37	
Male	38* (17%)	11 (44%)	9 (31%)	3* (7%)	61 (19%)**
Female	182* (82%)	14 (56%)	20 (69%)	34* (93%)	250 (80%)**
Age (yr) (mean)	55.5	55	49.4	39	50
Duration of disease (yr) (mean)	8.0	9.8	9.5	NA	9§

*Estimated values based on the percentage given by the authors
**Number and percentage estimated
§Mean value
NA = not available

Historically, exercise in general was prescribed for pain relief and improvement of joint mobility and flexibility. In recent decades exercise has increasingly been directed towards improving muscle strength and aerobic capacity in order to enhance functional ability and quality of life. Reduced function will result in decreased ability to perform activities of daily living, decreased independence, and adoption of a sedentary lifestyle with its resultant negative psychosocial impact and increased risk for cardiovascular disease [8].

Fatigue is a common complaint in RA and has wide-ranging consequences for quality of life

The 2012 Brazilian consensus group for RA recommends aerobic exercise such as cycling, walking, running and swimming. They advise exercise of 20 minutes or more at least twice a week, but limited to 60% of the heart rate based on the patient's age [9]. It is currently accepted that regular exercise can improve aerobic fitness, increase strength and alleviate pain in patients with autoimmune rheumatic diseases [2]. However, fatigue is rarely assessed as an outcome measure [10-12].

Given that fatigue in RA affects quality of life, functional capacity and daily activity, and that exercise can reduce pain and fatigue levels, once the latter is evaluated as an outcome measure to prescribe exercise (its type and/or duration), we reviewed the assessment of fatigue as an outcome measure and a predictor of exercise in rheumatoid arthritis. For the period August to October 2012, Medline (1985–2012), the Cochrane Collaboration Register of Controlled Trials (CCRCT), Lilacs, Pubmed (1985–2012), and Scopus databases were searched in Portuguese, English, Spanish, French and Italian. The keywords used in the search were rheumatoid arthritis, fatigue, fitness, physical activity, and exercise. Inclusion criteria were randomized controlled trials (with appropriate description of methods, materials and results) on the assessment of fatigue and exercise. Review articles, case reports, letters to the editor and editorials were excluded.

The title and abstract of the articles obtained in the initial research were revised by two independent observers in order to identify those that met the inclusion criteria. The articles selected were then revised, and their bibliographical references were analyzed to identify additional sources.Of the selected articles, the following data were examined: type of study, size of the sample, methods, statistical analysis, and results. The methodological quality of the papers was evaluated with the Jadad scale, comprising three items quantifying the probability of bias in the trial according to the description of randomization, masking, withdrawals and dropouts. Scores range from 1 to 5, with studies scoring 1 or 2 considered of low quality and those scoring 3 to 5 of high quality [12].

Of the 121 references initially identified in the cited databases, 37 were duplicates and 69 were considered irrelevant. Of the remaining 15 references 11 were excluded because they did not fulfill the inclusion criteria, leaving 4 randomized controlled trials that met the inclusion criteria. Figure 1 is a flow chart of reference selection. Using the Jadad scale, evaluation of the trials ranged from 2 to 5 (0–2 low quality, 3–5 high quality) with an average quality score of 3.25. One of the selected papers scored 5 [13], another scored 4 [10] and two studies scored 2 [14,15]. A total of 311 patients were evaluated in the trials, the mean number of patients in each trial was 77 (range 25–220), and the mean age ranged from 39 to 55.5 years. Table 1 presents a description of the patients.

All four articles evaluated the effects of exercise intervention on fatigue, assessing the latter as an outcome measure. Three scales were used to assess fatigue: the MAF [10,13] in two studies, the MAC [15] in two, and the POMS in all [Table 2]. All four trials conducted a 12 week program of 2 to 3 times/week and different periods of follow-up. Two studies involved low impact aerobic exercise (with one foot always on the ground and no running or jumping movements) [10,13], one used dance-based exercise [14], and one followed a home cardiopulmonary

MAF = Multidimensional Assessment of Fatigue
MAC = Mental Adjustment to Cancer
POMS = Profile of Mood States

conditioning program using a stationary bicycle [14]. Table 3 describes the protocol and scales employed in each study.

Neuberger et al. [13] and Daltroy et al. [15] established the target heart rate as 60–80% of the maximal heart rate achieved at baseline, while Noreau et al. [14] fixed the target heart rate at 50% of the maximal heart rate for the first 3 weeks, and 70% of the maximal heart rate for the last 9 weeks. Neuberger et al. [10] did not evaluate heart rate at baseline, nor did they affix a specific value to it.

Statistical analysis of change in the perception of fatigue in all studies, using POMS, MAF and/or MAC scales, showed a decrease in fatigue levels. Although statistical significance was not obtained ($0.03 \leq P \leq 0.10$), the results provide reasonable evidence that fatigue could influence exercise prescription (type of exercise and/or duration) and that the effects of exercise on fatigue are dose-related.

All trials were described as randomized, but only one study explained how the subjects were randomly allocated. The initial status was documented, and a homogeneity test was performed in all studies. Follow-up was completed in all studies, and subjects who were withdrawn from the study or who dropped out were documented.

Table 2. Sample, protocol and scales used

Author	Year	Sample			Protocol	Scales used
Neuberger et al. [13]	2007	Class*	Home**	Control	Low impact aerobic exercise: 12 wk, 1 hr, 3 times/wk	POMS MAF
		68	79	73		
Neuberger et al. [10]	1997	High§	Med^	Low°	Low impact aerobic exercise: 12 wk, 1 hour, 3 times/wk 15 wk follow-up	POMS MAF
		8	8	9		
Noreau et al. [14]	1995	Exercise		Control	Dance-based exercise: 12 wk, twice/wk counseling session once/wk 6 mo follow-up	POMS
		19		10		
Daltroy et al. [15]	1995	Exercise		Control	Cardiopulmonary conditioning with stationary bicycle: 12 wk, 3 times/wk 12 wk follow-up	POMS, MAC
		19		18		

*Classes at a fitness center, **classes at home using a videotape of the same exercise

§31 to 36 exercise classes, ^25 to 30 exercise classes, °24 or fewer exercise classes

POMS = Profile of Mood States, MAF = Multidimensional Assessment of Fatigue), MAC = Mental Adjustment to Cancer

RATIONALE

Several studies have evaluated the effects of exercise on fatigue, but only a few assessed it as an outcome measure. There are also several instruments to assess fatigue; some are brief, quantitative and symptom-focused, while others are multidimensional. However, only six scales show reasonable evidence of validation [6]. It should be recognized that fatigue is a common complaint in primary care, with a broad differential diagnosis – from physical to psychological – rendering its approach complex and difficult to treat [16].

Further studies should compare the available questionnaires and scales with the current core set measures to determine which better assesses fatigue in its multidimensional aspects

The present review aimed to analyze trials assessing fatigue as an outcome measure and a predictor of exercise in rheumatoid arthritis. The research yielded four papers meeting the inclusion criteria. The results showed reasonable evidence that the effects of exercise on fatigue are dose-related, although not statistically significant. It also shows

Table 3. Results and *P* values of each study

Author	Scales												*P* values
	POMS						MAF [10,13] / MAC [15]						
Neuberger et al. [13]	Class*		Home**		Control		Class*		Home**		Control		0.04
	BL	PT	BL	PT	BL	PT	BL	PT	BL	PT	BL	PT	
	1.53	1.35	1.16	1.23	1.52	1.37	24.91	20.74	20.08	19.23	21.88	20.88	
Neuberger et al. [10]	High§		Med^		Low°		High§		Med^		Low°		$0.05 \leq P \leq 0.10$
	BL	PT	BL	PT	BL	PT	BL	PT	BL	PT	BL	PT	
	1.23	1.05	1.39	0.83	1.13	1.36	19.79	17.1	18.5	13.7	17.5	19.4	
Noreau et al. [14]	Exercise				Control		–						$0.06 \leq P \leq 0.08$
	BL		PT		BL	PT							
	7.89		5.68		9.40	9.50							
Daltroy et al. [15]	Treatment				Control		Treatment				Control		$0.03 \leq P \leq 0.10$
	BL		PT		BL	PT	BL		PT		BL	PT	
	12.4		7.6		11.4	10.3	18.1		16.5		20.4	18.9	

*Classes at a fitness center, **classes at home using a videotape of the same exercise

§31 to 36 exercise classes, ^25 to 30 exercise classes, °24 or fewer exercise classes

BL = baseline, PT = post-test

that fatigue affects exercise performance and is a reliable measure for the prescription of physical activity.

On the other hand, the review shows a lack of studies with rigorous random sampling selection and blinding (single or double blinded), and the articles analyzed do not provide sufficient data to answer many questions with reliability. Future studies should provide the missing data, such as the type of training (i.e., strength training), as well as the average frequency, intensity and duration of the exercise intervention. Also required are more complete data on compliance with the exercise protocol. The issue of dose response is important given the recent recommendations from the Physical Activity Guidelines for Americans calling for additional dose-response analyses [17].

CONCLUSIONS

There is a lack of studies assessing fatigue as an outcome measure of patients with RA doing exercise; but the articles analyzed provide reasonable evidence that fatigue can be used both as a main measure in RA and as a good predictor of physical activity. Although there are several questionnaires and scales available to evaluate fatigue, clinical trials should be conducted to compare these tools with the current core set measures to determine which better assesses fatigue in its multidimensional aspects. Finally, fatigue appears to be a reliable outcome measure in the clinical management of RA, especially with regard to exercise prescription. However, there is a need for further research to evaluate the correlation between exercise, fatigue and quality of life, using validated fatigue scales, such as those described by Hewlett et al. [6] to explore the different components of fatigue and its wide-ranging consequences.

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"Knowledge comes, but wisdom lingers"

Lord Alfred Tennyson (1809-1892), Poet Laureate of Great Britain and Ireland during much of Queen Victoria's reign and remains one of the most popular British poets

"The true test of a civilization is, not the census, nor the size of the cities, nor the crops – no, but the kind of man the country turns out"

Ralph Waldo Emerson (1803-1882), American essayist