Journal of Science and Medicine in Sport 16 (2013) 99–104

Contents lists available at SciVerse ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Original research

Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors

Laurien M. Buffart[a,*], Ingrid C. De Backer[b], Goof Schep[b], Art Vreugdenhil[d], Johannes Brug[a], Mai J.M. Chinapaw[c]

[a] Department of Epidemiology and Biostatistics, VU University Medical Center, The Netherlands
[b] Department of Sports Medicine, Máxima Medical Center, The Netherlands
[c] Department of Internal Medicine, Máxima Medical Center, The Netherlands
[d] Department of Public and Occupational Health, VU University Medical Center, The Netherlands

ARTICLE INFO

Article history:
Received 29 September 2011
Received in revised form 20 February 2012
Accepted 30 May 2012

Keywords:
Physical endurance
Exercise
Value of life
Asthenia
Neoplasms
Mediation analysis

ABSTRACT

Objectives: This study aims to investigate whether fatigue mediates the association between physical fitness and quality of life.
Design: Uncontrolled pre–post intervention design.
Methods: Pre- and post-intervention measurements were conducted in 119 patients who completed chemotherapy treatment for various types of cancer. The intervention was an 18-week exercise programme consisting of high-intensity resistance and interval training. We assessed physical fitness – peak oxygen uptake and peak power output – self-reported fatigue (Multidimensional Fatigue Inventory – subscales general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue-, and fatigue symptom scale of EORTC QLQ-C30) and quality of life (EORTC QLQ-C30, subscale global quality of life). Linear regression analyses were conducted on the residual change scores of the variables. The mediated effect of fatigue on the association between physical fitness and quality of life was examined using the products of coefficient method. Bootstrapping was used to calculate the confidence intervals.
Results: We found significant associations between changes in physical fitness and global quality of life, between physical fitness and fatigue, and between fatigue and global quality of life. General fatigue mediated the positive association between peak power output and global quality of life, accounting for 82% of the total association. Physical fatigue, reduced activity, reduced motivation, and fatigue symptom were also mediators of this association. The mediation effects accounted for 91%, 76%, 38% and 71% of the total association, respectively. Reduced activity and reduced motivation mediated the association between peak oxygen uptake and global quality of life. Multiple mediation analyses showed that physical aspects of fatigue were stronger mediators than mental aspects.
Conclusions: General fatigue and physical aspects of fatigue mediate the relationship between physical fitness and quality of life in cancer survivors. We found no mediating effect of mental fatigue.

1. Introduction

Survival after cancer has improved substantially due to advances in early detection and treatment of cancer. In the Netherlands, 5-year cancer survival rates have improved up to 52% for male and 61% for female patients across all cancers.[1] However, cancer and its treatment are often associated with prolonged adverse psychosocial and physical symptoms including increased risk of anxiety, depression, fatigue, and reduced physical fitness and quality of life (QoL).[2–4]

Several literature reviews have reported that physical exercise may improve the QoL of cancer patients.[2,5] In a previous study, we evaluated the effects of an 18-week high intensity resistance exercise programme on physical fitness, fatigue and QoL in 57 cancer patients who completed chemotherapy.[6] We found significant improvements in patients' global QoL after completion of the intervention (effect size = 0.82; 95% confidence interval (CI) = 0.53; 1.11),[6] and these improvements persisted to 1 year follow up.[7] However, the mechanism (i.e. mediators) underlying improvements in QoL are unclear. A possible mediator of exercise-induced improvements in QoL is fatigue (Supplement 1).

Fatigue has been identified as one of the most common and distressing symptoms of cancer patients,[8,9] having a profound effect on QoL.[9,10] Previous meta-analyses have shown that physical exercise may reduce fatigue.[5,11,12] Schwartz[13] evaluated the

* Corresponding author.
E-mail address: l.buffart@vumc.nl (L.M. Buffart).

1440-2440/$ – see front matter © 2012 Sports Medicine Australia. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jsams.2012.05.014

Table 1
Characteristics of patients who did and did not complete the exercise program and of those with complete and incomplete data.

Variable	Exercise program			Measurements		
	Completers (n = 179)	Drop-out (n = 48)	p-Value	Complete (n = 119)	Incomplete (n = 60)	p-Value
Age, mean (SD) years	49.5 (10.1)	50.0 (9.8)	0.722	50.3 (9.1)	48.0 (11.7)	0.148
Gender, n (%) male	39 (20%)	13 (27%)	0.325	25 (21%)	11 (18%)	0.844
Type of cancer, n (%)			0.289			0.950
Breast	111 (62%)	27 (56%)		74 (62%)	37 (62%)	
Colorectal	19 (11%)	6 (13%)		14 (12%)	5 (8%)	
Genital organs	21 (12%)	3 (1%)		13 (11%)	8 (13%)	
Haematological	25 (14%)	9 (19%)		16 (13%)	9 (15%)	
Other	3 (1%)	3 (1%)		2 (2%)	1 (2%)	
Treatment, n (%)	N/A	N/A				
Chemotherapy				119 (100%)	60 (100%)	1.00
Radiotherapy				68 (57%)	31 (52%)	0.526
Surgery				102 (86%)	52 (87%)	1.00
Time between last chemotherapy and start training, n (SD) weeks	N/A	N/A		17.2 (9.5)	22.8 (13.6)	0.002

effects of an 8-week home-based, low-to-moderate intensity aerobic exercise programme on fatigue and QoL in a small sample of 27 women who received chemotherapy for breast cancer. She reported that functional ability and energy expenditure were associated with QoL, and that these associations were mediated by fatigue.[13] However, it is unclear whether these findings are valid for other parameters of physical fitness, for patients who are in a different phase of cancer treatment, or for other types of exercise programmes. More insight into the mechanisms of how exercise improves QoL is necessary for the systematic progression of research in this field and to better inform future exercise-based cancer rehabilitation. Therefore, the current study aims to investigate whether changes in fatigue mediate the association between changes in physical fitness and changes in QoL in a relatively large sample of patients who completed a high-intensity exercise programme after completion of chemotherapy for various types of cancer.

2. Methods

We conducted an uncontrolled clinical trial with a pre–post-test design in the Maxima Medical Centre, Veldhoven, the Netherlands. From March 2002 to January 2007, patients enrolled in an 18-week high-intensity exercise programme that was implemented as part of usual care for cancer survivors. Patients with histological confirmed cancer with no indication of recurrent or progressive disease and who had completed chemotherapy with curative intention were eligible. Exclusion criteria were: (1) not capable of performing basic skills like sitting or lying down, (2) cognitive disorders or severe emotional instability, and (3) other serious diseases that might hamper physical performance (e.g., heart failure, chronic obstructive pulmonary disease).

All patients signed an informed consent statement prior to participation. The Medical Ethics Committee of the Maxima Medical Centre approved the study. Patients started training at a minimum of 6 weeks after completing chemotherapy to a maximum of 52 weeks.

From March 2002 until January 2007, 227 patients were included in the study, of whom 48 did not complete the training programme; there were five deaths during the exercise programme due to the cancer, fourteen patients had recurrence or metastasis of cancer, sixteen patients had other medical reasons for which they were not capable to continue the programme, nine had personal or work-related problems, the programme was too strenuous for two patients, and for a further two patients the cause of non-completion is unknown. In total, 179 patients completed the exercise programme. Complete data regarding physical fitness, fatigue and HRQoL were available of 119 patients. Demographic and clinical characteristics did not differ between patients who completed the exercise program (n = 179) and those who did not (n = 48) and between patients who had complete data on the outcome measures (n = 119) and those who did not (n = 60), see Table 1. However, patients who completed all measurements started sooner after completion of therapy compared to patients with incomplete measurements (p = 0.002).

The 18-week exercise programme consisted of high-intensity resistance and interval training. Six resistance exercises targeting the large muscle groups were performed at 65–80% of one-repetition maximum and consisted of two sets of 10 repetitions. The interval training consisted of cycling two times for 8 min, before and after the resistance exercises at alternating workloads. The patients trained in groups of 6–8 on specialised resistance training equipment and on bicycle ergometers under the supervision of physical therapists. During the first 12 weeks, patients trained twice a week. In the last 6 weeks, patients trained once a week. Detailed descriptions of the training programme can be found elsewhere.[6]

Measures of body composition, physical fitness, fatigue and health-related quality of life were assessed before (T0) and after the 18-week exercise programme (T1).

Body mass index (BMI) was calculated from height and weight. Percentage body fat was determined from body weight and measurements of skinfold thickness at biceps, triceps, subscapular and suprailiac using the equation of Durnin and Womersley.[14]

Physical fitness was assessed during a maximum exercise test performed on a cycle ergometer (Corival, Lode, The Netherlands). Expired gases were collected and analysed breath by breath for O_2, CO_2, and flow and volume indices (Jaeger Oxycon Alpha, Jaeger, Hoechberg, Germany). Volumes and gas analyzers were calibrated before each test. Electrocardiogram was continuously monitored. Patients were instructed and encouraged to continue exercise until exhaustion. The test ended when patients were unable to maintain the required pedalling frequency of 70 rpm. At the end of the test, peak power output (PeakPO) and peak oxygen consumption ($peakVO_2$) were registered. This test was performed according to the standard protocol as described previously.[6]

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI).[15] This questionnaire consists of 20 statements for which the person indicates on a 7-point scale the extent to which the particular statement applies to him or her. The statement refers to aspects of fatigue experienced during the previous few days. Higher scores indicate a higher degree of fatigue. This self-report instrument consists of five subscales based on different dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The MFI subscales have good internal consistency (average Cronbach's alpha = 0.84).[15]