Effects of an endurance and resistance exercise program on persistent cancer-related fatigue after treatment

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Background: Fatigue is a relevant problem of cancer patients during and after treatment. Several studies have shown that exercise can improve quality of life and functional status of cancer patients undergoing chemo- or radiotherapy. However, there is a lack of information about the effects of this intervention on persistent cancer-related fatigue. Therefore, we assessed the effects of an exercise program on cancer-related fatigue after treatment.

Patients and methods: A consecutive series of 32 cancer patients with mild to severe persistent fatigue [scores on the Brief Fatigue Inventory (BFI) > 25] participated in a 3-week exercise program consisting of endurance (30 min walking on a treadmill) and resistance/coordination exercises for the major muscle groups. Fatigue, mood, and anxiety were assessed with questionnaires and physical performance with a stress test before and after the program.

Results: At the end of the program, we observed a significant increase of physical performance (workload at the anaerobic threshold pre 61 ± 26 W, post 78 ± 31 W, \( P < 0.0001 \)) and reduction of global fatigue (Functional Assessment of Cancer Therapy; pre 45.7 ± 13.4, post 52.6 ± 12.4, \( P < 0.0001 \); BFI: pre 37.9 ± 18.3, post 31.2 ± 17.1, \( P < 0.001 \)). However, no significant improvement of cognitive fatigue or reduction of anxiety was observed.

Conclusions: A 3-week exercise program leads to a substantial improvement of physical performance and reduction of mental and physical fatigue in cancer patients after treatment. However, this intervention does not affect depression, anxiety, or cognitive fatigue.

Key words: Anxiety, cognition, depression, exercise, fatigue, mood, supportive therapy

introduction

Most cancer patients experience a loss of energy and an impairment of physical performance in the course of the disease. It has been estimated that this problem affects up to 70% of cancer patients during chemo- and radiotherapy or after surgery [1]. Fatigue may affect not only the physical performance but also the cognitive function. In fact, patients report fatigue as a combination of symptoms including an inability to carry out physical exertion, tiredness, lack of interest, or motivation, and an impairment of short-term memory, attention, or concentration; these complaints are frequently associated with sleep disturbances (hyper- or insomnia), anxiety, and emotional reactivity [2]. On the basis of its characteristics, it has been proposed that fatigue is a syndrome rather than an isolated complaint [3].

For many patients, fatigue is a severe and limiting problem. The impairment of physical and mental performance prevents from working or carrying out regular daily activities and hence results in a substantial reduction of the quality of life. In response to fatigue, patients are usually advised to rest and down-regulate their level of daily activities. But since inactivity induces muscular catabolism, extended rest can actually help to perpetuate fatigue [4]. Furthermore, fatigue may be a persistent problem that continues for months after treatment, even in patients in complete remission [1, 5].

Several trials have evaluated different therapies for the treatment of cancer-related fatigue. However, therapeutic options for this problem remain limited. Recent studies have shown a lack of effect of antidepressants (paroxetine) and psychostimulants (methylphenidate) as treatment of cancer-related fatigue [6, 7]. Cognitive behavior therapies and psychotherapy may reduce fatigue in cancer patients [8]. However, these interventions do not correct the impairment of physical performance frequently observed in this patient group [9, 10].

Exercise has been proposed as a nonpharmacologic intervention for the treatment of cancer-related fatigue [11]. When carried out during chemo- or radiotherapy, exercise reduces the impairment of performance status related to treatment. It has been shown that exercise programs improve the quality of life in women treated for breast cancer [12, 13]. Furthermore, some evidence suggests that exercise may prevent fatigue related to cancer treatment. Women with breast cancer who carried out a home-based exercise program of moderate intensity during the initial phase of a chemotherapy
had a lower increase of fatigue scores compared with control patients [14]. However, the evidence about the effects of exercise on persistent cancer-related fatigue is still limited to pilot studies. In the first of them, five patients suffering from severe fatigue carried out an exercise program after chemotherapy; after 6 weeks, physical performance was substantially increased and fatigue reduced. However, the investigators assessed fatigue in an interview and did not use standard instruments or questionnaires to evaluate the severity of this symptom [9]. A further pilot study evaluated the effects of an individually adapted aerobic exercise program in 12 patients with severe fatigue following myeloablative therapy with allogeneic peripheral stem-cell support. After 12 weeks, the patients had significant improvement of physical performance and reduction of fatigue scores [15].

Exercise is a simple, low-risk intervention and is associated with positive effects on the cardiovascular system, the lean body mass and the risk of metabolic disorders. Therefore, it could play a relevant role in the rehabilitation and therapy of limitations associated with cancer and its treatment. On the basis of these considerations, we carried out a study to assess the effects of an exercise program on persistent cancer-related fatigue after treatment.

patients and methods

A consecutive series of patients consulting the Department of Hematology, Oncology and Transfusion Medicine of the Charité Universitätsmedizin Berlin due to fatigue between August 2004 and September 2007 was evaluated for participation in the study; a pretest, posttest trial. Inclusion criteria were age between 18 and 65 years, neoplastic disease (solid tumor or hematological malignancy), or peripheral blood stem-cell transplantation for the treatment of a hematological disorder, treatment concluded at least 4 weeks before screening for the trial or maintenance chemotherapy, a score of 25 or more on the Brief Fatigue Inventory (BFI) [16] indicating a mild, moderate, or severe fatigue syndrome (higher scores indicating more intense fatigue), independence from blood transfusion, ability to walk, and ability to understand German. Exclusion criteria were hemoglobin concentration < 8 g/dl, platelet count < 200 x 10^9/l, obesity (body mass index (BMI) > 30), cachexia, or malnourishment (BMI < 20), terminal disease, fatigue related to other conditions (i.e. autoimmune disease, chronic renal failure), chronic infection, treatment with high-dose corticoids (prednisone > 50 mg/day or equivalent dose of related agents), neurologic or muscular impairment precluding participation in an exercise program, chronic diseases which could be exacerbated or complicated by exercise (i.e. coronary artery disease, chronic obstructive pulmonary disease, osteoarthritis), skeletal metastases resulting in bone instability, or progressive disease with indication of new or additional therapy. A total of 32 eligible patients were enrolled after providing informed consent (Table 1). The study protocol was approved by the Institutional Ethics Committee.

Immediately after the first contact, an evaluation of fatigue was carried out with the BFI [17]. The BFI has been validated as a short and comprehensive instrument to assess the severity of fatigue and fatigue-related impairment in both clinical screening and trials. It consists of 10 items and may be completed by patients in <5 min. The questionnaire allows a basic assessment of the dimensions activity, ability to walk, mood, work, interpersonal relationship, and enjoyment of life. It uses simple designations to assess the severity of fatigue and the impairment of functional domains; however, it does not capture the multiple dimensions (cognitive, affective, and somatic) of fatigue.

| Age (years) | 52 ± 7 |
| Gender | 9 male, 23 female |
| Diagnosis |  |
| Solid tumor | 15 |
| Hodgkin’s disease | 1 |
| Chronic lymphocytic leukemia/non-Hodgkin’s lymphoma | 7 |
| Chronic myeloid leukemia | 1 |
| Multiple myeloma | 5 |
| Myelodysplastic syndrome | 2 |
| Acute myeloid leukemia | 1 |
| Treatment |  |
| Concluded treatment | 27 |
| Chemotherapy | 22 |
| Radiotherapy | 3 |
| Immune therapy | 6 |
| Maintenance chemotherapy | 5 |

As of 2020, the BFI has been validated as a short and comprehensive instrument to assess the severity of fatigue and fatigue-related impairment in both clinical screening and trials. It consists of 10 items and may be completed by patients in <5 min. The questionnaire allows a basic assessment of the dimensions activity, ability to walk, mood, work, interpersonal relationship, and enjoyment of life. It uses simple designations to assess the severity of fatigue and the impairment of functional domains; however, it does not capture the multiple dimensions (cognitive, affective, and somatic) of fatigue.

After recruitment, a baseline evaluation of physical performance was carried out. It consisted of a treadmill stress test using a Balke protocol. Respiratory and ventilatory parameters, heart rate, and electrocardiogram (ECG) were continuously registered. Lactic acid concentration was assessed at the end of each workload. Criteria for test termination were exhaustion, a respiratory quotient > 1.6, a heart rate >90% of the expected values, or signs or symptoms suggestive of cardiovascular pathologies (pathological ECG changes, systolic blood pressure > 220 mm Hg, inappropriate increase or decrease of heart rate or blood pressure, or angina pectoris). To determine the training intensity, we calculated the individual anaerobic threshold based on lactic acid concentration using the method described by Dickhuth et al. [18].

Patients received a comprehensive evaluation of fatigue with the Functional Assessment of Cancer Therapy—Fatigue Scale (FACT-F) [19]) and the MFIS (Multidimensional Fatigue Inventory [20]). Both instruments were specifically designed to evaluate fatigue in cancer patients. The FACT-F comprehends 13 items related to physical fatigue and its effect on functional status allowing an evaluation of the fatigue in the week before assessment. In this scale, lower scores indicate more intense fatigue. The MFIS consists of 20 questions on general complaints, physical, cognitive and mental fatigue, impairments caused by fatigue, and loss of motivation. Hence, the MFIS allows not only an assessment of the severity of fatigue but also an evaluation of its characteristics. These instruments and the BFI have been widely used in clinical trials with cancer patients. Values for reliability and validity have been published previously [17, 19, 20].

Depression and anxiety were evaluated with the German version of the Hospital Anxiety and Depression Scale (HADS) [21]. The HADS consists of 14 items grouped in a depression and an anxiety scale; this instrument evaluates the presence and severity of mild degrees of mood disorder, anxiety, and depression. A total score of 8 or more is indicative of clinically significant anxiety or depression, whereas values above 14 points indicate a severe disorder. The scale is widely used and found to be a reliable tool for detecting changes in psychological disturbances [21].

The patients carried out an endurance and resistance exercise program for 3 weeks. The endurance training consisted of walking on a treadmill.
on weekdays for 3 weeks. Training was carried out at a speed corresponding to a lactate concentration of 3 ± 0.5 mM/l in capillary blood or slightly below the individual anaerobic threshold; this intensity coincides with a heart rate of 80 ± 5% of the maximum reached during a stress test [22]. Heart rate during training was evaluated continuously and arterial blood pressure was assessed at the beginning and end of each workout. Lactate concentration was assessed every fifth training day. As lactate concentration sank <2.5 mM/l or exercise heart rate decreased as a result of training adaptation, the treadmill speed was increased by 0.5 km/h to maintain training intensity constant. During the first week, each patient walked five times for 3 min at the above-mentioned speed; between these training bouts, patients walked at half-speed for 3 min in order to recover. Patients unable to walk at a speed >3 km/h were allowed to sit during the intervals. Every five training sessions, exercise duration was increased by 5 min and the number of training bouts reduced accordingly to keep the duration of the workout constant at 30 min.

The resistance training consisted of a series of exercises using one’s own body weight, rubber bands, and dumbbells. The exercises were designed to increase the strength of major muscle groups (arms, pectoral and abdominal muscles, lower back, tights, and gluteus region). The patients carried out three sets of 20–30 dynamic repetitions or static isometric exercises for 45–60 s for each muscle group (one series) and rested 1–2 min between series.

In the week after concluding the training program, a second assessment of physical performance and severity of fatigue, anxiety, and depression was carried out. Since several patients terminated the stress test before exhaustion due to coordination problems or pain, changes in physical performance were evaluated by comparing the workload at the anaerobic threshold before and at the end of the program. If the tests could not be carried out at the scheduled time due to administrative or personal problems, a further workout was carried out in order to avoid a too long pause between the end of the training program and the second assessment.

**Statistical Analysis**

Primary end point of the study was the change of fatigue scores after the intervention. Secondary end points were the physical performance (watts at the anaerobic threshold) and scores of depression/anxiety. Hemoglobin concentration was assessed before and after the program to rule out confounding effects on physical or cognitive performance.

Pilot research on patients with a cancer fatigue syndrome showed a mean score of 45 ± 12 on the BFI. A difference of 6 points was considered as clinically relevant based on the generally accepted meaningful difference of a one-half standard deviation (SD) change for symptom assessment and quality-of-life measures. A calculation of sample size showed that 32 patients were required to detect a reduction of fatigue of this magnitude with a probability for an alpha error of 5% and a beta error of 20% using a two-tailed test.

The severity of fatigue was ranked according to previously published criteria [17] as mild (scores between 25 and 30), moderate (scores between 31 and 60), and severe (scores of >60). Data of patients before and after the program were compared using the Wilcoxon or the Student’s t-test, as indicated; a value of $P < 0.05$ was considered to be statistically significant. Tests were carried out using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA). Values are expressed as mean ± SD if not stated otherwise.

**Results**

All contacted patients agreed with participation and were recruited for the trial. During the study there were no adverse events and no dropouts. All patients completed all surveys.

During the 3 weeks of the trial, patients worked out a mean of 10 ± 3 days; hence, mean participation rate was 90% of the scheduled workouts (range 30%–100%). There were no complications during the training program. The hemoglobin concentration remained constant during the study (pre: 12.6 ± 1.7 g/dl; post: 12.8 ± 1.5; $P = 0.25$, Figure 1). All patients remained free of relapse and no patient required new chemoradiotherapy.

The exercise intervention led to a statistically significant improvement of physical performance. After the program, the workload at the anaerobic threshold increased from 63 ± 27 W to 80 ± 32 W ($P = 0.0001$; Figure 1).

The mean fatigue scores decreased in all evaluation instruments. Global fatigue was reduced by 25% (BFI pre: 37.9 ± 18.3, post: 31.2 ± 17.1, $P = 0.0007$; FACT pre: 45.7 ± 13.4, post: 52.6 ± 12.4, $P < 0.0001$). Before the intervention, five patients (15%) had mild fatigue (BFI scores between 25 and 30), 24 patients (63%) moderate fatigue (BFI 30–60), and four patients (12%) severe fatigue (BFI > 60). After 3 weeks, the figures were 10 patients (30%) with scores <25 (fatigue less than mild), two patients (6%) with mild, 19 (57%) with moderate, and one (3%) with severe fatigue. The subscales of the MFI showed a reduction of mental and physical fatigue (mental fatigue: pre 2.2 ± 0.7, post 1.6 ± 0.8, $P = 0.01$; physical fatigue: pre 2.4 ± 0.6, post 2.0 ± 0.7, $P = 0.004$). However, scores of cognitive fatigue at the end of the intervention were not statistically different compared with the baseline evaluation (pre: 2.1 ± 0.8, post: 1.9 ± 0.8, $P = 0.09$; Figures 2 and 3).

Finally, depression and anxiety scores at the end of the exercise program were unchanged (HADS A pre: 9.7 ± 3.8, post: 8.8 ± 4.1, $P = 0.15$; HADS D pre: 7.8 ± 3.8, post: 7.3 ± 4.5; $P = 0.37$).

**Discussion**

Fatigue is a frequent problem of cancer patients during and after chemotherapy. In recent years, exercise has been proposed...
tasks or a tendency to avoid social contacts and activities (volitional fatigue). These two latter forms of fatigue are rather primary indicators of psychological disturbance and increased mental distress than of physical disorder. Our findings show that both forms of fatigue require a different therapeutic approach.

In this study, a short-duration exercise program led to a substantial increase of physical performance. Global fatigue scores and the number of patients suffering from moderate to severe fatigue were lower at the end of the program. However, scores of cognitive fatigue did not improve at the end of the intervention. This observation suggests that cognitive impairment in cancer patients is independent of the loss of physical performance associated with treatment. Hence, the pathophysiology of the different forms of cancer-related fatigue is likely to be different, requiring further development of intervention strategies.

We have previously reported a lack of association between physical performance and fatigue in cancer patients [10]. This observation appears counterintuitive, but the findings of the present report provide an explanation for this phenomenon. Most questionnaires used for the assessment of fatigue allow a global evaluation of this symptom and do not consider the different components of the fatigue syndrome. Patients with impaired physical performance need a higher effort to carry out daily and work activities. The increased energy consumption and metabolic distress lead not only to fatigue but also to physical symptoms such as tachycardia, breathlessness, and muscle discomfort, which patients associate with a poorer health. The psychological stress related to this phenomenon probably contributes to mental fatigue. However, impaired cognition, the third component of the fatigue syndrome, may be not related to the latter two components. Actually, we have frequently observed patients with normal physical performance reporting a mild to moderate cognitive impairment, which manifests as loss of concentration and forgetfulness.

While depression and fatigue are frequently associated problems in cancer patients, the relationship between both disorders is not clear [10, 24–26]. Mental and physical fatigue is a common symptom of depression. However, impairments caused by the disease and its treatment may also cause a manifest depression in cancer patients. The results of the present study show that cancer-related fatigue and depression may require different therapeutic approaches. While exercise led to a substantial reduction of fatigue, no changes of depression or anxiety were observed. This observation mirrors previous findings showing that an antidepressant (paroxetine) reduces depression scores but does not affect fatigue in cancer patients [7].

The effects of physical activity on cancer-related fatigue are complex and not only limited to an improvement of cardiovascular or muscular function. Indeed, a higher performance status can increase the feeling of control, independence, and self-esteem, resulting in better social interaction and less anxiety and fear. Therefore, increased physical performance can result in secondary benefits such as an improved mood and reduced psychological stress. These changes have been associated with a reduction of fatigue in cancer patients [27].
The present study has some limitations. It cannot be ruled out that the increased social contact, motivation, and expectations related to participation in a trial may have led to a reduction of fatigue among study participants. In fact, studies evaluating psychostimulants for the treatment of cancer-related fatigue have shown a substantial placebo effect [6]. Due to the lack of a control group receiving only a psychological intervention, we cannot rule out effects of attention and social interaction on the outcomes of the present trial. However, it is suggestive that the exercise program only resulted in improvement of the areas associated with physical performance (i.e. physical and psychological fatigue), while anxiety, depression, and cognitive fatigue, which are more sensitive to psychosocial interventions, remained constant.

A further limitation of the study is the evaluation of the cognitive fatigue. While the used questionnaires allow a differentiation between several forms of fatigue, it is not possible to rule out some overlapping between the physical, mental, and motivational aspects of the problem. Further trials should carry out an evaluation of the cognitive function and the effects of exercise with more specific instruments.

The results of the present study show that exercise is a promising and effective therapeutic approach to persistent cancer-related fatigue. However, it does not affect all components of the fatigue syndrome, which are the cause of substantial impairment in cancer patients. Furthermore, the role of attention, motivation, and social interaction in connection with the positive effects of exercise on cancer-related fatigue needs to be further evaluated in future trials.

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references