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Original article

Correlation between physical performance and fatigue in cancer patients

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Summary

Background: Fatigue and a reduction in physical ability are common and often severe problems of cancer patients regardless of disease stage and modality of treatment. However, while physical performance can be assessed objectively with laboratory tests, fatigue is a subjective phenomenon whose perception is influenced by past experience and expectations for the future.

Patients and methods: To evaluate the correlation between fatigue and physical impairment, we assessed maximal physical performance with a treadmill test, and mental state with two questionnaires, the Profile of Mood States (POMS) and the Symptom Check List (SCL-90-R), in a successive series of 78 cancer patients with solid tumors or hematological malignancies.

Results: A weak association between fatigue and maximal physical performance was found ($r = -0.30$; $P < 0.01$). However, intensity of fatigue showed a strong correlation with several indicators of psychological distress such as depression ($r = 0.68$), somatization ($r = 0.64$) and anxiety ($r = 0.63$; P for all < 0.001). Furthermore, patients with lower levels of physical performance had significantly higher scores for depression ($P = 0.005$), somatization ($P = 0.03$) and anxiety ($P = 0.08$), and significantly lower scores for vigor ($P = 0.05$) than their counterparts whose physical performance was higher.

Conclusions: We conclude that fatigue in cancer patients may be related to mood disturbance but appears to be independent of physical performance. Moreover, low physical performance can be viewed as an independent predictor of mental distress in cancer patients.

Key words: cancer fatigue, physical performance, psychological distress

Introduction

Fatigue figures among the most common problems of cancer patients. According to several studies, this symptom affects up to 70% of patients during chemo- and radiotherapy [1–3]. It has been reported that impairment of physical functioning may persist for years after cessation of therapy in up to 30% of cancer survivors [3–5]. For many cancer patients, fatigue is severe and imposes limitations on normal daily activities. Postulated etiological mechanisms for the development of fatigue include anemia, impaired nutritional status, sleep disturbances, biochemical changes secondary to disease and treatment, psychosocial factors, and a reduced level of activity [6]. However, the causes of the impairment of physical functioning in this setting are not yet fully understood.

In fact, fatigue represents only one aspect of the problem of physical impairment experienced by cancer patients. Cancer is usually accompanied by an 'asthenic syndrome' consisting of two components, one objective (loss of physical performance) and one subjective (fatigue). This difference considerably complicates the study of asthenia in cancer patients. Physical performance can be directly determinated by laboratory tests and expressed in units (maximal oxygen uptake in ml/kg/min, maximal workload in km/h or watts). Fatigue, on the other hand, has to be assessed indirectly by self-ratings.

Another factor complicating evaluation of fatigue in cancer patients is that – as with every subjective phenomenon – perception of fatigue strongly depends on past experience. Since cancer-related decreases in physical activity can persist for a long time, perception of fatigue can change as it becomes chronic. It has been suggested that cancer patients gradually become accustomed to their impaired physical condition and finally experience it as normal [7]. Furthermore, the subjective and objective evaluation of the limitation in physical performance can produce different results: a substantial discordance has been observed in estimations of functional ability with the Karnofsky index by patients and medical staff [8]. Nevertheless, in some clinical situations fatigue can exist independently of deterioration in physical performance; for example, fatigue is frequently a symptom in patients with depressive disorders whose physical performance is not necessarily impaired.

In light of these considerations, we investigated the relationship between fatigue and physical performance in cancer patients.

Table 1. Baseline data of patients in the study (n = 78).

Gender	48 women, 30 men	
Age	40 ± 11.3 (18–60)	
Body mass index	23.9 ± 3.7 (18–34)	
	Number of patients	Percentage
Disease		
Breast cancer	25	32%
Metastatic breast cancer	9	11%
Testicular cancer	11	14%
Sarcoma	3	4%
Small-cell lung carcinoma	1	1%
Multiple myeloma	2	2%
Hodgkin's disease	6	8%
Non-Hodgkin's disease	21	27%
Maximal physical performance		
Very poor (50% of maximum)	49	62%
Poor (50%–54% of maximum)	6	8%
Fair (55%–65% of maximum)	7	9%
Good (66%–69% of maximum)	6	8%
Excellent (70%–75% of maximum)	8	10%
Superior (> 75% of maximum)	2	3%

Maximal physical performance of the patients was classified in accordance with tables of normal values for aerobic power tests for healthy adults [13]. Values are shown as mean ± standard deviation; ranges are shown in brackets.

Patients and methods

A series of 89 successive cancer patients with solid tumors or hematological malignancies were enrolled in the study (Table 1). Inclusion criteria were: age between 18 and 60 years, active malignancy, an absence of associated psychiatric, muscular, cardiovascular or pulmonary disease, and the ability to understand written German. All patients were considered for a high-dose chemotherapy (HDC) with peripheral autologous blood stem cell transplantation. In the weeks preceding hospital admission for HDC, all of them received one to four chemotherapy cycles consisting of etoposide 500 mg/m^2, ifosfamide 4 g/m^2, and cisplatinum 50 mg/m^2, with or without epirubicin 50 mg/m^2 (VIP/VIP-E).

After giving their informed consent, all patients underwent a treadmill stress test for assessment of maximal physical performance. The test began with 3 km/h and 1.5% elevation; the speed was increased by 1 km/h every third minute, while the elevation remained unchanged. The test was carried out under continuous ECG monitoring. The heart rate was assessed at the end of every workload. Eleven patients (13%) discontinued the test because of pain or coordinatory problems and were excluded from the study. Altogether, data on 78 patients were included in the statistical analysis.

Following evaluation of their physical performance, all patients underwent an assessment of their psychological state by completing two questionnaires, the short version of the Profile of Mood Status (POMS) [9, 10] and the Symptom Check List (SCL-90-R) [11, 12]. These instruments consist of statements about subjective experiences and allow an assessment of affective states during the past week (the SCL-90-R) or on the current day (the POMS). The short version of the POMS yields a total mood disturbance score (TMD) and separate subscale scores for depression, fatigue, anger-hostility and vigor. Similarly, the SCL-90-R yields a global severity index (GSI) and separate subscales for somatization, obsessivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Higher TMD and GSI scores indicate greater overall mood disturbance, while higher subscale scores indicate a greater intensity of disturbance in the examined areas. These instrument have been used in several clinical studies to evaluate affective states and mental symptomatology in different patient populations and have shown high reliability and validity.

Maximal oxygen consumption in ml O_2 per kg of body weight per minute was calculated according to the guidelines of the American College of Sports Medicine [13].

Statistical analysis

To evaluate the association between intensity of fatigue and physical performance, a partial correlation test, including age and gender as independent covariables, was carried out. Employing the Spearman rank correlation test, in a further analysis we calculated the correlation between fatigue and the remaining sub-scales of the POMS (vigor, anger, and depression), and between fatigue and the sub-scales of the SCL-90-R considered to be of relevance (somatization, depression, anxiety, hostility, and interpersonal sensitivity).

Maximal physical performance of the patients was compared with the values for aerobic power of healthy persons, obtained from standard tables [13]. In these tables, maximal physical performance can be assigned to one of six functional categories representing percentages of the maximal oxygen uptake (VO_2max) values recorded in healthy persons. The six categories are: very poor (VO_2max lower than 50% of the maximal observed value), poor (50%–54%), fair (55%–65%), good (66%–70%), excellent (71%–75%), and superior (higher than 76%). To evaluate the influence of physical performance on mental distress, the psychological scores of patients whose physical performance was in the lowest categories ('very poor' and 'poor') were compared with the remaining patients by the Mann–Whitney ranks test. To identify significant predictors of fatigue, a stepwise multiple regression analysis was carried out. It included all POMS subscales, the SCL-90-R subscales considered relevant (depression, somatization, and anxiety) and maximal physical performance as independent variables, and fatigue as a dependent variable. All statistical calculations were carried out using the Statistical Package for the Social Sciences (SPSS 6.1.2). A value of $P < 0.05$ was considered to show statistical significance, and a value of $r > 0.50$ to indicate relevant correlation.

Results

According to the guidelines of the American College of Sports Medicine, the physical performance of 55 of 78 patients in the study (70%) was classified as 'poor' or 'very poor' (Table 1). These patients had significantly more somatic complaints (P = 0.03), were more depressed (P = 0.005) and anxious (P = 0.08), had a higher insecurity in interpersonal contacts (P = 0.09) and significantly lower vigor (P = 0.05) than their counterparts with higher physical performance (Table 2). There was no difference in the extent of fatigue in the two groups (P = 0.30). Altogether, the global intensity of mental distress (GSI) in patients with reduced physical performance was more severe than for their counterparts with higher endurance ($P < 0.006$).

Statistical analysis showed a weak correlation between fatigue and maximal physical performance (Table 3). On the other hand, a strong correlation between fatigue and somatization, anxiety, and depression was observed. Multiple regression analysis showed depression, somatization and vigor/activity to be the only significant predictors of fatigue (f (3,73) = 39,5; $P < 0.0001$). These three parameters accounted for 61% of the variance in fatigue intensity.

Table 2 Differences of psychological distress between patients according to maximal physical performance.

	Patients in the lowest quartiles	Patients in the three highest quartiles	*P*-value
Number	56 (72%)	21 (28%)	
Maximal oxygen uptake (ml/kg/min)	21 ± 63	7 ± 3	<0 001
POMS			
Depression	14.4 ± 2.0 (0–70)	11.3 ± 3.1 (0–63)	0.46
Fatigue	10.9 ± 1 (0–42)	7 ± 1.5 (0–25)	0.30
Vigor-activity	18.9 ± 1.1 (0–37)	22.6 ± 1.6 (1–34)	0.05
Anger-hostility	5.7 ± 1 (0–36)	5.2 ± 1 5 (0–24)	0.83
Total mood disturbance	12.1 ± 33 (−30–115)	1 ± 29 (−31–93)	0.16
SCL-90-R			
Somatization	5.5 ± 0.7 (0–23)	2.8 ± 0.6 (0–10)	0.03
Obsessive-compulsive	4.6 ± 0.6 (0–21)	3.4 ± 0 7 (0–11)	0.27
Interpersonal sensitivity	3.7 ± 0.5 (0–19)	2.2 ± 0 6 (0–11)	0.09
Depression	7.4 ± 0.9 (0–35)	4.1 ± 1 2 (0–22)	0.005
Anxiety	4.7 ± 0.8 (0–28)	2.3 ± 0 8 (0–16)	0.08
Hostility	2.0 ± 0.35 (0–11)	1.1 ± 0 3 (0–5)	0.20
Phobic anxiety	1.6 ± 0.33 (0–13)	1.1 ± 0.4 (0–6)	0.50
Global severity index	39.2 ± 4.6 (4–173)	22 0 ± 5 (1–34)	0.006

Abbreviations: POMS – Profile of Mood States; SCL-90-R – Revised Symptom Check List 90
Data are shown as mean ± standard deviation; ranges are shown in brackets. Data were compared with the Mann–Whitney ranks test.

Discussion

Fatigue is a common and sometimes severe problem of cancer patients. The origin of fatigue in this setting is certainly multifactorial; however, psychological factors seem to play an important etiologic role. Fatigue in cancer patients has been related to depression, anxiety, distress, and global mood disturbance [1, 14–18]. Nerenz et al. found tiredness to be strongly associated with the emotional distress experienced during chemotherapy [15]. Depression in particular is considered to be a contributor to fatigue in cancer patients. Two reports found an association between fatigue and depression in a group of cancer patients undergoing radio- or chemotherapy [14, 19]. Furthermore, Fobair reported a strong correlation between energy loss and depression in lymphoma patients, evaluated several years after completion of treatment [20].

Table 3. Correlation between maximal physical performance and examined psychological domains.

	Correlation with fatigue	Significance of *P*
Maximal physical performance (VO_2max in ml/kg/min)	−0.30	<0.01[a]
Depression (POMS)	0.61	<0.001[b]
Vigor (POMS)	−0.52	<0.001[b]
Anger (POMS)	0.52	<0.001[b]
Depression (SCL-90)	0.68	<0.001[b]
Somatization (SCL-90)	0.64	<0.001[b]
Anxiety (SCL-90)	0.63	<0.001[b]
Hostility (SCL-90)	0.53	<0.001[b]
Interpersonal sensitivity (SCL-90)	0.47	<0.001[b]
Global severity index (SCL-90)	0.68	<0.001[b]

[a] Partial correlation including age and gender as covariates.
[b] Spearman rank-difference.

When considered from a teleological perspective, fatigue appears as a normal and necessary instrument of physiological self-regulation. Fatigue that appears after intense or prolonged activity protects the body from exaggerated or harmful effort. However, fatigue can also become pathological when it occurs during normal activity, persists for a long time, does not improve after rest, or becomes severe enough to force patients to reduce their level of activity [21]. The incidence of fatigue in healthy populations has been estimated to be between 21% and 47% [22–24]. Therefore, studies of the incidence and intensity of fatigue in cancer patients should include a comparison with sex- and age-matched healthy controls. Interestingly, when this methodology was used, mean fatigue levels in cancer patients were only slightly higher than those observed in controls [18, 25]. This is surprising, in view of the clinical observation that many cancer patients experience a severe diminution of their physical performance.

Our study suggests a possible explanation for this observation. Analyzing the subjective and objective data of our patients, we discovered a divergence between their objective life situation and their subjective perception of it. In fact, according to the standards of the American College of Sports Medicine, the physical performance of 70% of the patients in our study was 'poor' or 'very poor'; a similar percentage has been observed by other authors [3]. However, in our study, these patients did not experience more fatigue than their counterparts whose physical performance was higher. These data appear to be counterintuitive since many of these patients (especially those with a physical performance considered to be 'very poor') reported limitations in normal activities such as stair climbing or housekeeping. Thus, we wonder why patients do not feel fatigued despite impaired physical performance?

Breetvelt et al. [7] have proposed a theoretical explanation for this. Fatigue is a subjective experience. According to the North American Nursing Diagnosis Association, the major feature of chronic fatigue is verbalization or self-report of a sustained and significant lack of energy. However, since cancer fatigue can persist for a long time, the patient's subjective standards of measurement can change in the course of the disease. Therefore, patients affected by chronic loss of physical performance can gradually become accustomed to this impairment and finally experience it as normal.

The findings of the present study are clinically relevant, because our data show that evaluation of fatigue in cancer patients can be misleading, since many cancer patients deny feeling fatigued despite severe limitations in physical performance. To assess the actual degree of physical impairment, patients have to be explicitly asked about the objective limitations they experience in daily activities, such, for instance, as stair climbing or walking.

In our study, patients with impairment of physical performance had significantly higher scores of mental distress. Patients with the lowest performance level were significantly more depressed and anxious, had more severe obsessive-compulsive traits, were more insecure in social contacts, and had a higher intensity of somatic complaints than their counterparts with better physical performance. This association between impaired physical performance and increased psychological distress has been previously reported. In a study by Baker et al., the Karnofsky Index was the most significant predictor of satisfaction with quality of life, total mood disturbance and vigor [26].

Whether mood disturbance in these patients is a consequence or the cause of the impaired physical performance is difficult to determine; both possibilities seem plausible. Impaired physical performance can result in increased dependence, decreased self-esteem, reduction in social activities, limitations in family life, and a pessimistic mood. Furthermore, impaired physical performance can be interpreted by the patient as a sign of poor health and thereby increase his or her psychological distress. On the other hand, depressed and anxious patients are more likely to reduce their outdoor activity and revert to a passive lifestyle; this can result in muscular deconditioning and loss of physical performance. Clearly, the association between impaired physical performance and increased psychological distress in cancer patients can have therapeutical consequences. For example, an improvement of physical performance by a physical training program could reduce negative mood states in cancer patients; in fact, we have reported a substantial improvement of physical performance and emotional stability in cancer patients who participated in an aerobic training program [27–29].

To our knowledge, this report represents the first objective evaluation of impairment of physical performance and its relation to mood in cancer patients. All participants in our study were candidates for a high-dose chemotherapy with peripheral stem cell transplantation and had received treatment with identical doses of cytostatic drugs in the months preceding enrollment. Therefore, the sample evaluated in our study was homogeneous with regard to stage of disease, tumor burden and treatment modality.

Our study included a single evaluation of maximal physical performance and psychological status. This is a limitation of the study design, since cancer is a chronic disease and several factors (treatment, anemia, infection, recurrence, use of opioids or antihistaminic drugs) can modify physical performance and psychological distress during illness. Hence, the correlation between fatigue, physical performance and mood status can change in the course of disease. Moreover, as mentioned above, several studies have shown fatigue to be present for years after the conclusion of treatment. However, less is known about the limitations in physical performance suffered by these patients. Further research will be necessary to answer these important questions.

We conclude that cancer-related fatigue can be independent of the impairment of physical performance experienced by cancer patients; furthermore, low physical performance appears to be an independent predictor of mental distress in this group of patients.

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