

The Correlation between Fatigue, Physical Function, the Systemic Inflammatory Response, and Psychological Distress in Patients with Advanced Lung Cancer

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BACKGROUND. Functional disability is reported frequently in fatigued cancer patients, but little is known about the correlation between fatigue and objective physical function. In addition, from previous work, the systemic inflammatory response and psychological distress appear to be related to fatigue.

METHODS. Thirty-eight patients with metastatic or locally advanced lung carcinoma and 15 age-matched and gender-matched, healthy controls completed the Functional Assessment of Chronic Illness Therapy-Fatigue scale, a visual analogue weakness score, and the Hospital Anxiety and Depression (HAD) scale. Hemoglobin concentrations, C-reactive protein (CRP) concentrations, creatine kinase concentrations, white blood cell count, body composition, Karnofsky performance status (KPS), grip strength, and chair-rise time also were measured in both groups. The cancer patients were then grouped into tertiles on the basis of fatigue scores.

RESULTS. The cancer patients had greater fatigue compared with the control group ($P < 0.001$). They also weighed less, had lower hemoglobin and creatine kinase levels and higher CRP levels, and had lower KPS, poorer grip strength, longer chair-rise times, and increased HAD scale scores (all $P < 0.01$). KPS and chair-rise time were correlated strongly ($r^2 = 0.565$; $P < 0.001$). With increasing fatigue, KPS was lower, and chair-rise time and HAD scale scores were greater ($P < 0.01$). On multiple regression analysis, only KPS, weakness, and HAD scale scores were correlated independently with fatigue ($r^2 = 0.570$; $P < 0.001$).

CONCLUSIONS. Objective physical function (as measured by chair-rise time) in patients with advanced lung cancer was poorer with increasing fatigue. Results of the current study suggest that fatigue is not a result primarily of weight loss or anemia but is related to KPS and psychological distress. *Cancer* 2005;103:377–82.

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KEYWORDS: fatigue, physical function, performance status, systemic inflammatory response, psychological distress, depression, lung cancer.

It is now recognized that the majority of patients with advanced cancer will experience fatigue and that this will have a negative impact on their ability to carry out basic daily activities.^{1–3} Increased fatigue also may be related to poorer survival.⁴ However, despite the importance of fatigue, little is known about which factors are important in determining the severity of fatigue in patients with advanced cancer. In particular, the nature of the correlation between fatigue, which is a subjective symptom, and objective physical function is unclear.

It has been reported that fatigue is related to anemia⁵ and loss of weight, particularly loss of muscle bulk.⁶ Therefore, it is noteworthy that, in reports on patients with advanced cancer, the systemic inflammatory response has been associated with loss of lean tissue,⁷ anemia, poor performance status,^{4,8} and fatigue severity.^{9,10} In addition to the physical correlates of fatigue, previous studies have reported that psychological distress, and depression in particular, is related strongly to fatigue scores.^{11–14} However, the linear correlation between fatigue and depression is unclear.¹³ The objective of the current study was to examine the relationship between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer.

MATERIALS AND METHODS

Patients

Patients with a firm clinical or histologic diagnosis of locally advanced or metastatic lung carcinoma were recruited from two specialist palliative care centers and an associated hospital—Strathcarron Hospice (Denny, United Kingdom), Marie Curie Hospice Hunter's Hill (Glasgow, United Kingdom) and Stobhill Hospital (Glasgow, United Kingdom). Patient eligibility was identified by medical or nursing staff in the wards at each center, by the Respiratory/Oncology outpatient clinic, by the hospice day centers, or by hospice community specialist palliative care nurses. Patients were ineligible for the study if they had received surgery or had undergone chemotherapy or radiotherapy within the previous month or if they had an active connective tissue disease. A group of age-matched and gender-matched, healthy volunteers were recruited as a control group from Strathcarron Hospice volunteers and also through personal contacts at the University of Glasgow.

The control group and the patient group were assessed for fatigue, weakness, anthropometry, physical function, and psychological distress. A blood sample was collected for routine laboratory analysis of white blood cell count, hemoglobin, creatine kinase, albumin, and C-reactive protein.

The study was approved by the local ethics committees covering the participating units. All patients and healthy control participants were aware of the purpose of the study and provided written, informed consent.

Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which is a validated measure of fatigue, was used as described previously.⁵ The FACIT-F is a 13-item subscale of the larger, original

FACIT-F questionnaire (known originally as the Functional Assessment of Cancer Therapy-Fatigue) to assess quality of life in cancer patients suffering from fatigue and other anemia-related symptoms. Each item is scored between 0 (not at all) and 4 (very much) and asks the respondent how true each statement has been over the previous week. Low total scores represent a high level of fatigue.

The 3-item Fatigue subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30 (EORTC QLQ-C30) also was completed as a comparison measure.¹⁵ The three questions—"Did you need to rest?", "Have you felt weak?", and "Were you tired?"—are scored between 1 (not at all) and 4 (very much) and ask the respondent how true each question has been over the previous week. The total score for the 3 questions is transformed into a score out of 100 using a scoring algorithm. High scores represent high levels of fatigue.

Weakness Visual Analogue Scale

A simple 10-cm visual analogue scale (ranging from "I don't feel weak at all" to "I couldn't feel any weaker") was used as a measure of patient weakness at that time point. Patients were asked to mark the line at a point that they felt represented best how they were feeling currently. The score was in cm from point 0 on the far left.

Blood Parameters

Hemoglobin concentrations and white blood cell counts were measured on a SYSMEX NE 8000 analyzer (TOA Medical Electronics Company Ltd, Kobe, Japan). Intraassay and interassay coefficients of variation were < 10%.

Creatine kinase concentrations (as an indirect measure of muscle mass) as well as C-reactive protein (as a measure of the systemic inflammatory response) and albumin concentrations were assayed on an Olympus AU5200 analyzer (Olympus Optical Ltd., Tokyo, Japan) using standard methods. The minimum detectable concentration for C-reactive protein was 6 mg/L. Intraassay and interassay coefficients of variation were < 5% and 10%, respectively.

Body Composition

Height and weight were measured, and body mass index (BMI) was calculated using the formula $BMI (kg/m^2) = \text{weight (kg)} / \text{height (m)}^2$. Triceps skin-fold thickness and thigh skin-fold thickness were measured with Harpenden skin-fold calipers (British Indicator Ltd., West Sussex, United Kingdom) using established techniques. Midarm and midthigh cir-

cumferences were measured using a stretch-resistant measuring tape.

Patient Function

The Karnofsky performance status (KPS) was used as an observer-rated measure of functional ability; it has been used extensively in studies involving cancer patients.^{16,17} Hand-grip strength was measured in the dominant hand with a Takei Kiki Kogyo grip dynamometer (Takei and Company, Tokyo, Japan) using the best result from three attempts.

The chair-rise time was measured using a chair of square design with a firm seat and arm rests.¹⁸ The seat height was 43 cm (1 cm higher than the average British toilet): a functionally significant height.¹⁹ The patient was asked to rise from a seated position to a fully upright position as fast as they could, if possible without using the arm rests. The time taken to complete this maneuver was measured on a hand-held digital stopwatch (Lorus Watches, Austin, TX). The best time from three attempts was recorded.

Psychological Distress

The Hospital Anxiety and Depression (HAD) scale is a self-report questionnaire that originally was designed for use with medical patients, although it has been used extensively in cancer patients.^{20–22} It is a 14-item scale that originally was intended to be used as 2 7-item subscales measuring anxiety and depression. However, some of the depression scale questions, e.g., “I feel slowed down,” could apply equally to advanced physical illness and to depression. Recent studies in the palliative care population^{23,24} have suggested that the use of the entire scale is a better indicator of the presence of depression than the depression subscale alone. Each item has 4 possible answers (scored from 0 to 3, with higher scores more suggestive of psychological distress), and patients are asked to tick the answer that comes closest to how they have been feeling in the previous week. In terms of maximizing sensitivity and specificity, scores of 19 or 20 on the combined scale have been suggested as the most appropriate cut-off points for identifying a “case” of depression.^{23,24}

Statistics

Data are presented as medians with ranges. Where appropriate, group comparisons were carried out using contingency table analysis (chi-square analysis), the Mann–Whitney *U* test, and the Kruskal–Wallis test for analysis of variance. Given the number of comparisons made, a nominal *P* value of 0.01 was used as the criterion for statistical significance. Independent associations between FACIT–Fatigue and KPS, chair rise,

TABLE 1
Characteristics, Body Composition, Physical Function, and Fatigue in the Healthy Control Group and in Patients with Advanced Lung Cancer

Characteristic	Median (range)		<i>P</i> value
	Healthy controls (<i>n</i> = 15)	Cancer patients (<i>n</i> = 38)	
Gender (M/F)	7/8	23/15	0.541
Age (yrs)	64 (46–74)	64 (43–81)	0.358
BMI (kg/m ²)	24.6 (20.9–28.9)	21.2 (14.8–33.3)	0.011
White cell count (10 ⁹ /L)	6.5 (4.1–8.4)	9.2 (5.1–26.2)	<0.001
Hemoglobin (g/dL)	14.4 (12.3–16.1)	12.3 (9.6–16.3)	<0.001
Albumin (g/L)	44 (41–47)	39 (23–45)	<0.001
C-reactive protein (mg/L)	< 6 (<6–30)	59 (<6–214)	<0.001
Skinfold thickness (mm)			
Triceps	17.0 (6.5–32.0)	10.0 (3.0–33.5)	0.024
Midhigh	18.3 (8.5–56.5)	12.5 (3.5–36.5)	0.032
Circumference (cm)			
Middle-upper arm	31.2 (25.6–33.5)	24.8 (17.1–37.0)	<0.001
Midhigh	51.3 (44.8–59.1)	42.3 (32.3–57.1)	<0.001
Creatine kinase (IU/L)	105 (38–199)	35 (10–318)	<0.001
Karnofsky performance status	100 (90–100)	70 (30–100)	<0.001
Handgrip strength (kgW)	28.5 (20.0–49.0)	22.3 (6.5–51.0)	0.003
Chair rise (seconds)	0.97 (0.81–1.60)	1.50 (0.98–6.06)	<0.001
VAS weakness (cm)	1.0 (0.1–3.3)	4.1 (0.4–8.3)	<0.001
HAD scale	4 (0–13)	14 (0–26)	<0.001
FACIT–Fatigue scale	49 (43–51)	30 (4–45)	<0.001
EORTC QLQ–C30 Fatigue scale	0 (0.0–33.3)	55.6 (0.0–100.0)	<0.001

M/F: male/female; BMI: body mass index; VAS: visual analogue scale; HAD scale: Hospital Anxiety and Depression scale; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ–C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.

weakness, and HAD scale scores were examined by stepwise multiple regression analysis. Analyses were performed using SPSS software (SPSS Inc., Chicago, IL).

RESULTS

Fifteen healthy participants and 38 patients with lung cancer participated in the study (Table 1). Among the 38 patients, 29 patients had nonsmall cell lung carcinoma, 6 patients had small cell lung carcinoma, and 3 patients had no histology available. Eighteen patients had metastatic disease, and the remaining patients had locally advanced disease. Twenty-one patients were taking strong opioids, 13 patients were taking benzodiazepines, 5 patients were taking antidepressants, 11 patients were taking nonsteroidal antiinflammatory drugs (NSAIDs), and 14 patients were taking corticosteroids.

The healthy control group and the group of patients with cancer were similar in terms of age and gender. Compared with the control group, the cancer patients weighed significantly less (*P* < 0.01), had

TABLE 2

The Correlation between the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (Tertiles), Body Composition, Physical Function, and Quality of Life in Patients with Advanced Lung Cancer

Characteristic	Median (range)			ANOVA P value
	FACIT-Fatigue (n = 13)	FACIT-Fatigue (n = 13)	FACIT-Fatigue (n = 12)	
Median score	41	29	18	—
Gender (M/F)	10/3	7/6	6/6	0.332
Age (yrs)	64 (43–74)	63 (51–79)	65 (51–81)	0.718
BMI (kg/m ²)	19.7 (16.6–27.0)	22.2 (15.2–33.3)	20.7 (14.8–31.4)	0.801
White cell count (10 ⁹ /L)	7.7 (5.6–12.7)	10.4 (5.1–19.4)	11.6 (5.8–26.2)	0.079
Hemoglobin (g/dL)	12.7 (10.4–15.4)	12.2 (9.6–16.3)	12.0 (10.1–15.1)	0.231
Albumin (g/L)	40 (29–45)	39 (31–45)	35 (23–43)	0.095
C-reactive protein (mg/L)	19 (<6–175)	38 (<6–60)	128 (<6–214)	0.028
Skinfold thickness (mm)				
Triceps	10.0 (3.0–25.0)	10.2 (4.0–33.5)	10.0 (4.5–23.0)	0.903
Midthigh	10.0 (3.5–26.0)	13.5 (5.0–36.5)	14.5 (6.0–29.5)	0.500
Circumference (cm)				
Middle-upper arm	24.8 (18.1–31.0)	24.7 (17.6–36.4)	25.1 (17.1–37.0)	0.986
Midthigh	45.1 (32.3–55.2)	39.7 (32.5–55.7)	40.3 (34.2–57.1)	0.822
Creatine kinase (IU/L)	43 (16–100)	32 (17–151)	31 (10–318)	0.448
KPS	90 (40–100)	70 (60–80)	55 (30–80)	0.001
Handgrip strength (kgW)	24.0 (8.5–33.0)	22.0 (10.0–36.5)	18.5 (6.5–51.0)	0.331
Chair rise (seconds)	1.29 (1.05–1.66)	1.54 (0.98–3.80)	2.38 (1.31–6.06)	0.005
VAS weakness (cm)	2.4 (0.4–8.0)	3.6 (1.0–8.1)	6.0 (4.1–8.3)	0.001
HAD scale	10 (2–23)	18 (6–19)	21 (9–26)	0.001
EORTC QLQ-C30 Fatigue scale	33.3 (0.0–66.7)	55.6 (33.3–66.7)	72.2 (55.6–100.0)	<0.001

FACIT: Functional Assessment of Chronic Illness Therapy; ANOVA: analysis of variance; M/F: male/female; BMI: body mass index; KPS: Karnofsky performance status; VAS: visual analog scale; HAD scale: Hospital Anxiety and Depression scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.

lower albumin and hemoglobin concentrations ($P < 0.001$), and had elevated white blood cell counts and C-reactive protein concentrations ($P < 0.001$). The patient group had lower arm and thigh circumference measurements ($P < 0.001$), lower circulating creatine kinase concentrations ($P < 0.001$), lower KPS ($P < 0.001$), lower hand-grip strength ($P < 0.01$), and performed less well in the chair-rise test ($P < 0.001$) compared with the control group. The patient group reported greater levels of fatigue (both scales) and weakness as well as psychological distress (all $P < 0.001$).

In the group of patients with cancer, there were significant correlations between the FACIT-Fatigue and the EORTC QLQ-C30 Fatigue scales ($r^2 = 0.712$; $P < 0.001$) and between the KPS and the chair-rise time ($r^2 = 0.565$; $P < 0.001$). There was no correlation between fatigue and the presence of metastatic disease, prescription of opioids, opioid dose, or prescription of NSAIDs or steroids. However, fatigue was greater in the patients who were taking benzodiazepines compared with fatigue in patients who were not taking benzodiazepines ($P < 0.01$).

The patients with cancer were grouped (in tertiles)

according to the level of fatigue reported on the FACIT questionnaire (Table 2). The groups were similar in terms of age, gender, BMI, white blood cell count, hemoglobin, albumin, skin-fold and limb circumference measurements, and hand-grip strength. In contrast, with increasing fatigue, there were lower KPS scores ($P = 0.001$), slower chair-rise times ($P < 0.01$), higher weakness scores ($P = 0.001$), and higher HAD scale scores ($P = 0.001$). In a multiple regression analysis of these significant factors, only KPS scores, weakness scores, and HAD scale scores were correlated independently with fatigue ($r^2 = 0.570$; $P < 0.001$).

DISCUSSION

In the current study, the patients with advanced lung cancer had lost fat and muscle mass, had evidence of a systemic inflammatory response, had poorer physical function, had increased psychological distress, and had higher levels of weakness and fatigue compared with the control group. When the group of patients with cancer was subdivided on the basis of fatigue scores, it was clear that fatigue was associated with poor physical function and more psychological distress.

Whether fatigue is a cause or a consequence of poor physical function and psychological distress could not be determined in the current cross-sectional study. However, the current study did produce a number of interesting findings. There was no correlation either between the loss of fat/muscle mass and fatigue or between hemoglobin concentration and fatigue. These results suggest that neither cachexia nor hemoglobin concentrations, per se, play a major role in the etiology of fatigue. Previous work has suggested a correlation between fatigue and hemoglobin concentration.⁵ It is possible that the small numbers in the current study and the relatively narrow range of hemoglobin results may have contributed to the fact that no correlation was found. However, because other factors clearly were associated significantly with fatigue, the results suggest that hemoglobin concentrations on their own are not a primary determinant of fatigue in this patient group.

We previously reported that the presence of a systemic inflammatory response (as evidenced by an elevated circulating C-reactive protein concentration) is associated with increased fatigue and poorer performance status in patients with inoperable nonsmall cell lung carcinoma.^{4,10} However, in the current study, compared with physical function and psychological distress, the systemic inflammatory response appeared to be a relatively weak factor in determining fatigue levels. It is possible that the effect of the systemic inflammatory response on fatigue is secondary to the effect on physical function. For example, the systemic inflammatory response is associated with an increase in resting energy expenditure and, thus, may compromise the activity component of total energy expenditure.^{25,26}

It is noteworthy that fatigue scores were highest in the patients who were taking benzodiazepines. The reasons for this association are unclear. Ten of the 13 patients who were taking benzodiazepines were receiving night sedation with temazepam (9 patients) or chlorthalidopoxide (1 patient). In addition, 2 of those 10 patients also were receiving regular diazepam during the day. The remaining 3 of 13 patients were receiving diazepam alone during the day. Although sedation does not necessarily equate with fatigue, it is possible that the benzodiazepines were contributing to the fatigue. Use of alternative, less sedating medications may have led to lower levels of fatigue. However, because performance status also was lower ($P < 0.01$) in the group of patients who were taking benzodiazepines, it is possible that the association between the use of benzodiazepines and increased fatigue reflects only the poor physical function of these patients and more symptoms requiring benzodiazepines.

It also is interesting to note that the measures most closely related to fatigue, the KPS and the HAD scale, also are subjective measures. These results are consistent with previous reports that psychological distress, and depression in particular, is associated strongly with fatigue.^{11,12,14} In contrast, Visser and Smets¹³ found no longitudinal correlation between fatigue and depression, but it is clear that the two symptoms frequently coexist. The situation is complicated by the fact that fatigue is often a symptom of depression, and the answers to some of the questions on the HAD Depression subscale may be influenced by physical illness and functional disability. It seems logical that patients with increasing fatigue and impaired function would experience feelings of loss and, consequently, mood disturbance. It remains unclear whether there is a temporal correlation between decreasing physical function and increasing fatigue.

In the current study, we have showed for the first time that both fatigue and performance status in cancer patients are related to an objective measure of physical function, i.e., the time taken to rise from a chair. The chair-rise test has much to commend it, because it is objective, simple to perform, and can be applied to most patients with advanced cancer. Further work is warranted to test its reliability in the assessment and monitoring of physical function in patients with advanced cancer.

In summary, the results of the current study suggest that cancer fatigue is not primarily a result of weight loss or anemia, and other etiologic factors remain elusive. However, fatigue is related to performance status and psychological distress in patients with advanced lung cancer.

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