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ORIGINAL ARTICLE

Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study

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Chronic cancer-related fatigue in otherwise asymptomatic post-allogeneic hematopoietic stem cell transplant (HSCT) patients is common and debilitating. This pilot study investigated whether patients with no clinical or psychological abnormalities but severe fatigue would respond to an individually adapted aerobic exercise program. Participants were 12 patients (eight male, and four female patients), median age 47 years and 41 months post-HSCT with a variety of hematopoetic cancer diagnoses. All underwent a 12-week individualized mild aerobic exercise program, preceded by a 4-week introduction and baseline testing phase. Psychological measures included fatigue, mood and depression. Exercise-related physiological outcomes included power output at ventilatory threshold 2 (VT2) and associated changes in stroke volume, heart rate, blood lactate concentration and ratings of perceived exertion. Patients were assessed for fatigue before, immediately after and at 3, 6, 9 and 12 months post-program. Significant improvements were found on both measures of fatigue (both $P<0.001$), with a very large effect size of 1.82 on the The Functional Assessment of Cancer Therapy – Fatigue Module, which were maintained over the follow-up period. Exercise testing revealed a mean increase ($P<0.001$) of 28% in power output at VT2 with an increase ($P<0.001$) in stroke volume and a decrease ($P<0.001$) in heart rate, blood lactate and perceived exertion at pre-intervention VT2 power output.

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Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment for a number of hematological malignancies and bone marrow failure syndromes.[1–4] Factors limiting the efficacy of this treatment are death owing to recurrence or treatment-related death owing to infection or organ failure in the cytopenic and later immunosuppressed phase immediately post-HSCT. Over the last decades, the cumulative effects of improvements in supportive care, drug-dosing, stem cell technology and graft-versus-host disease (GvHD)-prophylaxis have led to an increase of the number of patients experiencing cure.[1–5]

Despite clinical cure in 20–70% of all patients (depending on disease presentation), long-term sequelae of immunosuppression, chemotherapy toxicities and GvHD debilitate a large number of patients over the long term.[6,7] With the increasing number of transplants performed and growing number of survivors, a shift is required in clinical focus from not only improving initial survival but also improving long-term quality of life.[8–11] Increasingly recognized as a problem is that 30–75% of all cancer survivors report fatigue continuing for months or years after completing active treatment.[12] Fatigue is a multidimensional concept with several modes of expression: physical, cognitive and emotional, often accompanied by inactivity and lack of motivation, with both acute and chronic presentations.[13–15] The term cancer-related fatigue (CRF) is defined by the National Comprehensive Cancer Network as 'a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning'.[12] It often persists over time and can interfere with usual activities. Cancer-related fatigue is more severe and distressing than the fatigue of everyday life, and rest does not always relieve it.

Long-term fatigue and impairment may be more frequent in patients after allogeneic (as compared to autologous) HSCT, despite similar acute toxicities and chemotherapy doses;[7,16] hence, we have chosen this population to sample. The fatigue observed in allogeneic HSCT recipients is often unexplainable from a medical standpoint.[16–18] Moreover, it has features in common with that seen in overtrained athletes, which led us to consider whether similar remedial approaches could be used. The

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causes of an impairment of physical performance in the cancer setting are not fully understood. Low physical performance has been postulated to be a substantial contributor to cancer fatigue.[19] The progressive loss of functional capacity associated with physical inactivity is attributed to the rapid decline in efficiency of multiple physiological systems, most apparent initially in the cardiorespiratory and muscular systems.[20,21] Such deconditioning can reduce work capacity and consequently a higher degree of effort is required to perform usual activities. To reduce fatigue, patients have traditionally been advised to avoid physical efforts and to downregulate their activity level,[22] which may paradoxically aggravate their fatigue.

Aerobic exercise, defined as the rhythmic contraction and relaxation of large muscle groups over a prolonged time, has been proposed as a method for rehabilitation of cancer patients affected by the problem of 'energy loss'.[23] An aerobic training program can break the vicious circle of lack of exercise, impaired performance and easy fatigability.[22] There is a burgeoning literature on the effects of exercise on cancer rehabilitation with promising results, particularly for breast cancer patients, on whom the majority of research has been conducted (for reviews see Schwartz,[24] McTiernan,[25] Stone,[26] Irwin,[27] Courneya[28]). Interventions both during and after treatment have been shown beneficial on outcomes ranging from overall quality of life, to more specific measures of mood and fatigue. A recent study showed that more physical activity after breast cancer diagnosis was related to enhanced survival.[29] One review concluded that future research is needed to extend our knowledge beyond breast cancer survivors, examine mechanisms for changes in quality of life, compare exercise with other interventions and examine biomarkers, cancer recurrence and survival.[28]

In terms of utilizing exercise interventions specifically in HSCT survivors, little work exists, and what has been carried out has largely been conducted by Dimeo *et al*., showing benefit in physical performance and decreases in fatigue in groups of early post transplant patients.[23,30] In one study, 16 patients participated in a 6-week program of walking on a treadmill, shortly after completing treatment. Physical performance and hemoglobin concentration improved following the intervention, and at that time no patient in the training group reported significant fatigue or limitations in daily activities due to low physical performance.[23] A recent report by Wilson *et al*.[31] described a home-based aerobic exercise program for HSCT survivors that consisted of 20–40 min of activity three to five times per week over a 12-week period. They found decreases in fatigue severity, improvements in physical well-being and increased aerobic fitness, but had high rates of attrition (46%). The Wilson study targeted patients who were inactive and largely obese, whereas we targeted those who were highly fatigued, irrespective of prior exercise frequency.

Despite the growing body of research on exercise as a treatment for fatigue in cancer survivors, none of the available studies have simultaneously evaluated the influence of training on metabolic and circulatory parameters, as well as subjective fatigue. This and the focus on highly fatigued survivors are unique features of this study that move a step beyond other reports. Another strength of this program is the full year of follow-up assessment of fatigue, which has not yet been reported.

Objectives

The primary objective of the study was to investigate whether HSCT patients with minor or no clinical and psychological abnormalities but with debilitating fatigue after HSCT exhibit changes over the course of an individualized aerobic exercise program on fatigue levels.

Secondary objectives were to evaluate the effect of the program on

1. depression levels,
2. mood states,
3. physiological markers of aerobic fitness.

Materials and methods

Subjects

Inclusion criteria:

1. Allogeneic stem cell transplant at least 6 months ago.
2. Complete remission of underlying disease, no active, malignancy-directed treatment in the past 6 months.
3. Age 18–60 years.
4. Able to give informed consent.
5. Graft-vs-host-disease: no GvHD > I° in the past 3 months or limited grade 1 GvHD not requiring therapeutic intervention.
6. Severe fatigue: Criteria – either (1) FACT-F score < 22; or (2) BFI > 5.5; or (3) FACT-F < 27 and BFI > 5.0.

Exclusion criteria:

1. Any untreated limited GvHD grade 2 or > grade 1 overall, any GvHD requiring treatment less than 3 months ago.
2. Donor lymphocyte infusion in the past 3 months.
3. Physical disability precluding ability to comply with the proposed exercise program.
4. Alcohol or substance abuse.
5. Insufficiently controlled diabetes (Hb A1c > 2 × UNL).
6. Chronic pain – medication with opioids.
7. Chronic inflammatory or rheumatoid disease.
8. History or symptoms of coronary artery disease, history of myocardial infarction, EF on MUGA of < 50%.
9. Pregnancy or lactation.
10. Score over 16 on the Centre for Epidemiological Studies – Depression Inventory (CES-D) and current major depressive episode.
11. Recurrent or severe infections in the past 3 months.

Recruitment

Allogeneic stem cell transplantation in Alberta is centrally carried out in Calgary. All patients are followed either at the Tom Baker Cancer Centre (TBCC) or in a transplantation outpatient clinic at the Cross Cancer Institute (CCI)

in Edmonton, with collaboration of the two institutions. Potentially eligible patients were identified by hematologists in Calgary and Edmonton through a fatigue questionnaire and routine clinical testing (as under inclusion criteria) at usual follow-up visits. As well, a mail-out of fatigue questionnaire to all potentially eligible patients was undertaken. Those who were identified as eligible after these routine tests were invited to participate, and at this point the study was explained to them and they were asked to provide informed consent. As this was a pilot study, a sample size of 12 patients was chosen as adequate and feasible to test over a 2-year period.

Measures
Medical/baseline:

1. *Endocrine status:* TSH, fT4, fT3, FSH, LH, testosterone, free androgen index, progesterone, estrogen, ACTH.
2. Erythropoetin serum levels, CRP, pulmonary function tests, Chest X-ray, ECG, MUGA.
3. Clinical chemistry and routine complete blood counts.

Psychological:

Fatigue: FACT-F – The Functional Assessment of Cancer Therapy – Fatigue Module (FACT-F) has been designed to measure the extent of 13 symptoms of fatigue, and has been shown to have very high internal consistency, a strong positive relationship with other fatigue measures and is able to differentiate patients by hemoglobin levels.[32] Items indicating higher fatigue are reversed scored and all items summed so that higher scores correspond with less fatigue.

Fatigue: BFI – In addition to the FACT-F, the Brief Fatigue Inventory (BFI) was also utilized.[33] This nine-item instrument measures a single dimension, severity of fatigue, and correlates well with the FACT-F. This second measure was included for validity and power purposes, as fatigue is a primary study outcome. As well, it was chosen to allow comparison of the data from this study with other data collected using this instrument in ongoing clinical research. The BFI total is calculated by summing scores on each item, then dividing by the number of items, resulting in an *average* score on the 10-point scale across the nine items. Higher scores indicate more fatigue.

Depression: As depression and reactive psychological changes through coping with the cancer diagnosis are frequent in the population under investigation,[8,34] it was essential to evaluate and follow depression or depressive reactions within the context of this study. Clinical levels of depression in this population might interfere with patients' ability to follow an exercise regimen, and would also require immediate attention from a psychiatrist or psychologist, perhaps biasing the results of the trial. Depression was screened using a questionnaire and a definitive diagnosis made with a clinical interview:

CES-D – Screening for depressive symptomatology was carried out using the Centre for Epidemiological Studies – Depression Inventory (CES-D), which serves as a reliable and valid tool for screening symptoms of a major depressive episode.[35]

SCID – The CES-D was followed by a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (SCID) mood disorders module,[36] administered by a clinical psychologist. If patients score over a pre-determined cutoff value on the questionnaire and met the criteria for a current major depressive disorder or bipolar II disorder, they were referred to Consultation-Liaison Psychiatry for treatment. Re-evaluation for the study was possible after 3–6 months of effective antidepressive treatment and scoring below the cutoff value.

POMS – In order to measure the effects of the program on more mild fluctuations in mood, the Profile of Mood States (POMS) was employed.[37] The POMS is a 65-item scale, which assesses six affective dimensions: tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia and confusion–bewilderment. It has been widely used in the assessment of mood changes resulting from a variety of interventions owing to its responsiveness, and has been used extensively with cancer populations.[38] The POMS measures state (vs trait) attributes and therefore previous administrations do not influence subsequent administrations, which makes it good for repeated measures designs.

Measures of physical performance. The following are parameters used in the measurement of physical performance and physiological fitness, with descriptions of their meaning and assessment procedures.

Oxygen Uptake (VO_2): Oxygen uptake is the rate at which oxygen can be consumed per minute by muscle. It was measured by the collection of expired air analyzed and recorded every 30 s using a TrueMax Metabolic Measurement Cart (ParvoMed; Salt Lake City, USA). Calibration checks occurred before and after every test with gases of known concentration.

Ventilatory threshold 1 (VT1): VT1 is defined as the oxygen uptake or intensity at which carbon dioxide increases more rapidly than oxygen uptake, and ventilation retains a constant relationship with the volume of carbon dioxide ($V\mathrm{CO_2}$), known as isocapnic buffering.[39] This is also referred to as the aerobic threshold. The proportion of oxygen in the expired air ($V_E/V\mathrm{O_2}$) increases whereas the proportion of carbon dioxide ($V_E/V\mathrm{CO_2}$) remains constant because the excess volume expired (V_E) is largely attributable to an excess $V\mathrm{CO_2}$.

Ventilatory threshold 2 (VT2): VT2 is defined as the oxygen uptake or intensity at which there is a nonlinear increase in ventilation and ventilatory equivalents ($V_E/V\mathrm{O_2}$; $V_E/V\mathrm{CO_2}$) relative to the increase in power output.[40] This is also referred to as the anaerobic threshold.

Power output: Power output is the rate of performing work and is measured in watts on a bicycle ergometer.

Respiratory exchange ratio (RER): This is the ratio of volume of $\mathrm{CO_2}$ produced by the body to the amount of oxygen consumed ($V\mathrm{CO_2}/V\mathrm{O_2}$).

Cardiac output: Cardiac output is the amount of blood pumped per minute through the heart. Cardiac output was determined using the open-circuit acetylene uptake method outlined by Barker *et al*.[41] The technique permits the simultaneous measurement of $V\mathrm{O_2}$ and cardiac output

during the test. The subjects were connected to a one-way valve assembly with dual inputs. One input was room air and the other was a gas mixture containing known concentration of acetylene (0.7%), helium (5%), oxygen (20.93%) and nitrogen (74.3%).[42] The subject sat on the bicycle and resting cardiac output was determined over approximately 8–10 min in conjunction with resting $V\dot{O}_2$. The subject then started cycling at 40 W of power at an individual cadence between 70 and 85 revolutions per minute. The workload was increased each 3 min by a further 20 W and cardiac output was measured at every other workload.

Stroke volume: Stroke volume is the amount of blood pumped through the left ventricle of the heart with each beat. This variable is determined from the measurement of total cardiac output (measured as above) divided by heart rate (beats/minute).

Blood lactate concentrate: Blood lactate concentration ($B[la^-]$) is the net result of the rate of lactate production and transport into the blood and rate of removal from the blood. It was used as a gauge of metabolic work intensity and was measured at rest and at workloads at and above an RER of 0.95 as measured on the TrueMax Metabolic Measurement Cart. $B[la^-]$ was also measured at 4 and 8 min into the final workload. Finger tip blood samples were taken by a trained technician and analyzed by a Lactate Pro measuring instrument.

Rating of perceived exertion (RPE):[43] The Borg scale for RPE is a self-report measure on a scale of 1–10 that asks how much physical effort and exertion a person experiences while exercising. The scale ranges from a perceived exertion of 'light', which corresponds to the number 1, to 'moderate' (RPE 3), 'somewhat hard' (RPE 4), 'hard' (RPE 5) and 'very hard' (RPE 7). Participants are asked to rate their exertion on this scale at each 3-min work stage during the protocol.

Baseline physical performance assessment: For assessment of baseline performance, subjects exercised on a SensorMedics electronically braked cycle ergometer beginning at 40 W for 3 min and thereafter increasing by 20 W every 3 min until VT2 was reached. When the power output at VT2 was identified, subjects exercised for a further 8 min at 20 W above threshold power output. The test finished at the end of this power output or earlier if the subject indicated that the RPE[43] reached a value of 7.

During the exercise test, oxygen uptake, cardiac output and $B[la^-]$s were measured using standard methodological protocols and monitoring equipment as described above.[41,44]

Procedures

Patients who were identified as eligible as described in the recruitment section and who met the inclusion and exclusion criteria provided informed consent. These patients were then assessed by a clinical psychologist for depression using the CES-D and SCID. Those who were identified as suffering from a major depressive disorder or bipolar II disorder were referred to consultation-liaison psychiatry for evaluation and treatment, and re-evaluated for eligibility after 3 and 6 months of treatment. Patients who were eligible for the exercise program were referred to the exercise physiologist for the 4-week initiation period and the first 12-week intervention program. In total, the exercise intervention took 16 weeks to complete.

Patients had limited clinical investigations at the post-test, 3, 6 and 9 months mark (POMS, FACT-F, BFI, blood counts, exercise testing), and the 12-month final investigation included a complete workup as by study entry, with the addition of exercise testing.

Training program

Overview weekly schedule:

Week minus 4	Initial screening and training education
Week minus 2	Familiarization with laboratory procedures
Week minus 1	Initial testing
Weeks 1–12	Training program implementation
Week 13	Post-testing of the 12-week training program, program design for subsequent 3 months

The training program consisted of three workouts per week at power outputs equivalent to (a) VT1; (b) VT2 and (c) 20 W above VT2. The power outputs and associated heart rates at these three intensities were determined from the $V\dot{O}_2$ data and additionally with the use of the $B[la^-]$. Workout number one consisted of 30 min at VT1, which corresponded to an RPE of 2, between 'light' and 'moderate'; workout number two was 15 min at 20 W above VT2 at an RPE of 6, between 'hard' and 'very hard' and workout number 3 was 20 min at VT2 with an RPE of 4. This third workout was also used as a monitoring ride each week, during which blood lactate samples were taken at 15 and 20 min into the program in order to determine if a training effect had been established. If the blood lactate concentration at 15 min was around 4 mmol/l and the 20-min sample was below 4 mmol/l, the power outputs for all workouts the following week were increased by 5–10 W. This procedure was used to ensure that the required relative training intensity was maintained and that improvements in fitness were compensated for during the 12-week training study. Training was conducted on Monark Ergometers 816E and monitoring rides were performed on a SensorMedics ergometer. Following completion of the 12-week exercise program, patients returned to the center for follow-up investigations as indicated in the measurement section.

Data analysis

Psychological measures: Changes over the course of the intervention (pre to post) were evaluated using paired-samples *t*-tests. Demographic variables were described using means, standard deviations and medians and ranges, where appropriate.

Measures of training effect: The power outputs, $V\dot{O}_2$ and heart rates at VT2 pre- and post-training were compared using paired-samples *t*-tests. In addition, stroke volume at VT2 power output was calculated and compared pre- and post-intervention.

Results

Subjects

In total, 222 of a potential 353 HSCT patients (the entire population who had received an allogeneic HSCT since 1983 and who were thought to be alive) returned fatigue screening questionnaires (62.8%). Of those who did not return the questionnaires, 32 were deceased, nine were lost to follow-up and 90 did not return the forms. Of the 222 screened, 106 who met the fatigue-related inclusion criteria were identified (47.7% – the other 52.3% were not severely fatigued). Of these, 52 were excluded owing to other criteria such as ongoing GvH or steroid use, 27 were excluded owing to geographical inability to travel to the weekly testing sessions, were not interested in participating or were busy with work or other obligations. Of the remaining patients, five were excluded owing to other medical limitations (outside of study criteria), 21 were lost to follow-up (did not return phone calls) and one elected not to participate owing to language difficulties.

A final sample of 12 patients (eight male and four female patients) participated in the study (Table 1). The median age was 47 years (range 28–55) and the median time post-allo-HSCT was 39 months (range 9–92 months). They had been diagnosed with a variety of hematopoietic cancer diagnoses including chronic lymphocytic leukemia (CLL, $n=3$), chronic myelogenous leukemia (CML, $n=3$), acute myelogenous leukemia (AML, $n=2$), and one each of non-Hodgkin's lymphoma, follicular lymphoma and myelodysplasia. Male participants were an average of 46 years of age (range 29–55), of height 177.3 ± 8.3 cm, of weight 79.8 ± 6.6 kg and of body mass index (BMI) of 25.3 ± 1.0 kg/m^2. Female participants were an average age of 36 years (range 28–40), of height 170.1 ± 7.4, of weight 74.4 ± 29.1 and BMI 25.7 ± 10.1 kg/m^2.

Psychological outcomes

Psychological scores are presented in Table 2. Of note, at the outset, in addition to the high scores on the fatigue measures, participants had depression scores on the CES-D of approximately 17 (s.d. = 12). This indicates that although participants were not diagnosed with major depressive disorder, some were experiencing a moderate level of depressive symptoms, which could be indicative of dysthymia, or subsyndromal depression. These scores may also be elevated by the items shared by both depression and fatigue, such as 'I could not get going' and 'I felt that everything I did was an effort'. Despite this underlying low mood, participants were able to complete the intervention.

Scores changed significantly over the course of the intervention from pre to post on the BFI ($t=4.89$, $P<0.001$) and FACT-F ($t=-5.32$, $P<0.001$), both in the direction of less fatigue. In addition, the POMS subscale of vigor improved ($t=-4.36$, $P<0.001$) and two other subscales were marginally significant: fatigue ($t=1.79$, $P=0.10$) and the total mood disturbance score ($t=1.75$, $P=0.11$). In order to better understand the nature of this improvement, individual items on the FACT-F were analyzed with paired-samples *t*-tests. These results are presented in Table 3. Of the 13 items, all but one improved

Table 1 Demographics

ID	*Gender*	*Age*	*Diagnosis*	*Time since BMT (months)*
1	M	47	CLL	43
2	M	48	CML	94
4	M	47	CLL	29
7	M	49	NHL	58
8	M	53	CLL	38
10	F	28	CML	47
11	F	39	CML	35
14	M	55	FL	70
15	M	30	AML	40
16	F	41	MM	7
18	F	40	AML	20
19	M	54	Myelodysplasia	13
Total	M = 8, F = 4	Mean = 44.3 (s.d. = 8.7), median = 47 (range = 28–55)		Mean = 41 (s.d. = 24), median = 39 (range = 7–94)

Abbreviations: AML = acute myelogenous leukemia; BMT = bone marrow transplant; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; FL = follicular lymphoma; NHL = non-Hodgkin's lymphoma; MM = multiple myeloma.

Table 2 Psychological scores pre- and post-intervention

Test	*Pre-intervention*		*Post-intervention*		*Mean change*	*Percentage change*	*Effect size (ES)*
	Mean	*s.d.*	*Mean*	*s.d.*	d = *(T2–T1)*	*(T2–T1/T1) × 100*	d/*pooled s.d.*
BFI	6.77	1.26	3.95*	2.07	−2.82	41.65	1.69
FACT-F	19.73	5.92	33.91*	9.31	14.18	71.87	1.82
CES-D	17.11	12.27	12.89	6.57	−4.22	24.66	0.45
POMS anxiety	5.27	7.48	5.45	4.97	0.18	3.41	0.03
POMS depression	9.55	11.70	6.55	5.47	−3.00	31.41	0.35
POMS anger	8.27	8.50	6.55	4.95	−1.73	20.92	0.26
POMS vigor	10.82	4.14	16.18*	5.13	5.36	49.54	1.16
POMS fatigue	15.64	5.87	11.27	6.96	−4.36	27.88	0.68
POMS confusion	11.27	6.96	7.01	6.24	−2.45	21.74	0.37
POMS total	35.00	36.53	18.27	24.41	−16.72	47.77	0.55

Abbreviations: BFI = Brief Fatigue Inventory; CES-D = Centre for Epidemiological Studies – Depression Inventory; FACT-F = Functional Assessment of Cancer Therapy – Fatigue Module; POMS = Profile of Mood States; s.d. = standard deviation.
*All $P<0.01$.

Table 3 FACT-F individual item scores pre- and post-intervention

Item	*Pre-intervention*		*Post-intervention*		*Mean change*	*Percentage change*	*Effect size (ES)*
	Mean	*s.d.*	*Mean*	*s.d.*	d = *(T1−T2)*	*(T2−T1/T1) × 100*	d/*pooled s.d.*
I feel fatigued	2.91	0.54	2.09*	0.94	0.82	28.18	0.94
I feel weak all over	2.55	0.82	1.18**	0.98	1.36	53.73	1.48
I feel listless ('washed out')	2.73	0.65	1.45*	1.04	1.27	46.89	1.00
I feel tired	3.00	0.63	2.18*	0.87	0.82	27.33	0.65
I have trouble starting things because I am tired	2.91	0.70	1.64*	1.43	1.27	43.64	0.76
I have trouble finishing things because I am tired	3.09	0.54	1.45**	1.13	1.64	53.07	1.59
I have energy	1.64	0.67	2.18	0.75	−0.55	−33.54	0.59
I am able to do my usual activities	1.82	0.75	2.73*	1.10	−0.91	−50.00	0.88
I need to sleep during the day	2.27	1.42	1.36**	1.43	0.91	40.08	1.30
I am too tired to eat	1.27	1.35	0.18*	0.40	1.09	85.83	0.89
I need help doing my usual activities	1.18	0.84	0.36*	0.67	0.82	69.49	0.84
I am frustrated by being too tired to do the things I want to do	3.09	0.70	1.82*	1.47	1.27	41.10	0.94
I have to limit my social activity because I am tired	2.73	1.01	1.27**	0.90	1.45	53.11	1.28

Abbreviations: FACT-F = Functional Assessment of Cancer Therapy – Fatigue Module; s.d. = standard deviation.
*$P<0.05$.
**$P<0.005$.

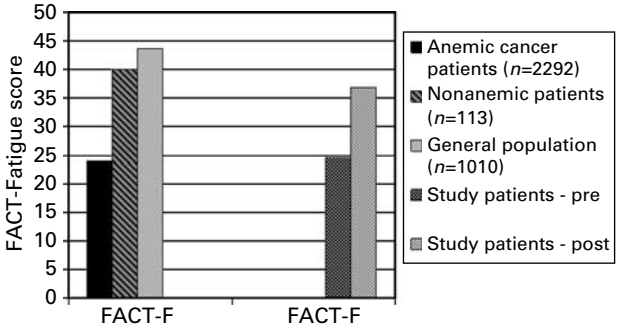

Figure 1 Fatigue in cancer reference patients, the general public and study patients pre- and post-intervention.

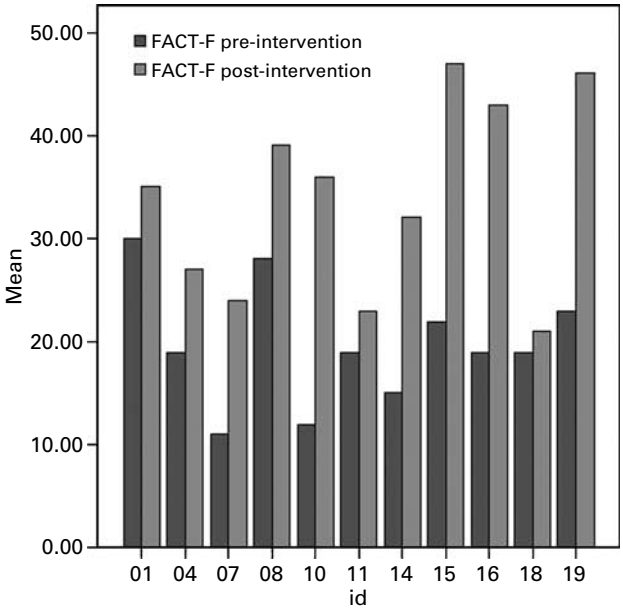

Figure 2 Individual study participants' fatigue scores pre- and post-intervention.

significantly, with the largest improvements on the following items: I have trouble finishing things because I am tired ($t=5.29$, $P<0.001$); I feel weak all over ($t=4.89$, $P<0.001$); I need to sleep during the day ($t=4.30$, $P<0.002$); and I have to limit my social activity because I am tired ($t=4.28$, $P<0.002$). Each of these items had effect sizes over 1.0.

Fatigue scores pre- and post-intervention were compared to published norms for cancer patients and the general public (Figure 1).[45] As can be seen, scores were similar in our participants pre-intervention to those of an anemic group of cancer patients. However, following the intervention, fatigue had improved to the level of other non-anemic patients and close to those of the general population. Individual fatigue scores on the FACT-F total are presented in Figure 2. The average improvement on the FACT-F was 71.87% (Table 2), which corresponds to a very large effect size of 1.86 (T1−T2/pooled s.d.).

On follow-up, data were collected post-intervention at 3 ($n=12$), 6 ($n=10$), 9 ($n=11$) and 12 months ($n=6$). Improvements on fatigue scores on both the FACT-F (Figure 3) and the BFI (Figure 4) were maintained over the entire year of follow-up, although there appears to be an increase in fatigue at the 3–6 month time point. Regardless, even the largest rise in fatigue, which occurred at 3-month follow-up on the FACT-F, is still significantly different from the pre-scores ($t=3.87$, $P<0.005$). On the BFI, the largest rebound effect occurred at 6-month follow-up, but even this level represents significantly less fatigue than at pre-intervention ($t=3.31$, $P<0.01$). This indicates sustained improvement over the entire course of follow-up on both measures of fatigue.

Physiological outcomes

Compliance with the full training program was $88.5\pm10.7\%$, indicating that almost 90% of all workouts were carried out as prescribed. Over the course of the exercise program from pre- to post-testing, power output at

VT2 increased from a mean of 92 to 118 W ($P<0.005$) after 12 weeks of exercise (Table 4). Blood lactate concentration at the pre- and post-VT2 were not different at 3.6 ± 1 and 3.8 ± 1 mmol/l ($P=0.44$), indicating that the body was working similarly hard at the pre- and post-training tests, but was able to produce more power at post-test – this demonstrates that a training effect had occurred. Stroke volume, the amount of blood pumped by the heart with each beat, at the same pre-power output of 92 W increased from 83 to 96 ml/beat ($P<0.005$), again demonstrating a positive training effect.

Furthermore, heart rate at the same pre-power output level (92 W) declined from 135 to 125 beats/min ($P<0.005$) and B[la$^-$] at that power level decreased from 3.5 to 2.7 mmol/l ($P<0.005$). Finally, the RPE decreased from 3.5 to 2.0 on the Borg scale ($P<0.005$), indicating that the exertion at the same pre-power level went from moderate to somewhat hard before the program, to between light and moderate afterwards.

The weekly training/monitoring session each week allowed participants to increase their absolute training intensity while maintaining relative intensity as training effects took place. This is illustrated for one individual in Figure 5. When the B[la$^-$] at the end of the weekly monitoring/training ride each week was below 4.0 mmol/l, the power output was increased for the following week. In week 8 (Figure 5) the participant had some non-physical stress in their life and there was a substantial increase in the blood lactate response for the same power output as the previous week. The corresponding heart rate response for the same individual and monitoring/training sessions as Figure 5 is illustrated in Figure 6.

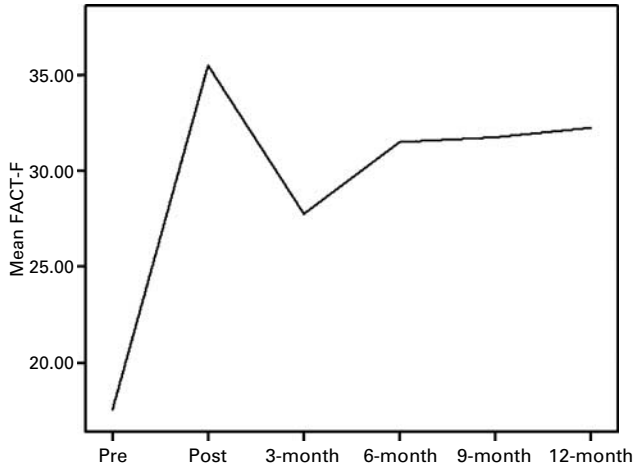

Figure 3 Follow-up scores on the Functional Assessment of Cancer Therapy – Fatigue Module.

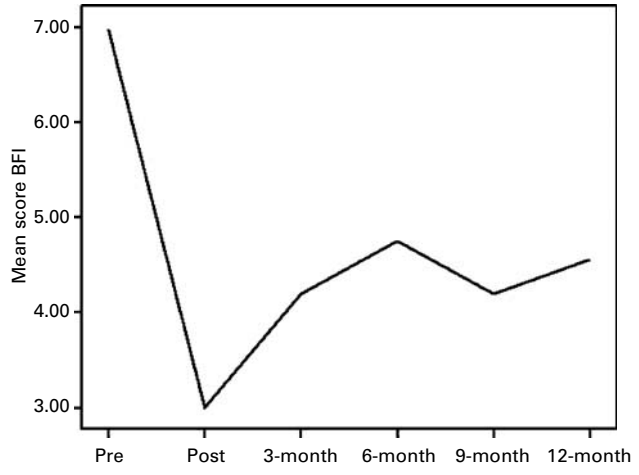

Figure 4 Follow-up scores on the Brief Fatigue Inventory.

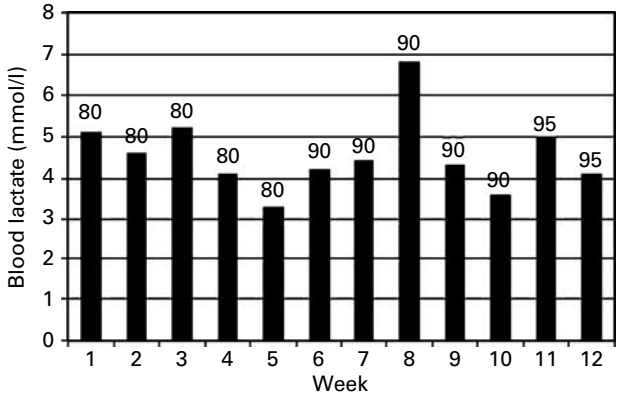

Figure 5 An individual example of blood lactate concentration response to 20 min of exercise at 80, 90 and 95 W measured during the monitoring/training ride at approximately VT2 intensity over 12 weeks.

Table 4 Physiological scores pre- and post-intervention

Test	*Pre-intervention*		*Post-intervention*		*Mean change*	*Percentage change*	*Effect size (ES)*
	Mean	*s.d.*	*Mean*	*s.d.*	d = *(T2−T1)*	*(T2−T1/T1) × 100*	d/*pooled s.d.*
VT2 power output (W)	92.0	34.0	118.0*	40.0	26.0	28.3	0.70
Stroke Volume at pre-power (mean 92 Ws)	83.0	21.0	96.0*	21.0	13.0	15.6	0.62
Heart rate at pre-power	135.0	13.0	125.0*	15.0	10.0	7.4	0.71
B[la$^-$] at pre-power	3.5	1.0	2.7*	1.0	0.8	21.1	0.80
RPE at pre-power	3.5	1.2	2.0*	1.1	0.5	14.3	0.43

Abbreviations: B[la$^-$] = blood lactate concentrations; RPE = rating of perceived exertion; s.d. = standard deviation; VT2 = ventilatory threshold 2.
*All $P<0.005$.

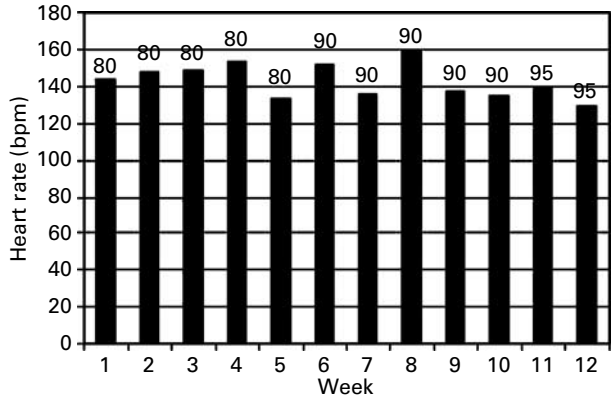

Figure 6 An individual example of heart rate response to 20 min of exercise at 80, 90 and 95 W measured during the monitoring/training ride at approximately VT2 intensity over 12 weeks.

Discussion

This study found very large improvements in fatigue over the course of an individualized aerobic exercise program in post-HSCT patients who were suffering from high levels of fatigue for which no morphological, biochemical, hormonal or psychological correlate could be identified. Patients were an average of over 3 years post-HSCT, yet still suffered steady, chronic and debilitating fatigue. The rapidity with which patients improved in fatigue over the course of the 16-week program is striking in view of the previous chronicity. Before the intervention, fatigue levels were similar to those seen in highly anemic patients, without any anemia or other medical cause identified in our patients. The entire cohort was meticulously screened for presence of GvHD, abnormal blood counts, hormone levels, immune function and cardiac function, all of which were in the normal range. After the intervention, their levels of fatigue improved with an effect size of almost two standard deviations on the FACT-F (ES = 1.82). To put this in perspective, one-half of one standard deviation, an ES = 0.5, is often considered a clinically significant improvement in outcome. Strikingly, fatigue levels were almost at the level of the general population following the exercise intervention. We also had excellent compliance with the intervention, with almost 90% of all sessions undertaken as prescribed. This is far superior to the Wilson *et al*.[31] home-based program which had almost 50% attrition. This high compliance and zero attrition may speak to the motivation level of participants, the benefits of lab-based supervised exercise testing and the use of heart rate monitors to capture all workouts.

In comparison of our study to the most methodologically similar studies, Wilson also found a small effect size of 0.3 on fatigue, and a larger 0.8 on aerobic fitness, in their group of inactive HSCT survivors who completed a 12-week program but were not selected for fatigue levels.[31] Dimeo *et al*.[23] did not directly assess fatigue levels of patients, instead inferring their ability to carry out activities of daily living by performance on the fitness test. They established a cutoff of 5.0 METS (standardized metabolic units of exertion) as consistent with the requirements for normal daily activities, and found more people in the exercise group reached that level than did those in the control group. Oxygen uptake at VT2 in our group was also in excess of the 5.0 METS requirement for normal daily activities used by Dimeo *et al*.[23] as a marker of fatigue, and confirms the improvement of fatigue seen by us on the other scales (FACT-F, BFI).

For many years, physicians' recommendations to cancer patients have been to rest and avoid physical effort.[46] As summarized by Wilson *et al*.,[31] although a majority of patients report rewarding lives following HSCT, a substantial proportion report problems with fatigue, physical functioning and physical role participation. However, the recent body of literature regarding the use of exercise clearly demonstrates that exercise is effective in preventing or reducing CRF.[47] From a functional point of view, the present study demonstrates a 28% improvement in power output at VT2 or a 17% improvement in oxygen uptake at VT2. Most of the exercise-related improvements in physiological functioning were in the effect size range of 0.5 – a medium-sized and clinically significant effect. This improvement is similar to the 15% change in oxygen uptake at VT1 reported by Wilson *et al*.[31] in a comparable patient population. These data demonstrate that patients post-allo-HSCT respond physiologically to exercise stimuli as do healthy individuals.

Our results also demonstrate that a physiological improvement occurred in calculated stroke volume determined from the open-circuit acetylene breathing measurement of cardiac output. This is likely owing to an increase in blood volume as a result of the exercise program that was designed to stress the participants for two of the three workouts per week at and in excess of VT2 intensity, which corresponds to the anaerobic threshold. The individually determined intensities were prescribed based on a long-term study of a sedentary population ($\dot{V}O_2$ max 32.9 ml/kg/min; age 34 years), which demonstrated that higher intensities of exercise, relative to the anaerobic threshold, resulted in larger gains in power output and $\dot{V}O_2$ at the anaerobic threshold when performing three exercise sessions per week for 20 weeks.[48]

As illustrated in Figures 5 and 6, individualized exercise prescription is very important to maximize the training effect. We suggest that blood lactate response may be a better measure of training intensity in cancer patients than heart rate or percentage predicted heart rate reserve. This is based on the observation that as stroke volume improves with training, the originally prescribed training heart rate zone may become too difficult, as heart rate declines for a given power output. In future studies, calibrated exercise ergometers with programmable power outputs, together with portable lactate analyzers, may offer participants the ability to individualize their training programs and monitor their progress with ease.

Despite this study's many advantages – intensive psychological and physiological assessment, comprehensive exclusion criteria, uniform fatigue-centered inclusion criteria and long-term follow-up – it is not without limitations. The primary limitations are the small sample size ($n = 12$), and the lack of a comparison or control group. Without a randomly assigned control group, it is

impossible to definitively conclude that the improvements seen over the course of the study were owing to the intervention itself, rather than the simple passage of time, maturation or natural healing of participants. However, the fact that on average participants were more than 3 years post-HSCT, and general clinical observation, argue against the likelihood that such severe chronic fatigue would spontaneously remit so rapidly. This observation in conjunction with the demonstrated improvements in physical fitness points to direct effects of the program on alleviating fatigue. The effect sizes seen in this sample are very large and clinically meaningful, and with a larger sample it is likely that outcome that were not significant with this sample size, such as overall mood disturbance, would be so. In fact, the ES of 0.55 on overall mood would easily be significant by only doubling this sample size.

These findings thus provide useful proof-of-principle evidence that can be employed to support proceeding to a full-scale randomized clinical trial. Indeed, future studies in this area would benefit from similarly comprehensive assessment, long follow-ups with monitoring of maintenance of exercise within randomized controlled study designs to allow determination of causality, and to control for nonspecific effects of the intervention that may have resulted from the supportive nature of the relationships between participants and the study team. This study remains a potent demonstration of the potential for individually tailored aerobic exercise interventions to return post-HSCT patients from states of disability and inability to carry out normal daily activities, to productive and involved members of society.

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