Post-transplant complications

Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme

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Summary:

The purpose of this investigation was to assess changes in total energy expenditure (TEE), body weight (BW) and body composition following a peripheral blood stem cell transplant and following participation in a 3-month duration, moderate-intensity, mixed-type exercise programme. The doubly labelled and singly labelled water methods were used to measure TEE and total body water (TBW). Body weight and TBW were then used to calculate percentage body fat (%BF), and fat and fat-free mass (FFM). TEE and body composition measures were assessed pretransplant (PI), immediately post-transplant (PII) and 3 months post-PII (PIII). Following PII, 12 patients were divided equally into a control group (CG) or exercise intervention group (EG). While there was no change in TEE between pre- and post-transplant, BW ($P<0.01$) and FFM ($P<0.05$) significantly decreased during the same period. Participation in the exercise programme led to increases in TEE to levels that were both higher than pre- and post-transplant measures ($P<0.01$). By PIII, the exercising patients also showed gains in FFM ($P<0.01$) in association with a reduction in %BF ($P<0.05$). Exercise has a functionally important role in preserving and increasing skeletal mass in the rehabilitation phase of cancer patients.

It is well recognised that if total energy expenditure (TEE) exceeds energy intake (EI), a reduction in body weight (BW) will result. A decrease in BW following transplant for cancer is a common side effect,[1] particularly for patients undergoing a peripheral blood stem cell transplantation (PBST). Elevated metabolic demands and impaired protein-sparing mechanisms, in conjunction with reduced energy intake, inactivity, and specific chemotherapeutic and steroid treatment regimens, may be contributing reasons for the negative energy balance, and therefore weight loss observed in some cancer patients.[2,3] However, the first step in learning the aetiology of weight changes following cancer treatment is to measure either one or both sides of the energy equation, TEE and total energy intake.

Total energy expenditure comprises resting energy expenditure (REE), thermogenesis, physical activity and the energy cost of growth.[4] Of the limited studies available that have assessed TEE in patients with cancer, TEE has been calculated by measuring REE and the energy cost of physical activity.[5–7] These studies usually maintain the assumption that thermogenesis accounts for approximately 10% of TEE, while the energy cost of growth is negligible. However, the former assumption may be violated because of the adverse effects that symptoms commonly experienced by cancer patients, such as nausea, vomiting and pain, have on appetite and food intake. Many chemotherapeutic agents, including dactinomycin, bleomycin, cyclophosphamide, 5-fluorouracil, methotrexate and vincristine, all have the potential to reduce food intake by causing nausea, vomiting, dry mouth and mouth sores.[2] Patients who have received high-dose chemotherapy or radiotherapy, such as PBST patients, are at a particularly high risk of experiencing these symptoms.[8] Although supportive care is continually improving the control of such symptoms,[9] some patients still find it difficult, if not impossible, to consume food.[8]

To date, no investigations could be identified that have used the most accurate method of assessing TEE, the doubly labelled water technique. By assessing TEE via this technique, all components of energy expenditure are encompassed within the measure and therefore no assumptions regarding TEF, the energy cost of physical activity or the energy cost of growth, are required. The use of this measure will aid research in determining the aetiology of energy imbalances and thus changes in weight associated with cancer and its treatment. It is not only crucial to determine the cause of weight changes associated with cancer and treatment, but it is also important to understand

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Received 23 January 2002; accepted 8 July 2002

body composition changes. Losses in fat mass (FM) and/or fat-free mass (FFM) could constitute BW changes observed, with losses in FFM having functional implications to the patient. A reduction in lean tissue will in turn lead to a greater degree of effort required by the patient to perform any given task. However, unless body composition as well as BW is studied, the functional ramifications of weight changes will be poorly understood.

Conventional medicine has failed to improve body composition following cancer treatment, and therefore other intervention strategies known to influence both EE and body composition need to be studied. Exercise is one such intervention strategy. However, a primary concern for patients, health professionals and carers might be that an increase in physical activity may correspond to an increase in energy expenditure and consequently an exacerbation of the patient's weight reduction. It is important to note that these concerns may be contributing to the common advice offered to patients such as 'take it easy' and 'get plenty of rest'. Evidence providing support for the use of exercise in correcting an energy imbalance and body composition is required to alter this notion.

Therefore, the purpose of this investigation was to determine the impact of undergoing high-dose chemotherapy treatment and autologous PBST on TEE and body composition. The study also assessed the impact of participation in a mixed-type, moderate-intensity exercise programme on TEE and body composition.

Patients and methods

Subjects

A total of 12 patients undertaking high-dose chemotherapy followed by an autologous PBST at the Wesley Hospital, Brisbane, Australia, provided consent to participate in this investigation. The high-dose chemotherapy (HDC) regimen administered at the Wesley Hospital is categorised as either a 'light' or 'heavy' programme. Women with breast cancer generally undertake a lighter programme while all other patients undertake a heavier HDC regimen. The HDC regimen, usually lasting 5 days, was different for various diagnoses. The majority of patients with haematological malignancies received busulphan melphalan-containing combinations. However, patients with Hodgkin's disease received BEAM, and the two patients with high-risk stage II breast cancer received high-dose cyclophosphamide and epirubicin with three high-dose cycles followed by stem cell support. Finally, one patient with stage IV breast cancer received an experimental programme of thiotepa, iphosphamide and taxol for three cycles with stem cell support.

After the treatment regimen, patients were divided into an experimental and a control group. Initially, patients were to be randomly divided into two groups, with age stratification, as they presented to the study. Unfortunately, a slow recruitment rate and hence low subject numbers meant that randomisation was difficult and could pose more problems during the statistical analysis when compared to patients being 'allocated' into a group. Therefore, the two groups were matched as closely as possible, by taking into account factors that had the potential to influence the level of change in an intervention project, notably those outlined in Table 1. Nonmedical factors that were deemed potential confounding variables and therefore considered when formulating the control and exercise group, included age, gender, previous exercise history, marriage status or support network, weight at PII and living distance from the exercise centre.

Medical variables considered when devising the experimental groups included original diagnosis, number of transplants undertaken and treatment regimen implemented. The degree of rigour posed by the hospitalisation experience could also influence the physical and psychosocial status of the patient, whereby the impact of undergoing a transplant would be less for those patients who experienced fewer post-treatment complications. For this reason, patients were not allocated a group until PII had been completed.

Treatment

The timing of medical events and testing phases has been outlined in Table 2. Although there were three testing phases scheduled, because of variations in the time patients were informed of, and recruited into the study, only seven patients were assessed during the first testing phase (Phase I, PI), which was scheduled pretransplant. Pretransplant assessment (PI) occurred between 7 and 10 days before admission into hospital for the start of the high-dose chemotherapy regimen. All 12 subjects were assessed during the second testing phase (PII), which occurred between 17 and 21 days following transplant. Treatment cessation was classified as the day of stem cell infusion. For those undertaking a three-transplant regimen, this reflects the day of stem cell infusion of the last transplant. Patients were then reassessed 3 months post-PII (PIII).

Exercise intervention

During PI and PII, the effect of the transplant was being assessed and all patients were considered to be in the same group (SG). Immediately after PII, patients were allocated to either the control/stretching group (CG) or the exercise intervention group (EG). Subjects within the CG were required to participate in a 3-month duration stretching programme, three times per week. Stretches were performed for all major muscle groups, with each stretch being performed twice and taken to the point of discomfort and not pain. To ensure that the same contact time was spent with the CG, compared with the EG, the number of stretches performed across the 3 months progressed from 20 to 30 and the duration each stretch was held increased from 15 to 30 s. While participation in the stretching programme could potentially lead to mobility improvements, it was unlikely that the programme would lead to improvements in the physiological variables being measured.

In contrast, the exercising subjects participated in a 3-month duration, moderate-intensity and mixed-type exercise programme. This exercise programme consisted of aerobic exercises (combination of treadmill walking and stationary cycling, 3 times/week, for 20–40 min, at an intensity of 70–90% maximum heart rate) and resistance

Table 1 Group characteristics

Variable	*Control group*	*Exercise group*
Age (years)		
Mean	54.5	39.5
Median	54	40.5
Range	46–64	16–64
Gender		
Males	4	3
Females	2	3
Marriage status		
Married/significant relationship	All six patients	Five out of six
Single		One out of six
Previous exercise history*		
1	One patient	One patient
2	Three patients	Three patients
3	One patient	One patient
4	One patient	One patient
Weight at PII (kg)		
Mean	71.82 kg	87.35
SD	23.71 kg	26.09
Range	62.9 kg	68.8
Living distance from the centre (km)		
Mean	80	33
Range	10–150	5–100
Diagnosis	1 × Acute myeloid leukaemia 1 × High-risk stage II breast cancer (BC) 2 × multiple myeloma 1 × Non-Hodgkin's lymphoma (NHL) 1 × Stage IV BC	1 × lymphoblastic lymphoma/leukaemia 1 × high-risk stage II BC 1 × rhabdomyosarcoma 3 × NHL
Number of transplants		
1 transplant	Four patients	Five patients
3 transplants	Two patients	One patient
High-dose chemotherapy regimen (HDC)		
'Lighter' programme	Two patients	One patient
'Heavy' programme	Four patients	Five patients

*1, 2, 3 or 4 is equivalent to no regular exercise, limited and sporadic exercise, regular exercise prior to diagnosis, and regular at diagnosis and up until transplant, respectively.

Table 2 Timing of medical events and testing phases

Medical events and testing phases	*Mean*	*s.d.*	*CV (%)*	*Range*
PI (no. of days before the start of HDC)	−8.43	−0.98	11.6	−7 to −10
HDC duration (number of days)	4.67	0.78	16.7	3–5
Day of stem cell infusion	0	0		0
Day of hospital discharge (no. of days from stem cell infusion)	1	0.6	60	0–2
PII (no. of days from stem cell infusion)	17.08	2.64	15.5	+14 to +21
PIII (no. days from PII)	85	2.26	2.7	82–89

PI: pretransplant testing session; HDC: high-dose chemotherapy regimen; PII: post-transplant testing session; PIII: testing session following the 3-month intervention period.

exercise (3–6 machine and free weight exercises, twice/week, with the weight set to induce failure between 8 and 20 repetitions). A maximal graded exercise treadmill was implemented at PII to determine each subject's maximum heart rate (HRmax) and training heart rate range. Progression was ensured throughout the 3-month programme by gradually increasing exercise intensity and duration. That is, at the start of the programme each participant performed 20 min of aerobic exercise at an intensity of 70% HRmax. By the end of the 3-month programme, all participants were performing 40 min of aerobic exercise, with up to 10 min at an intensity between 80 and 90% HRmax and the remainder of the time between 70 and 80% HRmax. Most importantly, all participants exercised within their calculated training heart rate range for the entire duration of the session.

The initial resistance training program consisted of a 'seated bench press', 'latissimus pulldown' and 'leg press' exercise using machine weights. Within the fifth to sixth week of the programme an additional exercise ('upright row' using a 'Smith machine') was introduced. By the final week of the programme patients were also performing 'a seated shoulder press' and 'lunges' using free weights. All exercises were performed until the participant was unable

to successfully complete one more repetition (ie, to failure). The weight was set so that failure occurred between 15 and 20 repetitions within the first 6 weeks of the program. To focus more on achieving strength gains, this repetition range decreased to 8–12 repetitions for the second half of the programme.

Height, weight and body mass index

Height and weight were measured to the nearest 0.1 cm and 0.01 kg, respectively. The variables were assessed with the subjects barefoot, using a wall-mounted Harpenden stadiometer™ (Holtain Ltd, Crymych, Dyfed) and a calibrated digital electric scale, Wedderburn Scales™ (Tanita BWB-600). Body mass index (BMI) was calculated from the formula weight (kg)/height^2(m^2).

Body composition – singly labelled water technique

The calculation of body composition is often derived from the measurement of total body water (TBW). The method employed to assess TBW in this investigation was through the use of the deuterium dilution technique. This method has been described elsewhere.[10] Suffice it to say here that each subject was given an oral dose of 10% ^2H_2O relative to body weight (0.5 g/kg) following collection of a predose urine sample. A further urine sample was collected between 4 and 6 h after the dose.

Total body water was calculated using a modification of the equation of Halliday and Millar.[11] The deuterium dilution space assessed exceeds TBW due to the exchange of the tracer with nonaqueous hydrogen atoms within the body. The difference in humans is believed to be 3–4%[10] and, hence, the ^{2}H dilution space can be converted to TBW by dividing TBW by 1.04.

When using this method, FFM is calculated by dividing the measured TBW by 0.73, the assumed hydration coefficient of the FFM in normal-weight healthy individuals. Fat mass is subsequently calculated by subtracting FFM from BW. While limited data are available on the hydration coefficient of the FFM in normal-weight or underweight cancer patients, Simons *et al*[12] reported unpublished laboratory work demonstrating that, through the use of deuterium dilution and DEXA scanning, the hydration coefficient of lung carcinoma patients (mean BMI, 20.8) was 0.73 ± 0.03 (range = 0.68–0.79). Therefore, to extrapolate to body composition, the following formula was applied:

$$\text{FFM} = \text{TBW (l)}/0.73.$$

Thus,

$$\text{FM} = \text{BW} - \text{FFM}.$$

Energy expenditure – doubly labelled water technique

Total energy expenditure was measured via the doubly labelled water (DLW) method in four of the exercising subjects only. The DLW technique is considered a valid tool for assessing energy expenditure in various populations including infants, young adults, healthy adults, patients with gastrointestinal disorders and subjects under metabolic ward conditions.[13] The accuracy (1–2% with a relative s.d. of 3–9%) and precision (approximately 4%) of the technique have also been shown previously.[10]

The details of this technique have been published elsewhere.[14] In short, following a loading dose of 0.125 g/kg body weight 100% $H_2{}^{18}O$ and 0.05 g/kg body weight 100% ^2H_2O, spot urine samples were collected daily for 14 days. The slope-intercept method was used to determine carbon dioxide production rate.[4] Assuming a respiratory quotient of 0.85, TEE was calculated using Weir's formula.[15]

Statistical analysis

Sample size calculations were based on the changes in body composition observed in the first two subjects recruited into this investigation. It was determined that 12 subjects, six in each group, were required to detect a 1 s.d. difference, with power and significance set at 80 and 5% (two-tailed), respectively. A two-way analysis of variance (ANOVA), with repeated measures on one factor (phase), was employed to determine the main effects of phase and group and the group-by-phase interaction for BW, BMI, FM, FFM and percentage body fat (%BF). A one-way ANOVA was implemented to determine the main effect of phase for TEE. Where significant interactions or main effects were observed, *post hoc* analysis (model-based contrasts performed within the model) was performed to determine the loci of the variance. Additionally, *t*-tests were used to detect differences in the change measured for BW, BMI, %BF, FM and FFM between PII and PIII, for the two groups.

Results

Table 1 summarises the characteristics of the control and exercise group. While certain variables such as the mean age, weight at PII and living distance from the centre appear different between the two groups, these differences were not statistically significant ($P = 0.052$, 0.466 and 0.209, respectively).

Changes in body composition and energy expenditure following the transplant are presented in Table 3. The transplant was associated with significant decreases in weight ($P < 0.01$), BMI ($P < 0.01$) and FFM ($P < 0.05$).

Figure 1 displays the TEE results recorded from four subjects in the EG. A Pearson correlation performed on FFM and TEE data ($R = 0.60$, $P < 0.05$) indicated that the level of FFM measured influenced TEE. Since the FFM of the subjects altered across the three testing phases, it was deemed crucial to appropriately adjust TEE with regard to these FFM fluctuations. A common method of adjusting for FFM changes is by dividing TEE by FFM. However, a second negative correlation ($R = -0.56$, $P < 0.05$) applied to TEE/FFM and FFM indicated that the ratio of TEE and FFM may not adequately account for FFM changes. In order to find an appropriate method of adjusting for FFM changes, TEE and FFM values were log-transformed and

Table 3 Body composition and energy expenditure measures at PI and PII for the study group (mean ± s.e.)

Study group	*PI (n = 7)*		*PII (n = 12)*		*P-value*
Variable	*Mean*	*s.e.*	*Mean*	*s.e.*	
Wt (kg)	87.6	1.4	79.5	0.9	0.000**
BMI (kg/m^2)	29.9	0.5	27.2	0.3	0.000**
%BF	34.3	1.5	33.6	1.1	0.736
FM (kg)	32.1	1.9	28.5	1.4	0.142
FFM (kg)	54.8	1.3	51.1	0.9	0.036*
TEE (kcal/day)/FFM (kg)$^{0.5}$	284 ($n = 4$)	84.6	260 ($n = 4$)	84.6	0.104

*$P < 0.05$, **$P < 0.01$.

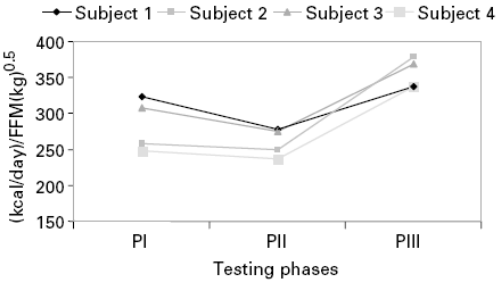

Figure 1 Changes in TEE for four subjects in the exercise group across the testing phases (TEE at each phase for each subject).

analysed by linear regression. The coefficient calculated in this case is the power to which FFM must be raised to completely adjust TEE for FFM. Since the linear regression coefficient was within two s.e. of either 0.5 or 1, TEE can be adjusted for FFM by expressing TEE/FFM (kg)$^{0.5}$ or, alternatively, TEE/$\sqrt{\text{FFM (kg)}}$.[16]

Across the sampling periods, there were no incidences of vomiting or diarrhoea, which could have potentially influenced the TEE results. While there was no change in TEE as a consequence of undertaking a PBST, following the 3-month exercise intervention, TEE increased ($P < 0.01$). TEE at PIII was also higher ($P < 0.01$) than that measured at PI.

As can be seen in Tables 4 and 5, weight and BMI at PIII remained lower ($P < 0.05$) than pretransplant measures for both the exercising and control group. The exercising subjects also recorded a lower FM at PIII ($P < 0.05$) when compared with pretransplant data (Table 4). Following the exercise intervention programme, those in the EG showed FFM increases ($P < 0.01$) as well as a reduction in %BF ($P < 0.05$). No statistical difference was found in the change in BW, BMI, %BF, FM and FFM between PII and PIII for the two groups (t statistics = −0.538, −0.421, 1.672, 1.734 and −1.949; and P-values = 0.604, 0.684, 0.129, 0.117 and 0.087, respectively).

Table 4 Body composition and energy expenditure measures across the testing phases for the exercise group (mean ± s.e.)

Variable	*n*	*Phase*	*Mean*	*s.e.*	*Comparisons*	*P-value*
Wt (kg)	5	I	95.5	1.8	PI–PII	0.007**
	6	II	87.4	1.4	PI–PIII	0.028*
	6	III	89.7	1.4	PII–PIII	0.315
BMI (kg/m^2)	5	I	32.3	0.6	PI–PII	0.010*
	6	II	29.2	0.5	PI–PIII	0.033*
	6	III	29.9	0.5	PII–PIII	0.369
%BF	5	I	34.9	1.8	PI–PII	0.980
	6	II	34.8	1.6	PI–PIII	0.051
	6	III	29.5	1.6	PII–PIII	0.041*
FM (kg)	5	I	37.0	2.2	PI–PII	0.201
	6	II	32.2	1.9	PI–PIII	0.032*
	6	III	28.2	1.9	PII–PIII	0.245
FFM (kg)	5	I	58.4	1.5	PI–PII	0.140
	6	II	55.1	1.3	PI–PIII	0.152
	6	III	61.6	1.3	PII–PIII	0.008**
TEE (kcal/day)/$^{0.5}$	4	I	284	11	PI–PII	0.185
FFM (kg)	4	II	260	11	PI–PIII	0.004**
	4	III	356	11	PII–PIII	0.001**

*$P < 0.05$, **$P < 0.01$.

Table 5 Body composition measures across the testing phases for the control group (mean ± s.e.)

Variable	*n*	*Phase*	*Mean*	*s.e.*	*Comparisons*	*P-value*
Wt (kg)	3	I	78.6	2.2	PI–PII	0.017*
	6	II	71.8	1.4	PI–PIII	0.041*
	5	III	72.8	1.6	PII–PIII	0.573
BMI (kg/m^2)	3	I	27.7	0.8	PI–PII	0.013*
	6	II	25.3	0.5	PI–PIII	0.032*
	5	III	25.7	0.6	PII–PIII	0.540
%BF	3	I	33.7	2.5	PI–PII	0.687
	6	II	32.4	1.6	PI–PIII	0.628
	4	III	32.1	1.8	PII–PIII	0.876
FM (kg)	3	I	27.2	3.1	PI–PII	0.318
	6	II	24.8	1.9	PI–PIII	0.416
	4	III	25.1	2.2	PII–PIII	0.867
FFM (kg)	3	I	51.5	2.1	PI–PII	0.145
	6	II	47.0	1.3	PI–PIII	0.213
	4	III	47.0	1.8	PII–PIII	0.996

*$P < 0.05$.

Discussion

Adverse changes in body composition were associated with a PBST, as was evident by the losses observed in both BW and FFM at PII. Only those patients who participated in the exercise intervention were able to regain FFM by 3 months post transplant. While participation in the exercise programme increased TEE to levels higher than that experienced pretransplant, body composition was not adversely influenced.

During the recruitment phase, the investigators tried to ensure that both the mean and range were similar for all

identified potential confounding variables, between the control and exercise group. While no statistical differences were found between the confounding variables of the control and exercise group, it was important to consider their potential effect on the results. An analysis of the raw data demonstrated that all subjects in the exercise group displayed a similar trend of change for body composition measures throughout the testing phases, and the differences in the magnitude of change were not related to any of the variables outlined in Table 1.

Undergoing the high-dose chemotherapy regimen and the autologous PBST had no effect on the TEE of the patients in this study. Although REE changes within the cancer population have been studied, limited research is available on the impact of cancer treatment on TEE.[6] Of those found, contrasting results have been reported. Insignificant increases were found in the TEE of premenopausal and perimenopausal women with breast cancer,[5] while decreases have been shown in a nonsmall cell lung cancer patient group when compared with age- and sex-matched controls,[6] as well as children treated for acute lymphoblastic leukaemia when compared with healthy sibling controls and other children treated for a variety of malignancies.[7] The reduction in TEE was explained by reduced patterns of physical activity.

A unique aspect of this study was the measurement of TEE via the DLW method. All other studies that have assessed TEE have done so by measuring REE and the energy cost of physical activity, rather than through its direct measurement. More studies employing the DLW method and involving greater subject numbers are required before the impact of cancer and its associated treatment on energy expenditure can be truly known.

While a relation between REE and FFM has been previously shown, with the results indicating that the lower the FFM, the lower the REE,[17] studies of patients with unresectable pancreatic cancer have shown that BW losses can also occur in the presence of increases in REE.[3] Therefore, although patients in this investigation showed a reduction in BW and FFM following the PBST, it cannot be assumed that REE also declined. Decreases in REE are not consistent findings, with the literature reporting increased, decreased and normal states following cancer treatment.[18] Factors including the type of tumour, type of treatment and the intensity of treatment,[19] as well as changes in BW and FFM[18] maintain the potential to influence changes in REE measured in patients with cancer.

Although the extent of the data regarding the energy expended on physical activity during or following cancer treatment is limited, a decline in energy spent on this component of TEE was observed.[6,20] With respect to the treatment regimen undertaken by the study patients, the hospitalisation period can last up to 1 month, with patients spending the majority of this time in a supine position. For those patients undergoing more than one transplant, the inpatient period is lengthened and thus the period of reduced physical activity is further prolonged. During the inpatient period, 'bed' or 'hallway' exercises are needed to maintain the energy spent on physical activity. However, it is not common practice to prescribe exercise to PBST patients in the hospital setting, and unless the patient has an intrinsic motivation to maintain physical activity, energy spent on physical activity during the treatment period is likely to decline.

There are also limited data available that directly assess the TEF in cancer patients, yet many studies maintain the assumption that TEF accounts for 10% of the TEE. Unfortunately, when dealing with the cancer population, this assumption may be violated, as conventional treatment regimens may lead to the presence of side effects including mucositis, nausea and vomiting. The presence of these side effects has the potential to alter food intake and thus TEF. The significant reduction in BW experienced by patients in this study highlighted the presence of an energy imbalance between PI and PII. Since TEE did not change during this period, energy intake must have declined, and consequently so too would the TEF.

The loss observed in BW ($P<0.05$) between PI and PII can be characterised by a disproportionate loss of FFM, as indicated by no change in FM, in conjunction with a 6% decline in FFM ($P<0.05$). The decline in functional tissue observed in this investigation supports previous findings demonstrating that children between the ages of 1.3 and 17.1 years experienced an 11% reduction in muscle protein reserves during the first month postautologous or allogeneic BMT.[21]

A similar disproportionate loss of FFM observed in the PBST patients within this research has consistently been shown in studies investigating body composition changes in HIV patients.[22] However, evidence within the cancer population is inconsistent. Data derived from the cancer population have shown equal FM and FFM losses,[23] greater FM losses when compared with FFM losses[24] and greater FFM losses when compared with FM losses.[6] Fat-free mass losses have also been demonstrated in patients who are gaining weight.[5,21] Of relevance to all findings is that positive or negative changes in BW can be at least partly accounted for by FFM losses. The loss in functional tissue has detrimental ramifications to the patient's ability to perform normally and without fatigue in daily activities, and it is therefore crucial that these losses be prevented, minimised and corrected.

The primary aim of implementing an exercise programme in the rehabilitation phase of cancer patients is to facilitate recovery and thus allow the patient to perform normal daily activities without undue fatigue. However, given the loss of BW observed during cancer treatment, and the relation between physical activity and energy expenditure, participation in an exercise programme may seem contraindicated. The results of this study demonstrate that aerobic and resistance exercise is crucial in regaining lean tissue that was lost during the transplant process.

Significant improvements in body composition were evident by PIII for the exercise group, with all six patients gaining lean tissue. While BW remained relatively stable between PII and PIII, %BF declined ($P<0.05$) in conjunction with an increase in FFM ($P<0.05$). That is, nonfunctional tissue was lost while functional tissue was gained. Due to the initial %BF of the subjects ($29.5\pm1.6\%$), the loss observed in FM by PIII was neither detrimental to the participants' energy reserves or their health. In contrast, the control group failed to regain any lean tissue that was lost

during the transplant process and one subject continued to show a decline. The adverse change in FFM of this subject highlighted the risk for continued declines in functional tissue following treatment cessation. As a result of these body composition changes during the recovery period, the control group would require a greater degree of effort, while the exercise group would require less effort to perform daily tasks, when compared with their pretransplant state. Interestingly, although BW was stable during the intervention period, TEE significantly increased. Taken together, these results indicate that energy intake must have also increased during the recovery period to maintain the energy balance.

The patient population studied in this investigation could be considered as overweight, as shown by BMI (mean = 31.85) or %BF (mean = 27.65) at PI. Therefore, a loss in BW as a consequence of the cancer treatment might be considered beneficial. However, irrespective of whether patients are overweight or underweight, a loss of FFM is detrimental to functional capacity. Unfortunately, if BW changes are the only factor assessed across time, patients, carers and health professionals could falsely perceive BW changes as positive. This highlights the importance of measuring body composition as well as body weight during the treatment and recovery phase of patients with cancer.

It has previously been reported that TEE is 'robust' and can remain relatively stable when challenged by such stimuli as an exercise intervention.[6,25] This lack of net TEE change is considered a consequence of one component of TEE compensating for changes in another. For example, given that an exercise intervention causes an increase in the energy spent on physical activity, people may correspondingly decrease the energy spent on daily tasks and spend more time during the day 'resting'. This would be considered an adverse consequence of physical activity in the cancer population given the objective of an exercise intervention. However, it was identified in this investigation that TEE did not remain stable, but was higher at PIII when compared with PI. These data suggest that the patients were able to maintain their participation in normal daily tasks, in conjunction with expending additional energy during their exercise sessions.

Inability to recruit adequate numbers of patients is a limitation in cancer research and has the potential to influence the success of a programme. During the subject recruitment phase of this study, it became evident that referral and encouragement by medical practitioners was crucial in attaining subjects. Willingness to participate during cancer treatment is no small endeavour for the patient. More specifically, recruiting patients prior to transplant is often at a time when patients are feeling depressed and have little energy to perform daily activities. Associated with these recruitment limitations is the influence of family and medical staff and their common recommendation that patients should 'take it easy' and 'get plenty of rest' during and following treatment. While this investigation provides evidence that an exercise programme should form a primary component of cancer rehabilitation, it also highlights the need for medical practitioners' support.

Another important consideration for the success of an intervention programme is programme acceptance and adherence. Previous exercise intervention programmes performed with BMT patients have reported a 90% acceptance rate[26] and have suggested that patients perceive their 'active' role in the rehabilitation process, compared with their previously 'passive' role in the diagnostic procedure and treatment process, as a 'welcomed change'. The program acceptance and adherence rate of this investigation supports these findings. All patients within the exercise group adhered to the programme, working within the prescribed intensity and duration of each exercise session. Additionally, only two patients failed to attend 1 week of the 12-week programme, because of illness. Comments regarding 'ownership' of the programme, or 'personal control', were commonly stated by exercising patients during informal interviews, and it was felt that these feelings may have contributed to the programme acceptance and adherence rate attained. Therefore, it seems evident that although difficulties are present during the recruitment phase, once patients have agreed to participate, programme adherence is not problematic, at least for a 3-month programme.

The small number of subjects in this investigation reflects the recruitment difficulties faced when dealing with patients with cancer. The recruitment problems experienced are not unique to this investigation, and small sample sizes are not uncommon in cancer research.[27] This limitation highlights the importance of further research within the area that both replicates and extends current studies. Nevertheless, while the sample size was relatively small, the statistical power was sufficient to detect many of the changes observed as statistically significant (at two-tailed, $\alpha = 0.05$). In addition, the assessment of individual change demonstrated that all subjects displayed a similar trend of change and magnitude of change. As such, the group mean change was representative of individual change.

Although undertaking HDC followed by an autologous PBST had no impact on TEE, adverse changes occurred in BW and body composition. Specifically, FFM declined as a result of the transplant. Importantly, this study has shown that the losses observed in functional tissue during the transplant period can be regained through participation in a 3-month duration, moderate-intensity, mixed-type exercise programme. Furthermore, participation in this type of exercise programme led to significant declines in fat or nonfunctional tissue. While the exercise program increased energy expenditure and was associated with positive changes in body composition, BW remained stable. Physical activity is an important rehabilitation strategy that can be used to improve body composition and in turn the functional capacity of cancer patients following transplant. Participation in moderate-intensity, mixed-type, regular activity should therefore be encouraged and not prevented.

Acknowledgements

We are indebted to the 12 committed patients who made this study possible. This study was supported in part by the National Breast Cancer Foundation, Australia.

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