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Attenuation of resting energy expenditure following hematopoietic stem cell transplantation in children

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Abstract

Background—Children undergoing hematopoietic stem cell transplantation (HSCT) typically receive parenteral nutrition (PN) due to gastrointestinal toxicities. Accurate determination of resting energy expenditure (REE) may facilitate optimal energy provision and help avoid unintended overfeeding or underfeeding.

Methods—In a multicenter, prospective cohort study of children undergoing allogeneic HSCT, REE was measured by indirect calorimetry at baseline and twice weekly until 30 days after transplantation. Change in percent predicted REE over time from admission was analyzed using repeated measures regression analysis.

Results—Twenty-six children (14 females) with a mean (SD) age of 14.9 (4.2) years who underwent an HLA-matched sibling or unrelated donor transplantation were enrolled. Mean (SD) percent predicted REE at baseline was 92.4 (15.2). Baseline REE was highly correlated with lean body mass measured by DXA ($r=0.78$, $p<.0001$). REE decreased significantly over time, following a quadratic curve to a nadir of 79% predicted at 14 days post transplantation ($p <0.001$) and returned to near baseline by day 30.

Conclusions—Children undergoing HSCT exhibit a significant reduction in REE in the early weeks after transplantation, a phenomenon that places them at risk for overfeeding. Serial measurements of REE or reductions in energy intake should be considered when PN is the primary mode of nutrition.

Keywords

parenteral nutrition; energy expenditure; energy balance; indirect calorimetry

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Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative therapy for malignancy and bone marrow failure with far-reaching nutritional consequences. Children undergoing HSCT are at high nutritional risk due to their underlying disease and the intensive medical therapy prior to and following transplantation [1]. The side effects of high dose chemotherapy and total body irradiation used as preparative treatment frequently cause anorexia with weight loss, mucositis and extensive gastrointestinal toxicity.

Parenteral nutrition (PN) is often used in HSCT since it has been associated with faster engraftment and improved survival[4, 5]. However, PN use has also been associated with complications including catheter-related blood stream infections, hepatotoxicity, suppression of oral intake, and metabolic abnormalities [6-8]. Knowledge of energy expenditure during HSCT could facilitate the provision of appropriate nutrition while minimizing potential risks.

In a previous study, we described REE changes in a cohort of 25 children undergoing allogeneic HSCT[15]. Children were enrolled in an open-label trial of a supportive care regimen that included a reduction in PN intake to meet estimated BMR or weekly measured REE. We observed a significant decline in REE from a pre-transplantation level of 95% predicted by standard equations, to a nadir of 80% by 3 and 4 weeks after transplantation ($P < 0.05$). These significant time-based changes were not explained by differences in body weight, time to engraftment, diagnosis, donor type, age, serum concentrations of C-reactive protein, or presence of infection [15].

In this earlier study, however, all subjects were generally prescribed energy intake less than typically provided to children undergoing HSCT, and subjects lost a significant amount of weight over the course of their hospitalization. Caloric deprivation [16] and weight loss [17] can reduce energy expenditure, via a process termed adaptive thermogenesis [18]. The decline in REE we observed could therefore have resulted from a physiologic adaptation to reduced energy intake [19].

To examine this effect further, we tested two approaches to nutritional intervention. Our study design included a standard arm with an energy intake equal to 140% estimated BMR, and an experimental arm with an energy goal of 100% measured REE. We hypothesized that children undergoing HSCT would have altered REE compared with published normal values, regardless of the amount of energy intake. In addition, REE was measured with greater frequency (twice per week vs. weekly) in order to measure more precisely possible REE changes over time. This study of REE changes in the entire cohort was a planned substudy of the parent randomized controlled trial.

Subjects and Methods

We performed a multicenter, randomized, double-blind controlled clinical trial of two approaches to the provision of PN to pediatric HSCT patients: 1) the standard of care (“standard PN”) in which energy intake was provided in the amount of 140% of estimated BMR, as calculated by standard reference equations [20] and 2) an alternative strategy

("experimental PN") in which energy intake was titrated to match REE, as measured by indirect calorimetry. Details of the main study methods have been published previously [21]. The Institutional Review Boards of Children's Hospital Boston and UCLA Mattel Children's Hospital approved the protocol. The study was registered in ClinicalTrials.gov ID: NCT00115258. The primary outcome of the main study was body composition as measured by dual energy x-ray absorptiometry (DXA) [22]. This ancillary study was designed to evaluate measurements of REE among all subjects over the course of HSCT, compared with estimates of BMR as calculated by the Schofield equations [20].

Inclusion criteria were age greater than or equal to 6 years in children who were scheduled for their first myeloablative, matched related or unrelated donor allogeneic HSCT at Children's Hospital Boston (n=21) or UCLA Mattel Children's Hospital (n=5). Children who were underweight [body mass index (BMI) z-score <-2] or overweight (BMI z-score >2) were excluded from participation, as were children already receiving PN at admission for HSCT, as well as those with hypo- or hyperthyroidism, insulin-dependent diabetes mellitus, or an allergy to egg or soy products. All subjects received standard medical care based on institutional HSCT guidelines and protocols. Preparative therapy included either total body irradiation (1400 cGy) or busulfan (0.8 mg/kg every 6 hours, intravenously, adjusted for levels) in addition to cyclophosphamide or other chemotherapeutic agents. Medications used for graft versus host disease (GVHD) prophylaxis included calcineurin-inhibitors, methotrexate and corticosteroids. Standard medications included oral non-absorbable antibiotics for gut decontamination, ursodeoxycholic acid and vitamin E for venoocclusive disease prophylaxis [23], and leucovorin calcium for recovery from methotrexate, when used for GVHD prophylaxis. Central venous catheters were used for administration of intravenous fluids and PN.

Nutritional management

PN was initiated when and if oral energy intake declined to less than baseline REE measurement for more than 3-5 days, but no earlier than the day of transplantation (day 0). Subjects were randomized using a computer-generated sequence of treatment assignments for each site in randomly permuted blocks of 2, 4, and 6. The patients, parents, physicians and nurses were blinded to treatment allocation, and were therefore not informed of the energy composition of the PN. The pharmacist and the registered dietitian were unblinded and planned the preparation of the PN solution according to the subjects' group assignment, but were not directly involved in the conduct of the study. The energy prescription of each group differed by alterations in dextrose and lipid to achieve either 100% of measured REE in the experimental group, or 140% of estimated BMR [24] as calculated by the Schofield method [20] in the standard PN group. Contributions of daily oral energy intake were subtracted from the total energy prescription to determine the energy allotted for PN. Total protein goals were similar in both study groups at 1.5 to 2.0 g/kg/day for children 6-13 years, and 1.0 – 1.5 g/kg/day for children over 13 years [25]. PN was discontinued when oral energy intake reached 50% of the most recent measured REE, or at the time of preparation for hospital discharge, whichever came first.

Anthropometrics and dietary intake

Body weight was measured daily during the hospitalization period by an electronic digital scale accurate to 0.1 kg. Standing height was measured by stadiometer to the nearest 0.1 cm at baseline [mean (SD) = 10 (3.75) days before transplantation] and 30 days post transplantation. Oral dietary intake was recorded daily throughout the inpatient admission using calorie counts. Oral energy and protein intake at baseline and 30 days post transplantation was calculated from 24-hour recall. Nutrient analysis software (Nutritionist Pro, ESHA Food Processor, and Nutrient Data Systems) and pharmacy specifications for parenteral solutions were used to calculate energy, macronutrient and micronutrient intake.

Resting energy expenditure

REE was measured prior to admission, twice weekly throughout the hospitalization, and again at 30 days after transplantation using the Vmax Encore® indirect calorimeter (Viasys Healthcare, Yorba Linda, CA). Patients were studied in a modified fasted state, i.e. ≥ 6 hours without any oral or enteral intake; intravenous fluids/PN were continued without interruption. The test was accomplished in the supine position, with a transparent canopy placed over the head. Each measurement was preceded by calibration with a gas mixture of known composition according to the manufacturer's instructions. The indirect calorimeter measures the inspiratory concentration of oxygen (FiO_2) and the difference between FiO_2 and expiratory concentrations of oxygen (FeO_2) using an electro-chemical cell, while the expiratory carbon dioxide ($FeCO_2$) is measured continuously with a non-dispersive infrared thermopile. Inspiratory CO_2 concentration of room air ($FiCO_2$) is measured every two minutes. Carbon dioxide output and oxygen consumption are calculated each minute and then converted to standard temperature and pressure using dry gas equations. REE, expressed in kcal per day, is calculated by the device using the modified Weir equation[26]. Steady state was defined as a time period of >5 minutes with <10% fluctuation in oxygen consumption and carbon dioxide production and <5% fluctuation in respiratory quotient (RQ)[27]. To achieve steady state, each test lasted 15-30 minutes. The average values of VO_2, VCO_2, REE and RQ over the steady state period were recorded. Percent predicted BMR was calculated[20] to normalize the data for age, sex, weight and height.

Body composition assessment

Whole body DXA was performed at baseline and day 30 in the anterior posterior position by a certified densitometry technologist using the Hologic Discovery A® (Hologic, Inc.) scanner, which generates X-rays at 2 energy levels (100 and 70 kV). DXA scanners were cross-calibrated at each site and weekly whole body phantom scans were performed as part of routine quality control measures. A series of transverse scans were made from the head to toe at 2 mm intervals. Area, body weight, fat mass, bone mineral content and lean tissue mass were recorded in grams for each region. Percent body fat was determined from the summation of the fat mass of each component divided by the total body mass, multiplied by 100. Data from both sites were analyzed and interpreted at Children's Hospital Boston using the Hologic Pediatric Upgrade for children and adolescents up to age 20 years[28].

Data analysis

Paired t-tests were used to compare baseline and day 30 measurements, and Pearson correlations to assess the association of REE with weight and energy-balance measures. The time course of REE was analyzed by repeated-measures regression, using a quadratic curve of REE vs. time to describe the dip suggested by the data and confirming the significance of the quadratic term by the appropriate F-test. Within-subject correlation was modeled by a compound-symmetric covariance structure. The level and time course of REE were compared between subgroups defined by clinical characteristics and treatment assignment by adding and testing interaction terms in the regression model. Smoothing spline analysis was used to corroborate the polynomial model and to conduct similar analyses of energy-balance measures [29]. All tests were two-sided with critical p-value <0.05. Analyses were performed with SPSS (PASW Statistics 17.0, Release 17.0.2, March 11, 2009) and SAS (version 9.2, Cary, NC).

Results

Baseline characteristics of the subjects are presented in Table 1. Children were generally well nourished at presentation with a mean (SD) BMI Z-score of 0.31 (0.83). Donor type and sex of the subjects was nearly equally distributed between the experimental and control groups. Hematologic malignancy was the diagnosis for transplantation in 23 (88%) subjects. Mean (SD) days to neutrophil engraftment was 24.1 (5.5) and length of hospital stay was 40.5 (10.9) days. Subjects received PN for 21.4 (10.1) days. None of these characteristics differed between the experimental and control groups ($p>0.30$).

REE was measured 253 times on the 26 subjects enrolled. Steady state was achieved in 93% of the measurements. Changes in weight, body composition and energy expenditure between baseline and 30 days after HSCT are noted in Table 2. Weight and lean mass as measured by DXA decreased significantly from baseline to day 30, while REE was not significantly different between these two time points. REE, expressed per kilogram of body weight and per kilogram of lean body mass, was also unchanged between baseline and day +30. The mean changes did not differ significantly between the two treatment groups ($p>0.20$).

The strongest correlate of measured REE at baseline and day 30 was lean mass measured by DXA, as noted in Table 3. Anthropometric assessments including weight, height and arm anthropometrics also showed moderate to strong correlations with measured REE. These correlations did not differ significantly between treatment groups at either time point ($p>0.70$).

Median weekly REE measurements and energy intake are listed in Table 4. All measures showed significant changes over the 7-week period except for VCO_2. RQ remained steady in the experimental subjects but rose by about 10% in the standard treatment group compared to the week before transplant ($p=0.0001$ for time × treatment interaction). Energy intake as a percentage of REE rose steeply from a low median of 48% in the week prior to transplantation, reaching a maximum of 156% by week 5.

During the conditioning period, 10 days preceding transplant, oral intake declined from median 114 kcal (range 37–215) to 22 kcal (0–149). There was no significant difference between treatment groups on any given day (p=0.85) nor in the pattern of decline (p=0.91). The median percentage of days that patients received more energy than their measured REE was 77% (range 56-92%) in the standard group, which as expected, was significantly higher than in the experimental group (median 56%, range 33-82%; p=0.006).

Over the 2 weeks prior to transplantation, REE was slightly, but significantly lower than BMR as predicted by the Schofield method [mean (SE) = 92.4 (3.0) % of predicted, $p<0.05$]. Mean REE declined significantly over time to a nadir of 79% predicted on day 14 after HSCT ($p<0.001$), with a subsequent increase suggesting a curvature as presented in the figure. Changes in REE over time were not significantly different between groups (experimental vs. standard PN, p=0.78) (Figure) with both treatment groups showing substantial reductions in REE, expressed as percent predicted, by days 7-14 following transplantation. This pattern was not altered by removing data from days when a subject received less than 50% of REE. These changes in REE were not related to clinical covariates including donor type (p=0.36), diagnosis for transplantation (p=0.10), cancer vs. non-cancer diagnosis (p=0.11), peak mucositis score (p=0.19), diagnosis of veno-occlusive disease (p=0.21), amount of steroids received (p=0.29), days to engraftment (p=0.11), presence of infection during the study period (p=0.61), or diagnosis of graft versus host disease (p=0.62).

Discussion

In this group of 26 children undergoing allogeneic HSCT, we observed significant changes in REE over the first month following HSCT. At baseline, mean measured REE was significantly lower than estimated BMR, and REE declined further along a quadratic curve to its lowest point at 2 weeks following HSCT, followed by a return to baseline level. This decline in REE was not related to the provision of more or less parenteral energy, nor other factors including infectious or other morbidities of HSCT. In addition, we documented reduced oxygen consumption and carbon dioxide production over the course of HSCT, alongside a significant rise in RQ in patients assigned to receive standard nutrition.

Variations in measured REE during HSCT have previously been reported in adults and children [11-14]. In a group of 6 children undergoing autologous HSCT for malignant disease, mean REE was 111% of predicted BMR in those receiving PN before high dose chemotherapy conditioning, and 128% of predicted BMR in those receiving PN after conditioning[13]. Following engraftment, REE significantly increased to 128% of BMR in the early PN group, and 146% of BMR in the late PN group [13]. A similarly designed study of 7 adults undergoing allogeneic HSCT found REE values ranging from 79% to 121% of BMR over the 1 week prior and 3 weeks following HSCT [11]. Others have found individual differences in REE measurements compared to predicted BMR in adults prior to autologous (-19 to 9%) or allogeneic (-11 to 32%) HSCT [12]. Significant differences in REE measured over the course of post-HSCT aplasia were also observed [12]. The mean increase in REE in autologous HSCT recipients and a mean decrease in allogeneic HSCT recipients [12] suggests

that changes in energy expenditure might relate to differences in diagnosis, HSCT treatment regimens or effects of allogenicity.

Since chemotherapy is also associated with declines in lean body mass and energy intake[2,3], maintaining or improving nutrient intake in children undergoing HSCT is an important component of post-transplantation care. Standard practice has suggested energy prescriptions at 130-150% of equation-estimated basal metabolic rate (BMR) [1, 4, 9-11]. However, estimates of BMR using equations developed from studies of healthy children are likely a poor reflection of the true energy expended during recovery from HSCT. Due to the gastrointestinal toxicities associated with chemotherapy and radiation used in the myeloablative preparation for HSCT, many children will require parenteral feeding. While enteral feeding has been utilized with some success, intolerance remains a problem. Thus, improving the precision and quality of PN prescriptions should be valuable to patient care regimens.

Declines in energy expenditure have been associated with intentional weight loss over 1-3 months in healthy adults [16]. However, the impact of acute, catabolic illness on metabolic demand may also influence the effect of reduced energy intake. Daily measurements of REE in critically ill children studied during the first week of hospitalization were stable and did not correspond with significant changes in energy balance [30]. We found no significant differences between REE measurements related to energy intake in our cohort, suggesting no impact on REE from the reduced energy intake of the experimental group. Our previous cohort exhibited baseline REE measurements near normal compared to age and sex matched standard equations[15]. With energy provided to match REE measured by indirect calorimetry, REE declined significantly over time to a nadir of ∼80% of predicted REE by 3 weeks after HSCT[15]. Our current findings are similar in the degree of reduction in REE observed, but extend these findings by confirming that the amount of energy provided to the subjects was not a correlate of this trend. Patients received an energy amount that was greater than or equal to their measured expenditure on most days, with a significant rise in RQ noted in the standard group. Since changes in REE were similar in both groups despite differences in energy intake, we are confident that the reduction in REE was not a result of metabolic adaptation to hypocaloric feedings and thus represents a calorie intake independent physiologically relevant outcome for children undergoing HSCT.

As assessed by DXA, a precise measure of body composition, we found a strong correlation between baseline and day 30 REE and lean body mass. Lean body mass significantly declined over the course of the study. As lean body mass is known to be the primary contributor to REE, the reduction in lean body mass is a plausible explanation for the attenuation in REE over time. However, we were unable to measure lean mass as frequently as REE during the course of HSCT, and thus were unable to determine if the timing of REE changes were related to sequential changes in lean mass. In this setting, the accuracy and reliability of frequent body composition measurements to define this trend at the bedside remains unknown.

A previous study examining REE in children undergoing autologous (n=10) and allogeneic HSCT (n=24) found significant variations in median REE from baseline to day 21 after

HSCT [14]. In more than 77% of cases, REE differed by more than 10% from predicted BMR, as determined by the WHO equation, the Harris-Benedict equation, or the Seashore equation [14]. Contrary to our findings, at 2 weeks following HSCT, the authors observed a significantly higher REE compared to baseline and day 7 levels [14]. Energy intake exceeded expenditure in 10-50% of patients at any point during this early transplantation period, with 30% of all measured respiratory quotients >1.0, further suggesting overfeeding. Differences in regimens, pre-transplantation therapy and time to engraftment among allogeneic and autologous HSCT recipients may have influenced the observed changes in REE. The conditions and methods by which REE has been measured vary substantially among studies of REE in HSCT patients. Although these differences may explain inconsistences between published results, they are unlikely to provide a rationale for changes within groups.

Our study has several limitations. The sample size of the current study is insufficient to analyze all of these possible influences. Although all patients underwent allogeneic HSCT, such patients have significant diversity in their underlying diagnoses, prior treatment, myeloablative therapy, and regimen-related toxicities. Such variables, as well as therapeutic maneuvers including the use of analgesics and corticosteroids, could potentially contribute to changes in energy expenditure or alterations in body weight and body composition. Children with cancer are routinely treated with corticosteroids and have a higher fat mass adjusted for stature than healthy controls[31, 32]. Our study included patients with and without previous and concurrent steroid treatment, perhaps contributing to our inability to discern its cumulative effect on body composition. Furthermore, HSCT patients typically are less active and require narcotics and sedatives for pain relief and anxiolysis, both of which may contribute to reductions in REE during hospitalization. Another limitation of this study was the inability to accurately measure body composition serially. However, the correlation of measured REE with the significant decline in lean body mass 30 days after transplantation suggests that depletion of lean mass could explain the REE changes.

The energy requirements of children undergoing HSCT are important to determine for the provision of safe and effective nutrition, while minimizing risks for metabolic and other complications. Survivors of pediatric cancer have significantly higher risks of cardiovascular disease [33] and obesity [34] than their siblings, and HSCT survivors have high rates of insulin resistance [35]. Our study confirmed significant declines in REE over the course of transplantation, compared to values predicted by the commonly used Schofield equation. Standard nutritional regimens are therefore likely excessive, especially during the 2 - 3 weeks following transplantation, and may predispose to subsequent metabolic complications.

Standard equations are frequently inaccurate in children with a variety of illnesses [36-38]. The American Society for Parenteral and Enteral Nutrition guidelines have recommended the use of measured REE to best determine energy prescriptions in critically ill children[39]. Optimal conditions for steady state REE measurements have been proposed[40], and should be incorporated into future protocols of REE measurements in children. The results of our current study suggest that indirect calorimetry should be considered in children undergoing HSCT to determine individual variations in REE over time. When indirect calorimetry is unavailable, systematic lowering of standard energy prescriptions from 140% to 100% of

estimated BMR would be reasonable to avoid excessive delivery of energy. Studies of critically ill adults have demonstrated improvements in clinical outcomes with reductions in energy intake [41-43]. Examination of clinical outcomes is warranted for HSCT patients who are provided reduced parenteral nutrition therapy.

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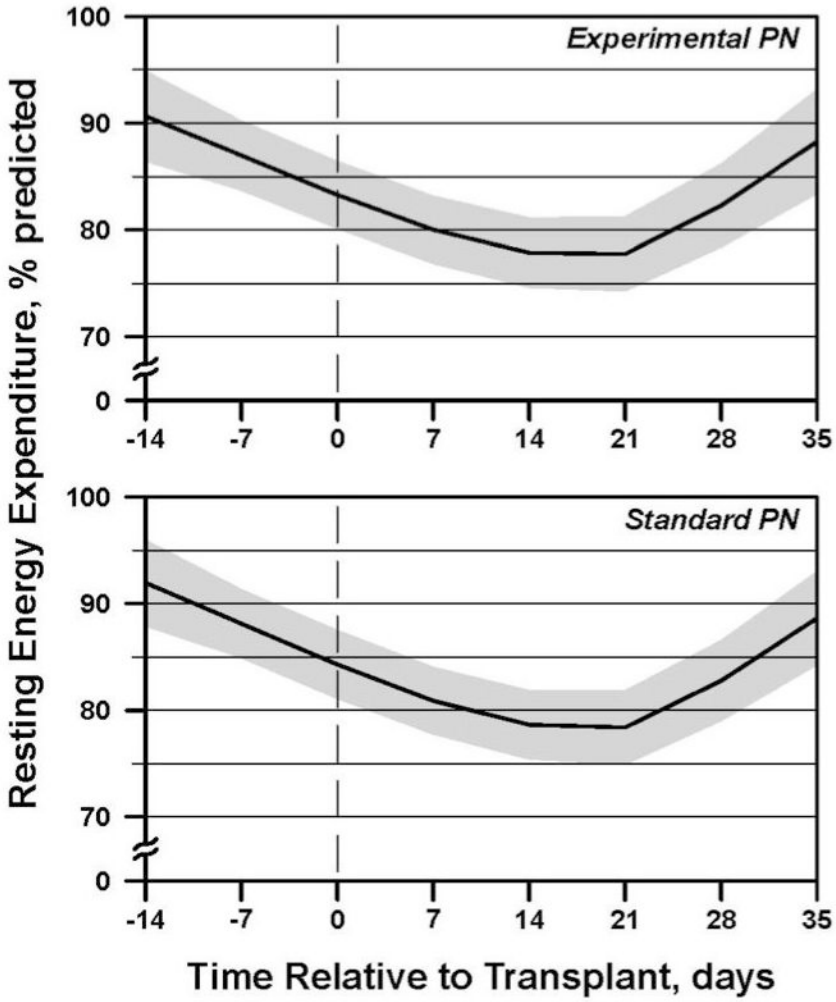

Figure.

Changes in measured REE following HSCT in children with different energy intakes; REE compared to BMR calculated by Schofield equations.

Table 1
Baseline characteristics of 26 children undergoing HSCT

Characteristic	Mean (SD)
Age, years	14.9 (4.2)
Weight, kg	52.6 (17.9)
Weight for age and gender, Z-score	0.09 (1.03)
Height, cm	154.7 (19.3)
Height for age and gender, Z-score	−0.37 (1.23)
BMI Z-score	0.31 (0.83)
Predicted BMR*, kcal/day	1430 (282)
Donor type	
Sibling related	12 (46)
Unrelated	14 (54)
Sex	
Male	12 (46)
Female	14 (54)
Diagnosis for transplantation	N (%)
Acute lymphoblastic leukemia	7 (27)
Acute myelogenous leukemia	7 (27)
Myelodysplastic syndrome	3 (12)
Chronic myelogenous leukemia	3 (12)
Lymphoma	2 (8)
Aplastic anemia	1 (4)
Other	3 (12)

*Calculated from Schofield equations

Note: no significant differences between treatment groups

Table 2

Changes in body composition and energy expenditure in children 30 days after HSCT

Measure	Baseline, Mean (SD)	Day 30 sample	Day 30, Mean (SD)	Change, Mean (SE)	p*
Weight, kg	52.6 (17.9)	26	50.1 (16.0)	−2.5 (0.6)	<0.001
DXA lean mass, kg	35.4 (13.3)	23	33.1 (12.4)	−1.7 (0.5)	0.003
Measured REE, kcal/day	1313 (320)	24	1259 (304)	−59 (53)	0.28
% Predicted BMR†	92.4 (15.2)	24	88.6 (13.2)	−4.4 (3.5)	0.23
Measured REE, kcal/kg/day	27.4 (9.3)	24	27.3 (7.3)	−0.8 (1.1)	0.47
Measured REE, kcal/kg DXA lean mass/day	40.6 (12.6)	22	40.4 (10.3)	−1.8 (1.5)	0.22

*Testing H_0: mean change = 0 by paired t-test.

†Using Schofield equations.

Note: no significant differences between treatment groups

Table 3

Pearson correlation of measured REE with body composition and anthropometry in 26 children undergoing HSCT

	Correlation with REE			
Variable	**Baseline**	**p**	**30 days**	**p**
DXA lean mass, kg	0.78	<0.0001	0.90	<0.0001
Weight, kg	0.71	<0.0001	0.86	<0.0001
Height, cm	0.66	0.0002	0.84	<0.0001
BMI, kg/m^2	0.59	0.0015	0.70	0.0004
Midarm circumference, cm	0.64	0.0005	0.80	<0.0001
Midarm muscle area, cm^2	0.67	0.0002	0.83	<0.0001

Note: no significant differences between treatment groups

Table 4

Weekly energy expenditure and intake in children undergoing HSCT

Measure	Median (interquartile range)							p†
	Week pre- transplasntation		Weeks post-transplantation					
	2	1	1	2	3	4	5	
REE, kcal/day	1140 (444)	1227 (481)	1144 (528)	1131 (391)	1043 (428)	1074 (387)	1253 (489)	0.0002
REE, % predicted	94.5 (17.7)	87.5 (19.0)	80.3 (18.4)	80.7 (16.0)	75.8 (22.7)	84.8 (23.1)	86.1 (17.8)	0.0004
RQ: standard	0.97 (0.11)	0.85 (0.06)	0.95 (0.08)	0.96 (0.07)	0.91 (0.15)	1.00 (0.17)	0.96 (0.16)	<0.0001
experimental	0.86 (0.09)	0.85 (0.10)	0.88 (0.06)	0.88 (0.09)	0.89 (0.09)	0.86 (0.10)	0.89 (0.20)	0.68
VCO_2, ml/min	147 (42)	152 (59)	141 (56)	150 (47)	134 (53)	145 (46)	151 (66)	0.18
VO_2, ml/min	161 (63)	174 (75)	164 (71)	159 (59)	142 (60)	152 (65)	178 (79)	<0.0001
Intake, kcal/day*	1840 (629)	516 (603)	1416 (999)	1476 (879)	1403 (986)	1411 (824)	1410 (2022)	0.003
Intake:REE, %	158 (75)	48 (60)	128 (56)	138 (68)	137 (100)	128 (79)	156 (154)	<0.0001

*Energy from oral and parenteral intake combined

†From smoothing spline analysis, testing for significant variation over time.