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Low Levels of Energy Expenditure in Childhood Cancer Survivors: Implications for Obesity Prevention

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Abstract

Childhood cancer survivors are at an increased risk of obesity but causes for this elevated risk are uncertain. We evaluated total energy expenditure (TEE) in childhood cancer survivors using the doubly labeled water method in a cross-sectional study of 17 survivors of pediatric leukemia or lymphoma (median age 11.5 years). Mean TEE was 2,073 kcal/day, which was nearly 500 kcal/day lower than estimated energy requirements with recommended levels of physical activity. This energy gap is likely to contribute to the risk of obesity in this population and future trials are needed to assess implications and potential treatment strategies.

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INTRODUCTION

Childhood cancer survivors are at a high risk of becoming overweight or obese. Increases in weight occur early in treatment and are maintained throughout treatment and beyond.^{1–5} Obesity adds risk to the already elevated chronic health conditions in childhood cancer survivors,⁶ and can adversely impact survivors' morbidity and mortality.⁷ The causes of increased risk of obesity in childhood cancer survivors are speculative, and this knowledge is needed to for obesity prevention and treatment in this vulnerable population.

Obesity can result from reduced energy expenditure and/or increased energy intake (EI) but only a few studies have examined these factors in childhood cancer survivors.^{8,9} Self-reported energy expenditure is subject to bias but few studies of energy expenditure in childhood survivors have employed objective assessments of energy expenditure such as the doubly labeled water (DLW) method. The DLW method measures total energy expenditure (TEE) over an extended period (1–3 weeks) under free-living conditions, and is the reference method for measuring TEE.^{10,11} The DLW method is highly accurate, does not depend on subjects' cooperation or memory, requires no restrictions on subjects' daily activities, and can therefore accurately reflect children's habitual energy expenditure.

Total energy expenditure is the sum of resting energy expenditure (REE), diet-induced thermogenesis (DIT), and energy expended on physical activity, i.e., activity energy expenditure (AEE).¹² In children, growth also accounts for 1–2% of TEE. However, in children who have survived cancer or are undergoing cancer treatment, factors related to the underlying or other diseases, cancer treatment, or survivorship might also influence total energy expenditure. In weight stable persons TEE equals EI. However, commonly used methods to assess dietary intake are known to have poor accuracy in estimating the absolute value of total EI.^{13,14} The DLW method represents the only accurate method to measure TEE in free living humans. In this pilot study, we measured the TEE in survivors of childhood acute lymphoblastic leukemia (ALL) and lymphoma using the DLW method, and compared TEE data to the Estimated Energy Requirement (EER), established by the Institute of Medicine as part of the Dietary Reference Intakes.¹⁵ In addition, we explored whether the energy expenditure in childhood cancer survivors differed by patient and treatment characteristics.

PATIENTS AND METHODS

We conducted a cross-sectional study to evaluate levels of TEE in childhood cancer survivors. Eligible participants were identified from the records of the Pediatric Hematology/Oncology Clinic of the Floating Hospital for Children at Tufts Medical Center, Boston, MA. To be eligible, patients had to (1) be diagnosed with ALL or lymphoma at age younger than 21 years, (2) be between the ages of 3–25 years at study enrollment, and (3) have completed all cancer treatment within the past 15 years and. (4) be in remission or on-treatment receiving maintenance therapy. Exclusions included relapse, allogeneic bone marrow transplant, conditions known to influence food intake or energy expenditure, or pregnancy or lactation.

Demographic variables and medical history (including receipt of cranial radiation therapy, CRT) were extracted from medical records. Non-fasting weight was measured in light clothing, without shoes, on a standing scale to the nearest 0.1 kg. Height was measured using a wall-mounted stadiometer to the nearest 0.1 cm. Body composition including fat-free mass (FFM), fat mass (FM), and percent of body fat (%BF) were assessed by whole body dual x-ray absorptiometry (DEXA) (Hologic Discovery A. software version 12.6, Hologic Inc., Bedford, MA). FFM was calculated as the sum of lean body mass and bone mineral contents. FM was calculated as the difference between total weight and FFM. Percent BF was calculated as the percentage of FM divided by total weight. Dietary intake was assessed by a set of three 24-hour diet recalls (two weekdays and one weekend day) as well as a self-administered Block food frequency questionnaire. The initial 24-hour diet recall was administered in person and two additional unannounced recalls were conducted by phone within seven days of the first recall. Dietary recalls were conducted by trained staff using the standardized multiple pass method developed for national dietary surveillance.^{16,17} Dietary recall data were analyzed using the Nutrition Data System for Research software (NDSR, version 2011), developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN.

The study was approved by the institutional review board at Tufts Medical Center/Tufts University. All subjects provided informed consent prior to enrollment, and if under 18 years of age, parent consent and child assent were obtained.

Total Energy Expenditure (TEE)

TEE was measured using the DLW method. Participants completed two study visits approximately one week apart: at the first visit, participants provided a baseline urine sample and then received orally 0.08g of $^2\text{H}_2\text{O}$ at 99.9 atom % and 1.25g/kg of H_2^{18}O at 10% per kg of body weight, and two post-dose urine samples were collected at 4 and 5 hours; one week after dosing, the final post-dose urine sample was collected. All urine samples were shipped on dry ice to the USDA/ARS Children's Nutrition Research Center in Houston, TX for mass spectrometry measures.¹⁸ Carbon dioxide production rate (VCO_2) was calculated from the fractional turnover rates of ^2H and ^{18}O using the equation of Schoeller¹¹ with TEE based on an energy equivalent of a liter of CO_2 to be $3.815/\text{RQ} + 1.2321$ according to Ravussin et al.¹⁹ Respiratory quotient (RQ) was assumed to be 0.86.²⁰ Reliability of the TEE measurements was assessed by analyzing two duplicate samples collected from the same participant. The results were highly reproducible with a correlation of 0.98.

Statistical Analysis

TEE (kcal/day) was evaluated in association with demographic and treatment characteristics of using Analysis of Variance (ANOVA). We then assessed the association between TEE and anthropometrics including weight, body mass index (BMI) z-score, FFM, and % BF. BMI z-score was calculated using the 2000 Center for Disease Control and Prevention (CDC) growth charts for children.²¹ Obesity was defined as BMI z-score ≥ 1.645 (95th percentile), overweight as BMI z-score $= 1.036$ – 1.644 (85th–94.9th percentile), healthy weight as BMI z-score $= -1.645$ – -1.035 (5th–84.9th percentile), and underweight as BMI z-

score < -1.645 ($<5^{\text{th}}$ percentile), based on the current recommendations of the US CDC²² and in accordance with previous studies.²³ To control for the effect of body weight and FFM on TEE, TEE per kg of weight and per kg of FFM were calculated.

Last, we compared the mean difference between TEE and EER using a paired t-test. EER was estimated using the national equations by the IOM.¹⁵ EER is calculated based on age, gender, height, weight, physical activity level, and energy requirement for growth. We calculated EER assuming the recommended active healthy physical activity level. All statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

RESULTS

Clinic records identified 67 eligible patients. An informational letter about the study was sent to potential participants. The letter contained an opt-out card, which, if returned, would preclude further contact by study staff. Five patients returned the opt-up card, 12 declined to participate during follow-up contacts, 28 did not respond after attempts to contacts by phone or mail, resulting in 22 patients enrolling in the study between October 2011 and June 2012. Of the 22 enrolled participants, five were not able to return for the last urine sample collection required for the TEE assessment, so 17 participants with complete urine samples were included in this analysis (Figure 1).

The median age at enrollment of all participants was 11.5 years (range: 4.7–22.3) (Table 1), with males (77%) and non-Hispanic whites (77%). The median age at cancer diagnosis was 4.0 years (range: 0.9–15.1). The median interval from cancer diagnosis was 5.8 years (range: 2.3–17.0). The mean BMI z-score at study enrollment was 1.0 (SD = 0.9), corresponding to the 84th BMI percentile. No survivors were underweight, while 12% were overweight and 35% were obese. The mean FFM was 35.4 (SD=16.4) kg, and the mean %BF was 29.0 (SD=7.4).

Mean TEE was 2,073 (SD = 665) kcal/day. TEE was positively associated with body weight and FFM (Pearson $r = 0.84$ and 0.90 respectively, both $p < 0.001$) and with age (Pearson $r = 0.84$, $p < 0.001$). Young survivors had higher TEE per kg of weight than older survivors (56 vs. 39 kcal/day/kg, $p = 0.01$) (Table 2). Survivors who received CRT had a significantly lower TEE per kg of weight than survivors who did not receive CRT (29 vs. 50 kcal/day/kg, $p = 0.049$). Other demographic and cancer-related variables were not significantly correlated with TEE.

Childhood cancer survivors had a significantly lower level of TEE than predicted EER with recommended physical activity level. The difference between TEE and EER was -491 (95% CI: -686 , -295 , $p < 0.0001$) kcal/day (Figure 2). TEE remained significantly lower than EER after adjustment for body weight, -12 (95% CI: -16 , -7 , $p < 0.0001$) kcal/day.

DISCUSSION

Childhood cancer survivors are known to be at a high risk for obesity. However, the role of low energy expenditure versus high energy intake developing obesity for childhood cancer survivors is poorly understood. Our study is only the second to assess TEE in childhood

cancer survivors using DLW.²⁴ Our results indicated that childhood cancer survivors have an energy deficit of nearly 500 kcal/day compared to the estimated energy requirement.

The TEE we observed in 17 childhood cancer survivors (2,173 kcal/day) with a median age of 11.5 years was similar to that (2,150 kcal/day) reported in a previous study by Reilly et al. that assessed 20 British survivors of pediatric ALL with a mean age of 10.9 years.²⁴ In another study by Warner et al. of 34 British survivors of pediatric ALL with a similar age (12.3 years), the TEE was 1,557 kcal/day,²⁵ much lower than that in our study and the study of Reilly et al.²⁴ This difference may be explained by the different methods used to assess TEE: both our study and the study of Reilly et al. used the DLW method to assess TEE whereas the study of Warner et al.²⁵ estimated TEE by adding REE assessed by indirect calorimetry and AEE by heart rate monitoring. Compared to other methods measuring energy expenditure such as accelerometers, physical activity questionnaires and heart rate monitors, the DLW method offers a direct and highly accurate assessment on total energy expenditure and does not depend on human's recall or indirect derivations from its components.¹¹

Reduced TEE may result from decreased REE, AEE or DIT. Although we did not directly measure REE in our study, existing evidence does not support an important role for REE in development of obesity in childhood cancer survivors. Three prior studies found no alteration in REE in childhood cancer survivors,^{26–28} and in the two studies reporting a slightly reduced REE in survivors of childhood cancer,^{24,25} the magnitude of the reduction in REE was far less than could explain the difference between EER and TEE that we observed. Survivors are also unlikely to have reduced energy expenditure from DIT because the main dietary macronutrient composition (protein: 15%, carbohydrate: 52%, and fat: 33%) of the survivors, as measured by multiple 24-hour diet recalls in our study, was within the typical range for Americans and within the ranges recommended by the 2010 Dietary Guidelines for Americans. In children and adolescents, the reduction in TEE may reflect reduced energy cost associated with growth deficiency. However, survivors in our study did not have reduced height (mean height z-score = 0.5, $p = 0.69$).

AEE is the most variable part of TEE. Low levels of TEE in childhood cancer survivors are most likely explained by their low levels of physical activity. When Schofield equations²⁹ were used to estimate basal metabolic rate (BMR), the physical activity level (PAL) of our study participants, expressed as the ratio of TEE/BMR, was close to the lower end of the “low active” physical activity categories (i.e., PAL=1.4). This suggests that childhood cancer survivors are largely sedentary. Future DLW studies in this population should ideally also include measures of BMR (essentially identical to REE) and AEE so that remaining questions regarding the associations between the components of TEE and reduced TEE can be directly assessed.

Similar to previous studies,^{24,25} our study also found that TEE in childhood cancer survivors is strongly correlated with FFM. The correlation is similar to, if not stronger than, what has been reported in the general population of healthy children.³⁰ This may imply that the reduced levels of energy expenditure in childhood cancer survivors are due to reduced FFM.

However, our study was too small to allow for comparison with age and gender matched levels of TEE.

Our study provided direct evidence that childhood cancer survivors' daily TEE is below the EER for the recommended level of physical activity. The energy gap we identified could be partially addressed by promoting an average of 60 minutes a day of moderate-to-vigorous physical activity such as brisk walking and swimming (~250 – 400 kcal/day). However, if the energy deficit we observed was due to reduced FFM, there may be potential benefit of both aerobic and resistance exercise to reduce FM and increase FFM. Physical activity alone may be insufficient to increase TEE by an average of 500 kcal/day. Thus reduction of EI may also be needed to achieve energy balance in childhood cancer survivors.

Our study has limitations. The cross-sectional design does not permit causal inferences on the relationship between reduced TEE and obesity in childhood cancer survivors. Given weight gain occurs early in treatment, it is important to longitudinally study energy balance during and after cancer treatment in order to identify a sensitive window for weight gain that can be targeted in future interventions. The DLW method requires multiple urine collections, and we had nearly 25% of the families failing to provide the last urine sample. Childhood cancer is a rare disease and many survivors do not regularly attend long-term follow-up visits. All of these pose challenges in assessing TEE using the DLW method in this population. We were unable to ascertain an impact of CRT on TEE since only two of our study participants were treated with CRT. However, use of CRT is decreasing in contemporary treatment protocols and an increasing number of studies have reported a high rate of obesity in survivors treated without CRT.³¹ Although hypothalamic-pituitary axis abnormalities have been observed in childhood cancer survivors,³² the link between energy balance and biological mechanisms for obesity remains to be studied in this population. Future studies with a prospective design and a larger sample size, preferably incorporating biomarkers of growth and energy regulation, are required to further elucidate the mechanisms and implications of low TEE in childhood cancer survivors.

Despite these limitations, our study is one of the few studies assessing TEE in childhood cancer survivors using the DLW method, an accurate and objective method of measuring habitual energy expenditure. Our results suggest that childhood cancer survivors have low levels of total energy expenditure. Future studies are needed to determine if the energy gap can be addressed by physical activity in combination with dietary modification to achieve energy balance and prevent obesity in this at-risk population.

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Figure 1.
Study Flow Chart

Panel A

Panel B

Figure 2.

Bland and Altman plot of the difference between total energy expenditure (TEE) and estimated energy requirement (EER) with recommended amount of physical activity in 17 childhood cancer survivors. Panel A: The mean difference between TEE and EER is -491 (95% CI: -686, -295) kcal/day; Panel B: The mean difference between TEE and EER after adjusting for body weight is -12 (95% CI: -16, -7) kcal/day per kg of weight.

Table 1

Characteristics of childhood cancer survivors, the Healthy Living Study, 2011–2012

Characteristics	
Age at study enrollment, <i>years</i> , median (Q1, Q3)	11.5 (7.5, 14.8)
Gender, n (%)	
Male	13 (76.5)
Female	4 (23.5)
Race/ethnicity, n (%)	
Non-Hispanic white	13 (76.5)
Other	4 (23.5)
Treatment status, n (%)	
On-treatment	2 (11.8)
Off-treatment	15 (88.2)
Age at diagnosis, <i>years</i> , median (Q1, Q3)	5.1 (2.3, 5.9)
Years since diagnosis, median (Q1, Q3)	6.8 (2.8, 8.3)
BMI z-score, mean (SD)	1.0 (0.9)
Weight status, n (%)	
Healthy weight	9 (52.9)
Overweight/obese	8 (47.1)
Fat-free mass, <i>kg</i> , mean (SD)	35.4 (16.4)
Percentage of body fat (SD)	29.0 (7.4)

Table 2

Total energy expenditure (TEE) (kcal/day) in childhood cancer survivors by demographic and treatment characteristics

	n	TEE (kcal/day)	P value *	TEE per kg of weight (kcal/day/kg)	P value *
Mean (SD)					
Age at study, years					
< 11.5	9	1,571 (258)		56 (14)	
11.5	8	2,637 (498)	<0.0001	39 (8)	0.01
Sex					
Male	13	2,135 (729)		48 (16)	
Female	4	1,870 (405)	0.50	46 (7)	0.81
Race/ethnicity					
Non-Hispanic white	13	2,175 (684)		46 (12)	
Other	4	1,741 (546)	0.27	53 (22)	0.44
Age at diagnosis, years					
< 4.5	9	1,891 (736)		54 (15)	
4.5	8	2,278 (550)	0.24	42 (11)	0.08
Years since diagnosis					
< 10	7	1,955 (616)		50 (14)	
10	3	2,623 (727)	0.12	36 (11)	0.12
Treatment status					
On-treatment	2	1,390 (164)		65 (11)	
Off-treatment	15	2,164 (655)	0.13	46 (14)	0.08
Cranial radiation					
No	15	2,024 (693)		50 (13)	
Yes	2	2,440 (224)	0.42	29 (85)	0.049
Weight status					
Healthy weight	8	1,988 (657)		50 (10)	
Overweight/obese	9	2,168 (707)	0.59	45 (19)	0.44

* P values were obtained from ANOVA