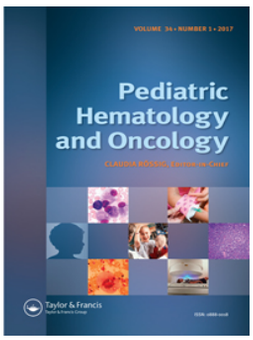

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Association of energy intake and expenditure with obesity: A cross-sectional study of 150 pediatric patients following treatment for leukemia

Richa Srivastava, Atul Batra, Deepa Dhawan, and Sameer Bakhshi

Department of Medical Oncology, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

ABSTRACT

Increased obesity in leukemia survivors has been attributed to chemotherapy and radiation. Data on total energy intake (TEI) and total energy expenditure (TEE) are lacking in obese childhood leukemia patients after completion of therapy from India. We conducted a cross-sectional study in pediatric acute leukemia patients after completion of therapy wherein energy intake was assessed by 24-hour recall method. TEE was calculated using Harris–Benedict equation, by assessing the physical activity level using Physical Activity Questionnaire for children and basal metabolic rate by World Health Organization equation. Indian Academy of Pediatrics 2015 guidelines for BMI were used for defining overweight and obesity. Nutritional status was assessed in 150 leukemia patients after completion of therapy. Twenty-five percent of leukemia patients after completion of therapy were overweight and obese versus 11% of healthy controls ($p = 0.042$). The mean ratio of TEI/required energy intake (REI), TEE/required energy expenditure (REE), and (TEI:REI)/(TEE:REE) were significantly higher in overweight and obese group versus nonobese survivors ($p < 0.001$, $p = 0.091$, $p < 0.001$, respectively). Multivariate analysis showed higher income (HR-2.3, $p = 0.04$), increased TEI/REI (HR-4, $p = 0.049$) and higher (TEI:REI)/(TEE:REE) (HR-3.1, $p = 0.039$) to be significant factors predicting obesity. Obesity in leukemia patients after completion of therapy is associated with increased energy intake, causing imbalance between energy intake and TEE in these patients.

Abbreviations: TEI: Total energy intake; TEE: Total energy expenditure; PAQ-C: Physical activity questionnaire for children; BMR: Basal metabolic rate; IAP: Indian academy of pediatrics; REI: Required energy intake; REE: Required energy expenditure; BMI: Body mass index; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; FAO: Food and Agriculture Organization; WHO: World Health Organization; UNU: United Nations University

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, associated with high cure rates of more than 80% in the Western population [1]. Late effects constitute a major health hazard in ALL survivors. Obesity is one such recognized late effect. The risk of

CONTACT Sameer Bakhshi sambakh@hotmail.com Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India.

cardiovascular diseases is increased with obesity and thus preventing obesity can prevent the associated morbidity and mortality [2]. Various reports have suggested increased propensity of obesity in ALL survivors [3–5]. Weight gain has been reported to start as early as interim maintenance phase [6]. The prevalence of overweight and obesity in this population has been reported from 11% to 57% with varying definitions of obesity [3]. Obesity in childhood acute myeloid leukemia (AML) survivors has not been systematically analyzed, possibly due to lower frequency of AML patients in pediatric age group and further to limited number of long-term survivors.

Steroid use is one of the reasons implicated for obesity in ALL patients after completion of therapy. Moreover, chemotherapy and cranial irradiation alter the hypothalamic–pituitary axis, which may cause obesity [4]. The current protocols use either no irradiation or minimal radiation to the brain, and the use of steroids early in the course may not be a major cause for obesity. Some studies have reported that female sex and young age at initial diagnosis predict occurrence of obesity in ALL patients after completion of therapy [5–8], but these findings are inconsistent [9–12].

There are no data from India on total energy intake (TEI) and total energy expenditure (TEE) in childhood leukemia patients after completion of therapy. This study was aimed at determining the prevalence of obesity in childhood leukemia patients after completion of therapy and the relationship, if any, between their nutritional status with TEI and TEE.

Material and methods

Patients and treatment

This was a cross-sectional study conducted in pediatric oncology outpatient of the cancer center at All India Institute of Medical Sciences, New Delhi between Jan 2010 and Sep 2012. The inclusion criteria included childhood leukemia patients (ALL and AML) who had completed treatment and are aged 5–18 years. The inclusion criteria for the control group included apparently healthy siblings of patients after completion of therapy with nearest age to the patient and aged 5–18 years. The Institute Ethics Committee approved the study, and informed consent was obtained from guardian before enrolment.

Patients with ALL were treated with induction, consolidation, re-induction followed by 18 months of maintenance therapy; cranial irradiation was administered as central nervous system prophylaxis at a dose 12 Gy to all patients aged older than 3 years. Patients with AML received "3+7" induction followed by 3 cycles of consolidation using high-dose cytosine arabinoside. Demographic and detailed socioeconomic data were recorded for each patient.

Assessment of nutritional status

Nutritional status was assessed by anthropometric assessment of the patients after completion of therapy including height (cm), weight (kg), and body mass index (BMI). Height was measured with the help of height measuring scale and rounded off to the nearest half cm. Weight was measured by a standardized analog weighing machine and rounded off to nearest kg. BMI was calculated from formula of weight (kg)/height (m) [2]. The BMI was then plotted on the Indian Academy of Pediatrics (IAP) BMI-for-age growth charts for girls and boys, respectively, to obtain a percentile ranking [13]. The cut-offs used for overweight and obesity were 23 and 27 as these are more appropriate for use in Asian children because Asians are known to have more adiposity and increased cardiometabolic risk at a lower BMI as per World Health

Organization (WHO) Expert Consultation [14]. Childhood leukemia patients after completion of therapy were grouped as "overweight and obese" or "nonobese."

Assessment of physical activity

A Physical Activity Questionnaire for children (PAQ-C) was used for determining physical activity level in children, which has been validated previously [15]. This questionnaire consists of 9 items, and each item has a 5-point response scale ranging from low (score of 1) to high activity (score of 5). Few activities were replaced in "physical activities or games" section in the questionnaire (rowing, tag, ice-skating, cross-country skating, and ice-hockey) by more commonly participated activities (cricket and kabaddi–a game of Indian origin, played between two teams of seven players, in which individuals take turns to chase and try to touch members of the opposing team without being captured by them). Physical activity level was graded as low, moderate, and high based on the average scores obtained from the questionnaire (1–2.33: low, 2.34–3.66: moderate, and 3.67–5: high).

Assessment of TEI

The 24-hour dietary recall for 3 consecutive days was used for obtaining the information on dietary intake. Mean value as obtained for 3 consecutive days before the medical visit was used for calculating TEI by "Diet Soft" software (www.dietsoft.in).

Assessment of TEE

Basal metabolic rate (BMR) of all the children was calculated using Food and Agriculture Organization/WHO/United Nations University equation based on the body weight in kilograms [16]. After determining BMR of individuals, Harris–Benedict principle was used to calculate TEE. Multiplication factors of 1.28, 1.55, and 1.8 were used for low, intermediate, and high activity levels, as determined by PAQ-C score. BMR multiplied by the multiplication factor provided the TEE.

Parameters used for assessing the role of TEI and TEE

The following parameters were compared to assess the role of TEI and TEE:

Ratio of total energy intake/required energy intake (TEI/REI): Recommended dietary allowances chart for Indians was used as reference for obtaining required energy intake (REI).

Ratio of total energy expenditure/required energy expenditure (TEE/REE): Required energy expenditure (REE) means energy requirement for maintaining the present body weight. To maintain body weight, it is necessary to balance the energy derived from food with that spent in physical activity. To lose weight, energy expenditure must exceed intake and to gain weight, energy intake must exceed expenditure. To maintain body weight, it is necessary to balance the energy derived from food with that expended in physical activity. REE used was the same as TEI for that patient.

Ratio of TEI/REI to TEE/REE: This was evaluated to assess the relative contribution of energy intake versus energy expenditure.

Statistical analysis

Descriptive statistics were used in the study including mean, median, range, and standard deviation for demographic characteristics and to evaluate the distribution of leukemia patients after completion of therapy and healthy controls according to grading of nutritional status.

For inferential statistics, Student's *t*-test and chi-square test were used to determine the differences between sample means and frequencies. The level of significance was set at 0.05. Student's *t*-test and chi-square test were used to compare the basic demographic characteristics with mean ratios of TEI/REI, TEE/REE and TEI/REI to TEE/REE in overweight and obese and nonobese groups. Multivariate analyses using logistic regression were performed to predict the factors associated with obesity in leukemia patients after completion of therapy. SPSS (version 19) was used for statistical analysis.

Results

One hundred fifty leukemia (122 ALL and 28 AML) and 38 sibling controls were assessed for nutritional status. The median age at diagnosis in the leukemia group after completion of therapy and siblings was 11 months (range, 6–19) and 12 months (range, 6–18), respectively. The male:female ratio was 3:1 in leukemia group after completion of therapy, compared to 3:2 in the sibling group. The median duration from completion of treatment was 36.8 months (range, 14–127); 37.8 months (27–127) for ALL patients and 20.2 (14–83) months for AML patients. As per the IAP guidelines 2015 BMI-for-age, 25% of the leukemia patients after completion of therapy were in overweight and obese group (30/122 [24.6%] ALL and 7/28 [25%] AML) versus 4/38 (11%) in healthy controls ($p = 0.042$). The prevalence of obesity was similar for ALL patients after completion of therapy for less than or more than 5 years (26/103, 25% vs 4/19, 26%, $p = 0.47$).

With respect to the leukemia patients after completion of therapy, obesity was associated with higher education status of both father and mother ("$p < 0.001$ for both") and higher income ($p = 0.003$) (Table 1).

Relationship of TEI and TEE with obese versus nonobese survivors

The mean ratio of TEI/REI and (TEI:REI)/(TEE:REE) were significantly higher in the overweight and obese leukemia patients group after completion of therapy versus the "nonobese" group of off-therapy patients leukemia ("$p < 0.001$ for both"), whereas no significant difference was observed in TEE/REE between the two groups (Table 2).

Factors associated with obesity

Baseline factors including age, sex, parent's educational status, father's occupation, income group, and energy-related variables (TEI/REI, TEE/REE, and TEI:REI/TEE:REE) were analyzed for association with obesity. A multivariate analysis on factors that emerged significant ($p < 0.1$) on univariate analysis was performed to predict the factors associated with obesity in leukemia patients after completion of therapy. Higher income, increased TEI/REI, and increased ratio of intake to expenditure emerged as significant factors (Table 3).

Table 1. Basic socioeconomic variables of overweight and obese versus nonobese (healthy) survivors.

Socioeconomic variables	Nonobese group ($N = 113$)	Overweight and obese group ($N = 37$)	P value (chi-square test)
Religion			
Hindu	99 (88%)	30 (81%)	0.214
Muslim	13 (11%)	5 (14%)	
Others	1 (1%)	2 (5%)	
Father's education			
Illiterate	9 (8%)	1 (2.5%)	0.007
High school	61 (54%)	11 (30%)	
>High school	43 (38%)	25 (67.5%)	
Mother's education			
Illiterate	23 (20%)	4 (11%)	<0.001
High school	43 (38%)	5 (13.5%)	
>High school	47 (42%)	28 (75.5%)	
Father's occupation			
Farmer	17 (15%)	2 (5.5%)	0.112
Businessman	26 (23%)	13 (35%)	
Servicemen	44 (39%)	19 (51.5%)	
Other	24 (21%)	3 (8%)	
NA	02 (2%)	—	
Mother's working status			
Working	17 (15%)	8 (21%)	0.375
Housewife	94 (83%)	29 (79%)	
NA	2 (2%)	—	
Income group (Rs./month)			
<5000	33 (30%)	3 (8%)	0.014
5000–10,000	67 (59%)	25 (67.5%)	
>10,000	13 (11%)	9 (24.5%)	

NA: Not Available; INR: Indian Rupees.

Table 2. Mean ratio of TEI, REI, TEE, and REE in "overweight and obese" survivors and "nonobese" survivors.

	Overweight and obese survivors N = 37 [mean/SD]	Non-obese survivors N = 113 [mean/SD]	P Value
TEI/REI	1.032 ± 0.22	0.83 ± 0.19	<0.001
TEE/REE	0.96 ± 0.16	0.91 ± 0.14	0.091
TEI/REI	1.07 ± 0.16	0.92 ± 0.16	<0.001
TEE/REE			

TEI, total energy intake; REI, required energy intake; TEE, total energy expenditure; REE, required energy expenditure.

Discussion

The increased prevalence of overweight and obesity in childhood leukemia patients after completion of therapy has been noted in many studies, and a recent meta-analysis confirmed the same observation [3–5]. This study also noticed an increased prevalence of obesity in this population as compared to the sibling controls, thus confirming the observation in Indian population. A recent systematic review reported that the prevalence of childhood overweight and obesity in Indian children is 19.3% [17]. Compared to this, the sibling group of our study had lower prevalence (11%) and leukemia group after completion of therapy had higher prevalence (25%). Lower prevalence in sibling group may be due to smaller sample size and demographic differences within India.

TEI and TEE are simple yet important concepts in obesity. An imbalance between the two, either increased intake or decreased expenditure or both cause weight gain. Whether the imbalance is caused predominantly because of increased intake or decreased expenditure of energy in leukemia patients after completion of therapy has not been assessed previously. One study till date in 20 ALL patients evaluated the TEE and concluded that decreased energy

Table 3. Multivariate for predicting obesity in acute leukemia survivors.

Multivariate analysis	OR	(95% CI)	*P* Value
Father's education			
Illiterate	1		
High school	1.41	(0.5–4.4)	0.61
>High school	1.22	(0.8–3.9)	0.32
Mother's education			
Illiterate	1		
High school	1.37	(0.6–3.9)	0.29
>High school	1.26	(0.4–2.9)	0.58
Father's occupation			
Farmer	1		
Businessman	0.8	(0.4–1.3)	0.51
Servicemen	1.1	(0.6–2.5)	0.36
Income group (Rs./month)			
<5000	1		
5000–10,000	1.8	(1.1–2.1)	0.03
>10,000	2.3	(1–5.4)	0.04
TEI/REI	4	(1–15.9)	0.049
TEE/REE	0.6	(0.2–2.3)	0.45
TEI/REI	3.1	(1.1–9.1)	0.039
TEE/REE			

OR: Odds Ratio; TEI: Total Energy Intake; REI: Recommended Energy Intake; TEE: Total Energy Expenditure; REE: Recommended Energy Expenditure.

expenditure is the predominant cause of obesity; however, this study was limited by small sample size [18]. In our study, both increased TEI/REI and increased (TEI:REI)/(TEE:REI) were found to be associated with obesity. Patients after completion of therapy belonging to higher income group had a significant predisposition to obesity in multivariate analysis. This may be due to the overprotective behavior of parents associated with unhealthy eating habits.

The demerits of the study include a cross-sectional design and predictive values of BMR and TEE, rather than direct measurements. However, it has been shown previously that the resting metabolic rate is not affected in ALL patients and hence predicted values can be used for the analysis [19]. The strength of this study is that this is first of its kind that evaluates the relative roles of energy intake and expenditure in predicting obesity in leukemia patients after completion of therapy.

To conclude, acute leukemia patients after completion of therapy have increased prevalence of overweight and obesity, which is associated with increased TEI/REI, resulting in an imbalance between energy intake and expenditure. Thus, diet counseling for appropriate energy intake and food faddisms should be a regular part of counseling in childhood leukemia patients after completion of therapy to prevent overweight and obesity.

Declaration of interest

The authors declare that they have no conflict of interest.

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