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Dietary intake and childhood leukemia: The Diet and Acute Lymphoblastic Leukemia Treatment (DALLT) cohort study

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Abstract

Objective—Children with acute lymphoblastic leukemia (ALL) are at elevated risk for nutrition-related morbidity both during and after therapy. We present the demographic characteristics and

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nutrient intake at study entry of a prospective cohort in which evaluating dietary intake in children diagnosed with ALL was investigated.

Methods—Dietary intake data were collected for participants enrolled on the Dana-Farber Cancer Institute ALL Consortium Protocol. Dietary intake was assessed with a food frequency questionnaire and was compared with the dietary reference intake by ALL risk group (standard and high risk).

Results—Dietary intake data were collected from 81% of participants (n = 640). We found that 27% of participants were overweight/obese. Intake of total calories and other nutrients exceeded the dietary reference intake in up to 79% of children. This was evident in both risk groups and was pronounced among younger children. For micronutrients, dietary intake of calcium, vitamin D (females only), and zinc differed significantly between patients with standard-risk and those with high-risk ALL.

Conclusions—This study was successful in collecting dietary intake data at the time of cancer diagnosis in a multicenter setting in a pediatric population at high-risk for nutrition-related morbidity. We identified “at-risk” dietary intakes, which vary by sex and ALL risk group; such patients may benefit from future dietary interventions.

Keywords

Dietary intake; Nutritional status; Micronutrient intake; macronutrient intake; Obesity; Pediatric oncology; Acute lymphoblastic leukemia

Introduction

Over the last 50 years, overall survival for children and adolescents with acute lymphoblastic leukemia (ALL) has increased from 10% to more than 90% [1]. This improvement in outcome was fostered by the establishment of cooperative research groups that have provided an infrastructure for the systematic collection of data and successful conduct of randomized clinical trials.

Despite the dramatic improvement in cure rates, treatment-related toxic effects remain a significant problem. Children and adolescents with ALL experience a spectrum of nutrition-related diseases or disorders during and after treatment. For example, a small retrospective review reported that during the initial phase of therapy (induction phase), nearly 35% of children and adolescents develop hypertriglyceridemia [2]. Others have reported that up to 68% of survivors of ALL have low bone mass [3], a percentage higher than that of the general population. Although reduced bone mass is due largely to the treatment for ALL, studies have suggested that poor dietary intake of nutrients may also contribute to bone morbidity. Tylavsky et al. reported that less than 30% of survivors met the recommended dietary intakes for bone-metabolizing nutrients, lower than reported in the general population [4]. Additionally, there are also data suggesting that modification of the diet may have an effect on the development of therapy-related toxicity [5,6]. ALL has also been described as a “preobese state” based on the increasing number of patients who develop obesity during and after treatment [7]. The impact of obesity is not trivial. Recent meta-analyses found that the presence of obesity at diagnosis is a poor prognostic indicator in

children and adults with leukemia [8–10]. In children with leukemia, those classified as obese at diagnosis have a 35% increased risk of mortality compared with those who are not obese [10]. Importantly, several studies have suggested that remediation of either under- or overweight during therapy eliminates the adverse association with survival [11,12].

To date, no large, prospective dietary studies have been performed in a homogenous pediatric population with cancer. Moreover, much of the published data on dietary intake in childhood cancer has been conducted in small, underpowered studies, preventing meaningful conclusions from being drawn. We present the baseline characteristics of a prospective cohort study describing dietary intake during cancer therapy among children with ALL. To the authors' knowledge, this study represents the largest dietary study performed in children and adolescents receiving cytotoxic therapy in a single-treatment regimen for a single diagnosis.

Materials and methods

Study objectives and participants

The Diet and Acute Lymphoblastic Leukemia Treatment (DALLT) study is a prospective cohort study exploring dietary intake at predefined points in treatment and the association of dietary intake with treatment-related toxicity in children and adolescents undergoing treatment for ALL and enrolled in a single clinical therapeutic trial. Children and adolescents (aged 1–18 y) with newly diagnosed ALL who were enrolled in Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocol 05-001 were eligible to participate in DALLT. Ten institutions in the United States, Canada, and Puerto Rico participated in DFCI ALL Consortium Protocol 05-001 (Supplementary Table 1). Details of this trial are described elsewhere [13]. The study was approved by the institutional review boards at all participating centers and was performed in accordance with the Helsinki Declaration. Informed consent for participation in DALLT was obtained from parents or guardians at the time of enrollment in DFCI ALL Consortium Protocol 05-001.

Clinical data collection

The DFCI ALL Consortium study coordinating center, located at DFCI, was responsible for the collection of ALL risk group (standard risk [SR] or high risk [HR]) [13], date of diagnosis, nutrition anthropometrics (height and weight), and therapy-related toxicity data obtained from each consortium center. The team of investigators at Columbia University Medical Center held primary responsibility for the collection, management, and analysis of all dietary data obtained through the food frequency questionnaires (FFQs) at each consortium center.

Dietary data collection and instruments

Dietary intake was measured at three points in therapy (Supplementary Table 2). A designated research assistant at each of the participating institutions administered the age-appropriate FFQ to study participants. Completed surveys were then processed by the research group at Columbia University Medical Center, in accordance with the guidelines set forth by the Channing Laboratory at Harvard University [14–16]. Two dietary instruments

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were administered to participants to gather information on dietary intake during the previous month, The Harvard Service Food Frequency Questionnaire (HSFFQ) [16] and the Youth and Adolescent Food Frequency Questionnaire (YAFFQ) [14, 15]. The HSFFQ was administered to children 5 y of age or younger and completed by the parent or guardian [16]. The YAFFQ was administered to children and adolescents 6 to 18 y of age and completed by the parent or patient. Both survey instruments were available in English, Spanish, and French, and surveys were completed in the parents' language of choice. The YAFFQ asks participants how often, on average, they consume each of the 131 foods listed, and food portion sizes are determined by comparison with national standard surveys and the "natural" serving size of foods (e.g., bread slice, apple). The HSFFQ contains 103 items, including 84 questions on foods and 19 questions on food habits and supplements. The reliability and validity of the instruments among healthy children and children diagnosed with a pediatric malignancy have been reported [5,6,14–16].

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For standardization of data collection, a medical nutrition therapy form was developed to collect information on the provision of enteral feeds (nasogastric feeds, gastrostomy tubes), oral nutrition supplements (e.g., Pediasure, Ensure), and total parenteral nutrition at each of the designated time points. The medical nutrition therapy form provided information on the brand of nutrition formula and the prescribed dose. The nutrients delivered by the scheduled dose were then calculated by the study's nutritionist at Columbia University Medical Center and manually added into the individual's dietary analysis produced by the FFQ. Detailed nutrient information on patients who received total parenteral nutrition was not available. Use of total parenteral nutrition was captured by institutions indicating its administration at the time point as "yes" or "no."

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Classification of dietary intake

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The dietary reference intakes (DRIs) are the most widely used reference guide for determining the adequacy of individual and group diets and provide a systematic framework within which dietary data, obtained in individuals or groups, may be compared. For the present study, dietary intakes of children with ALL were compared with the values set forth by the DRIs of the Institute of Medicine, National Academy of Sciences [17]. For calories, reference values for dietary intakes were calculated for each age and sex category assuming a sedentary activity level. Caloric intake for each patient was classified into four groups: 1) under caloric intakes, which are lower than the recommended values by more than 10%; 2) met caloric intakes, which are within 10% of recommended values; 3) caloric intakes that exceed the recommended values by more than 10% to 24%; and 4) caloric intakes that exceed the recommended values by more than 25%. Dietary intakes for fat, protein, and carbohydrate were classified according to the acceptable macronutrient dietary ranges (AMDRs), which are macronutrient distribution ranges as a percentage of total calories [17]. For micronutrients, recommended daily allowances (RDAs) for micronutrient intakes, by age and sex, were classified into three categories (under, met, or exceeded). Dietary intake greater than the RDA was classified as dietary intake at or greater than the upper tolerable limit as indicated in the DRIs.

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Demographic and anthropometric data

All participating centers provided information on demographic characteristics as part of the standardized data collection procedures described in the treatment protocol. Demographic variables were collected from the medical chart and included country of residence, date of birth, sex, race, and ethnicity. Height and weight were abstracted from the medical records. Body mass index (BMI) percentile for age and sex were determined per guidelines from the Centers for Disease Control for children and adolescents between 2 to 17 y of age [18]. For participants younger than 2 y, weight for length percentile was determined for children whose height was greater than 77 cm.

Statistical considerations

In this article, we report on dietary intake of participants at study entry (diagnosis). Demographic information was screened and then summarized by using descriptive statistics for the entire cohort ($n = 794$), baseline survey completers ($n = 640$), and baseline survey non-completers ($n = 154$). We removed 14 cases from baseline dietary analysis because the data met outlier criteria (± 3 SD from the mean caloric intake by age and sex), intakes did not appear to be credible, or participants completed the incorrect survey, which resulted in 626 cases with dietary data at study entry. All demographic variables were nominal; hence frequencies and proportions were reported for the categorical variables and the associations between them were assessed with Pearson's χ^2 test. Little's Missing Completely at Random test was also performed to evaluate the missing data pattern at baseline.

The Mann–Whitney U test was used to quantify the association by sex in DRI-classified nutrient intakes between leukemia risk groups at diagnosis. Considering the aim of the present study was to describe the baseline characteristics of the participants as opposed to testing a statistical hypothesis, we did not adjust for multiple comparisons. Statistical analysis was conducted with SPSS Version 20 software (IBM, Armonk, NY). A P value 0.05 was considered to indicate statistical significance.

Results

Demographic characteristics at study entry

The demographic characteristics of the 794 evaluable participants at time 1 are summarized in Table 1. Of the 794 children and adolescents recruited into the treatment study, dietary data at diagnosis were obtained on 81% of the study cohort ($n = 640$). A total of 154 surveys were not collected at time 1. Reasons for missing data include administrative errors ($n = 91$); failure of parent or participant to complete dietary survey ($n = 37$); change in clinical condition of the participant, including death, change in diagnosis, or revised treatment plan ($n = 13$); or other circumstances ($n = 13$).

The demographic characteristics of the dietary cohort ($n = 640$) were reflective of features typically associated with childhood ALL [19], including a slight male predominance (56%), a higher proportion of patients considered to be standard risk (58%), and younger age at diagnosis (72% ≤ 8 y old). Classification of the cohort by BMI percentile revealed that the majority of participants were within a normal weight classification at diagnosis, and 27%

were classified as either overweight or obese. Pearson's χ^2 test of demographic variables of completers and non-completers of the dietary survey revealed significant differences in the distribution of ethnicity, language, and institution location between the two groups ($P < 0.001$ for each). Furthermore, investigation of missing data with Little's Missing Completely at Random test suggested that the data were missing completely at random ($\chi^2 = 0.87$, $df = 49$, $P > 0.05$, data not shown).

Dietary intake at study entry

Figure 1 illustrates mean caloric intake by age and sex in comparison to DRIs. At each age, mean caloric intake was greater than the DRI; however, this disparity was most apparent for younger children compared with the adolescent group.

Caloric and macronutrient intake was examined further by comparing dietary intake with DRIs and AMDRs, with respect to risk group, age, and sex (Table 2). For total caloric intake, no significant differences were observed between SR and HR ALL for both males and females ($P = 0.30$, $P = 0.98$, respectively). For males, significant differences between SR and HR ALL were found in the proportions of participants who were under, met, or exceeded the AMDRs for carbohydrate and fat ($P = 0.04$ and $P < 0.001$, respectively). At diagnosis, we found similar proportions of children with SR and HR ALL within the AMDRs for most macronutrients, a finding that was counterintuitive considering the increased leukemic burden and/or disease aggressiveness associated with HR ALL. A notable finding was the proportions of males not meeting or exceeding the AMDR for fat intake ($P < 0.001$). A greater proportion of males with SR ALL were in the "under" category, whereas a greater proportion of males with HR ALL were in the "exceeded" category, but similar proportions were observed for the "met" category. No significant differences in dietary intake of fat were observed between females with SR ALL and those with HR ALL.

For micronutrients, there were no significant differences in dietary intake of vitamins C and E between participants with SR ALL and those with HR ALL. However, evaluation of dietary intake of zinc revealed that for both males and females with SR ALL, proportionally more participants either met or were above the DRI ($P < 0.001$; $P < 0.001$, respectively), with a small proportion under the DRI. We observed a significant difference in the dietary intake of vitamin D between females with HR ALL and those with SR ALL ($P = 0.02$), but not in males ($P = 0.15$). Compared with females with HR ALL, more females with SR ALL did not meet the DRI for vitamin D. A clinically important finding was that for vitamin D, greater than 90% of participants in almost every group were under than the DRI. For calcium, proportionally more children with HR ALL were in the under category while proportionally more children with SR ALL were in the met category. The uneven calcium DRI distribution between risk groups was observed in both males and females ($P = 0.03$ and $P = 0.02$, respectively).

Discussion

To the authors' knowledge, our study is the first prospective dietary study performed in a large cohort of children and adolescents receiving a uniform treatment for ALL. The study

was successful in illustrating the acceptability and feasibility of performing dietary assessment at diagnosis in children and adolescents undergoing treatment for cancer. Collection of dietary data was achieved in the majority of participants, with response rates similar to those of other studies assessing diet in individuals with cancer [20]. The baseline characteristics of participants that completed the dietary surveys were comparable to the demographic characteristics of childhood ALL, suggesting that the cohort is reflective of the larger population of children with ALL. Although significant differences were observed between completers and non-completers, missing data analysis revealed that this was random, suggesting that the survey completers are representative of the entire cohort. Successful collection of dietary information from children diagnosed with both SR and HR ALL further strengthens the investigators' ability to compare dietary intake between the risk groups and, thus, examine the relationship of diet with different intensities of therapy.

We found that BMI percentile at diagnosis was similar to published data from other group studies. At diagnosis, 27% of our cohort were either overweight or obese, a figure slightly lower than that in one study [21], but similar to those in other studies [12,22,23]. Simultaneously, we found that 7% of children and adolescents were classified as underweight, compared with the 16% underweight at diagnosis reported in two other studies [22,24]. Our results are similar to those of one recent report of children participating in a treatment study for HR ALL sponsored by the Children's Oncology Group [12]. The National Health and Nutrition Examination Survey reported that 17.3% of children were classified as obese and 32.2% as overweight [18], whereas 13% of participants in DALLT were obese and 14% were overweight. The disease process might plausibly contribute to the classification of a smaller proportion as overweight, or the geographic and ethnic distribution of our cohort may be responsible. These findings are intriguing and are the focus of ongoing analysis, particularly in the light of recent data correlating BMI percentile with mortality in children with ALL [8,10].

Evaluation of dietary intake at diagnosis revealed that children and adolescents with ALL are meeting the DRIs suggesting the children participating in this study were well nourished when diagnosed with ALL, before the initiation of corticosteroid therapy. Moreover, we found that the majority of participants exceed the recommended calories, a finding supported by some studies [7,25,26] but not others [27,28]. However, it should be recognized that most studies reporting on dietary intake during treatment for childhood ALL are small and do not involve children treated with modern protocols. Importantly, the finding that most children with ALL have an excessive caloric intake at diagnosis suggests the need for early nutritional intervention, as this may reduce the risk of nutrition-related diseases throughout the 2-year treatment.

Interesting findings were observed in the proportion of HR compared to SR children that were under, met, or above the DRI for zinc. High or low dietary intakes may have clinical relevance to the development of infections, a serious complication of treatment for ALL. The implication of excess zinc intake on therapy-related toxicities requires further investigation, as up to 60% of respondents were above the RDA for this nutrient. Finally, the clinical implication of the combination of low calcium and vitamin D dietary intake is related to the development of bone morbidity warrants further study. This observation was

especially pronounced among children with HR ALL, a population composed primarily of older children and adolescents, and a group that has been reported to be at higher risk for development of bone complications [29,30].

There are several limitations to the described study. Our decision to set the RDA as the reference value rather than the estimated average requirement may lead to overestimation of the numbers of children and adolescents not meeting the RDA. There remains controversy over which reference value is best suited for the evaluation of populations with a chronic disease [31–33]. Moreover, neither reference value considers the risk factors associated with childhood ALL. The goal of this study was to identify dietary risk factors amenable to intervention, thus maximizing the potential benefit of dietary intervention on clinical outcomes. Our study administered the FFQ for the measurement of dietary intake due to the ease of its use in a multi-center study. The FFQ was designed to be self-administered, which was particularly relevant for institutions without access to a trained dietitian or adequate research staff to administer the survey in person. Despite the use of this tool, overreporting appears to be limited, given that reported nutrient intakes in this study were similar to those of previous reports [5]. Our study did not account for other lifestyle factors affecting dietary intake such as physical activity; therefore, comparison with the DRIs for calories assumed a sedentary lifestyle for patients at time of diagnosis of ALL. This weakness was minimized by the categorization of dietary intake by age and sex, which inherently controls for confounding variables related to energy intake such as sex, age, height, lean mass, physical activity, and metabolic efficiency, per the national standards [34]. The assumption of a sedentary lifestyle shortly before diagnosis is also not an unreasonable assumption because of the clinical signs and symptoms that precipitate a diagnosis of childhood ALL.

DALLT was designed to provide an understanding of how fluctuations in dietary intake during therapy affect the development or severity of therapy-related toxic effects in children with ALL. The National Cancer Institute has highlighted the importance of studies of this nature, especially studies conducted on a homogenous cohort of patients with restrictive eligibility criteria and ability to correlate nutritional indices with meaningful clinical and patient outcomes [35]. Thus, DALLT represents a unique data set in which investigators will be able to examine the role of diet during cancer therapy. The results reported here describe dietary intake of the cohort at diagnosis. Subsequent analyses will extend the described analysis, particularly to include associations with toxicity and outcomes in ALL. The results of DALLT may identify at-risk patterns of dietary and nutrient intake that may serve as targets for future dietary intervention clinical trials in children with cancer.

Conclusions

We describe dietary intake and nutritional status, defined by BMI percentile, in a cohort of children with ALL. Our study found that most children with ALL are not malnourished at diagnosis. In fact, the majority of children exceeded caloric recommendations for intake of calories and select micronutrients, despite the disease process of ALL. This finding was counterintuitive and will be the subject of future investigation. Variations in dietary intake were observed with respect to SR and HR ALL, suggesting that disease characteristics may have an effect on dietary intake at diagnosis. Subsequent studies will determine if these

relationships persist throughout treatment and determine if “at-risk” groups stand to benefit from proactive dietary intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Mean caloric intake by age and gender.

Table 1

Demographic characteristics at study entry

Demographic	Total (N = 794)		Complete survey (N = 640)		Did not complete survey (N = 154)		P value*
	No	%	No	%	No	%	
Sex							
Male	444	56%	359	56%	85	55%	0.84
Female	350	44%	281	44%	69	45%	
Age							
1–3 y	308	39%	248	39%	60	39%	0.46
4–8 y	262	33%	213	33%	49	32%	
9–13 y	137	17%	114	18%	23	15%	
14–18 y	87	11%	65	10%	22	14%	
Ethnicity							
White, non-Hispanic	507	64%	425	66%	82	53%	<0.001
Hispanic (white, Hispanic; other, Hispanic)	142	18%	120	19%	22	14%	
Black (non-Hispanic, African-American, black)	38	5%	25	4%	13	8%	
Asian	24	3%	16	3%	8	5%	
Other (non-Hispanic, other, Alaskan, American/Indian)	83	10%	54	8%	29	19%	
Language [†]							
English	415	59%	360	56%	55	83%	<0.001
Spanish	87	12%	85	13%	2	3%	
French	204	29%	195	31%	9	14%	
Risk group							
Standard	456	57%	372	58%	84	55%	0.42
High	338	43%	268	42%	70	45%	
Geographic location							
Continental US	429	54%	322	50%	107	69%	<0.001
Canada	308	39%	264	41%	44	29%	
Puerto Rico	57	7%	54	9%	3	2%	
BMI at diagnosis [‡]							

Demographic	Total (N = 794)		Complete survey (N = 640)		Did not complete survey (N = 154)		P value*
	No	%	No	%	No	%	
<5% (underweight)	58	7%	44	7%	14	9%	0.38
6–84% (normal)	508	65%	417	66%	91	61%	
85–94% (overweight)	120	15%	92	14%	28	19%	
>95% (obese)	100	13%	83	13%	17	11%	

BMI, body mass index

* Statistical comparisons were made using the Pearson's χ^2 test. Percentages were rounded to the nearest whole number and may not total 100%.

† Primary language information was missing for 88 patients because they did not complete dietary surveys at any point.

‡ BMI information was missing for 8 patients at diagnosis because their heights were <77 cm.

Table 2

Proportion classified as not meeting, meeting, or exceeding DRIs by risk group* (N = 626)

Nutrient	Male		Female		P value [†]
	Standard risk	High risk	Standard risk	High risk	
Calories					
Did not meet	35 (19%)	34 (21%)	33 (19%)	14 (14%)	0.98
Met	12 (6%)	14 (9%)	4 (2%)	7 (7%)	
>10–24% DRI	26 (14%)	23 (14%)	22 (13%)	14 (14%)	
>25% DRI	116 (61%)	90 (56%)	117 (67%)	65 (65%)	
% Calories carbohydrate					
Did not meet	7 (4%)	10 (6%)	6 (3%)	2 (2%)	0.83
Met	166 (88%)	145 (90%)	161 (92%)	95 (95%)	
Exceeded	16 (9%)	6 (4%)	9 (5%)	3 (3%)	
% Calories fat					
Did not meet	49 (26%)	21 (13%)	40 (23%)	14 (14%)	0.18
Met	124 (66%)	110 (68%)	124 (71%)	80 (80%)	
Exceeded	16 (9%)	30 (19%)	12 (7%)	6 (6%)	
% Calories protein					
Did not meet	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.13
Met	186 (98%)	161 (100%)	172 (98%)	100 (100%)	
Exceeded	2 (1%)	0 (0%)	4 (2%)	0 (0%)	
Vitamin C (mg)					
Did not meet	8 (4%)	11 (7%)	13 (7.4%)	12 (12%)	0.20
Met	181 (96%)	150 (93%)	163 (92.6%)	88 (88%)	
Exceeded	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Vitamin E (mg)					
Did not meet	148 (78%)	118 (73%)	136 (77%)	70 (70%)	0.18
Met	41 (22%)	43 (27%)	40 (23%)	30 (30%)	
Exceeded	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Zinc (mg)					
Did not meet	5 (3%)	12 (8%)	8 (5%)	10 (10%)	<0.001

Nutrient	Male		Female		P value [†]
	Standard risk	High risk	Standard risk	High risk	
Met	86 (46%)	102 (63%)	63 (36%)	54 (54%)	
Exceeded	98 (52%)	47 (29%)	105 (60%)	36 (36%)	
Calcium (mg)					
Did not meet	62 (33%)	72 (45%)	55 (31%)	45 (45%)	0.02
Met	126 (67%)	87 (54%)	121 (69%)	55 (55%)	
Exceeded	1 (1%)	2 (1%)	0 (0%)	0 (0%)	
Vitamin D (IU)					
Did not meet	179 (95%)	146 (91%)	167 (95%)	87 (87%)	0.02
Met	10 (5%)	15 (9%)	9 (5%)	13 (13%)	
Exceeded	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

DRIs, Dietary Reference Intakes

* Classifications of dietary intake were based on the DRIs by age and sex.

[†] Statistical comparisons were performed using the Mann–Whitney *U* test. Percentages were rounded to the nearest whole number and may not total 100%.