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Obesity and Acute Lymphocytic Leukemia

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OBESITY AND ACUTE LYMPHOCYTIC LEUKEMIA

by

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ABSTRACT

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Obesity rates for pediatric acute lymphocytic leukemia (ALL) survivors vary from 11%-57%. The purpose of this study was to evaluate the relationship between caloric and macronutrient intake on the incidence of obesity in survivors of pediatric ALL. A retrospective study of 137 participants using existing data collected from the Bone II study was evaluated. Participants were grouped into categories based on BMI for adults and CDC growth charts for children. Data was collected from 24 hour food recalls at time of enrollment. No statistical significance was found between BMI groups. Forty percent of participants were overweight or obese, but 69% were below the DRI for calorie intake. Half the participants consumed above the AMDR for percentage of calories from fat and 96% of participants consumed above the AMDR for percentage of calories from sugar. Based on these findings there is no association between obesity status and caloric and macronutrient intake.

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CHAPTER I

REVIEW OF LITERATURE

Introduction

Adult obesity rates are increasing rapidly with rates in many states doubling and tripling since 1989. Childhood obesity is following a similar trend with obesity rates increasing from 6.5% in 1980 to 17% in 2006 (1). Obesity is linked with several health-related consequences including cardiovascular disease, asthma, hepatic steatosis, sleep apnea, diabetes, and psychosocial risks such as early and systemic social discrimination (1). As a way to combat the widespread prevalence of obesity, many health-focused, obesity prevention programs have been implemented by public health organizations. However, one group often not considered are those with acute or chronic illness, particularly those with childhood illnesses. Obesity rates for pediatric acute lymphocytic leukemia (ALL) survivors vary from 11%-57% (2). In these survivors, obesity compounds the known increased risks for developing type 2 diabetes, hypertension, dyslipidemia, glucose intolerance, and secondary cancers later in life (2). Survivors of ALL often have low self-esteem and depression that may be negatively impacted by increased body weight. While there is conflicting evidence, Withycombe et al. (2) showed that children with ALL who are obese at the time of diagnosis exhibited a higher probability of relapse than those who were of normal weight at diagnosis. Treatment advancements of cancer have resulted in a growing population of survivors in whom long-term consequences are now becoming apparent. To clearly understand the factors that affect the

incidence of obesity in this population, we investigated multiple factors present before, during, and after treatment.

Before Diagnosis

Researchers have sought to identify potential indicators of obesity existing before diagnosis of ALL. One study enrolled 54 pediatric ALL patients who were treated with chemotherapy alone (3). The investigators found that 48% of ALL survivors were overweight or obese 5 years after diagnosis as compared to the general population where 21% were overweight or obese. They found that BMI at time of diagnosis and maternal BMI were significant factors that may predict greater weight gain after disease remission (3). Razzouck and colleagues (4) reported similar results; individuals who were overweight or obese at diagnosis were 9.2 times more likely to be overweight or obese when they reached adult height and 14.7 times more likely to be obese as compared to patients who were normal weight at diagnosis. Gofman and Ducore (5) enrolled 95 patients aged 18 years or older at diagnosis and free from disease for 2 years after treatment. They investigated the association of age at diagnosis, gender, race, median treatment, central nervous system disease and radiation, radiation field, and metabolic history including antihypertensive medications, hyperglycemia, and thyroid disease with obesity. Based upon BMI at time of diagnosis, 6% of participants were overweight and 2% were obese. At the end of treatment, 20% were overweight and 12% were obese. Follow-up was performed 2 years after completion of therapy revealed that 16% of patients were overweight and 24% were obese. Thus, patients gained weight during treatment for ALL at a rate

similar to weight gain seen in the non-ALL pediatric population. Of the patients who survived for 3 years after completion of therapy, 24% were obese which is equivalent to the obesity rate seen in the United States population as a whole (1). The only factors found to be significant in predicting obesity at diagnosis were younger age at diagnosis (participants ages ranged from six months to16.7 years), BMI at diagnosis, and Hispanic race (5). These studies showed that factors that impact the incidence of obesity in ALL survivors exists even prior to diagnosis.

During and After Treatment

Identification of factors associated with weight gain during and after treatment have similarly been sought in an attempt to develop interventions to modify weight gain. One study examined whether or not drug therapy alone during treatment was associated with an increase in weight gain and hypertension in ALL patients (6). Similar to the predictors of obesity present before diagnosis, the study results indicated that those who were younger at diagnosis, female, and overweight or obese at baseline were at higher risk for obesity later in life. A unique finding from this study was that most of the weight gained during treatment was maintained over time. At the end of therapy, 38.2% were overweight/obese and 41.2% were overweight/obese 5 years from diagnosis as compared to 23.6% at diagnosis. Since corticosteroid dose was associated with increased BMI z-scores, researchers concluded that corticosteroids given during treatment were the main factor associated with obesity at follow-up (6).

Additional studies identified other factors of ALL treatment on obesity. Garmey et al. (7) compared pediatric ALL survivors to childhood cancer survivor siblings and found that BMI increased 2.7 units and 1.7 units in females and 2.2 units and 1.5 units in males from baseline to completion of follow-up (mean of 7.8 years), respectively. Though BMI increased from baseline in both groups, only the ALL group treated with cranial radiation therapy (CRT) showed a significant increase in BMI over the control group ($p<.01$). Furthermore, the younger the patient at the time when radiation was given, the more weight they gained over time (7). However, other studies such as Withycombe and colleagues (2) were unable to show treatment with CRT to be a valid predictor of increased BMI.

Since the acquisition and distribution of fat in patients receiving CRT have been linked to increased BMI, investigators assessed the association of CRT and gender, with abdominal adiposity, liver fat, and muscle composition (8). Researchers concluded that despite having similar BMI and waist circumference, the survivors treated with CRT had a greater amount of abdominal and visceral fat compared to survivors treated with chemotherapy alone. Subcutaneous abdominal fat was similar in amount and distribution in CRT and non-CRT survivors. The distribution of fat was found to be gender-specific with males having a greater amount of visceral fat, but less subcutaneous fat than females in their respective groups. Independent of gender, survivors treated with CRT had a higher percent body fat than survivors treated with chemotherapy alone due to increased fat mass and decreased lean mass. Total fat mass was higher and lean mass was lower in females than males (8).

Similar to most medical conditions, individuals with pediatric ALL experience different severities of the condition (2). Depending on the severity of disease, the aggressiveness of treatment will vary. Therefore, the aggressiveness of treatment and the influence on weight gain must also be considered. Withycombe et al studied high risk, newly diagnosed children with ALL who received more aggressive treatment than given to those with low risk ALL (2). Researchers enrolled 1,638 high risk ALL patients who were treated on the Children's Cancer Group protocol CCG 1961 from November 1996 to May 2002 aged 2-20 years and determined weight patterns in order to identify factors influenced body mass index (BMI) during treatment. The treatments used in this protocol included vincristine, prednisone, daunomycin, asparaginase, methotrexate, cytosine arabinoside, and cranial irradiation. The investigators found a 14% incidence of obesity at diagnosis and 23% incidence at the end of therapy. Thus, treatment of high risk ALL was linked with an increased frequency of obesity but was similar to that of standard risk ALL patients. Other variables associated with increased weight gain included female participants, being 5-9 years of age, obesity at diagnosis, being of Black or Hispanic race, and having additional health issues such as grade 3 or 4 pancreas/glucose toxicity (2). Though treatment with cranial irradiation in this study did not predict obesity, other studies suggest that cranial irradiation of greater than 20 Gy is a significant indicator in predicting obesity (2,5).

Robien et al. compared the usual dietary intake of adult survivors of childhood ALL to the Dietary Approach to Stopping Hypertension (DASH) diet

recommendations (9). A DASH diet concordance score was calculated to determine patients compliance with dietary recommendations. Results showed that patients followed the DASH diet guidelines for total and saturated fat intake, but consumption of added sugars was more than double the recommendation. These intakes were similar to that of the general population. Though compliance with the DASH diet was not found to be associated with BMI or waist circumference, poor compliance to the DASH diet made findings inconclusive (9).

Conclusion

In summary, many factors influence development of overweight and obesity in pediatric ALL survivors. Factors known to be associated with increased weight gain include age at diagnosis, being female, being overweight or obese at baseline, receiving cranial radiation therapy, being treated with corticosteroids, and being of Black or Hispanic race. To date no studies have evaluated the impact of diet on the incidence of obesity in pediatric ALL survivors. Therefore, the aim of this study was to evaluate the relationship between caloric and macronutrient intake on the incidence of obesity in survivors of pediatric ALL.

CHAPTER II

METHODS

Subjects

This retrospective study comprises analysis of existing data that was collected for the Diminished Bone Mineral Density In Survivors Of Childhood Acute Lymphoblastic Leukemia (ALL): A Severity-Adapted Clinical Trial (Bone II) (10). Bone II was approved by the St. Jude Children's Research Hospital Internal Review Board. Participants consist of survivors of ALL (treated on Total XI, XII, or XIII protocols) who were at least 5 years from completion of therapy and were in first remission. All data was managed according to the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Participant Grouping

Participants were grouped by BMI into the under/normal weight group and the overweight/obese group for comparison. For children less than 20 years of age, CDC growth charts and percentiles were used (11). Under/normal weight is defined as being below the 85^{th} percentile in weight for age, and overweight/obesity was defined as being at of above the 85^{th} percentile in weight for age (12). For adults 20 years of age and older, BMI was used to assess weight status. Under/normal weight was defined as a BMI of less than 25 kg/m^2 and overweight/obesity was defined as 25 kg/m^2 and greater. BMI and growth chart data for the participants was calculated at the time of the 24-hour recall (11,12).

Nutrient Analysis

Food records and macronutrient levels were evaluated to assess dietary intake. Twenty-four hour food recall records collected during the first 6 months of the study were retrieved from the existing data entered in the Nutrition Data System for Research (NDSR) 2009 database. From these recalls, the amount of food eaten, how it was prepared, and a detailed description of the food was used to assess macronutrient intake. Macronutrient levels evaluated in this study included: Kilocalories (kcal), grams of fat, percent kcal from fat, grams of carbohydrates, percent kcal from carbohydrates, grams of sugar, grams of protein, and percent kcal from protein. In addition to macronutrient levels, a Healthy Eating Index (HEI) was also evaluated (13). The HEI is a measure that compares dietary adherence to the Dietary Guidelines for Americans and MyPyramid by using the amount of intake per 1,000 kilocalories. This index evaluates nutrient intake based upon: total fruit (includes 100% juice), whole fruit (not juice), total vegetables, dark green/orange vegetables/legumes, total grains, whole grains, milk, meats and beans, oils, saturated fat, sodium, and calories from solid fats/alcoholic beverages/added sugars. Patient scores were compared to the mean scores from the U.S. population (13).

Data Analyses

Statistical analyses were performed using SAS statistical software (14). The data collected was compared to the United States Department of Agriculture (USDA) recommendations for healthy eating using Dietary Reference Intake (DRI) and Acceptable Macronutrient Distribution Range (AMDR) based on

age/gender. DRI is a measurement that uses Recommended Dietary Allowance (RDA), Adequate Intake (AI), Estimated Energy Requirements (EER), and Tolerable Upper Intake Levels (UL) to establish levels of macronutrients and micronutrients needed daily to maintain a person's health. AMDR is the range of intake from an energy source such as fat, carbohydrates, and protein that is associated with decreased risk of chronic disease development (15). Demographic and treatment related variables were used to identify confounding factors discussed in the background. Descriptive data included: BMI at enrollment, age at diagnosis, ethnicity, gender, corticosteroid use, cranial radiation therapy, and standard/high risk. Descriptive statistics were provided to compare dietary intake to USDA recommendations. Wilcoxon's rank sum test was used to compare dietary intake between under/healthy weight survivors and overweight/obese survivors. Fisher's test and Chi-square test were also performed for statistical analyses.

Inclusion Criteria

The inclusion criteria followed the same guidelines as the BONE II protocol: survivors of ALL who were at least 5 years from completion of therapy, were in first remission, and were treated on Total XI, XII, or XIII protocols (10). For inclusion in the current study, participants must also have had a 24-hour food recall obtained within the first 6 months from the start of the study, and demographic and anthropometric data recorded.

Exclusion Criteria

The exclusion criteria were any participants who were enrolled on the BONE II protocol who did not have a 24-hr food recall obtained within the first 6 months of the study, or were missing demographic or anthropometric data.

CHAPTER III

RESULTS

Patient Demographics

One hundred forty-six patients were enrolled for medical chart review; 4 were excluded due to missing 24-hour recalls within the first 6 months of BONE II study enrollment. Five additional patients were excluded for missing patient demographic and anthropometric data. Thus, final analysis included 137 patients. Of the 137 participants eligible for the study, 91% were white, 7% black, 1% Asian, and 1% were of other race. Gender was dispersed almost evenly with 55% being male and 45% being female.

Confounders Examined

Only 34% of patients enrolled received cranial radiation therapy with the majority (66%) receiving 1,800 cGy and 34% receiving 2400 cGy. In examination of risk categories, 16 of the 137 patients (11%) were missing risk category data, but were not excluded from the study due to having all other data available. Of the remaining participants, 63% were classified as high risk and 37% classified as standard risk. While there was no statistical significance when comparing age at diagnosis and likelihood of being overweight/obese, the median age of the overweight/obese category was younger at diagnosis than the under/healthy weight group with a median age of 3.5 years and 4.8 years, respectively. Also, all participants received steroid therapy; however, steroid therapy differed depending on time of enrollment and treatment protocol. Regardless, there was no differentiation between obesity rates and type of steroid therapy received.

Body Weight Status

BMI categories consisted of 82 participants (60%) in the under/healthy weight category and 55 participants (40%) into the overweight/obese category.

Calorie and Macronutrient Intake

No statistical significance was observed in the comparison of calorie and macronutrient intake with DRI/AMDR between the two BMI groups; however, certain dietary behaviors were identified among participants. Ninety-four participants (69%) were below the DRI for calorie intake while only 4% were below the DRI for intake of protein and carbohydrates. Half the participants on the study consumed above the AMDR for percentage of calories from fat, while 4% and 0% were above the AMDR for carbohydrate and protein, respectively. In relation to percentage of calories derived from sugar (a form of carbohydrate), 96% of participants consumed above the AMDR. To clarify, the AMDR is based on ranges, participants could meet protein and carbohydrate intake, exceed fat intake, and still be below calorie needs. Descriptive statistics, anthropometrics, and dietary intake of pediatric ALL survivors can be seen in Table 1, and the AMDR ranges can be seen in Table 2. HEI was excluded from analysis due to missing data.

Table 1. Descriptive statistics, anthropometrics, and dietary intake of pediatric ALL survivors

Variable	N	Min	Median	Max	Mean	Std Dev
Age at diagnosis (yrs)	137	0.9	4.25	17.44	6.38	4.78
Age on study (yrs)	137	9.36	17.01	35.26	17.81	6.31
Height (cm)	137	78	157.6	190.6	156.19	19.44
Weight (kg)	137	11	57	115.5	57.89	20.9
BMI (kg/m^2)	137	12.2	21.8	39.6	23.04	5.22
Growth Chart Percentile	82*	1	73.5	98	66.09	29.89
Calories	137	791	2172	4819	2330.1	768.3
Fat (g)	137	18	86	250	93.04	38.6
% calories from fat	137	14	36	57	35.56	6.97
Carbohydrate (g)	137	85	286	708	292.09	103.8
% calories from carbohydrate	137	29	51	73	50.39	8.63
Sugar (g)	137	11	146	301	149.15	60.9
% calories from sugar	137	6	26	57	26.03	9.16
Protein (g)	137	28	78	208	87.47	33.1
% calories from protein	137	6	15	27	15.28	3.92

*55 patients were from the adult group, and thus don't have a growth chart percentile

Table 2. Acceptable Macronutrient Distribution Ranges based on gender and age

Macronutrient	Age/Gender grouping	AMDR %
Fat	Males	
	9−13 y	25-35
	14−18 y	25-35
	19−30 y	25-35
	31-50 y	25-35
	Females	
	9−13 y	25-35
	14−18 y	25-35
	19−30 y	25-35
	31-50 y	25-35
Carbohydrates	Males	
	9−13 y	45-65
	14−18 y	45-65
	19−30 y	45-65
	31-50 y	45-65
	Females	
	9−13 y	45-65
	14−18 y	45-65
	19−30 y	45-65
	31-50 y	45-65
Sugar	There is no DRI for sugar intake but the USDA recommends consuming no more than 6-10% of your total calories from sugar.	
Protein	Males	
	9−13 y	10-30
	14−18 y	10-30
	19−30 y	10-35
	31-50 y	10-35
	Females	
	9−13 y	10-30
	14−18 y	10-30
	19−30 y	10-35
	31-50 y	10-35

CHAPTER IV

DISCUSSION

Research and literature has shown that in the United States ALL is more common in whites than blacks with the incidence of 3 out of every 4 cases (16,17). Most occurrences of ALL occur between the ages of 2-5 years and occur more often in males than females (18). This sample size rendered similar results with median age at diagnosis of 4.25 years, and 55% of our sample consisting of males. With respect to race, whites were slightly more prevalent in our study than in the ALL population (90%).

When examining known confounders to BMI during ALL treatment, in contrast to some published literature, no significant results were observed when comparing BMI groups at enrollment to gender, race, CRT, steroid therapy, or age at diagnosis (19). These results were not consistent with results from other literature, which may be attributed to the limited sample size of the study (5-8). Even though results were not significant, the median age at diagnosis for the under/healthy weight group was 4.82 years while the overweight/obese group was 3.49 years and was consistent with prior studies showing that the younger the age at diagnosis the more likely to be overweight/obese (6).

Caloric and macronutrient intake was also compared to BMI at Bone II enrollment. While no results were significant, some dietary trends among ALL survivors were detected. Sixty-nine percent of study participants were below the DRI for calorie intake. The interesting factor about this statistic is that the majority of patients in both BMI groups were below the DRI for calories, 67% in the

under/healthy weight group and 71% in the overweight/obese group. It is common knowledge that excess calorie consumption will cause weight gain in individuals, but our results were not indicative of this. It is possible there were some additional confounders that were not examined that may have had an influence. For instance, estimated calorie needs were based on DRI; however, individuals with ALL may not have the same energy needs due to treatment factors, such as hormonal and cranial radiation therapy, which may influence metabolic function (7). On a positive note, even though most individuals were not meeting caloric needs, 96% of participants met or exceeded the DRI for protein. This data suggests that the focus on dietary intervention should be less about consuming adequate protein and more focused on other criteria. Other variables that exhibited a trend included percentage of calories from fat and percentage of calories from sugar. The majority of participants consumed above the AMDR for calories from fat, which suggests that participants on our study consumed too many high fat foods during their 24-hour food recall; however, it does not differentiate whether these fats were unsaturated or saturated. Also, an astonishing 96% of participants were above the AMDR for percentage of calories from sugar. This data implies that participants' diets were derived too heavily from sugar and may have been lacking in critical nutrients found in from other sources of energy. Since 73% of participants were within the AMDR for percentage of calories from carbohydrates and also consumed an excess amount of sugar, foods containing other forms of carbohydrates may have been lacking. Often, high sugar foods are lacking in fiber and other beneficial nutrients,

so participants in this study may have been consuming diets less than ideal for good health. This indicates that dietary intervention should be more focused on the amount and types of fats to consume and on limiting the consumption of high sugar foods in the diet.

Limitations

Limitations include having a limited sample size, using 24-hour food recalls to assess dietary intake, and using growth percentiles and BMI as a measurement of fat mass. Having a limited sample size may not have given enough data to accurately assess confounders and/or dietary behaviors in comparison to BMI at Bone II enrollment. This study also does not accurately portray results across all races and ethnicities. The sample size used contained 90% whites and data represented in literature associates only 75% of ALL cases occurring in whites (16,17). Therefore, our results may not be consistent among all ALL survivors. Using 24-hour food recalls may not accurately represent an individual's actual dietary intake since it is simply a snap shot of an individual's diet based on recollection of what food what consumed, how it was prepared, what amount was consumed, and how closely the item eaten was to what was entered into the food analysis software. In addition, due to the fact that participants on our study were seen outpatient, many of them were traveling on the days that the 24-hour food recall was taken. Therefore, this record may not have been reflective of the participants' usual dietary intake. Using food frequency questionnaires or three day food records to better encompass individuals usual dietary intake may help get a better idea of how an individual

actually eats. Also, having to eliminate the HEI from the study affected the ability to not only assess caloric and macronutrient levels, but also how healthy the diet was in comparison to the U.S. population. Another limitation involved how weight status was assessed. When using growth percentiles and BMI as a measurement weight status it doesn't differentiate between fat and lean tissue and may not accurately assess an individual being overweight or obese. In future studies using bioelectric impedance, dual x-ray absorptiometry, air displacement plethysmography, or hydrostatic weighing may better distinguish the effects of diet on weight status.

Conclusion

In summary, based on these findings there is no association between obesity status at enrollment and caloric and macronutrient intake (as compared with AMDR/DRI). However, dietary trends of ALL survivors observed from this data showed participants were more likely to be below the DRI for calories regardless of BMI group, most participants met or exceeded the DRI for protein and carbohydrate intake, over half the participants consumed above the AMDR for percentage of calories from fat, and almost every participant consumed above the AMDR for percentage of calories from sugar. Additional research still needs to be done to determine whether caloric and macronutrient intake are associated with the incidence of obesity using larger samples, better measures to assess weight status, and using food frequency questionnaires or three day food records to assess usual dietary intake. The long term effects of ALL treatment and diet on the incidence of obesity is still lacking research; however, survivors may benefit

from dietary intervention after completion of therapy to help educate on the benefits of consuming a healthy diet and its impact on quality of life and BMI status.

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APPENDICIES

APPENDIX A

GUIDELINES FOR HEALTHY EATING

Macronutrient	Age/Gender grouping	DRI in grams/day	Acceptable Macronutrient Distribution Range (%)
Calories *For males, subtract 10 calories per day for each year of age above 19 *For females, subtract 7 calories per day for each year above 19	Males* 0-6 months 6 months-1 year 1-3 4-8 9-13 14-18 19-30 31-50 >50 Female* 0-6 months 6 months-1 year 1-3 4-8 9-13 14-18 19-30 31-50 >50	 570 743 1046 1742 2279 3152 3067 3067 3067 520 676 992 1642 2071 2368 2403 2403 2403	Category not applicable for calories