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Research Article

Excessive Weigth in Survivors of Acute Lymphoblastic Leukemia: What's Going on with Children and Adolescent in Northeast Brazil?

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Therapeutic advances increased survival rates to more than 90% at 5 years. However, this treatment may have unfavorable consequences. Obesity is a well-recognized late effect in these survivors, which increases cardiovascular morbidity and mortality. This research aims to describe the prevalence of excessive weight in ALL survivors, to test the association between clinical, laboratory and treatment characteristics and excessive weight.

Method: Cross-sectional study including ALL survivors from a tertiary pediatric oncology hospital in Bahia. Results were described with measures of central tendency and dispersion for numeric variables and absolute and relative frequencies for categorical variables. To test the association between ALL and excessive weight, Fisher's exact test or chi-square test were performed, when appropriate. P values < 0.05 were considered significant.

Results: We evaluated 128 patients with a mean age of 12.3 ± 3.4 years, most of them male. Of the examined sample, 45 patients (35%) had excessive weight, of which 26 (20.3%) overweight, 15 (11.7%) obesity and 4 (3.1%) severe obesity. There was an association between family history of obesity and excessive weight (56.3% vs 14.1%; p <0.001), and between family history of obesity and increased waist circumference (24% vs 15%; p = 0,002) with no association with gender, type of ALL, treatment protocol used and time after the end of treatment.

Conclusion: In this sample, there was a high prevalence of excessive weight in children and adolescents after ALL treatment and an association of excessive weight and increased waist circumference with a family history of obesity.

Keywords: Acute Lymphoblastic Leukemia, Obesity, Childhood Cancer Survivors, excessive weigth.

Abbreviations: ALL: Acute Lymphoblastic Leukemia; GBTLI: Brazilian Group of Childhood Leukemia Treatment; BFM: Berlin-Frankfurt Münster backbone.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, accounting for nearly a quarter of all childhood cancers [1]. While advances in treatment strategies have led to five-year survival rates approaching 90% [1], curative therapy for pediatric ALL is associated with an increased risk for numerous chronic health conditions [2]. The St. Jude Lifetime Cohort Study report

states that at 45 years of age, 95.5% of childhood cancer survivors have at least one chronic disease, including obesity [2,3]. As obesity is known to contribute to an increased risk of hypertension, type 2 diabetes, cardiovascular disease, cancer, and premature death, it is imperative to develop and apply interventions in this at-risk population. However, effective intervention strategies for ALL survivors requires a clear understanding of those who are at greatest risk of becoming obese and the mechanisms of obesity in survivors [4]. Some etiologic mechanisms have been proposed, including patient characteristics and treatment received [5,6]. Nevertheless, the factors related to excess weight in patients treated even with the most modern protocols have not yet been fully elucidated[6]. Even so there are few studies reporting this risk in developing countries especially in Brazil in which the problem of dietary deficiency was rapidly shifting to one of dietary excess in last decades. The aim of this study was (1) to assess the frequency of excessive weight in children and adolescents' survivors of ALL, (2) to identify the clinical and laboratory findings of these individuals and (3) to test their association with excess weight gain in an important public hospital that is reference in childhood cancer in Bahia-Brazil. We intend to contribute for evidence about the characteristics of ALL survivors in Brazilian children.

Material and Methods

This is a cross-sectional study based on a convenience sample of 128 patients with a previous diagnosis of ALL, in regular follow-up with pediatric endocrinology at *Martagão Gesteira* Hospital, in Salvador, Bahia, from October 2016 to December 2021. In this Hospital, all ALL cases are referred and regularly followed with endocrinological evaluation, regardless of nutritional status. The primary objective of a descriptive study was followed. Considering an estimated prevalence of 30% of excessive weight after ALL treatment, 127 patients were needed to estimate the prevalence of excessive weight in this sample, with 8% precision and an alpha of 5%. The sample calculation was performed using a specific calculator (WinPepi Version 11.65 of 2016). Patients, of both genders, were included if, at first endocrinological evaluation, aged between 2 and 18 years old, and had completed curative treatment for ALL at least 12 months before. Patients excluded from the study were those who undergone bone marrow transplantation, who had secondary obesity or any concomitant diseases that could serve as confounding factors, such as Cushing's syndrome and Prader Willi syndrome. This study was approved by a local Research Ethics Committee under protocol 48166121.5.0000.5544, available at the "Plataforma Brasil". Informed consent was obtained from all subjects and/or their families before enrollment in the study, after explaining the purpose of the study and the procedure.

Three treatment protocols for the underlying disease were identified using a medical record review: Brazilian Group of Childhood Leukemia Treatment-1999 (GBTLI 99) [7], Berlin-Frankfurt-Münster-backbone (BFM 2002 [8] and BFM 2009 [9] protocols). In these treatment protocols, prednisone and dexamethasone were equivalent in terms of glucocorticoid effect. It was not possible to access the complete anthropometric measurements of these patients before the ALL diagnosis or upon admission. Anthropometric and pubertal development data were obtained during the appointment with a pediatric endocrinologist. Anthropometric measurements were made with the children wearing light clothing and without shoes. Measurements of height were obtained in duplicate with an accuracy of 0.1 cm. Weight was measured using a digital scale with a capacity of 2 to 150 kg and an accuracy of 0.1 kg. The average of the two height measurements was used to calculate BMI [BMI = weight (kg)/height^2 (cm)]. The boys and girls were classified according to BMI Z-score ranges (BMI curves established for each gender and age), using the parameters of the population curves defined by the World Health Organization (WHO) in 2007 [10]. The children's nutritional status was categorized according to BMI z-score. A second categorization was performed: all overweight, obese, or severely obese individuals were considered as excessive weight. The waist circumference was measured using an inelastic tape measure graduated in centimeters. The reference point was the midpoint between the lower costal margin and the anterior superior iliac crest. Furthermore, the patient was upright, presenting a relaxed abdomen after a gentle exhalation. The reference value used was the North American standard described by Fernandez in 2004 [11]. Values over the 90 percentile were considered increased for both gender. Blood pressure was measured in the right arm using an aneroid sphygmomanometer, with appropriate cuffs for the patient's size. As a reference, we used the values recommended by the Department of Nephrology of the Brazilian Society of Pediatrics [12]. The pubertal staging was also assessed using the Marshall and Tanner criteria to dichotomize into prepubertal (stage 1) and pubertal (from stage 2 on). The family history of obesity variable was defined if the father, mother and/or grandparents were obese by measuring their weight and height (BMI).

Blood samples were collected after overnight 12-hour fasting to measure total cholesterol, Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fasting glucose (mg/dL); glycated hemoglobin (A1c %) by the HPLC method (high performance liquid chromatography); insulin (µUI /mL), TSH (mUI/mL) and free tiroxin T4L (ng/dL) by electrochemiluminescence. The reference values from the Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis [13] were adopted for the lipid profile. The HOMA-IR (homeostatic model assessment) calculation was based on fasting insulin and glucose levels to assess insulin resistance; the HOMA-IR cut-off point was > 4.07 for pubertal adolescents and > 2.91 for non-pubertal adolescents [14]. Hand and wrist radiography to evaluate bone age was determined by the Greulich-Pyle method [15]. Statistical analysis: All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS) software version 26.6 [16]. The results were described with measures of central tendency and dispersion for numeric variables and absolute and relative frequencies for categorical variables. Frequencies were compared using the Chi-square test or Fisher's exact test, when appropriate. Statistical tests with a p-value < 0.05 were considered statistically significant.

Results

Among 128 ALL survivors patients, 74 (57.8%) were male, 43.8% were treated by GBTLI 99 protocol, 24.2% by BFM 2002,

and 32% by BFM 2009. At diagnosis, the mean age was 5.2 ± 3.6 years, and 116 individuals (92.1%) presented an immunophenotypic classification of B-precursor ALL. In the sample, eight patients (6.3%) underwent cranial radiotherapy (Table 1). The duration of treatment ranged from 2.0 to 2.6 years, with a median of 2.4 years; the time between concluding this treatment and the first endocrinological evaluation had a median of 4 years, with 52.5% of patients between 1 and 4 years out of therapy and 47.5% over 4 years. At the endocrinological appointment, the mean age was 12.3 ± 3.4 years, and most patients were already in puberty (68.5%). Fifty percent had mother and/or father and/or grandparents with history of obesity. Forty-five (35.2%) patients presented with excessive weight. Of these, 26 (20.3%) were overweight, 15 (11.7%) obese, and 4 (3.1%) severely obese. Thirty-three (27.5%) patients had altered waist circumference (>P90) (Table 2). The mean systolic blood pressure (BP) was 106,3 ± 14,8 mmHg, and the mean diastolic BP was 68,6 ± 11,6 mmHg. When BP was analyzed according to gender, age, and height, no blood pressure abnormalities were found. Increased HOMA-IR was identified in 31.4% of the individuals. The lipid and glycemic profiles and thyroid function were not significantly altered. Furthermore, no significant difference was found between bone ages and chronological ages. Table 3 shows the laboratory characteristics of the sample studied. Individuals with a family history of obesity were observed to have a higher frequency of excessive weight than those without a family history (56.3% vs. 14.1%; p <0.001). Besides, no differences were observed between the presence of excessive weight and gender, type of ALL, treatment protocol used, and time after the end of treatment (Table 4) Furthermore, it was observed that individuals with a family history of obesity had a higher frequency of increased waist circumference than those without this family history (24% vs. 15%; p = 0.002). No differences were observed between the presence of increased waist circumference and gender, type of ALL, treatment protocol used, and time after the end of treatment (Table 4).

Table 1: Demographic characteristics of the study participants.

Variable	n 128	%
Gender		
Male	74	57.8
Age group		
Child	119	93.0
Adolescent (≥ 12 years old)	9	7.0
Type of ALL		
B Cells	116	92.1
T Cells	10	7.9
Treatment protocol		
GBTLI 99	56	43.8
BFM 2002	31	24.2
BFM 2009	41	32.0
Radiotherapy		
No	120	93.8

ALL = Acute Lymphoblastic Leukemia; GBTLI 99 = Brazilian Group of Childhood Leukemia Treatment -1999; BFM 2002 = Berlin-Frankfurt- Münster-backbone of 2002; BFM 2009 = Berlin Frankfurt-Münster- backbone of 2009. Source: Elaborated by the authors (2023)

Table 2: Characteristics of the survivors at the endocrinology appointment.

Variable	n=128	%
Age group at appointment		
Child	50	39.1
Adolescent (≥ 12 years old)	78	60.9
BMI		
Severe Thinness	0	0
Thinness	4	3.1
Eutrophia	79	61.7
Overweight	26	20.3
Obesity	15	11.7
Severe Obesity	4	3.1

Waist circumference		
Normal	87	72.5
Abnormal (> P90)	33	27.5
Tanner Stage		
Prepubertal	40	31.3
Pubertal	87 68.5	
Excessive weight		
No	83	64.8
Yes	45	35.2
BMI = Body Mass Index; P90 = 90% percentile Source: Elaborated by the authors (2023		

Table 3: Laboratory characteristics of ALL survivors.

Variable	Mean	Standard Deviation
Total cholesterol (mg/dL)	170.7	32.6
LDL (mg/dL)	104.4	29.6
HDL (mg/dL)	48.8	12.9
TG 1 (mg/dL)	85.9	14.4
TG 2 (mg/dL)	83.8	7.6
Blood glucose (mg/dL)	90.3	6.6
HbA1c (%) *	5.1	4.9-5.3
Insulin (uUI/mL) *	10.2	6.9-16.5
HOMA-IR*	2.1	1.4-3.4
TSH (mUI/mL)	2.2	1.1
T4L (ng/dL)	1.2	0.2
* Median and quartiles ALL = Acute Lymphoblastic Leukemia ; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG 1 = Triglycerides up to 9 years of age; TG 2 = Triglycerides from 10 to 18 years of age; HbA1c = Glycated hemoglobin; HOMA-IR = Homeostasis model assessment of insulin resistance; TSH = Thyroid-stimulating hormone; T4L = Free thyroxine. Source: Elaborated by the authors (2023)		

Table 4: Association between clinical variables with excessive weight and increased waist circumference in ALL survivors.

Variable	Excessive weight			Increased WC		
	n	%	p-valor	n	%	p-valor
Gender			0.457			0.352
Female	17	31.5		13	26	
Male	28	37.8		20	35	
FH obesity			<0.001			0.002
No	9	14.1		9	15	
Yes	36	56.3		40	24	
Time to the end of treatment			0.826			0.392
1 – 4 years	22	34,.9		18	30	
> 4 years	21	36.8		15	27.8	
Type of ALL			0.163			0.440
B cells 43 37.1				32	29.1	
T cells	1	10.0		1	12.5	
Treatment protocol			0.924			0.457

GBTLI 99	20	35.7	13	24.1		
BFM 2002	10	32.3	7	24.1		
BFM 2009	15	36.6	13	35.1		

ALL = Acute Lymphoblastic Leukemia ; FH = Family history; GBTLI 99 = Brazilian Group of Childhood Leukemia Treatment-1999; BFM 2002 = Berlin-Frankfurt- Münster- backbone of 2002; BFM 2009 = Berlin-Frankfurt- Münster- backbone of 2009; WC = weist circumference Source: Elaborated by the authors (2023).

Discussion

The findings of this study indicated a high prevalence of excessive weight (35.2%) in children and adolescents who survived ALL. These findings are according with other Brazilian studies, as well as from other countries. Moreover, the numbers reflect the magnitude of the problem since excessive weight at the end of treatment was higher than in the Brazilian population aged 5-9 years (29.3%) [17] and 12-17 years (25.5%) [18] in general. At the endocrinological appointment, excessive weight had a frequency like that reported by Alves et al[19] (38.3%) in a study with Brazilian children. In international literature, there are even higher prevalence, such as those reported by Asner et al. (48%) and Breene et al. (47.2%) [20,21]. However, it is relevant to highlight that differences can be attributed to the diversity of protocols, excess weight definitions, and small sample size in these studies [6,22]. There is a strong relation between the quantity of adipose tissue and their disfunction. Adipose tissue quantity, as measured with either BMI or waist circumference (WC) is related to plasma concentrations of adipokines, to morphologic characteristics of adipose tissue, and to the development of the metabolic syndrome[23]. Given the importance of insulin resistance in the pathophysiology of metabolic syndrome, it is relevant to emphasize that we found 27.5% of patients with increased abdominal circumference (>P90) – all of whom were part of the excessive weight group. The present study also observed a 31.4% frequency of HOMA-IR elevation, a method to assess insulin resistance that is closely related to childhood obesity. This percentage is like that found in other studies with ALL survivors [24,25]. There is well-documented evidence linking the risk of obesity after ALL treatment with older protocols. Former late effects studies in ALL survivors demonstrated that CRT was a major risk factor for overweight/obesity in the long-term. Discussed hypotheses and mechanisms suggested that radiation damage to hypothalamic neurons controlling eating behaviors and leptin resistance were mainly involved in the development of late excessive weight gain in this population[20]. In this sample, only eight patients underwent cranial radiotherapy, all children with B-cell ALL.

However, after the 1990s, there was progress in therapies, with the development of protocols that include replacing cranial radiotherapy by intrathecal chemotherapy, more intense systemic chemotherapy, and the use of high-dose corticoids. Despite this changes and the use of the most modern protocols, some studies still mention the risk of obesity [20,26]. The analysis of associated factors in the present sample does not show that excessive weight is associated with the type of leukemia or with the treatment received. However, a statistically significant association was observed between excessive weight and family history of obesity. Family history is important in determining obesity and the result of the present study is consistent with those in the literature. In a study with a sample of 699 children in the second largest city in Bahia, Oliveira AL, et al [27], identified parental obesity as a significant risk factor in the development of childhood overweight/obesity, especially when both parents had this condition. - Children of obese parents were 3.5 times more likely to have excessive weight. The genetic factor is sufficient cause to determine obesity, but it is not always necessary. This factor is strongly influenced by the environment in which children live, and it is known that the lifestyle adopted by parents is generally transferred to their children, which perpetuates the overweight phenotype[27]. It is important to notice that the association between a family history of obesity was also demonstrated with an increase in waist circumference, which reinforces the role of family history in the genesis of obesity, whether global or central, thus suggesting the etiopathogenesis of obesity after treatment for ALL is not different from that of children in the general population.

Research in healthy children shows that the parents' eating behavior (i.e., the way and frequency they feed their children) is closely related to caloric intake and children's BMI [28]. Thus, it is relevant to note that, to minimize weight loss during the disease, there is a tendency to provide more calories to children and adolescents affected by ALL, which often lasts for years after the end of treatment [29]. Other possible contributing mechanisms to the development of excessive weigth after ALL therapy are increased sedentary behavior and reduced physical activity [3]. The strength of this study includes that children and adolescents survivors of ALL of the main pediatric oncology center in Bahia were studied for the first time. Furthermore, the importance of this research is also the demonstration of the high frequency of excessive weight and increased abdominal circumference in this group. With this knowledge, plans and guidelines can be drawn up for an adequate approach to obesity, already at that time, to avoid future complications. Joint monitoring of all ALL survivors with an endocrinologist, nutritionist and psychologist is planned to be implemented, with periodic reassessments of excessive weight cases. We know that obesity is a chronic and multifactorial disease that causes damage to individual health and increases the costs of the public health system. In the case of childhood patients, guidance from caregivers regarding eating habits, physical activity and mental health care is essential. This investigation presented some limitations: there was no systematic record of the nutritional status of patients before and during treatment for ALL. When analyzing factors associated with obesity, the literature suggests that excess baseline weight could be one of the factors associated with excess weight after treatment [30]. Therefore, the treatment period would be critical for nutri-

tional intervention and preventing future complications. Although a control group with minimal pairing by sex and age group was desirable, this was not possible since the Pediatric Oncology at *Martagão Gesteira* Hospital is a tertiary service, however this limitation does not invalidate the results presented, considering that they were compared with those of the general population with the same sociodemographic profile and ALL survivors from other centers.

Conclusion

In the present study, a high prevalence of excessive weight was found in a sample of children and adolescents post-leukemia treatment (from a specialized service in oncologic treatment in a public hospital of Salvador - BA), as well as an association of excessive weight with a family history of obesity and increased waist circumference. However, no association was found between excessive weight and some characteristics of the patient (such as gender and age), of the disease (cell type of the ALL), or of the treatment received (protocol; cranial radiotherapy; corticosteroid therapy), suggesting that the development of excess weight in this population presents association with genetic and/or epigenetic characteristics, but not to factors directly related to ALL. Thus, a careful look at childhood obesity (which is known to increase the risk of cancer and numerous associated diseases), especially in a specific pediatric population such as leukemia survivors, has become a necessity and a significant challenge today.

Declaration of interest

All authors declare that they have no conflict of interest.

Ethical approval

The study was approved by the local ethical research committee.

Informed consent

For this type of study, formal consent was required through the Informed Consent Form.

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