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Evaluation of Obesity, Insulin Resistance and Metabolic Syndrome in Childhood Leukemia Survivors

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Abstract

Background: Leukemia is one of the most common malignancies in childhood, accounting for about 40 per million children under the age of 15 years. Acute lymphoblastic leukemia accounts for about 75% of these cases of leukemia. Regarding the improvement in life expectancy and the prolonged life of patients with acute lymphoblastic leukemia, identifying the long-term complications and effects of treatment in patients is necessary.

Methods: The present applied study is a cohort study based on the case-control method. In order to achieve the purpose of the study, 50 patients who had improved acute lymphoblastic leukemia were selected as a case group; the selections were conducted in a sequential manner in Mofid Children Hospital. 50 other people who had no history of ALL disease were selected as the control group. All information gathering processes including patient history, physical examination, and necessary tests were done by a pediatric hematology oncology subspecialties fellow and trained personnel with full supervision of Pediatric hematologist - oncologist. Blood samples were taken at 10-cc of fasting blood. Blood samples after centrifugation and storage at 20 ° C were used to measure serum fasting blood glucose, triglyceride (Slovak based on serum lipid profile), and insulin levels. All demographic information, BMI, clinical symptoms, laboratory tests, and treatments were recorded in both forms. Data were finally entered into SPSS version 21 and analyzed using the GEE method.

Results: the incidence of obesity was significantly higher in patients with ALL as compared with the controls. The risk of obesity in ALL patients was found to be approximately 9 times higher than the controls. In this study 6 (12%) patients in cases and 4 (%8) patients in controls had metabolic syndrome. There was no statistically significant difference between the groups in the incidence of metabolic syndrome, insulin resistance, and visceral obesity.

Conclusion: It is suggested that after acute lymphoblastic leukemia treatment in children, in addition to regular follow up for disease recurrence, the patients should be monitored about metabolic syndrome or any of its components, especially weight gain, and obesity.

Key Words: Acute lymphoblastic leukemia, Insulin resistance, Metabolic syndrome, Obesity.

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1- INTRODUCTION

Acute Lymphoblastic Leukemia is the most common type of leukemia in childhood (1). This type of malignancy includes 25% of childhood malignancy cases. Currently, the full recovery rate for children with acute lymphoblastic leukemia is around 80% (2, 3). However, success in treating children with malignancy and prolonging the life of this group of patients is associated with an increased risk of complications and deaths (4–7). Cohort studies in children with improved malignancies in St. Jude Hospital have indicated that the incidence of a chronic and severe) disabling and life-threatening (complication until the age of 45 years is 95% and 80%, respectively (4).

It seems that Childhood Leukemia Survivors, are susceptible to clinical and biochemistry manifestations of the metabolic syndrome, including visceral obesity, insulin resistance, glucose tolerance, dyslipidemia, arterial hypertension and endothelial dysfunction, which is a risk factor for Cardiovascular Complications (1). Obesity is one of the major risk factors. Long-term studies on the weight pattern of ALL children at different stages during and after treatment indicate a significant increase in weight and the incidence of obesity (8–10). Obesity and physical inactivity increase the risk of diabetes, dyslipidemia and metabolic syndrome in these patients (11). Determining the risk factors for obesity and chronic obesity-related disorders plays a significant role in improving the long-term health status and quality of life among these patients. In a meta-analysis, Faienza et al. (12), reviewed 12 articles, comprising 2,337 participants (1,462 cases and 875 controls). Only three of them were case–control studies eligible for the meta-analysis. The childhood leukemia survivors showed an increased risk of MetS as compared to healthy controls (OR = 4.36; 95% CI 1.19–16.22). The risk was significantly increased only in patients treated with chemotherapy and radiotherapy (OR = 7.79; 95 % CI 1.27–47.77), and not in patients treated with only chemotherapy (OR = 2.35; 95 % CI 0.40–13.78). Childhood leukemia survivors, in particular, if treated also with radiotherapy, are prone to develop MetS more than healthy controls. So, monitoring MetS components in these patients is necessary to avoid cardiovascular consequences later in life. In this regard, the aim of this study was to evaluate the rate of obesity, insulin resistance and metabolic syndrome in childhood leukemia survivors in Mofid children's hospital.

2- MATERIALS AND METHODS

2-1. Design and participants

In this cohort study, 50 patients with ALL aged 6 - 21 years old, all treated in Mofid children's hospital were selected as the case group. Sampling method was sequential (individuals in the case control group included 27 siblings, and 23 non siblings) Exclusion criteria were leukemia recurrence, secondary malignancy and history of hyperlipidemia in the patient's family. A total of 50 other patients who had no history of ALL were selected as the control group. The data used to support the findings of this study were supplied by authors under license and so cannot be made freely available. Requests for access to these data should be made to [Zahra khafaf pour, Zahra.khafaf@gmail.com].

2-2. Data collection

All data gathering processes including patient history, physical examination and necessary tests were done step-by-step by a pediatric hematology oncology subspecialty fellow and trained personnel with complete supervision of Pediatric hematologist - oncologist. Blood samples were taken from patients at 10 cc of fasting blood. Blood samples after

centrifugation and storage at -20° C were used to measure the serum fasting blood sugar level, triglyceride (Slovak Based on serum lipids curve (Lipid Community Study)), and insulin levels.

2-3. Statistical analysis

In this study, mean, standard deviation, upper and lower limits were used to describe quantitative variables. In addition, Frequency and ratio were measured for qualitative criteria. In order to compare the research variables among the experimental groups, the Generalized Estimation Equations (GEE) method was used. For this purpose, an Exchangeable correlation matrix and logit function were used for the statistical model. The level of significance was considered $P< 0.05$ for the 95% confidence interval.

3- RESULTS

The demographic and clinical characteristics of children are shown in **Table 1**. 54% of the cases and 32% of the controls were male. The mean ages of children in case and control groups were 12.9 and 11.75 years, respectively. Type of ALL in all of the survivors was B cell acute lymphoblastic leukemia. The mean age of diagnosis in survivors was 6.9 ± 3. 21 years. The lowest diagnosis age was 2 and the highest was 12 years. All cases received a complete course of chemotherapy based on protocols. Three patients (6%) also had radiation therapy with a dose of 1800 cGr. Based on children's BMI, 30% of survivors and 20% of controls were overweight and obese. In 22% of children in the case group and 16% in the control group, insulin resistance was observed. Details of height, weight, waist circumference, systolic and diastolic blood pressure, triglyceride levels, HDL-C, insulin and fasting glucose of children in two groups of case and control are presented in **Table 1**. Control group information for siblings and non-relatives is also separately provided.

The Most common metabolic syndrome components, in the group of survivors, were low HDL-C levels (32%) and central obesity (28%). Central obesity in the control group was (34%); and then triglyceride and high glucose (10%), respectively, were the most common MS components. In total, 6 (12%) of the survivors and 4 (8%) controls had metabolic syndrome (**Table 2**).

None of the patients with history of Radiotherapy had metabolic syndrome. 5 of the 6 children with metabolic syndrome in the survivor group had Pre B cell acute lymphoblastic leukemia. Regression analysis with age, gender and consanguinity adjustment showed that there was no statistically significant difference between the incidence of metabolic syndrome and insulin resistance in both case and control groups. However, there was a significant difference in obesity between the two groups (**Table 3**).

4- DISCUSSION

Leukemia is one of the most common malignancies in childhood, which affects about 3.3 per 100,000 children. About 75% of leukemia is considered as acute lymphoblastic leukemia (1). Regarding the improvement of life expectancy in ALL patients, it is necessary to identify the long-term complications and effects of treatment. In this regard, the present study was conducted at the Blood and Cancer Clinic of Mofid Children's Hospital of Shahid Beheshti University of Medical Sciences on a population of survivors with acute lymphoblastic leukemia referred for follow-up after treatment. Complications such as obesity, insulin resistance, and metabolic syndrome were compared in these children with those in non-infected children. Studies show that the peak incidence of acute lymphoblastic leukemia is during 2 to 5 years of age and its prevalence in boys is higher than in girls (13).

Table-1: Metabolic characteristics of child survivors of acute lymphoblastic leukemia and the controls

Variables		Case group	Control group		
			All	B&S	Non-relative
n		50	50	27	23
Sex (M) n (%)		27 (54%)	16 (32%)	10 (37%)	6 (26%)
Current age (Y)a		12.9 (6.30, 21.30)	11.75 (6, 21)	12.99 (6.30, 21)	10.29 (6,20)
Height (cm)b		145.66±20.47	143.47±18.43	146.37±20.92	140.07±14.71
Weight (kg)b		47.96±22.92	44.37±17.13	48.26±19.37	39.80±13.03
Waist (cm)[b]		73.06±16.71	74.60±11.08	74.30±12.39	74.96±9.58
Nutritional status	Normal	20 (40%)	29 (58%)	16 (59.30%)	13 (56.50%)
	Low weight	15 (30%)	11 (22%)	4 (14.80%)	7 (30.40%)
	Overweight	7 (14%)	9 (18%)	6 (22.20%)	3 (13%)
	Obesity	8 (16%)	1 (2%)	1 (3.70%)	0
Blood pressure	Systolic (mmHg)[b]	100.83±11.30	108.10±11.28	103.8±12.49	113.13±7.07
	Diastolic (mmHg)[b]	70.82±8.53	71.68±8.59	72±9.23	71.30±7.96
	Triglycerides (mg/dl)[b]	79.48±36.30	89.68±42.38	77.30±39.84	104.22±41.42
HDL-C (mg/dl)[b]		42.57±8.48	43.40±10.56	44.11±12.17	42.57±8.48
Insulin (µU/mL)b		12.41±10.93	9.83±6.48	10.21±7.57	9.38±5.03
Glucose (mg/dl)b		90.54±6.19	89.78±8.75	89.04±7.37	90.65±10.24
Insulin resistance n (%)		11 (22%)	8 (16%)	5 (18.5%)	3 (13%)

[a]Values are mean (min,max); [b]Values are Mean ± Standard Deviation; Abbreviations: B&S Brothers & Sisters

Table-2: Prevalence and components of metabolic syndrome in child survivors of acute lymphoblastic leukemia and controls

Variables	Case group	Control group		
		All	B&S	Non-relative
n	50	50	27	23
WC[a] ≥ 90pc[b]	14 (28%)	17 (34%)	7 (25.90%)	10 (43.50%)
Triglycerides ≥150 mg/dL	3 (6%)	5 (10%)	1 (3.70%)	4 (17.40%)
HDL-C[c] <40 mg/dL	16 (32%)	3 (6%)	3 (11.11%)	0
High BP[d]	0	0	0	0
Glucose>100 mg/dL	4 (8%)	5 (10%)	2 (7.40%)	3 (13%)
Metabolic Syndrome	6 (12%)	4 (8%)	4 (14.80%)	0

Values are number (percentage); Abbreviations: [a]WC Waist Circumference, pc[b] percentile, [C]HDL-C High density lipoprotein cholesterol, [d]Systolic blood pressure ≥90 pc or Diastolic pressure ≥90 pc

Table-3: Odds ratio of metabolic syndrome, obesity and insulin resistance in case and control groups

Parameter	P-value	OR	95%CI	
MetS [a]	0.43	1.56	0.52	4.65
Obesity	0.03	9.16	1.23	68.05
Insulin resistance	38	1.59	0.57	4.43

Abbreviations: MetS Metabolic Syndrome

As in the present study, in which most of ALL survivors were boys, in the study by Farhangi, et al., 63 patients were male and 37 patients were female (14). And in the study by Moradveisi et al., 65.5% of ALL patients were boys (15).

The results of the current study showed that 14% of the survivors were overweight and 16% had obesity in the case group. Considering that the prevalence of obesity among people under the age of 18 years in Iran is estimated to be between 3.29-11.9% (16), the prevalence of obesity in patients with treated leukemia in this study is more than the prevalence of obesity in the community. The results of this study are consistent with the findings of the study by Zareifar et al (17). In Zareifar et al.'s study, the prevalence of obesity in survivors was reported as 23.53%. Similarly, in Garmey et al.'s study, in the United States, increased BMI in female adults was confirmed after childhood leukemia treatment (8). The present study showed that the prevalence of obesity in the case group was significantly more than that in the control group. Based on the results, the risk of obesity in ALL survivors is approximately 9 times more than in non-All patients (OR = 16.19).

In this study, visceral obesity was also studied along with BMI. The results showed that 28% of survivors had visceral obesity; however, there was no significant difference between the two groups in this variable. It was also found that 12% of the survivors had metabolic syndrome. This rate was higher than the rates determined by Kourti (5.8%) (2), Trimis (11.2%) (18), Chow (10.8%) (19), Oudin (2.9%) (20), and Similar to the reported rates in Barbosa-cortes (13.5%) (21) and Reisi (20%) (22). In the study by Faienza et al. (12) the overall rate of MetS in 12 reviewed studies was 13.1 % (95 % CI 8.4–17.7). In the three case–control studies reviewed, the rate of MetS was 13.5 % (95 % CI 7.3–23.3) and 4.1 % (95 % CI 1.3–10.4) in leukemia survivors and controls, respectively. The childhood leukemia survivors showed an increased risk of MetS as compared to healthy controls (OR = 4.36; 95 % CI 1.19–16.22).

It seems that the reported incidence rate has been different from one study to another, due to differences in diagnostic criteria and cut off points. In this study, none of the patients with history of radiotherapy had metabolic syndrome. The results showed that 14.8% of siblings in the control group had metabolic syndrome; but there was no evidence of metabolic syndrome in Non-relative controls. Regarding the incidence rate of metabolic syndrome, the results showed that there was no statistically significant difference between the two groups.

In the present study, 22% of the patients had insulin resistance. In 8% of these patients, fasting blood glucose levels above 100 mg/dl were reported. However, statistical analysis of insulin resistance showed that there was no significant difference between the studied groups. The mean systolic and diastolic blood pressure of survivors was 100.83±11.30

and 70.82±8.53, respectively. The mean systolic and diastolic blood pressure was lower in the survivors as compared with the siblings and non-relative controls. Based on the results of this study, 6% of the survivors had high triglyceride levels. The results, further, showed that there was no statistically significant difference in triglyceride levels between the experimental and control groups.

5- CONCLUSION

Regarding the fact that the prevalence of obesity with or without consanguinity was significantly more in ALL patients than in healthy controls, it can be concluded that obesity prevalence in these patients can be influenced by their treatment process in addition to the patient's lifestyle. The study also revealed that the risk of obesity in ALL survivors was 9 times higher than in the controls. Considering that obesity is a significant risk factor for cardiovascular diseases, it is recommended that acute lymphoblastic leukemia patients be examined for the incidence of obesity before and during the treatment process and the necessary therapeutic interventions should be done during the course of treatment and follow up.

6- ETHICAL CONSIDERATIONS

The protocol of the present study was presented at the ethics committee of Shahid Beheshti University of Medical Sciences and confirmed with the code of ID IR.SBMU.RETECH.REC.1396.434. All subjects entered the study after receiving individual or parental consent (according to the age range of the subjects).

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8- AUTHORS' CONTRIBUTION

Shahin Shamsian and Zahra Khafafpour participated in the design of the study, the acquisition and interpretation of the data, and drafted the manuscript. Marjan Shakiba participated in critically reviewing the final manuscript. Mohammadreza Shamshiri participated in data analyses.

9- CONFLICT OF INTERESTS

None.

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