

Adiponectin correlates with obesity: A study of 159 childhood acute leukemia survivors from India

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Abstract

BACKGROUND: Acute lymphoblastic leukemia survivors are predisposed to obesity. However, the exact underlying mechanisms are not known. **AIMS:** The study was done to assess the role of biomarkers of obesity in acute leukemia survivors. **SETTINGS AND DESIGNS:** This is a cross-sectional study conducted at All India Institute of Medical Sciences in survivors of acute leukemia who had completed treatment at least 1 year before enrollment in this study. **MATERIALS AND METHODS:** Obesity was studied by determining the body mass index. Potential biomarkers were studied by assessing serum leptin, resistin, and adiponectin by enzyme-linked immunosorbent assay, and the results were compared in obese versus nonobese survivors. **STATISTICAL ANALYSIS:** Descriptive analysis for baseline demographic factors and Student's *t*-test for comparing the mean levels of biomarkers among the obese and nonobese survivors. **RESULTS:** One hundred and fifty-nine acute leukemia patients were enrolled in this study with a median follow-up of 36.8 months. The median age was 10 (range: 3–18) years, and 123 (77.3%) patients were males. The overall prevalence of overweight/obesity was 26.4%, and this was similar in acute myeloid leukemia and acute lymphoblastic leukemia sub-groups (26.2% vs. 27.3%, *P* = 0.9). Mean serum leptin and resistin were similar in obese and nonobese leukemia survivors (3.7 vs. 2.85 pg/mL, *P* = 0.064; 8.01 vs. 9.33 ng/mL, *P* = 0.36). However, mean serum adiponectin was significantly lower in obese leukemia survivors (7.97 vs. 11.5 µg/mL, *P* = 0.023). **CONCLUSIONS:** Obese leukemic survivors had lower serum adiponectin levels than nonobese survivors. However, serum resistin and leptin levels were similar in the two groups.

Key Words: Acute lymphoblastic leukemia survivors, adiponectin, biomarkers, leptin, obesity, resistin

Introduction

Cure rates of acute lymphoblastic leukemia (ALL) have improved significantly.^[1] With the improving survivorship of childhood leukemias, the long-term treatment-related effects are being observed more frequently and need to be addressed. Obesity is one such dreaded late effect, which increases the risk of death from cardiovascular diseases^[2] and being a modifiable risk factor, primary and secondary prevention can decrease the associated morbidity and mortality.

Increased prevalence of overweight and obesity in ALL survivors has been noted in various studies.^[3–7] The mechanism underlying this observation has been hypothesized to the use of steroids and effect of chemotherapy and cranial irradiation on the hypothalamic-pituitary axis; however, this association is inconsistent.^[8] The predictive factors in some studies^[9–12] were female gender and younger age at diagnosis, but these were not observed in other studies.^[13–16] Hence, the mechanism of obesity in leukemia survivors seems to be interplay of many factors.

Leptin and adiponectin are peptide hormones secreted by adipocytes. Leptin is proportional to total body fat mass and communicates primarily with the hypothalamus regarding satiety and energy usage.^[17] Adiponectin is inversely proportional to fat mass and appears to communicate primarily with skeletal muscle and the liver with respect to energy storage.^[18] Both adipokines are part of a larger system of communication between the hypothalamus, the adipocyte, and the gut with respect to hunger, satiety, energy usage, and energy storage. Resistin is secreted by monocytes

and is linked with chronic inflammation that accompanies obesity.^[19,20]

This study was done with the aim of assessing serum levels of adiponectin, leptin, and resistin in acute leukemia survivors and correlates the same with obesity in these patients.

Materials and Methods

Patient and treatment

This was a cross-sectional study conducted in pediatric oncology outpatient of the cancer center at All India Institute of Medical Sciences, New Delhi, between January 2010 and September 2012. The Institutional Review Board approved this study. The inclusion criteria included acute leukemia survivors aged ≤18 years who had completed the treatment at least 1 year before enrollment in this study. Random sample technique was used to identify the patients eligible for enrollment. Patients with ALL were treated with chemotherapy which included induction, consolidation, re-induction followed by 18 months of maintenance therapy; specifically cranial irradiation was administered as central nervous system prophylaxis at a dose 12 Gy to all patients more than 3 years of age. Patients with acute myeloid leukemia (AML) received “3 + 7” induction followed by three cycles of consolidation using high-dose cytosine arabinoside.

Collection of blood samples

The parents were explained about the study procedure and 12 h overnight fasting, 5 ml of venous blood sample was drawn from each participant.

Classification of leukemia survivors into obese and nonobese

Body mass index (BMI), a reliable indicator of body fat, was calculated from the formula of child's weight (kg)/height (m)². After calculating BMI for children, the BMI was plotted on the Centers for Disease Control BMI-for-age growth charts for girls and boys to obtain a percentile ranking.^[21] A BMI of more than 85th percentile was classified as overweight and more than 95th as obese.

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Assessment of biomarkers

Collected blood samples were immediately centrifuged, and serum was frozen at -20°C until assay. Estimation of serum level of leptin, adiponectin, and resistin were done using enzyme-linked immunosorbent assay kits were obtained from R to D (USA). The minimum detectable dose of adiponectin, resistin, and leptin were 0.246 ng/mL, 0.026 ng/mL, and <7.8 pg/mL, respectively.

Ethics

The Institute Ethics Committee approved this study. Informed consent was obtained from parents of all participating survivors. The procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki declaration of 1975, as revised in 2000.

Statistical analysis

For analysis, obese and overweight were grouped together as obese, whereas healthy and underweight subjects were grouped together as nonobese. For inferential statistics, Student's *t*-test was used to detect the difference between sample means. The level of significance was set at 0.05.

Table 1: Baseline characteristics of acute leukemia survivors

Characteristics	Number of patients (n=159)
Age (years)	
Median	10
Range	3–19
Mean±SD	10.7±4.2
Sex (%)	
Male	123 (77.4)
Female	36 (22.6)
Diagnosis (%)	
ALL	126 (79.2)
AML	33 (20.8)
Obesity (%)	
Obese/overweight	42 (26.4)
Nonobese	117 (73.6)
Follow-up duration (months)	36.8 (range, 14–127)

ALL=Acute lymphoblastic leukemia; AML=Acute myeloid leukemia; SD=Standard deviation

Results

One hundred and fifty-nine acute leukemia survivors were enrolled in this study. The baseline characteristics of survivors are shown in Table 1. Overall 42/159 (26.4%) were obese, and the prevalence of obesity was similar in ALL and AML subgroups (33/126 [26.2%] vs. 9/33 [27.3%], $P = 0.9$).

Biomarkers in “obese” leukemia survivor group and “nonobese” leukemia survivor group

The mean serum leptin and resistin levels were similar in obese and nonobese leukemia survivors (3.7 vs. 2.85 pg/mL, $P = 0.06$; 8.01 vs. 9.33 ng/mL, $P = 0.36$) [Table 2]. However, the mean serum adiponectin levels were significantly lower in the obese leukemia survivors as compared to nonobese leukemia survivors (7.97 vs. 11.5 $\mu\text{g/mL}$, $P = 0.01$). Similar results were observed when serum leptin, resistin, and adiponectin were compared in obese and nonobese AML and ALL patients separately [Table 2].

Discussion

Higher serum leptin levels have been associated with body fatness in ALL survivors.^[22–24] A study reported the high resistin levels in *de novo* and relapsed ALL patients.^[25] In a study of nine ALL patients, serum resistin and levels were reported to be higher during therapy, and the levels progressively normalized toward the end of the treatment. Serum leptin and resistin levels in our study were similar between obese and nonobese survivors, and this was in contrast to the previously reported observation.

Serum adiponectin levels have been observed to be low during therapy of ALL and continue to be so at the end of treatment.^[26] Low serum adiponectin levels have been reported consistently in ALL patients.^[23,25,27] Association of lower adiponectin levels with insulin resistance, body fatness, and metabolic syndrome has been reported.^[23,24] Our study also reported the lower levels of serum adiponectin in obese acute leukemia survivors as compared to nonobese survivors which are in accordance with previous data.

Table 2: Mean of biomarkers in “obese” leukemia survivor group and “nonobese” leukemia survivor group

Biomarkers	Obese (n)	Mean±SD	Nonobese (n)	Mean±SD	P
All survivors (n=159)					
Leptin (n=127)	24	3.70±2.27	103	2.85±1.91	0.06
Resistin (n=152)	40	8.01±6.75	112	9.33±8.21	0.36
Adiponectin (n=143)	36	7.75±4.59	107	11.55±8.79	0.01
ALL survivors (n=126)					
Leptin (n=99)	17	3.31±1.96	82	2.99±2.03	0.55
Resistin (n=120)	32	8.58±7.28	88	8.98±7.19	0.81
Adiponectin (n=113)	28	6.67±3.88	85	11.76±9.51	0.007
AML survivors (n=33)					
Leptin (n=28)	7	3.81±2.86	21	3.01±2.19	0.44
Resistin (n=32)	8	5.75±3.48	24	10.63±7.21	0.08
Adiponectin (n=30)	8	7.81±3.12	22	11.51±4.12	0.05

ALL=Acute lymphoblastic leukemia; AML=Acute myeloid leukemia; SD=Standard deviation

Interestingly, the high prevalence of obesity in AML survivors was observed in this study, which has not been reported previously. However, this was not the primary aim of this study, and such a conclusion cannot be made. Notably, the results of biomarkers assessment were similar for overall group and sub-groups of AML and ALL survivors. Such an observation may point toward factors other than treatment-related factors in the pathophysiology of obesity in acute leukemia survivors.

AdipoRon, an orally active compound, binds to and activates adiponectin receptors. Preclinical studies in mice have shown amelioration of undesirable effects of obesity and insulin resistance leading to prolonged lifespan.^[27] This novel therapy, if found safe and efficacious in human studies may be useful in obese leukemia survivors in whose significant low levels of adiponectin are observed.

The strength of this study was a large sample size. The study was limited by a cross-sectional design and 1-time measurement of biomarker levels. To conclude, we found the lower levels of adiponectin in overweight/obese acute leukemia survivors as compared to the nonobese survivors. Contrary to few previous reports, serum resistin and leptin levels were similar in obese and nonobese acute leukemia survivors in our study. The lower serum levels of adiponectin in obese acute leukemia survivors may suggest the existence of a negative feedback mechanism between adipose mass and the production of adiponectin in humans.

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