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FULL LENGTH ARTICLE

Glucose metabolism abnormalities among pediatric acute lymphoblastic leukemia survivors: Assessment and relation to body mass index and waist to hip ratio

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KEYWORDS

Acute lymphoblastic leukemia survivors;
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Abstract *Background:* As survival rates of pediatric acute lymphoblastic leukemia (ALL) improve, attention is turning to side and late effects of therapy including glucose metabolism abnormalities.

Objective: To asses the presence of abnormal glucose metabolism in pediatric ALL survivors and its possible relation to body mass index (BMI), waist to hip ratio and treatment related factors.

Subjects and methods: Retrospective study with a prospective follow-up of 12 ALL survivors who had been off chemotherapy for >9 months was done. Fifteen healthy sex and age matched children were involved as controls. Body mass index (BMI) waist to hip ratio (WHR), and Oral glucose tolerance test (OGTT) were performed with assessment of glycated hemoglobin (Hb A1C) and insulin sensitivity indices.

Results: At study time the mean BMI, WHR, all components of the OGTT (except the 2 h post load glucose), all indices of insulin sensitivity and the mean Hb A1C% were significantly higher compared to those of the controls. Two survivors (16.6%) developed transient hyperglycemia

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during therapy, one (8.3%) had pre-diabetes, seven (58.3%) had a risk level of Hb A1C but no one had diabetes mellitus (DM) or insulin resistance (IR). At study time the two survivors with transient hyperglycemia during therapy had a significantly high WHR compared to the remainders. WHR of the survivors at study time correlated significantly with fasting plasma glucose and area of insulin under the curve (AUC). The 2 h post-prandial plasma glucose correlated with the duration after therapy completion.

Conclusions: WHR may play a better role than BMI in the prediction of insulin resistance in those patients. Hb A1C may increase earlier than other indices of glucose tolerance.

1. Introduction

Survival after childhood acute lymphoblastic leukemia (ALL) has improved dramatically during the last decades, which emphasizes the importance of long-term treatment complications.[1]

ALL survivors are known to experience a variety of late effects that could impact on their future health, including abnormalities of growth and endocrine function,[2] cardiac dysfunction,[3] and subsequent malignant neoplasms.[4]

Obesity is a well-recognized treatment-related complication, particularly following childhood ALL.[5,6]

Excessive weight gain during ALL treatment is usually related to steroid effects and CNS treatment on appetite regulation, as well as less energy expenditure. Nevertheless, these factors do not fully explain overweight in this group of patients.[7]

Body mass index (BMI) is a number calculated from a child's weight and height. BMI is a reliable indicator of body fatness for most children and teens.[8]

Besides obesity ALL survivors are recognized to present clinical features of metabolic syndrome,[9] and therefore increased risk factors for visceral obesity[10] insulin resistance (IR) and glucose intolerance.[11]

IR is defined as an impaired ability of plasma insulin at usual concentrations to adequately promote peripheral glucose disposal, suppress hepatic glucose, and inhibit very low density lipoprotein (VLDL) output, but it can be inferred on strong clinical evidence and confirmed by insulin and glucose measurements.[12]

It is associated with numerous physical health findings that have serious consequences such as obesity, hyperlipidemia, hypertension, cardiovascular disease, and type 2 diabetes. The clustering of these diseases is termed insulin resistance syndrome.[13]

Waist to hip ratio, is an indicator of abdominal obesity and is a predictor of glucose metabolism abnormalities in children and adults.[12]

The objective of this study was to assess the presence of abnormal glucose metabolism in pediatric (ALL) survivors and its possible relation to body mass index (BMI), waist to hip ratio and treatment related factors.

2. Subjects and methods

2.1. Subjects

The present study recruited ALL survivors who were diagnosed, treated and received their follow up care in Pediatric department, Menoufiya University Hospital, Hematology and Oncology unit on cancer study group (CCG) protocol during the period 2000–2008. This treatment protocol did not involve cranial radiotherapy. The eligible population consisted of children (age $\geqslant 1$ year and $\leqslant 18$ years) who had not received chemotherapy in at least 9 months. Patients were ineligible if they had relapsed, had pre-existing type 1 diabetes (before diagnosis of ALL) leaving 15 potentially eligible survivors. The rationale for the exclusions was to leave a sample to which abnormalities in weight status or body composition might be attributable to ALL or its treatment. The eligible survivors were invited to participate but only 12 (80%) had agreed. The included ALL survivors (seven males and five females) had age ranging between 3 and 12 years (7 ± 3) at the time of diagnosis. At study time, their ages ranged between 7 and 18 years (11.5 ± 3.4). Five of them (41.7%) had family history of type 1 diabetes mellitus.

Fifteen healthy children with matched age (11.6 ± 3.74), sex (nine males and six females) and family history of type 1 diabetes (four out of 15; 26.7%) were enrolled as a control group.

The Ethics Committee approved the study. Study participants' caregivers provided informed consent to their children's participation.

2.2. Methods

All participations were subjected to the following:

(I) Full history taking including family history of diabetes mellitus. Data regarding the subject's ALL treatment were collected from the medical record on a separate occasion. Information gathered included date of diagnosis, age, height and weight at diagnosis, first recorded serum glucose level, three highest serum glucose levels recorded during treatment, details of chemotherapy including type of steroid used, total cumulative doses of asparaginase, dexamethasone, and/or prednisone, and date of completion of therapy. All survivors had received dexamethazone. The total asparaginase dose was expressed as the number of courses of asparaginase. One course of L-asparaginase refers to either the nine injections of 6000 units/m^2 used in the induction phase of chemotherapy or the six injections of 6000 units/m^2 used in other chemotherapy phases.
Subjects were defined as having transient hyperglycemia if they had greater than two random glucose levels greater than 200 mg/dl.[14]

(II) Thorough clinical examination.

(III) Anthropometric measurements including:

Height and weight were measured to 0.1 cm and 0.1 kg, respectively, using a Scale-Tronix stand on scale 5002 while patients removed shoes and outdoor clothes.

Body mass index was calculated as weight in kilograms divided by height in meters squared (BMI, kg/m^2) both at diagnosis and at study time for survivors.

The BMI was expressed as an age and sex specific *z*-score or centile. Egyptian BMI reference data are available[15] in the form of centile charts for boys and girls and so these were used in the present study. Various international BMI for age reference data are available, the most widely used are probably those provided by the US Centers for Disease control and prevention (CDC).[16] Both of these were used in the present study. BMI *z*-scores were calculated from WHO 2007 reference data using WHO Anthro version 3.2.2, January 2011 software.[17] BMI *z*-scores were calculated relative to US CDC reference data. When using Egyptian and US CDC BMI for age reference data obesity was defined conventionally, as $\geqslant$95th centile, overweight as 85th to 94th centile, and underweight as $<$5th percentile.[16] According to WHO classification of BMI 2007,[17] a person with BMI *z*-score $>$ 2SD is considered obese, this with $>$1SD is considered overweight and if $<$2SD is considered thin.

Waist and hip circumferences (cm) were measured while the subjects were wearing light clothing. Waist circumference was measured at the minimum circumference between the iliac crest and the rib cage. Hip circumference was measured at the maximum protuberance of the buttocks, and the waist/hip ratio (WHR) was calculated.[18]

(IV) Laboratory investigations including:

Oral glucose-tolerance test (OGTT):

At 8–9 AM, after a 10-h to 12-h overnight fast, baseline blood samples were obtained for measurements of glycosylated hemoglobin (Hb A1c), fasting plasma glucose and fasting insulin. Thereafter, glucose in a dose of 1.75 g/kg of body weight (up to a maximum of 75 g) was given orally, and blood samples were obtained every 30 min for 120 min for measurements of plasma glucose and insulin.

Blood samples were transferred into sodium fluoride tubes and then centrifuged. Blood glucose level was plotted against time to draw glucose tolerance curve.

Blood glucose was determined by enzymatic colorimetric test using Spin react kit, SPAIN.[19]

Impaired glucose tolerance (IGT) was defined, according to the American Diabetes Association guideline, 2012[20] as a fasting plasma glucose level of 101–125 mg/dl and a 2-h plasma glucose level of 140–199 mg/dl; diabetes was defined as a fasting plasma glucose level of 126 mg/dl or higher or a 2-h plasma glucose level of more than 200 mg/dl or higher.

Fasting and 2-h postprandial serum insulin levels (μU/mL) were determined by enzyme linked immunosorbent assay method, using DRG® Insulin ELISA kit, Germany.[21]

IR is diagnosed when person has fasting insulin level $>$15 μU/mL or if the peak insulin level $>$150 μU/mL.[12]

The results were used to calculate the insulin and glucose area under the curve (AUC) and the homeostatic model assessment of IR [(HOMA index) = fasting glucose (mg/dl) $\times$ fasting insulin (μU/mL)/constant (405)].[22] According to Valerio et al.[23] a cut-off HOMA level of $>$2.5 in children and $>$4.0 in adolescents was used to identify an insulin-resistance status.

Glycated hemoglobin (Hb A1c) was determined by quantitative colorimetric measurement as percent of total hemoglobin using kits supplied by Teco diagnostics, USA.[24]

According to the American Diabetes Association guideline, 2012[20] normal level of Hb A1C is that $<$5.6%, if between 5.7% and 6.4% the person is of the category of an increased risk for diabetes and diabetes is diagnosed if it is $\geqslant$6.5%.

2.3. Statistical analysis

Results were collected, tabulated, statistically analyzed by IBM personal computer and Statistical Package for the Social Sciences (SPSS) version 16. Differences between the groups were evaluated by the non-parametric Mann–Whitney test. Chi-square test (χ^2) was used to study the relation between two qualitative variables. Spearman rank test for *p*-value of $\leqslant$0.05 was considered statistically significant.[25]

3. Results

All of the involved survivors had received dexamethasone with the mean cumulative dose of 869 ± 150 mg/m^2. The mean percentage of L-asparginase courses taken was 90 ± 10%.

The subjects had been off therapy for a mean of 24.33 months (SD ± 18.18, range 9–60 months).

The mean BMI at the time of the diagnosis did not differ than that of the control while, at study time the mean BMI and WHR were significantly higher compared to those of the controls.

According to the WHO BMI *z*-score and CDC classification of BMI centiles, 16.6% of the studied survivors were overweight and obese at the time of diagnosis, that increased to be 25% at the study time percentages that were higher compared to the controls (Table 1).

On individual level, all the included 15 healthy children had normal OGT values and Hb A1C% with no one having IR.

While among the studied 12 ALL survivors two (16.6%) developed transient hyperglycemia during therapy, one (8.3%) had IGT = pre-diabetes (2 h post load glucose $>$140), seven out of the 12 survivors (58.3%) had a risk level of Hb A1C (between 5.7% and 6.4%) but no one had DM or IR.

All components of the OGTT except the 2 h post load glucose were significantly higher in the ALL survivors compared to those of the controls.

Also the means of all indices of insulin sensitivity (fasting, 2 h post load insulin, HOMA IR index and area of insulin under the curve) together with the mean glycated Hb% of the ALL survivors were significantly higher compared to those of the controls (Table 1).

The overweight and obese ALL survivors according to the WHO BMI *z*-score classification (either at the time of diagnosis or at study time), did not differ in WHR ratio or any of insulin sensitivity indices compared to non-overweight survivors at the corresponding times (Table 2).

At study time the two survivors with transient hyperglycemia during therapy had a significantly high WHR compared to

Table 1 Comparison between survivors and the control group regarding clinical and demographic data.

	Survivors	Controls	Test value	*p*-Value
Age at study (years)	11.5 ± 3.4	11.46 ± 3.74	−0.099	0.92
Age at diagnosis (years)	7 ± 3			
Sex (male/female)	7/5 (58.3/41.7%)	9/6 (60/40%)	0.008	0.93
Family history of DM (yes/no)	5/7 (41.7/58.3%)	4/11 (26.7/73.3%)	0.675	0.411
BMI at diagnosis	16.12 ± 2.07		−1.860	0.06
BMI at the time of the study	17.86 ± 2.96	14.59 ± 0.46	−3.202	0.001[a]
BMI z-score for age at diagnosis				
Normal	10 (83.3%)	15 (100%)		
> 1SD (overweight)	1 (8.3%)			
> 2SD (obese)	1 (8.3%)			0.1
Non overweight	10 (83.4%)			
Overweight	2 (16.6%)		2.700	
BMI z-score for age at study time				
Normal	8 (66.7%)			
> 1SD (overweight)	3 (25.0%)			
< 2SD (thin)	1 (8.3%)			
Non overweight	9 (75%)		4.21	0.04[a]
Overweight	3 (25%)			
BMI centiles at diagnosis				
< 5	1 (8.3%)	0		
5–85	9 (75.1)	15 (100%)		
85–95	1 (8.3%)	0		0.1
> 95	1 (8.3%)	0		
Non overweight	10 (83.4%)			
Overweight	2 (16.6%)		2.700	
BMI centiles at study time				
< 5	2 (16.67%)			
5–85	7 (58.3)			
85–95	3 (25%)			
> 95	0			
Non overweight	9 (75%)		4.21	0.04[a]
Overweight	3 (25%)			
WHR at study time	0.92 ± 0.022	0.75 ± 0.06	−4.40	0.000[a]
Random blood sugar (mg/dl)	128.17 ± 13.16	98.93 ± 8.87	−4.29	0.000[a]
Fasting glucose in OGTT (mg/dl)	80.58 ± 9.85	71.40 ± 5.38	−2.65	0.008 [a]
1/2 h glucose in OGTT (mg/dl)	125.58 ± 20.49	108.40 ± 5.38	−2.21	0.027[a]
1 h glucose in OGTT (mg/dl)	103.84 ± 15.36	92.20 ± 9.77	−2.22	0.026[a]
2 h glucose in OGTT (mg/dl)	85.25 ± 26.98	70.66 ± 15.35	−1.35	0.177
Fasting insulin (μU/mL)	3.27 ± 2.32	1.59 ± 1.29	−2.20	0.028[a]
2 h post-prandial Insulin (μU/mL)	7.58 ± 3.42	3.36 ± 1.24	−3.08	0.002[a]
Homa IR	0.63 ± 0.44	0.28 ± 0.23	−2.489	0.013[a]
AUC	34.98 ± 28.18	7.44 ± 6.09	−3.230	0.001[a]
Glycated Hb%	5.74 ± 0.79	3.80 ± 0.26	−4.427	0.000[a]
Cumulative dose of steroid (mg/m^2)	869 ± 150			
Percentage of asparginase courses (%)	90 ± 10			
Type of steroid during induction	Dexamethasone			
Duration after therapy range (months)	9–60			
	24.33 ± 18.18			

[a] Significant.

the remainders without significant differences in any of the insulin sensitivity indices (Table 3).

There were non significant correlations between any of the insulin sensitivity indices at the time of the study and patients data (age at study and at diagnosis, mean BMI at diagnosis and at study time, duration after completion of chemotherapy, cumulative dose of steroid (mg/m^2), the % of L-asparginase courses) (Table 4).

WHR of the survivors at study time correlated significantly with fasting plasma glucose and area of insulin under the curve (AUC) (Figs. 1 and 2). While the 2 h post-prandial plasma glucose correlated with the duration after therapy completion (Fig. 3).

Table 2 Comparison between survivors according to BMI *z*-score categories regarding WHR and insulin sensitivity indices at the time of the study.

Item		WHR	Fasting glucose	Fasting insulin	2 h post-prandial Insulin	HOMA index	Insulin AUC
Overweight at diagnosis	Non overweight ($n = 10$)	0.92 ± 0.02	79.9 ± 9.87	3.5 ± 2.5	6.99 ± 3.30	0.69 ± 0.47	33.95 ± 30.10
	Overweight and obese ($n = 2$)	0.91 ± 0.02	84.0 ± 12.73	1.9 ± 0.6	10.50 ± 3.11	0.39 ± 0.06	40.12 ± 22.80
Test value		−0.439	−0.538	−0.859	−1.50	−0.859	−0.645
p-Value		0.66	0.591	0.390	0.132	0.390	0.519
Overweight at study	Non overweight ($n = 9$)	0.92 ± 0.02	82.11 ± 8.19	3.05 ± 2.45	6.90 ± 3.53	0.62 ± 0.49	30.61 ± 29.15
	Overweight ($n = 3$)	0.93 ± 0.035	76.0 ± 14.93	3.93 ± 2.15	9.6 ± 2.51	0.68 ± 0.31	48.07 ± 25.03
Test value		−0.44	−1.02	−0.86	−1.51	−0.86	−0.64
p-Value		0.66	0.32	0.39	0.13	0.39	0.51

Table 3 Comparison between hyperglycemic and non-hyperglycemic patients during therapy regarding WHR and insulin sensitivity indices at the time of the study.

Item		WHR	fasting OGTT (mg/dl)	Fasting insulin	2 h post-prandial insulin	HOMA index	Insulin AUC
Hyperglycemia during therapy	No ($n = 10$)	0.915 ± 0.15	80.80 ± 9.91	3.0 ± 2.4	7.67 ± 3.74	0.59 ± 0.47	34.90 ± 30.74
	Yes ($n = 2$)	0.95 ± 0.02	79.50 ± 13.43	4.65 ± 1.3	7.10 ± 1.27	0.89 ± 0.11	35.37 ± 15.37
Test value		−2.19	−0.43	−1.5	0.000	−1.72	−0.43
p-Value		0.028[a]	0.67	0.13	1.00	0.09	0.67

[a] Significant.

5. Discussion

The presence of glucose metabolism abnormalities among pediatric ALL survivors has been documented in different studies.[26–28]

Mohn et al.[27] reported an impaired insulin response in patients who had been off therapy for 1 year, but over time, this impairment resolved.[29] However, some studies suggest that some childhood ALL survivors, depending on therapy, may have a persistent risk of insulin resistance in their young adult years.[11,28]

Compared to the controls, the mean values of all components of the OGTT except the 2 h post load glucose, all indices of insulin sensitivity (fasting, 2 h post load insulin, HOMA IR index and area of insulin under the curve) together with the mean % of glycated Hb were significantly higher in the involved ALL survivors.

While on an individual level, among the studied 12 ALL survivors, only one (8.3%) had been found to have impaired glucose tolerance in the form of high 2 h post load glucose (148 mg/dl = pre-diabetic level) with high Insulin AUC (47.61) and with Hb A1C level of 6.4% (category of increased risk for diabetes) but other wise he did not have any symptoms of DM and his other laboratory data are within normal range. This survivor was 13 years at the study time, and was not overweight either according to BMI centiles or BMI *z*-score. His cumulative dose of steroids was the highest among the 12 survivors (1000 mg/m^2) and completed 80% of his asparaginase

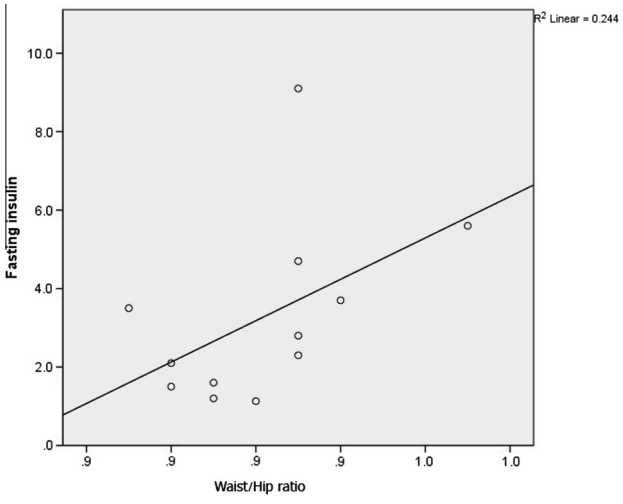

Fig. 1 Correlation between WHR and fasting insulin.

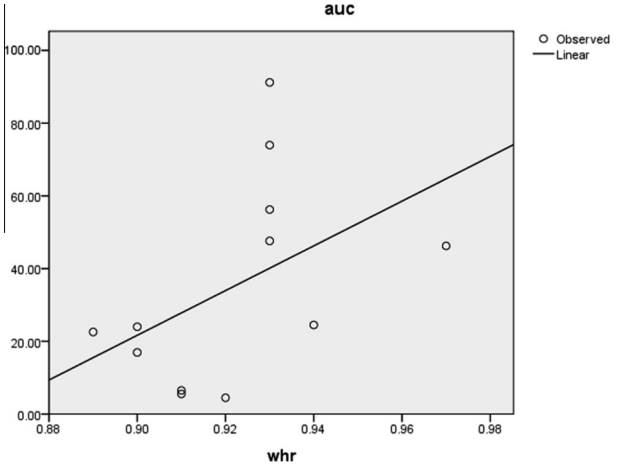

Fig. 2 Correlation between WHR and area of insulin under the curve.

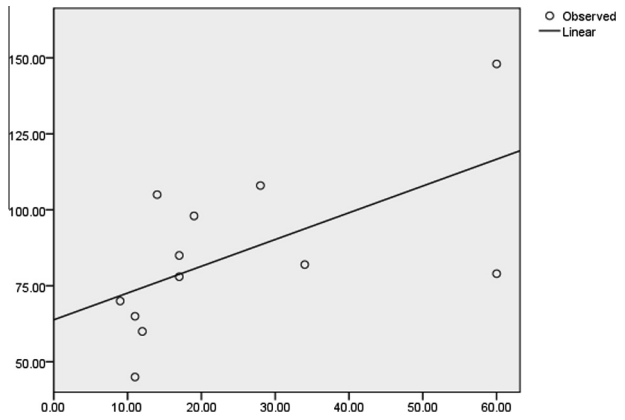

Fig. 3 Correlation between duration after therapy completion and 2 h post load glucose.

courses without any documented transient hyperglycemia during therapy. This adolescent survivor had completed his therapy since 60 months (the longest duration among the studied survivors).

IR is not documented in any of the ALL survivors or the controls.

Against these results, Lowas et al.[30] documented IR in eight out of the studied 27 ALL survivors (29.6%) and one subject had pre-diabetes (with a fasting glucose level of 101 mg/dl, but this subject's 120-min glucose level was less than 140 mg/dl). Also Surapolchai and co-workers[31] had reported IGT in 10 out of 131 Thailand ALL survivors (7.6%) whereas 40 (30.5%) had IR. These two studies did not involve healthy control group.

Recent studies suggest that ALL survivors have an increased prevalence of obesity.[5,6,32,33]

We have selected BMI as a surrogate measure of body fatness. BMI is the standard index used in clinical studies of obesity in adults and has been shown to correlate with other indices of body fat in children and adolescents.[34]

In the present study, two out of the 12 survivors (16.8%) were overweight or at risk at the time of diagnosis by applying the international approaches based on BMI (centiles and *z*-score) that did not differ significantly compared to the controls. This percentage increased to be 25% (three out of 12) at the study time (an average of 5 years after completion of chemotherapy) and this differed significantly with controls. Also the mean BMI of the survivors at study time was significantly higher than that of the controls that was not true at the time of diagnosis.

Based on U.S. Centers for Disease Control and Prevention (CDC) definition growth charts, Salazar-Martinez et al.[35] reported that the prevalence of overweight and obesity was 12.1% and 6.2%, respectively, among the healthy Egyptian adolescents. Back to the results of this work, it could be observed that, overweight and obesity were more prevalent in ALL survivors compared to general Egyptian population. This supports the role of chemotherapy in acquiring overweight in ALL survivors.

The results of this study come in agreement with those of Lowas et al.[27] who documented overweight or at risk in seven out of 27 studied group (25.9%) at the time of diagnosis that increased to 15 (55.6%) at study time after an average of 2.8 years off therapy. The higher percentage of overweight in the latter study can be explained by the involvement of cranial or cranio–spinal radiotherapy in three out of the 27 survivors (11.1%) as children with ALL given cranial radio-therapy (CRT) developed increases in their BMI-standard deviation score (*z*-score) early on and during treatment and remain at a significant risk for becoming overweight as young adults.[36]

One previous study also based on Korean children with ALL found a trend toward continued increase in BMI even after treatment completion.[37]

In Saudi study performed on 56 adolescent ALL survivors, with a mean age of 13.4 years a mean of 9.1 years post-diagnosis who did not receive CRT, the prevalence of BMI for age defined overweight and obesity (combined 28.5%) were actually lower than in the general population in Saudi Arabia. The authors suggested that overweight and obesity observed are probably not an ALL specific problem.[38]

It is known that adiposity, particularly abdominal adiposity, is associated with increased insulin resistance.[12,39]

Lowas et al.[30] reported that the elevated BMI for age at the time of study was a strong, consistent predictor of insulin resistance as it correlated significantly with several measures of insulin resistance. Waist/hip ratio and BMI at ALL diagnosis also correlated with insulin resistance. Variations in

ALL therapy, total doses of steroids and presence of transient hyperglycemia did not appear to increase risk of glucose intolerance or insulin resistance.

Table 4 Correlations between insulin sensitivity indices and clinical assessment data at the time of the study.

Hb A1C		Insulin AUC		HOMA index		2 h post-prandial insulin		Fasting insulin		Item
Sig.	*r*	Sig.	*r*	Sig.	*r*	Sig.	*r*	Sig.	*r*	
0.643	−0.150	0965	−0.014	0.877	−0.050	0.960	−0.016	0.991	−0.004	Age at study
0.163	0.43	0.645	−0.148	0.785	−0.088	0.537	−0.198	0.983	−0.007	Age at diagnosis
0.590	−0.173	0.863	−0.056	0.372	−0.284	0.854	0.060	0.359	−0.291	BMI at diagnosis
0.768	−0.095	0.240	−0.368	0.121	−0.473	0.279	−0.340	0.158	−0.434	BMI at study
0.363	−0.288	0.047[a]	0.582	0.101	0.497	0.488	0.222	0.044[a]	0.589	WHR
0.365	0.287	0.965	0.014	0.888	0.046	0.650	−0.146	0.820	0.074	Duration after completion of chemotherapy (months)
0.412	0.261	0.545	0.194	0.084	0.518	0.688	0.130	0.139	0.453	Hyperglycemia during therapy
0.169	0.599	0.931	−0.028	0.697	0.126	0.888	−0.046	0.681	0.133	Cumulative dose of steroid (mg/m^2)
0.785	0.088	0.925	0.030	0.981	−0.008	0.860	−0.057	0.768	0.095	Courses of L-asparginase

[a] Significant.

In this study, overweight and obese ALL survivors (either at time of diagnosis or at study time), did not differ in any of insulin sensitivity indices compared to non-overweight survivors at the corresponding times. Further more BMI (either at time of diagnosis or at study time) did not correlate to any of insulin sensitivity indices.

Warner et al.[40] found that the BMI for age provided a poor indicator of excess adiposity in patients with childhood cancer and other chronic diseases.

Studying WHR as another indicator of central obesity, the mean WHR of the studied survivors was significantly higher compared to that of the controls. It was the only variable that correlated to some of insulin sensitivity indices (fasting insulin and insulin AUC) while other variables including cumulative steroid dose and courses of L-asparginase percentage did not.

Several studies have noted an increased incidence of transient hyperglycemia during remission induction treatment for childhood ALL.[26,30,41,42] Some have suggested that there may be a lasting hyperglycemic effect on patients with or predisposed to diabetes.[43]

Among the studied 12 ALL survivors, two (16.6%) developed transient hyperglycemia during therapy.

At the study time these survivors had a significantly high WHR compared to the remainders without significant differences in any of the insulin sensitivity indices. This strengthens the relation of WHR to insulin sensitivity indices in ALL survivors.

Presence of hyperglycemia during therapy did not have any relation to insulin sensitivity indices at study time. This comes in accordance with previous studies which found no relationship between transient hyperglycemia during treatment and glucose intolerance in the first several years after treatment completion.[30,44]

In this work duration after therapy completion had correlated to 2 h post load glucose and this may denote that long term follow up for these survivors is needed to demonstrate the possible disturbance in glucose metabolism that may occur.

The present study was limited by small sample size, 12 subjects were studied instead of the 15 originally planned. One reason for this was the difficulty in subject recruitment due to lack of interest of the parents. Another limitation was the short time between end of the therapy and the present study.

Additional limitations include the variation in age and time off therapy of the subjects. These, too, were related to the few adolescents who participated.

6. Conclusions

It can be concluded that, although the mean values of OGT test and IS indices were higher in ALL survivors compared to healthy controls, none of the values were high enough to indicate a disease process such as insulin resistance on an individual level.

There was no role of BMI in the prediction of insulin resistance as a late effect of chemotherapy in pediatric ALL survivors, but WHR may play a better role in the prediction of insulin resistance in those patients.

Hb A1C may increase earlier than other indices of glucose tolerance.

The potential for late-onset of metabolic syndrome still exists, demanding a long-term longitudinal research and longer follow-up to gain better understanding of predisposing factors of glucose metabolism alteration in ALL survivors. The late effects of chemotherapy on glucose metabolism still deserve further research on a study of a larger population sample.

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