INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. Cure rates of ALL have improved significantly and with the improving survivorship of childhood ALL, long-term treatment related effects are being observed more frequently and need to be assessed. Survivors are at increased risk for obesity, insulin resistance, and increased visceral and subcutaneous adiposity ***(Tonorezos et al. 2013; Srivastava et al. 2015)***.

Obesity is well recognized problem for children treated for ALL and is present in roughly one fourth of children by end of therapy. Obesity may lead to immediate health issues such as increased risk for cancer relapse or may cause future health issues such as DM, metabolic syndrome, hypertension, additional cancers or cardiovascular diseases ***(Withycombe 2012).***

The mechanisms underlying obesity in ALL has been hypothesized to the use of steroids, effect of chemotherapy and cranial irradiation on the hypothalamic pituitary axis. However, the mechanisms of obesity in ALL survivors seem to be interplay of many factors ***(Siviero-Miachon et al. 2007).*** Obesity is a modifiable risk factor; primary and secondary prevention can decrease the associated morbidity and mortality ***(Srivastava et al. 2015)***.

Metabolic syndrome (MS) is a common complication encountered in children surviving ALL. Affected patients develop obesity, insulin resistance, hypertension and hyperlipidemia. Metabolic syndrome is a consequence of multiple factors, particularly hormonal imbalance induced by various ALL treatment. Clinicians should continue to identify patients at risk early and use therapeutic approach that combines dietary restrictions and enhanced physical activity ***(Abu-Ouf & Jan 2015)*.**

The pathophysiological and biological mechanisms underlying the association between MS and cancer remain unexplained and are starting to be understood. Survivors of various malignancies may present metabolic syndrome traits several years after cancer therapy withdrawal ***(Siviero-Miachon et al. 2012)***.

Leptin, a hormone secreted mainly by adipocytes, regulates appetite and energy expenditure by acting in hypothalamus. Leptin and leptin resistance has been hypothesized to play a role in the development of obesity or weight gain in ALL survivors ***(Arguelles et al. 2000; Davies et al. 2004)***. Leptin is also an important nutritional marker and adiposity index during and after ALL therapy and is strongly correlated with BMI ***(Arguelles et al. 2000; Adan et al. 2001)*.**

AIM OF THE WORK

The main objectives of this study were to:

- Assess the frequency of obesity and metabolic syndrome in survivors of childhood ALL.
- Identify alterations in body composition of survivors of childhood ALL.
- Identify the risk factors for obesity and metabolic syndrome among this group of patients.

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Acute Lymphoblastic Leukemia (ALL) represents one third of pediatric cancer cases, accounting about 75-80% of all cases of acute leukemia in children ***(Lim et al. 2014)***.

The incidence rate of childhood ALL is now stable at 3 to 4 new cases per year per 100,000 children who are younger than 15 years, with a peak incidence at approximately 2–5 years of age ***(Swensen et al. 1997; Greenlee et al. 2000)***.

In Egypt, the incidence of lymphatic and hematopoietic cancers increased dramatically over the period from 1972 to 2001. The lymphatic and hematopoietic cancer incidence in 2001 have increased approximately 11 times cancer incidence in 1972 ***(Hosny & Elkaffas 2002)***. In the years 2002-2005, the overall incidence of childhood cancer was approximately 78,010 new patients, seen at the National Cancer Institute, Cairo, Egypt; among which leukemia represents the most common childhood cancer, representing almost 35% of all cases ***(El-Attar 2005)***.

Remarkable advances have been made over the past 55 years in both the treatment of ALL and the improved understanding of the biology of the disease. Pediatric ALL is often cited as one of the true success stories of modern medicine, with the cure rate improving from virtually zero in

the 1950s to current overall and event-free survival (EFS) rates of approximately 80% ***(Schrappe et al. 2000; Pui et al. 2004).***

Treatment of Childhood ALL:

Treatment of childhood ALL includes four components: remission induction, consolidation, continuation, and treatment of subclinical central nervous system (CNS) leukemia.

1- Remission induction

The goal of remission-induction therapy is to eradicate more than 99 percent of the initial burden of leukemia cells and to restore normal hematopoiesis and a normal performance status. This treatment phase almost always includes the administration of a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and at least one other agent (usually asparaginase, an anthracycline, or both). Improvements in chemotherapy and supportive care have resulted in complete remission rates of about 98 percent for children ***(Pui & Evans 2006).***

2- Intensification (consolidation) therapy

When normal hematopoiesis is restored, patients in remission become candidates for intensification therapy. Commonly used regimens for childhood ALL include high-dose methotrexate with mercaptopurine, high-dose asparaginase given for an extended period, and re-induction treatment ***(Silverman et al. 2001; Pui & Evans 2006)***.

3- Continuation treatment:

Patients with ALL generally require prolonged continuation therapy, for reasons that are still poorly understood. A combination of methotrexate administered weekly and mercaptopurine given daily constitutes the basis of most continuation regimens ***(Pui & Evans 2006)***.

4- Treatment directed to the central nervous system

Factors associated with an increased risk of relapse in the CNS include high risk genetic features, T-cell immunophenotype, a large leukemia-cell burden, and the presence of leukemia cells in the cerebrospinal fluid ***(Burger et al. 2003; Pui 2003)***. Cranial irradiation is still recommended for patients at very high risk for relapse, such as those with leukemia of the CNS or those with T-cell ALL, especially with presenting leukocyte counts of more than 100×10^9 per liter ***(Howard et al. 2002; Pui 2003)***. However, because cranial irradiation can cause many acute and late complications, including second cancers, late neurocognitive deficits, and endocrinopathy ***(Pui 2003)***, it has largely been replaced by intrathecal and systemic chemotherapy. In a growing proportion of patients, prophylactic cranial irradiation, once a standard treatment, is being replaced by intrathecal and systemic chemotherapy to reduce radiation-associated late complications such as second cancers, cognitive deficits, and endocrinopathy ***(Pui et al. 2003; Geenen et al. 2007; Hijiya et al. 2007; Waber et al. 2007)***.

Late and Long-term Effects of ALL Therapy

Using modern treatment regimens, the 5-year survival rate of ALL has improved from virtually zero (in the 1950's) to approximately 80% ***(Silverman et al. 2001)***. A significant improvement in patient survival has led to a heightened focus on the long-term complications associated with this disease and corresponding treatments.

Unfortunately, long-term survivors of childhood cancer are at risk of developing a spectrum of late adverse effect, such as reduced growth, obesity, decreased fertility, high blood pressure, cardiovascular diseases (CVD), impaired glucose metabolism, another form of cancer, and organ dysfunction ***(Barnea et al. 2015)*.**

In the last decades, cranial radiotherapy has been replaced by intra thecal chemotherapy, as standard CNS prophylaxis and treatment, and a reduced percentage of children have received cranial radiation with a consequent reduction of sequelae related to this treatment modality. However, it has been suggested that also chemotherapy can negatively affect growth and endocrine functions ***(Breene et al. 2011)*.**

Childhood acute leukemia survivors exhibit a more than 4-fold increase in cardiovascular-related mortality rates, including congestive heart failure, coronary artery disease including myocardial infarction, cardiac arrest and stroke, compared with

siblings or the general population ***(Mertens et al. 2008; Mody et al. 2008)***. Anthracyclines, which have been linked to cardiac toxicity, are only partly responsible for this increased cardiovascular mortality ***(Chen et al. 2011)***. Furthermore, childhood ALL survivors have been shown to have early signs of atherosclerotic lesions ***(Gurney et al. 2012; Dengel et al. 2014)***. The natural evolution of atheromatous disease begins years before the onset of a lesion with clinical impacts.

CHILDHOOD OBESITY AND METABOLIC SYNDROME

Childhood obesity is one of the most important public health challenges. It is strongly associated with risk factors for cardiovascular disease ***(Han et al. 2010)***, type 2 diabetes (T2DM), orthopedic problems, mental disorders, under achievement in school and lower self-esteem ***(Fruhbeck 2000)***, cholesterol gallstone disease ***(Di Ciaula et al. 2012),*** and dysfunctional gastrointestinal motility ***(Nacci et al. 2013).***

Definition of obesity

For children, the use of body mass index (BMI) is the common basis for defining weight status, and standard deviation scores for BMI (BMI-SDS), also referred to as z scores, have become widely accepted. BMI is defined as weight (in kg) divided by height (in m^2). For children and adolescents, overweight is defined as BMI > 85^{th} percentile, obesity as ≥ 95^{th} percentile for age and severe obesity is considered to be > 99^{th} percentile ***(Rosenblum & Venkatesh 2017)***.

Using BMI to define overweight and obesity has limitations, for example, people with well-developed muscularity but little fat will have a high BMI ***(Sweeting 2007).*** Body mass index also does not give any indication as to the distribution of fat in the body: in adults, central adiposity is

more closely associated with health risks than general adiposity ***(Coutinho et al. 2013)*.**

Indices predictive of adolescent central obesity include waist circumference (WC), waist-to-hip ratio (WHR and waist-to-height ratio (WHtR). Waist circumference is a highly sensitive and specific measure of upper body fat in young people and thus it is valuable for identifying overweight and obese adolescents at risk of developing metabolic complications. The same applies for risk factors of cardiovascular disease in children and adolescents, in whom WC and WHtR are better predictors than BMI ***(Savva et al. 2000)*.**

Obese children are at higher risk of being obese as adults ***(Llewellyn et al. 2016)*.** Adult obesity is associated with significantly increased risk of morbidity, including T2DM, CVD and cancer, and hence with premature mortality ***(Vucenik & Stains 2012)*.** However, the increase in risk is not large enough for childhood BMI to be a good predictor of the incidence of adult morbidities, as most of adult obesity-related morbidity occurs in adults who were of healthy weight in childhood. Using BMI as a screening tool for childhood obesity may help identify obese or overweight children who would benefit from weight management intervention, but does not identify the majority of children who will go on to develop obesity related morbidities in adulthood ***(WHO 2012)*.**

Metabolic Syndrome

Metabolic syndrome (MS) comprises a cluster of cardiovascular risk factors (hypertension, altered glucose metabolism, dyslipidemia and abdominal obesity) that occur in obese children. However, MS can also occur in lean individuals, suggesting that obesity is a marker for the syndrome, not a cause ***(Meinardi et al. 2000; Weiss et al. 2013).***

Different criteria have been developed for the diagnosis of metabolic syndrome (Table 1). National Institutes of Health (NIH) has defined MS by having at least three of the following conditions: central obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), hypertension or elevated fasting plasma glucose ***(Smith & Ryckman 2015).***

The International Diabetes Federation (IDF) defines MS in children >10 years of age as abdominal obesity, plus at least two of the following clinical features: hyperglycemia, hypertriglyceridemia, reduced HDL cholesterol, and hypertension.

Table 1: Definitions of Metabolic syndrome

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia† (plasma insulin >75th percentile	Central obesity (WC ≥ 99cm (M), ≥ 80 cm (F)
Criteria	Any 3 of the 5 criteria below	Insulin resistance or diabetes, plus 2 of the 5 criteria below	Hyperinsulinemia plus 2 of the 4 criteria below	Obesity plus 2 of the 4 criteria below
Obesity	WC > 40 inches (M), > 35 inches (F).	WHr > 0.90 (M), > 0.85 (F) or BMI > 30 Kg/m^2	WC > 94 cm (M), > 80 cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥ 100 mg/dl or	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥ 100 mg/dl
Dyslipidemia	TG ≥ 150mg/dl or	TG ≥ 150 mg/dl or HDL cholesterol < 35 mg/dl (M), < 39 mg/dl (F)	TG ≥ 177 mg/dl or HDL cholesterol < 39 mg/dl	TG ≥ 150 mg/dl
Dyslipidemia (2nd separate criteria)	HDL cholesterol < 40 mg/dl (M), < 50 mg/dl (F) or			HDL cholesterol: < 40 mg/dl (M), < 50 mg/dl (F):or Rx
Hypertension	> 130 mmHg systolic or > 85 mmHg diastolic or	≥ 140/90 mmHg	≥ 140/90 mmHg or Rx	> 130 mmHg systolic or > 85 mmHg diastolic or Rx
Other criteria		Micro albuminuria*		

NCEP: National Cholesterol Education Program Expert Panel; WHO: World health organization; EGIR: European Group for the Study of Insulin Resistance; IDF: International Diabetes Federation; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; T2D: type 2 diabetes; IR: insulin resistance; other evidence includes euglycemic clamp studies; Rx: Pharmacologic treatment.

*Urinary albumin excretion of > 20 microgram/min or albumin–to-creatinine ratio of > 30mg/g; †: Reliable only in patients without T2D

(Huang 2009)

In 2007, the IDF attempted a definition of pediatric metabolic syndrome using age-specific diagnostic criteria and proposed that metabolic syndrome be considered in (1) children aged 6–10 years who are obese (defined as waist circumference (WC) ≥90th percentile) and have other relevant risk factors (such as family history of cardio metabolic disease) and in (2) children aged 10–16 years who are obese defined as WC ≥ 90th percentile) and meet the adult metabolic syndrome criteria for triglycerides TGs), HDL-cholesterol (HDL-C), blood pressure and glucose concentrations ***(Zimmet et al. 2007)*.**

Causes and risk factors for developing MS

Although the risk for MS has largely been attributed to adult lifestyle factors such as poor nutrition, lack of exercise, and smoking, there is now strong evidence suggesting that predisposition to the development of MS begins in utero ***(Smith & Ryckman 2015)*.** Obesity during pregnancy is associated with an increased risk of short- and long-term metabolic dysfunction in the mother and her offspring ***(Catalano & deMouzon 2015)*.**

Among risk factors predisposing to the development of MS in childhood, genetic factors, low birth weight, and early adiposity rebound, obesity, insulin resistance (IR), physical inactivity and unhealthy diet may all contribute to a child's future risk ***(Nesto 2003; Poeggeler et al. 2010)*.**

Insulin resistance

Insulin resistance (IR) is defined as the decreased tissue response to insulin-mediated cellular effects ***(Weiss et al. 2013)***. Multiple clinical characteristics related to IR and compensatory hyperinsulinemia can help to identify children and adolescents with IR ***(Calcaterra et al. 2008)*.** These include acanthosis nigricans, polycystic ovary syndrome, hypertension dyslipidemia, and nonalcoholic fatty liver disease ***(Ho et al. 2014)*.** With the development of IR, the individual progresses to impaired glucose tolerance, pre-diabetes and finally to T2DM when the pancreatic β-cell reserve diminishes ***(Weiss et al. 2005)*.**

Body fat amount and distribution as well as physical activity, are related to IR accordingly, weight loss and increase in physical activity improve IR and MS ***(Inoue et al. 2015)*.** The association between body fat, physical activity and insulin resistance is mediated by several adipocytokines, such as leptin and adiponectin ***(Koerner et al. 2005)*.**

Insulin resistance plays a major pathophysiological role in MS ***(Vukovic et al. 2015)***. Obesity and IR promote release of free fatty acids and various adipokines from adipocytes, which lead to acute changes in vascular reactivity and chronic endothelial injury through inflammatory responses and oxidative stress ***(Singleton et al. 2003)*.** Obesity is regarded as a low-grade chronic inflammation, further contributing to IR

because inflammation increases IR through multiple pathways ***(Bastard et al. 2006)*.**

Insulin resistance is also related to the development of hypertension and/or an abnormal lipid profile, characterized by elevated triglycerides, low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) in overweight and obese children and adolescents ***(Ho et al. 2014)*.**

Body composition and Fat Distribution:

The amount of fat and lean body mass and the distribution of fat are important risk factors for the prediction of cardiovascular disease and T2DM. The body composition of childhood cancer survivors (CCS) should be considered even if they are not overweight or obese ***(Sohn et al. 2011)*.**

BMI is only a crude indicator of body fat mass. The amount of fat and the distribution of fat, are more important risk factors for prediction of cardiovascular disease and T2DM ***(Jarfelt et al. 2005)*.**

Lipid partitioning (i.e., the distribution of fat among its potential depots) is much more related to the metabolic phenotype of obese children and adolescents than the degree of obesity Thus; lipid partitioning is a major determinant of peripheral insulin sensitivity and is strongly associated with other metabolic biomarkers ***(Weiss et al. 2004)***.