HHS Public Access

Author manuscript

Curr Treat Options Oncol. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Curr Treat Options Oncol. 2016 April ; 17(4): 17. doi:10.1007/s11864-016-0393-5.

Obesity and Metabolic Syndrome among Adult Survivors of Childhood Leukemia

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Opinion statement

Treatment-related obesity and the metabolic syndrome in adult survivors of childhood acute lymphoblastic leukemia (ALL) are risk factors for cardiovascular disease. Both conditions often begin during therapy. Preventive measures, including dietary counseling and tailored exercise should be initiated early in the course of survivorship, with referral to specialists to optimize success. However, among adults who develop obesity or the metabolic syndrome and who do not respond to lifestyle therapy, medical intervention may be indicated to manage underlying pathology, such as growth hormone deficiency, or to mitigate risk factors of cardiovascular disease. Because no specific clinical trials have been done in this population to treat metabolic syndrome or its components, clinicians who follow adult survivors of childhood ALL should use the existing American Heart Association/National Heart Lung and Blood Institute Scientific Statement to guide their approach.

Keywords

Acute lymphoblastic leukemia; childhood; pediatrics; survivor; obesity; metabolic syndrome; lifestyle; growth hormone deficiency; cranial radiation; glucocorticoids

Introduction

Advances in treatment and supportive care have improved five year survival rates for children diagnosed with acute lymphoblastic leukemia (ALL) to over 90% [1].

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Unfortunately, treatment is not without consequence; 50% of childhood ALL survivors in their twenties will have at least one chronic medical condition [2]. Early death is also a recognized problem; the standardized mortality ratio among those who survive five years from diagnosis is 9.5 (8.8–10.2) [3] with non-cancer related mortality frequently attributed to a cardiovascular cause [3]. Although chronic cardiac conditions and early cardiac deaths in this population have been linked to treatment exposures during childhood, recent data indicate that the presence of any one or multiple cardiovascular risk factors, including obesity and/or other components of the metabolic syndrome, can multiply this risk by as much as 40-fold [4]. Unlike treatment, many of these risk factors, also common in the general population, may be preventable or modifiable. Even with known treatment-related risk factors for chronic disease, survivors who adopt a healthy lifestyle may be able to modify their risk for adverse outcomes [5, 6]. This review summarizes recent literature describing the prevalence and risk factors for obesity and metabolic syndrome among childhood ALL survivors. We also provide suggestions for lifestyle modifications that have potential to mitigate risk and summarize existing medical management guidelines for these adverse health outcomes.

Obesity

Obesity is an abnormal or excessive accumulation of body fat, defined by the World Health Organization as a body mass index (BMI) of ≥ 30 kilograms of body weight per square meter of height (kg/m^2). The reported prevalence of obesity among adult survivors of childhood ALL ranges from 11 to 56% and varies based on reporting method and cohort characteristics.[7] Data from the North American Childhood Cancer Survivor Study (CCSS), using self-reported height and weight values to calculate BMI, indicated that 17% of ALL survivors (N=1,765), with a mean age of 24.1 (range 18–42) years, had BMI values ≥30 kg/m2 [8]. As in the general population, higher rates of obesity among ALL survivors were associated with increasing age [9, 8] In addition, longitudinal data from the CCSS cohort show increasing rates of obesity over time; 31.7% of ALL survivors meet BMI criteria for obesity by age 32 years [9]. Self-report data from the CCSS are supported by self-report measures in other cohort studies [10]. However, data from clinical cohorts, where BMI is ascertained using objective measures, indicate obesity rates ranging from 31% at a mean age of 22.3 years [11] to 42.8% at a median age of 32.4 years [12]. These rates are higher than expected given that the proportion of 20–39 year olds in the general population who are obese is 30.3% [13].

Body Composition

While BMI is the accepted standard for obesity screening, it is a somewhat crude measure of body fat and fat distribution, particularly among ALL survivors (reference) [14, 15]. Survivors often have other body composition abnormalities [14, 15], like abdominal obesity or high body fat percentage, that may contribute to an increased risk for chronic disease despite a normal BMI [16]. In fact, use of other anthropometric or imaging measures to characterize adiposity in ALL survivors suggests that using BMI to classify obesity may underestimate the prevalence of this problem. In a cohort of 35 adult survivors of childhood ALL, Jarfelt et al [14] reported that mean body fat percentages measured by dual x-ray

absorptiometry (DEXA) were more than 8% higher among males, and more than 4% higher among females when compared to age-, sex-, and BMI- predicted values. No survivor in this cohort was classified as obese by BMI. Similarly, we reported higher mean body fat percentages (4.5% males, 2.0% females) and lower mean percent skeletal muscle mass (2.6% males, 2.2% females), but no difference in BMI, comparing 75 ALL survivors (mean age 30.2 years) to age and sex matched controls [17]. These results were replicated in a larger study (365 ALL survivors, 365 age and sex matched controls) among survivors treated with cranial radiation therapy (CRT) (4.5% higher body fat among males; 3.5% higher body fat among females), as well as among males treated with CRT (6.4% higher body fat) [18].

Treatment-Related Risk Factors for Obesity

The most frequently documented risk factors for obesity following treatment for childhood ALL are CRT, younger age at diagnosis, and female sex [11, 8, 12]. In the CCSS, females who received CRT doses in excess of 20 Gy had the highest odds (OR 3.81, 95% CI 2.34–5.99) of obesity when compared to siblings [8]. The hypothesized mechanism for this association suggests that CRT induced neuronal damage to the hypothalamus and pituitary results in growth hormone deficiency (GHD) [19, 14, 20] and/or leptin insensitivity [21, 20, 22, 23]. Chemaitilly et al [19] reported that 46.5% of adult survivors of childhood cancer (mean age 34.2 years, 72.6% of whom were ALL survivors) exposed to CRT had fasting insulin like growth factor 1 (IGF-1) z-scores < -2.0 (a surrogate marker for GHD). In this study, risk factors for GHD included younger age at diagnosis, older age at follow-up, and higher doses of CRT. Additionally, survivors with evidence of GHD were more likely than those without to have central adiposity and low lean muscle mass. Skoczen et al [22] and Tonorezos et al [23] both reported higher serum leptin levels and higher rates of obesity in ALL survivors (N=82, median age 13.2 years; N=116, median age 23 years respectively) who received CRT when compared to those who did not receive CRT. Obesity was associated with higher serum leptin in both studies. These data are supported by a report from Janiszewski et al [24], who evaluated 114 young adult survivors of childhood ALL, and found lower IGF-1 values and increased total body fat, abdominal fat, visceral fat and serum leptin levels among survivors treated with CRT when compared to those not treated with CRT.

Other treatment-related risk factors independent of CRT that may impact adult obesity among survivors of childhood ALL include the type and dose of glucocorticoid exposure [25], the development of medication induced insulin resistance or diabetes during therapy [26, 27], and the amount of on therapy weight gain [25]. While the mechanisms underlying weight gain in children who do not receive CRT during treatment for ALL are unclear [28, 29], adiposity in these children is associated with increasing serum leptin levels and cumulative doses of glucocorticoids [26, 22]. It is possible that steroid therapies influence long-term adiposity by disrupting fat metabolism and distribution and/or by promoting an increase in energy intake during treatment [30, 31]. Nevertheless, the impact of on-therapy exposures and toxicities highlights potential opportunities for early intervention aiming to mitigate these long-term impacts of cancer therapy.

Genetic Mediators of Obesity

Several candidate gene studies, and one genome wide association study (GWAS), have evaluated potential genetic risk factors for overweight and obesity among adult survivors of childhood ALL. Ross et al, using data from the CCSS, reported that female survivors (N=600) with BMI ≥ 25 mg/m^2 were twice as likely as those with BMI < 25 mg/m^2 to be homozygous for the Arg Allele on the leptin receptor gene (*LEPR*, Gln223Arg, rs1137101) [32]. This finding is consistent with other reports suggesting that leptin levels are highest in female survivors of childhood ALL [33], and that soluble leptin receptor levels are negatively correlated with body mass [22]. Another group of investigators evaluated associations between obesity and polymorphisms of the fat mass and obesity associated (*FTO*) gene. Among ALL survivors treated with CRT, they found lower rates of obesity in those homozygous for the T allele at rs9939609 when compared to those with at least one copy of the A allele [34]. While the exact function of the *FTO* gene is unknown, it has been associated with regulation of global metabolic rate, energy expenditure, energy homeostasis, body size, and body fat accumulation [35, 36]. Wilson et al [12] conducted a GWAS among 1,996 adult survivors of childhood cancer (42% were ALL survivors) and found potential genetic predictors of obesity on chromosomes 13 *(FAM155A)*, 2 (*SOX11*), 4 *(GLRA3)* and 5 (*CDH18 and BASP*1) among those exposed to CRT. *FAM155A* is expressed in the hypothalamus and pituitary, *GLRA3* codes for a receptor protein involved in signaling the glycine neurotransmitter, and *CDH18* and *SOX11* influence neuronal growth, repair and connectivity, so these findings may support the hypothesis that CRT induced neuronal damage influences obesity.

Adiposity Onset

Weight gain among children treated for ALL often begins during therapy, persists following cessation of treatment, and is associated with younger age at diagnosis, even among children treated without CRT [37–39]. Data from the Children's Oncology Group (COG) Study CCG 1691 that included 1,638 children with high risk ALL indicated that 23% of children had BMI values indicative of obesity (≥ 95th percentile) at the end of therapy, compared to 14% at diagnosis. In two other studies, Esbenshade et al [40] and Chow et al [38] also reported higher prevalence of obesity at the end of therapy than at diagnosis (23 versus 19%, 21 versus 11%) among 183 pediatric and 165 children with ALL, respectively. In the study by Chow et al [38], the prevalence five years after completion of therapy remained essentially unchanged (20.0%) compared to the end of therapy. Finally, Winkler et al evaluated trajectories of weight gain among 62 children treated for ALL without CRT. Children in all age groups were at risk for weight gain during therapy, and for persistent obesity. The highest post-treatment prevalence of obesity was among those diagnosed at 3 to 5 years of age [41].

Metabolic Syndrome

Obesity, or excess adiposity, is just one component of a constellation of cardiovascular disease risk factors experienced by adult survivors of childhood ALL. As many as 33.6% of adult survivors of childhood ALL have the metabolic syndrome [42], a cluster of risk factors

for diabetes and cardiovascular disease defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) as the presence of at least three of the following criteria: 1) waist circumference > 102 centimeters (cm) in males and > 88 cm in females; 2) triglyceride levels > 150 milligrams per deciliter (mg/dL); 3) high density lipoprotein cholesterol (HDL-C) <40 mg/dL; 4) blood pressure ≥ 130/85 millimeters of mercury (mmHg); and 5) glucose ≥ 100 mg/dL [43].

Like obesity, rates of metabolic syndrome (or similar clusters of cardiovascular disease risk factors) in ALL survivors increase with increasing age, are more prevalent among females than males, and are associated with exposure to CRT and/or growth hormone abnormalities [44, 45, 11, 46, 42, 47–49]. Gurney et al reported metabolic syndrome among 16.6% of 75 ALL survivors a mean age of 30.2 years and a mean time since diagnosis of 25 years. Females were more likely than males to have metabolic syndrome, and 9 of 11 participants with metabolic syndrome had received CRT [46]. Nottage et al reported metabolic syndrome among 33.6% of 784 ALL survivors (median 31.7 years of age and 26 years after diagnosis). Rates of metabolic syndrome increased with age and were higher among those exposed to CRT than among those not exposed to CRT [42]. Similar to these cohort studies, a case control study by Link et al [20] reported higher waist to height ratio, higher serum triglycerides and glucose, and lower HDL-C among 44 adult ALL survivors (median age 25 years) previously treated with CRT compared to controls matched on age, sex, smoking habits and rural/urban residential status. They also found increased fat mass, lower lean mass and impaired indicators of cardiac function (ejection fraction, shortening fraction) among survivors when compared to controls. In this study, 91% of survivors were growth hormone deficient. Furthermore, peak growth hormone levels during stimulation testing were negatively correlated with measures of adiposity, plasma insulin, and leptin, and positively correlated with HDL-C levels.

Similar findings are presented in other studies of adult survivors of childhood ALL [47–49]. However, prevalence rates for components of metabolic syndrome vary widely, due in large part to heterogeneity in diagnostic criteria and study reporting methods (Table). Rates of adiposity range from 5.8 to 41.7%, elevated triglyceride levels from 13.0 to 58.2%, low HDL-C from 9.8 to 63.5%, hypertension from 19.5 to 46.4% and elevated fasting glucose from 4.7 to 31.4%.

Abnormalities of individual components of the metabolic syndrome often begin during cancer therapy, do not completely recover after cessation of therapy, and are associated with other markers of abnormal metabolism and cardiovascular disease in fairly young survivors. Esbenshade et al documented hypertension (41.5% systolic; 24.0% diastolic) among 184 children during treatment for ALL, and increasing insulin resistance during maintenance therapy among 34 ALL patients [50]. Chow et al documented hypertension in 63.3% of children with ALL at the end of induction, in 15.3% at the end of therapy and in 14.1% five years from diagnosis [38]. In a smaller study of 23 young survivors of childhood ALL (median age at evaluation 10.7 years), two had metabolic syndrome and all but eight had at least one component of the metabolic syndrome. The most prevalent components were hypertension (N=10) and high triglycerides (N=10) [51]. In this cohort, abdominal obesity, diastolic hypertension, and higher fasting glucose were associated with higher serum levels

of leptin, while systolic and diastolic hypertension and triglycerides were associated with low T-adiponectin. In an older population (mean age 18.6 years) of childhood ALL survivors (N=55), Sivero-Miachon et al evaluated components of the metabolic syndrome for associations with other markers of cardiovascular disease, and reported a positive correlation between systolic blood pressure and carotid intima-media thickness [52].

Prevention and Treatment Approaches

The high prevalence of obesity, the metabolic syndrome and other constellations of cardiovascular disease risk factors among ALL survivors is particularly concerning given their increased risk for both GHD and adverse cardiovascular outcomes [4, 53, 54]. Although previous treatment exposures are a fixed risk factor in the long-term follow-up setting, individual components of the metabolic syndrome are potentially modifiable, representing an area where targeted surveillance and secondary prevention strategies are needed.

Lifestyle Modifications

For both prevention and management of obesity and the metabolic syndrome, lifestyle interventions should be recommended to ALL survivors to avoid or remediate body composition and metabolic abnormalities. ALL survivors who are overweight or obese (or whose waist circumference exceeds 35 inches for women or 40 inches for men) should be offered a formal weight loss program that includes physical activity, dietary modification, and behavioral counseling [43]. Those who participate in less than the minimum recommendation of 150 minutes of moderate or 75 minutes of vigorous physical activity per week [55] should be encouraged to increase activity, aiming for at least 30–60 daily minutes of aerobic activity and bi-weekly resistance training. To optimize success with physical activity, ALL survivors who have medical co-morbidities or neuromusculoskeletal impairments that interfere with their ability to exercise should be referred to an exercise professional who can tailor an activity program to accommodate their impairments [17, 18]. ALL survivors whose diet is not consistent with recommended guidelines [56] should receive appropriate dietary counseling. A daily diet consistent with the WCRF/AICR guidelines [1) 5 servings of fruit and/or vegetables, 2) ≥400 grams (g) of complex carbohydrates, 3) <14 g (females), <28 g (males) alcohol, 3) <80 g red meat, and 4) < 2400 mg sodium] is associated with a decreased prevalence of the metabolic syndrome among cancer survivors [5], is easy to follow, and is appropriate for most adults [57].

Medical Management

In ALL survivors with specific components of the metabolic syndrome that do not respond to lifestyle interventions, pharmaceutical management may be required. In survivors with documented GHD, replacement therapy may be a viable option. A non-randomized study among 18 young adult (19–32 years) childhood ALL survivors with GHD [58] reported significant decreases in serum leptin, leptin per kg fat mass, plasma glucose, and waist and hip circumference after 12 months of growth hormone replacement (GHR) therapy. Unfortunately, no randomized GHR study has been done in childhood ALL survivors to date, largely because of concerns about the potential role of growth hormone in the

development of subsequent neoplasms (SN) [59]. Data from the CCSS and from post marketing studies estimated a five year cumulative incidence of 6.2% for any SN among pediatric cancer survivors treated with GHR [60, 61]. This risk appears to decrease over time [62], does not include increased risk for central nervous system SNs [63], and was estimated primarily in survivors who received replacement as children. Further data are needed to determine the efficacy and safety of GHR for adults who are GHD as a result of their treatment for childhood ALL.

Additional studies addressing the long-term impact of medical intervention for obesity and individual components of the metabolic syndrome on subsequent cardiovascular outcomes in childhood ALL survivors are largely unavailable due to issues of cost, cohort size, and duration of follow-up. In the absence of population-specific data to inform decision-making in childhood cancer survivors, leading organizations such as the American Heart Association have endorsed adaptation of risk-reduction strategies recommended for children and adults in the general population [64]. In general, pharmacologic intervention is recommended when aggressive lifestyle modifications fail to normalize individual components of the metabolic syndrome. As an example, a consensus statement from the American Heart Association/National Heart Lung and Blood Institute outlines parameters for pharmaceutical management of dyslipidemia, elevated blood pressure and elevated plasma glucose among adults based on specific risk categories for coronary heart disease (CHD) derived from large, long-term observational studies such as the Framingham Heart Study [43].

It is important to note, however, that even among non-cancer populations, risk scores such as these are limited in their ability to predict adverse cardiovascular events for individuals <40 years of age.[65] In addition, they do not account for cancer-treatment specific cardiac risk factors (e.g. cardiotoxic chemotherapy and/or radiation exposure), leaving their utility in survivor cohorts unknown. It is therefore important that clinicians consider the complex etiologies often contributing to cardiovascular risk factors in cancer survivors when determining best practical management.

Summary

Advances in therapy and improvements in risk stratification have inspired substantial changes in childhood ALL treatment in recent decades, with the dual goals of improving cure rates and reducing the incidence of late health effects. Although these changes may yield lower incidence rates of obesity and metabolic syndrome among at least some groups of newly-diagnosed childhood ALL survivors, there is a clear need for additional research into the etiology, prevention and management of these conditions. For example, CRT has been replaced by chemotherapy in contemporary protocols for the treatment of standard risk ALL, yet children treated with chemotherapy alone are still at risk for excess adiposity and metabolic abnormalities. Thus it is crucial that mechanisms by which specific chemotherapeutic agents increase risk of metabolic dysfunction are identified. Beyond treatment changes, improved prevention of obesity and metabolic syndrome in survivors requires evidence-based intervention strategies, tailored to the specific demands of children undergoing or having recently completed cancer therapy. Although, existing guidelines for

the general population can be useful for directing management of obesity and metabolic syndrome in survivors, further research should evaluate a) the need for modified diagnostic criteria (e.g. lower thresholds for high blood pressure) in the context of prior cardiotoxic treatment exposures, and b) survivor-specific interventions for monitoring metabolic status and improving diet and physical activity. Finally, long-term studies in large survivor cohorts are needed to inform the most appropriate strategies for medical management in this unique population.

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Table

Summary of studies of metabolic syndrome among adult survivors of childhood ALL

Author Year	Time since diagnosis	Age at evaluation	Metabolic syndrome	Increased waist circumference/ adiposity	Elevated Triglycerides	Low HDL-C	Hypertension	Elevated blood glucose	Risk factors identified
(N)	years	Years	%	%	%	%	%	%	
Talvensaari [48] 1996 (28/50 with ALL)	Range 8–21	10–31	16.0%	32% obese	No mean difference survivors vs. controls	Survivors lower mean values vs. controls	No mean difference survivors vs. controls	Higher mean values survivors vs. controls	GHD
Kourti [66] 2005 (52)	Median (since completion of therapy) 37 mo 3.1 years	Median 15.2	5.8%	5.8% obese	23.1%	32.7%	–	–	–
Gurney [46] 2006 (75)	Mean 25.0	Mean 30.0	16.6%	41.7%	20.6%	63.5%	21.1%	9.9%	GHD and CRT
Trimis [67] 2007 (80)	Median (since completion of therapy) 6.3 years	Median 13.9	11.3%	25.0% obese	21.3%	12.5%	21.3%	15.0% (high HbA1c)	CRT
van Waas* [49] 2010 (164/500 with ALL)	Median 19.0	Median 28.0	13.0%	9.2%	NR	9.80%	19.50%	1.0%	CRT
Oudin [47] 2011 (184)	Median 15.4	Median 21.2	9.2%	14.5%	13.0%	31.8%	25.3%	5.7%	HCT with TBI
Nottage [42] 2014 (784)	Median 26.1	Median 31.7	33.6%	39.9%	28.2%	44.6%	46.4%	31.4%	CRT
Gunn [68] 2016 (N=226)	Mean 12.6	Mean 18.0	–	32% obese	50.0% with dyslipidemia among CRT exposed	=	19.0%	30.8% among CRT exposed	CRT

HDL-C=High density lipoprotein cholesterol, GHD=Growth hormone deficiency, HCT=Hematopoietic cell transplantation, HbA1c=hemoglobin A1c, CRT=Cranial radiation Therapy, NR=Not reported,

*Used a modified definition of metabolic syndrome with four components.