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CLINICAL RESEARCH

Increased Cardiometabolic Traits in Pediatric Survivors of Acute Lymphoblastic Leukemia Treated with Total Body Irradiation

Eric J. Chow,[1,2] Jill H. Simmons,[3] Christian L. Roth,[2]
K. Scott Baker,[1,2] Paul A. Hoffmeister,[1] Jean E. Sanders,[1,2] Debra L. Friedman[3]

Survivors of childhood acute lymphoblastic leukemia (ALL) may face an increased risk of metabolic and cardiovascular late effects. To determine the prevalence of and risk factors for adverse cardiometabolic traits in a contemporary cohort of pediatric ALL survivors, we recruited 48 off-therapy patients in remission treated with conventional chemotherapy and 26 treated with total body irradiation (TBI)-based hematopoietic cell transplantation (HCT) in this cross-sectional pilot study. At a median age of 15 years (range, 8-21 years), HCT survivors were significantly more likely than non-HCT survivors to manifest multiple cardiometabolic traits, including central adiposity, hypertension, insulin resistance, and dyslipidemia. Overall, 23.1% of HCT survivors met the criteria for metabolic syndrome (≥3 traits), compared with 4.2% of non-HCT survivors ($P = .02$). HCT survivors also had increased C-reactive protein and leptin levels and decreased adiponectin, suggestive of underlying inflammation and increased visceral fat. In multivariate analyses, history of HCT remained associated with ≥2 traits (odds ratio [OR]. 5.13; 95% confidence interval [CI], 1.54-17.15) as well as with ≥3 traits (OR, 16.72; 95% CI, 1.66-168.80). Other risk factors included any cranial radiation exposure and family history of cardiometabolic disease. In summary, pediatric ALL survivors exposed to TBI-based HCT as well as to any cranial radiation may manifest cardiometabolic traits at an early age and should be screened accordingly.

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INTRODUCTION

The cure rate of childhood acute lymphoblastic leukemia (ALL) now exceeds 85%, resulting in a growing cohort of long-term survivors who potentially face adverse long-term health sequelae as a result of their cancer therapy [1]. There is evidence that ALL survivors treated with conventional therapy alone or with hematopoietic cell transplantation (HCT) are at increased risk of developing multiple related cardiovascular/metabolic risk factors, inluding obesity, hypertension, dyslipidemia, and insulin resistance [2-6]. Together, these components make up the metabolic syndrome, which is associated with a significantly increased risk of both atherosclerotic cardiovascular disease and diabetes mellitus [7-9]. Among ALL survivors, risk may be increased secondary to growth hormone deficiency occurring after cranial radiotherapy and total body irradiation (TBI), which has been associated with obesity and dyslipidemia [3,10]. Because chronic inflammation may have an important role in mediating obesity, insulin resistance, and related cardiovascular diseases [11], chronic graft-versus-host disease (cGVHD) posttransplantation also may increase the risk in affected survivors [12,13]. Other exposures, such as high-dose glucocorticoids (as part of both primary leukemia treatment and GVHD treatment) and more widespread use of immunosuppressive medications, such as calcineurin inhibitors used to prevent or treat GVHD, also have been associated with obesity, hypertension, and dyslipidemia [14,15].

Because current ALL therapy is characterized by reduced use of cranial radiotherapy and increased use of more-intensive chemotherapy, including more potent glucocorticoids, we conducted this prospective cross-sectional pilot study to determine the prevalence of and risk factors for cardiometabolic traits in pediatric ALL survivors treated since 1990 with conventional chemotherapy and with HCT. We hypothesized that childhood HCT survivors would be at increased risk for these traits compared with ALL survivors treated without HCT, and that this risk would be further modified by a history of GVHD and cranial radiotherapy exposure. In exploratory analysis, we also measured selected cytokines in an attempt to determine whether levels of cytokines associated with inflammation, adiposity, and endothelial dysfunction would be altered in survivors with multiple cardiometabolic traits.

SUBJECTS AND METHODS

Subjects

Eligible subjects for this prospective cross-sectional study were diagnosed with ALL at age <22 years; treated at Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, or Vanderbilt Children's Hospital between 1990 and 2008; and currently aged 8-21 years. Two patient cohorts were recruited, one consisting of individuals in first complete remission after treatment with conventional chemotherapy and the other consisting of individuals treated with HCT, currently in remission, and off any immunosuppressive therapy for GVHD. All subjects had to be at least 1 year off therapy or out from the date of HCT. Subjects were recruited in Seattle between July 2007 and June 2009 and in Nashville between April and June 2009. Among the 41 HCT and 83 non-HCT patients approached for this study, 63.4% and 66.3%, respectively, were enrolled. Seven enrolled non-HCT patients were subsequently excluded (because of Down syndrome in 3 and incomplete data in 4). Final data analysis included 26 HCT and 48 non-HCT survivors. The Institutional Review Boards at all participating centers approved the study protocol, and all participants/guardians provided written informed consent before participation.

Exposure and Outcome Measurements

Medical records were abstracted for previous chemotherapy and radiotherapy doses, including those associated with HCT, history of extensive or moderate/severe cGVHD, and any clinician-reported growth hormone deficiency. Medical histories were updated for any patient who was not seen within the previous year at one of the participating centers. Participants and their parents also completed questionnaires on physical activity [16], diet/food frequencies [17], and family history of cardiovascular disease (ie, coronary heart disease, stroke, hypertension, dyslipidemia) and/or diabetes [18]. Positive family history was defined as having a first-degree relative with the relevant disease.

Height, weight, and waist and hip circumferences were measured, and body mass index (BMI) and waist-to-hip ratio were calculated. Resting blood pressure was measured twice, with a third measurement obtained if systolic or diastolic pressures were >10 mm Hg apart; the most extreme measurement was excluded. Pediatric normative data were used to determine BMI z score [19], waist circumference [20], and blood pressure percentiles [21].

At the same research visit, when possible, following an 8-hour overnight fast, blood samples were obtained for a lipid profile (total cholesterol, high-density lipoprotein [HDL], and triglycerides), glucose, insulin, and selected cytokines (leptin, adiponectin, high sensitivity C-reactive protein [CRP], interleukin [IL]-6, tumor necrosis factor [TNF]-α, E-selectin, and soluble intercellular and vascular cell adhesion molecules [sICAM, sVCAM]). Lipid profiles were collected and processed at the participating institutions' hospital laboratories. Glucose was measured using an automated hexokinase method (Roche Diagnostics, Indianapolis, IN), and insulin was measured using an automated immunoenzymometeric assay (Tosoh Bioscience, San Francisco, CA). Cytokines were collected and processed under a standardized protocol [22] and then stored at −80°C before being batch analyzed using a commercially available fluorokine multianalyte profiling kit (R&D Systems, Minneapolis, MN) on a Luminex 200 analyzer (Luminex, Austin, TX). As a measure of insulin resistance, the homeostasis model assessment (HOMA) was calculated from fasting glucose and insulin values [23], based on the following formula: glucose (mmol/L) × insulin (mU/L)/22.5.

Cardiometabolic traits were defined a priori via current adult International Diabetes Foundation Consensus criteria [9] for subjects aged ≥18 years and pediatric-adapted values for those aged <18 years (Table 1). Sensitivity analysis used criteria based on the older but still widely used National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines [7,8], with a fasting glucose level ≥100 mg/dL defined as abnormal. For this study, we tabulated the number of abnormal components present in each individual and categorized individuals as having the metabolic syndrome if any 3 or more of the 5 criteria were present.

Statistical Analyses

Continuous parameters with skewed distributions were transformed when possible. Differences in

Table 1. Cardiometabolic Trait Definitions*

Trait	Consensus Criteria		NCEP-ATPIII Criteria	
	Adult [9]	Pediatric Adaptation	Adult [7]	Pediatric [8]
Obesity	BMI ≥30 kg/m² or waist circumference ≥94 cm in males and ≥80 cm in females	BMI ≥95th percentile for age and sex or waist circumference ≥90th percentile for age, sex, and ethnicity	Waist circumference >102 cm in males and >88 cm in females	Waist circumference ≥90th percentile for age and sex
High blood pressure	≥130/85 mm Hg	≥90th percentile for age, sex, and height or ≥120/80 mm Hg (adult prehypertension threshold)	≥130/85 mm Hg	≥90th percentile for age, sex, and height
Insulin resistance	Fasting glucose ≥100 mg/dL (5.6 mmol/L)	Same	Fasting glucose ≥110 mg/dL (6.1 mmol/L)†	Same†
High triglyceride level	≥150 mg/dL (1.7 mmol/L)	≥110 mg/dL (1.24 mmol/L)	≥150 mg/dL (1.7 mmol/L)	≥110 mg/dL (1.24 mmol/L)
Low HDL cholesterol level	Males, <40 mg/dL (1.03 mmol/L); females, <50 mg/dL (1.29 mmol/L)	≤40 mg/dL (1.0 mmol/L)	Males <40 mg/dL (1.03 mmol/L); females <50 mg/dL (1.29 mmol/L)	≤40 mg/dL (1.0 mmol/L)

*Any subject currently taking drugs for hypertension, diabetes, and dyslipidemia was classified as fulfilling the criterion associated with blood pressure, insulin resistance, and high triglyceride/low HDL levels, respectively.

†Redefined as ≥100 mg/dL in this study.

continuous parameters were compared using the *t* test (or Wilcoxon's rank-sum test for nonnormal distributions), and differences in proportions were assessed by Fisher's exact test. All tests were 2-sided. Multivariate linear regression models that included current age, sex, and participating institution (Seattle vs Nashville) were used to assess differences in physical activity and diet (ie, calories, fat intake) between patient cohorts. Linear regression models that also included BMI *z* scores and the presence of multiple cardiometabolic traits (≥2 vs <2) were used to assess differences in cytokine levels between patient cohorts. Logistic regression models that included the foregoing adjustment variables plus race/ethnicity (white v. nonwhite) and family history of cardiovascular disease/diabetes were also used to estimate the odds ratios (OR) and 95% confidence intervals (CI) of having ≥2 cardiometabolic traits associated with potential risk factors of HCT status, cranial radiotherapy, cGVHD, and growth hormone deficiency. All analyses were performed using Stata version 10 (Stata-Corp, College Station, TX).

RESULTS

Demographic Data and Treatment Characteristics

Basic demographic characteristics were similar for the 2 survivor cohorts (Table 2). Compared with responders, nonresponders were slightly more likely to be female (55.8%), but the 2 groups were of similar current median age (16 years; range, 8-21 years) and median years since ALL diagnosis (9 years; range, 3-19 years). The proportion of subjects with any family history of cardiovascular disease and/or diabetes was greater in the HCT survivors compared with the non-HCT survivors (61.5% vs 37.5%; *P* = .06). Reflecting contemporary treatment, only 10.4% of the non-HCT group received any cranial radiotherapy (all 1800 cGy), in contrast to the HCT group, in which 38.5% received some form of cranial radiotherapy, either as upfront therapy or as salvage therapy for recurrence (median, 1000 cGy; range, 600-2400 cGy). All HCT patients were conditioned with myeloablative doses of cyclophosphamide and TBI (median dose, 1320 cGy; range, 1200-1575 cGy). In the HCT recipients, bone marrow was the predominant stem cell source (n = 19; 73.1%), followed by peripheral blood (n = 5) and cord blood products (n = 2). Twenty-one transplants (80.8%) were HLA-matched, 11 with a matched unrelated donor. No patient underwent more than one HCT procedure. Thirteen HCT survivors and 1 non-HCT survivor subsequently developed growth hormone deficiency. Nine subjects were currently receiving growth hormone supplementation.

Table 2. Demographic and Treatment Characteristics of ALL Survivors Stratified by HCT Status

Characteristic	Non-HCT (n = 48)	HCT (n = 26)	P Value
Site, n (%)			
Seattle	30 (62.5)	21 (80.8)	.12
Nashville	18 (37.5)	5 (19.2)	
Female, n (%)	26 (54.2)	10 (38.5)	.23
Nonwhite race/ethnicity, n (%)	10 (20.8)	8 (30.8)	.40
Median current age, years (range)	14 (8-21)	15 (8-21)	.36
Median years (range) since diagnosis	10 (3-18)	10.5 (1-15)	.83
Median years (range) since HCT	–	6 (1-13)	–
History of relapse, n (%)*	–	16 (61.5)	–
Radiation exposure, n (%)			
Cranial radiotherapy	5 (10.4)	10 (38.5)	.007
TBI	–	26 (100)	–
History of chronic GVHD, n (%)	–	16 (61.5)	–

HCT indicates hematopoietic cell transplant; TBI, total body irradiation; GVHD, graft-versus-host disease.

*Eligibility for the non-HCT cohort was restricted to those in first complete remission. Ten HCT patients underwent transplantation while in first complete remission because of very-high-risk disease in accordance with institutional practice.

Anthropometric and Standard Laboratory Measurements

Although HCT survivors were significantly shorter than non-HCT survivors, the distribution of BMI z scores and the proportion of overweight or obese individuals as defined by BMI were similar in the 2 groups (42.3% vs 39.6%, respectively; Table 3). The proportions defined as obese using BMI versus waist circumference also were similar in the 2 groups; however, the HCT survivors had significantly greater waist-to-hip ratios, even after adjustment for sex and current age (Table 3).

HCT survivors were more likely to have blood pressures ≥90th percentile for age, sex, and height (or absolute values ≥120/80 mm Hg) compared with non-HCT survivors (Table 3). However, the proportions with blood pressures ≥95th percentile or ≥140/90 mm Hg were similar (11.5 vs 8.3%; $P = .69$). Whereas median glucose values were similar for the 2 survivor cohorts, HCT survivors had significantly higher fasting insulin levels and measures of insulin resistance as estimated by HOMA (both $P < .01$). HCT survivors also had significantly more adverse lipid profiles with higher triglyceride levels and lower HDL levels (both $P < .01$).

When the number of survivors meeting cardiometabolic trait criteria was tabulated, compared with non-HCT survivors, significantly greater proportions of HCT survivors met at least 1 criterion (84.6% vs 50.0%) and met at least 3 criteria (23.1% vs 4.2%; global P value $< .01$) (Table 3). When criteria were reanalyzed using the ATP III guidelines, the burden of traits remained greater in the HCT survivors ($P = .04$). However, obesity, as defined by BMI, was more common in non-HCT survivors with ≥2 traits compared with HCT survivors (9 [90%] vs 5 [35.7%]; $P = .01$).

Cytokine Levels

Compared with non-HCT survivors, HCT survivors had significantly lower adiponectin and higher CRP levels, and borderline higher leptin levels (Figure 1). Markers of endothelial dysfunction (sICAM, vCAM, and E-selectin) were similar in the 2 groups. We obtained IL-6 and TNF-α levels in a subset of subjects in each group (non-HCT, n = 23; HCT, n = 14), and found no significant differences between the groups. When HCT and non-HCT survivors were combined and stratified by the presence of <2 versus ≥2 cardiometabolic traits, leptin, CRP, and E-selectin levels were significantly higher and adiponectin level was significantly lower in those with ≥2 traits. Among HCT recipients alone, history of HLA disparity and chronic GVHD were not associated with significant differences in cytokine levels.

Multivariate Analyses

In adjusted analyses, a history of HCT remained a significant risk factor for having ≥2 cardiometabolic traits (OR, 5.13; 95% CI, 1.54-17.15), as well as for meeting criteria for metabolic syndrome (≥3 traits; OR, 16.72; 95% CI, 1.66-168.80). Using ATP III criteria instead, a history of HCT remained significant (≥2 traits: OR, 4.16; 95% CI, 1.07-16.10; ≥3 traits: OR, 22.99, 95% CI, 1.41-373.65). Compared with those who had no radiotherapy exposure to the brain, survivors treated with cranial radiotherapy/TBI alone and cranial radiotherapy plus TBI had a similar risk of manifesting ≥2 cardiometabolic traits (OR, 5-6). Positive family history also was significantly associated with ≥2 traits independent of HCT status (OR, 3.65; 95% CI, 1.15-11.57). However, diagnosis age, time since diagnosis, sex, and history of cGVHD or growth hormone deficiency (even if those currently receiving supplementation were considered separately) were not associated with having ≥2 traits.

Risk estimates were not associated with or modified by the addition of physical activity or caloric intake levels, even though HCT survivors had lower activity scores and borderline lower caloric intake compared with non-HCT survivors (Table 4). However, the proportion of calories from fats was similar in the 2 groups (data not shown).
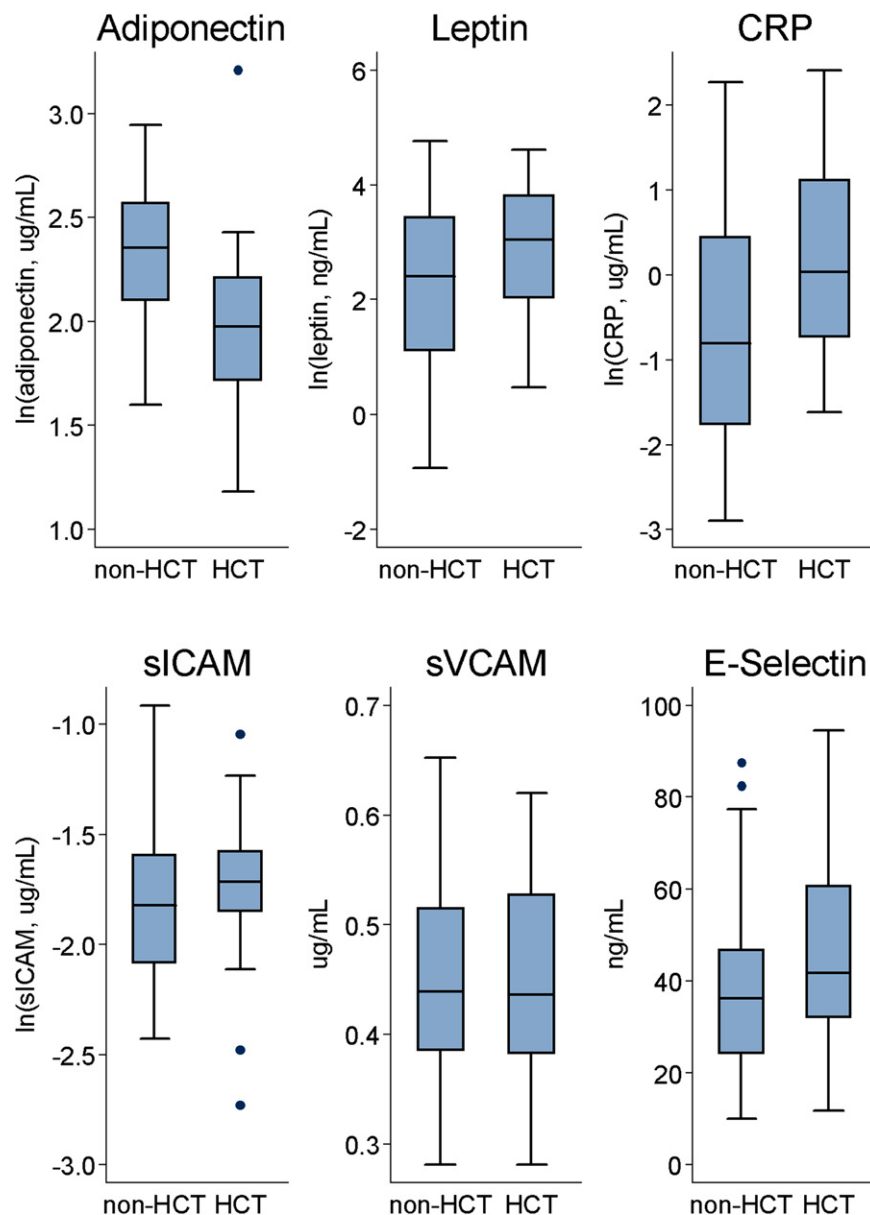
Figure 1. Distribution of selected biomarkers stratified by HCT status: adiponectin, leptin, CRP, sICAM, sVCAM, and E-selectin. Boxes show median values and interquartile ranges, with whiskers denoting upper and lower adjacent values; outside values are denoted by closed circles. Differences between HCT survivors and non-HCT survivors were significant for adiponectin and CRP ($P < .001$ and $P = .02$, respectively); the distributions of other biomarkers were not significantly different in unadjusted analyses (leptin, $P = .08$; sICAM, $P = .17$; sVCAM, $P = .96$; E-selectin, $P = .19$).

In linear regression models, HCT status was significantly associated with lower adiponectin levels and higher leptin levels (Table 4); however, HCT status was no longer associated with increased CRP level independent of the presence of ≥2 traits. History of HLA disparity, cGVHD, growth hormone deficiency, and radiation exposure to the brain were not associated with differences in cytokine levels in our adjusted analyses.

DISCUSSION

Various follow-up studies of adult survivors of pediatric ALL have reported increased obesity, insulin resistance, and dyslipidemia [3,5,6]. Among studies that have specifically examined transplant survivors, both pediatric and adult HCT recipients appear to be at increased risk of cardiometabolic traits, particularly dyslipidemia [2,4,24-27]. HCT survivors also have been reported to have an increased risk of developing diabetes [25,28,29] and cardiovascular disease [30-32]. However, few previous studies have directly compared pediatric ALL HCT and non-HCT survivors, particularly survivors treated in the contemporary era when cranial radiotherapy is used less commonly but chemotherapy is more intensive. Our results suggest that young HCT survivors uniformly treated with TBI are at significantly greater risk for developing cardiometabolic traits and the

Table 3. Metabolic Parameters of ALL Survivors, Stratified by HCT Status

Outcomes	Non-HCT (n = 48)	HCT (n = 26)	P Value
Height z score, mean ± SD	0.30 ± 0.99	−0.59 ± 1.19	<.01
BMI z score, mean ± SD	0.80 ± 0.92	0.54 ± 1.29	.31
BMI ≥25 or ≥85th percentile for age and sex, n (%)	19 (39.6)	11 (42.3)	1.00
BMI ≥30 or ≥95th percentile for age and sex, n (%)	13 (27.1)	6 (23.1)	.79
Waist ≥90th percentile for age and sex, n (%)*	13 (27.1)	7 (26.9)	1.00
Waist-to-hip ratio, mean ± SD	0.83 ± 0.07	0.90 ± 0.068	<.01
Blood pressure ≥120/80 mm Hg or ≥90th percentile for age, sex, and height, n (%)	8 (16.7)	11 (42.3)	.03
Glucose, mg/dL, median (range)	82 (43-96)	82 (63-110)	.76
Insulin, mU/L, median (range)	6.5 (1.0-26.9)	11.7 (1.0-39.6)	<.01
HOMA-IR, median (range)	1.32 (0.11-5.51)	2.64 (0.18-10.76)	<.01
Triglycerides, median (range), mg/dL	63 (16-177)	127 (63-327)	<.01
HDL, median (range), mg/dL	54 (33-108)	45 (32-63)	<.01
Cardiometabolic traits, n (%)†			
0	24 (50.0)	4 (15.4)	Overall
1	14 (29.2)	8 (30.8)	<.01
2	8 (16.7)	8 (30.8)	
≥3	2 (4.2)	6 (23.1)	

HCT indicates hematopoietic cell transplantation; HOMA, homeostasis model assessment.
*Or if waist circumference ≥80 cm in females and ≥94 cm in males.
†As defined by the consensus criteria (Table 1).

metabolic syndrome compared with similar-aged non-HCT survivors not exposed to cranial radiotherapy. Although the power of the present study was limited, additional cranial radiotherapy did not appear to markedly increase the risk beyond that associated with TBI. Although no standard pediatric definition of metabolic syndrome exists, and prevalence estimates can vary depending on the criteria used [33], our findings were consistent across 2 classification schemes.

The finding that cardiometabolic changes may occur soon after treatment in childhood is important, given that data from the general population suggest that cardiometabolic traits that develop in childhood often persist into adulthood [34,35]. However, in contrast to findings from the general population [8] and in our non-HCT ALL survivors, HCT survivors often manifest cardiometabolic traits, such as dyslipidemia and insulin resistance, without being "obese"

Table 4. Multivariate Regression Estimates (Coefficients with 95% CIs) for Selected Parameters in ALL Survivors, Adjusted for Sex, Current Age, Race/Ethnicity, and Institution

Parameter	Non-HCT	HCT	P Value
Physical activity*	Ref	-1.62 (-2.90 to -0.34)	.01
Calories*	Ref	-0.21 (-0.42 to -0.002)	.048
Biomarkers†			
Adiponectin*	Ref	-0.32 (-0.52 to -0.13)	.01
Leptin*	Ref	1.01 (0.55 to 1.46)	<.01
CRP*	Ref	0.43 (-0.33 to 1.19)	.26
sICAM*	Ref	0.14 (-0.01 to 0.30)	.07
sVCAM	Ref	0.03 (-0.02 to 0.08)	.24
E-selectin	Ref	2.54 (-8.11 to 13.19)	.64

Ref indicates referent group; ALL, acute lymphoblastic leukemia; HCT, hematopoietic cell transplantation; CRP, C reactive protein; sICAM, soluble intercellular cell adhesion molecules; sVCAM, soluble vascular cell adhesion molecules.
*Logarithmically transformed to normalize data distribution.
†Also adjusted for BMI z score and the presence of ≥2 metabolic syndrome traits.

as defined by BMI [24,27,29]. Instead, more direct measures of central/abdominal adiposity, such as waist-to-hip ratio, may be a more useful screening tool in the HCT population. In the general population, central adiposity is correlated with visceral fat and has been shown to be an independent risk factor for cardiovascular disease and diabetes, even after adjusting for BMI [8,9,36].

Consistent with previous studies [3,4,6,25,37], we found that both TBI and cranial radiotherapy were strongly associated with subsequent metabolic abnormalities. Both of these are known risk factors for subsequent growth hormone deficiency. Although we did not find a history of growth hormone deficiency (regardless of supplementation) to be an independent risk factor for increased cardiometabolic traits, our patients were not prospectively tested for this study, and it is possible that some patients might have undiagnosed deficiency, particularly postpubertal patients, for whom short stature is less of a concern. Other studies that prospectively tested all participants for growth hormone deficiency found that those with growth hormone deficiency were at increased risk [3,38].

In addition to TBI, other factors associated with allogeneic HCT might be associated with an increased risk for cardiometabolic complications. Large adult series have found an increased risk of cardiovascular complications in allogeneic HCT recipients compared with autologous HCT recipients, even after adjusting for TBI exposure [25,30]. Some evidence suggests that GVHD following allogeneic HCT can result in chronic low-level inflammation, endothelial dysfunction, and an atherosclerotic phenotype [12,13,39]. Although we did not find history of cGVHD to be associated with differences in cytokine levels or to be an independent risk factor for the development of multiple cardiometabolic traits, this might be related

to our limited sample size and our exclusion of patients still being actively treated for GVHD. A larger study with a more detailed analysis of GVHD (eg, duration of treatment, severity/extent) might yet reveal more subtle effects of GVHD, as well as other factors, such as stem cell source and HLA disparity, that may influence immune tolerance, inflammation, and the development of cardiometabolic outcomes.

Chronic inflammation appears to be a central pathophysiological mechanism underlying the development of diabetes and atherosclerotic cardiovascular disease in the general population [11]. For example, levels of CRP, E-selectin (which mediates leukocyte recruitment and rolling in inflamed tissues), and adipose tissue cytokines such as adiponectin and leptin are known to be altered in patients with the metabolic syndrome [36]. Adiponectin enhances insulin sensitivity, with favorable effects on endothelial function, whereas leptin promotes atherogenesis and is an independent risk factor for cardiovascular disease [40,41]. Leptin is produced primarily by subcutaneous adipocytes, whereas adiponectin levels are strongly correlated with visceral fat [40,41]. Childhood ALL survivors treated with cranial radiotherapy have been shown to have increased visceral fat versus subcutaneous fat on computed tomography scans [42].

Other factors that may contribute to development of cardiometabolic traits include sedentary lifestyle, diet, and family history (both genetic and environmental influences) [43]. Studies of adult and pediatric cancer survivors have found that survivors tend to be less physically active compared with the general population [44]. Dietary studies have generally reported low adherence to recommended dietary guidelines in childhood cancer survivors, suggesting another potential area for intervention [45]. Although the proportion of survivors with a positive family history of cardiovascular disease and/or diabetes was greater in HCT survivors compared with non-HCT survivors, HCT status remained a significant independent risk factor in our multivariate analyses. Nevertheless, genetic polymorphisms in selected pathways (eg, adiponectin and leptin receptor genes) might be important in mediating the variation in risk in the general population [46] as well as in cancer survivors [47].

In conclusion, we found that cardiometabolic traits, including meeting metabolic syndrome criteria, were more common in pediatric ALL survivors treated with TBI-based HCT compared with those treated with conventional chemotherapy. Manifestations appeared at an early age and suggest that ALL survivors treated with TBI or cranial radiotherapy should be closely followed and screened for dyslipidemia and diabetes, even if not overweight or obese by BMI standards. Alternative simple measures of central adiposity, such as waist-to-hip ratio, may better identify individuals at potentially greater risk. The important role of central adiposity and inflammation in mediating cardiometabolic complications is supported by alterations in cytokine levels, corresponding to a proinflammatory state, including decreased adiponectin levels, in HCT survivors.

ACKNOWLEDGMENTS

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