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Adipokines, Inflammation, and Adiposity in Hematopoietic Cell Transplant Survivors

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Abstract

Adult survivors of acute leukemia in childhood have a higher than expected frequency of obesity, an increased risk for metabolic syndrome and early mortality from cardiovascular disease (CVD). Adipose tissue has been recognized as an endocrine and paracrine organ that secretes various adipokines involved in metabolic regulation and inflammatory processes. Examine inflammatory factors [IL-6 and TNF-] and adipokines (adiponectin, leptin) in addition to body composition and adiposity in cancer survivors who underwent hematopoietic cell transplantation (HCT) during childhood in comparison to sibling controls. Over 2-year survivors of HCT for hematologic malignancies during childhood were recruited from 2 institutions along with a control population of siblings. Participants underwent evaluation for body composition, anthropometrics and

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measurement of cardiovascular (CV) risk factors and adipokines. Cases were stratified by radiation exposure in the preparative regimen (total body irradiation (TBI) + central nervous system (CNS) irradiation, TBI only, chemotherapy only) and adjusted least square means were estimated for each adipokine and adjusted by age, sex, race, Tanner stage, and percent fat mass (PFM) percentiles (0–24, 25–74, 75+). 151 HCT survivors and 92 siblings underwent evaluation. Significant differences were detected in mean adipokine levels between survivors and siblings: leptin was significantly higher and adiponectin significantly lower in HCT survivors who received TBI with or without central nervous system (CNS) compared with siblings. Interleukin 6 (IL-6) was significantly higher in all groups of HCT survivors compared to siblings. Body mass index (BMI) was similar between survivors and controls although PFM was significantly higher in all groups of HCT survivors and lean body mass (LBM) was lower in survivors who received TBI with and without CNS radiation compared with siblings. HCT survivors show unfavorable profile of inflammation, adipokines, and adiposity, despite similar BMI, when compared to controls. Higher PFM and lower LBM may contribute to these findings. Total body irradiation exposure is correlated with greater severity of these observations. Increasing lean body mass may serve as a tangible target in mitigating the high cardiometabolic risks of HCT survivors.

Keywords

Adiposity; Adipokines; Inflammation; Survivorship; Sarcopenia

Introduction

The use of hematopoietic cell transplantation (HCT) for the treatment of malignant and nonmalignant conditions in children has increased over the past 5 decades (1). Along with the larger number of children who have undergone HCT, survival after HCT has significantly increased as well, resulting in a growing population of long-term survivors. Unfortunately, childhood HCT survivors are also demonstrating an increased prevalence of many chronic conditions (2) and a higher risk of late mortality after HCT (3). In particular, childhood cancer survivors, as well as HCT survivors, have a higher than expected frequency of multiple cardiovascular disease risk factors and early mortality from cardiovascular disease (CVD) (4–6). These risk factors, comprised of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension mirror the metabolic syndrome that has been described in the obese general population where they are associated with a substantially increased risk for type 2 diabetes mellitus (T2DM) and atherosclerotic CVD (7,8).

In recent years, adipose tissue has been recognized as an endocrine and paracrine organ that secretes various adipokines, involved in metabolic regulation and inflammatory processes (9). The effect of obesity on adipocytes has been shown to cause dysregulated endocrine/paracrine function and macrophage accumulation in the adipose tissue resulting in low level inflammation (9). Differences in adipokine levels including high leptin and low adiponectin as well as elevated inflammatory makers have been observed between pre-HCT and approximately 6 months post-HCT in children (10). There are differences in adipokine levels and inflammatory markers between individuals with metabolic syndrome post-HCT and

spontaneously occurring metabolic syndrome (11). Exposure to TBI and prolonged immunosuppressive treatment during the HCT process and post-transplantation endocrine dysfunction and/or leptin resistance have been suggested to play a role in alterations to adipokine and inflammatory cytokine concentrations (7,12,13). Inflammation has been shown to be an integral component of the atherosclerotic process in CVD that is in part regulated by the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (14–16).

A thorough understanding of the pathophysiology and etiology in the development of cardiometabolic risk factors and early mortality from cardiovascular disease in HCT survivors is not known. Alterations in adipokines and low-grade systemic inflammation may be a catalyst for the development of metabolic and CVD complications. Therefore, we examined inflammatory factors [IL-6, TNF-α] and adipokines (adiponectin, leptin) in addition to body composition and adiposity in cancer survivors who underwent HCT during childhood with sibling controls for comparison.

Materials and Methods

Study Design

The study was approved by the institutional review board human subjects committees at the University of Minnesota and the Fred Hutchinson Cancer Research Center/Seattle Children's Hospital (FHCRC/SCH). Consent and ascent was obtained from participants. Hematopoietic cell transplantation survivors were selected from transplantation databases at each institution and were eligible to participate if they were diagnosed with a primary hematologic malignancy at age ≤21 years, received HCT at either the University of Minnesota Medical Center or the FHCRC/SCH, were ≥ 9 years of age at the time of study participation, survived a minimum of 2 years after transplantation, and were currently in remission. Sibling controls were eligible to participate if they were ≥ 9 years of age at the time of examination and never had cancer. Controls were frequency matched to HCT survivors by age and sex. Pregnant women were excluded until 3 or more months after the end of their pregnancy. Of the 339 potentially eligible survivors identified, 60 refused participation and we were unable to establish contact (passive refusal) with 125 survivors. The remaining 154 survivors (45% of those potentially eligible, 72% of those contacted) provided consent to participate along with 92 of their siblings. Three HCT survivors were found to be ineligible at the time of study because of previously undiagnosed diabetes mellitus (n = 1), severe hypertension (n = 1), and multiple medical issues (n = 1) that all required immediate medical attention. This left the final study population of 151 subjects.

Data Collection

All participants underwent a 2-day examination. Height, weight, waist circumference (WC), and blood pressure were assessed according to a standard protocol, as previously described (17). BMI was calculated using height and weight. Fat mass and lean body mass were measured using dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy scanner, software version 9.3; General Electric Medical Systems, Madison, WI).

Adipokine/Cytokine Assays

Blood samples were obtained for serum adiponectin, leptin, IL-6 and TNF-α. Plasma/serum concentrations of adiponectin IL-6, leptin and TNF-alpha were measured by Luminex multiplex assay (R&D Systems, Minneapolis, MN). Samples and cytokine standards were incubated with Luminex microbeads (one unique bead population per cytokine) coated with cytokine-specific antibodies. Beads are washed then incubated with biotinylated cytokine antibodies, washed again then incubated with a phycoerythrin-streptavidin conjugate. After a final wash the assay is read on a Luminex 200 instrument (Luminex Corporation, Austin, TX), classifying each bead as to its cytokine-specificity and phycoerythrin fluorescence intensity. Phycoerythrin fluorescence of each bead will be proportional to the cytokine concentration in the samples or standards. A standard curve was generated for each cytokine, with sample concentrations calculated from these curves. Participant lab results of IL-6 that were less than the laboratory detection limit of 2.0 pg/ml were imputed to 1.9 pg/ml for analysis. Participant lab results of TNF-α that were less than the laboratory detection limit of 1.5 pg/ml were imputed to 1.4 pg/ml for analysis.

Statistical Analysis

Descriptive statistics are expressed as frequencies and percents or mean ± SE as appropriate. HCT survivors were grouped into 3 treatment groups based on their HCT preparative regimen: 1) total body irradiation (TBI) and CNS radiation (given pre-HCT or as a ‘boost’ with TBI), 2) TBI without CNS radiation, and 3) chemotherapy without TBI. Comparisons between the survivor treatment groups and siblings were estimated using multivariable linear regression and adjusted for age at study, sex, race/ethnicity and Tanner score. Adjusted means are reported for all outcomes based on the original outcome scale though models were fit using log-transformed measures. Adjusted means were evaluated at the mean levels of covariates included in the models. A 2-sided P value < 0.05 was considered to be statistically significant, although because of the high number of statistical tests carried out, the significance of those between 0.01 and 0.05 should be viewed cautiously. All analyses were conducted with SAS version 9.2 (SAS Institute, Inc., Cary, NC). Logistic regression analyses to estimate odds of developing elevated cytokine levels (reduced levels in adiponectin) in allogenic vs. autologous transplants after adjustment for age, sex, race, tanner stage, and percent fat mass were performed. A similar analysis was performed to explore the potential impact of having had acute and/or chronic GVHD.

Results

On average, HCT survivors and siblings were similar in age, race and gender (Table 1). All participants received a myeloablative conditioning regimen. The majority of survivors (76.8%) received a HCT preparative regimen that included TBI and 20.5% received CNS radiation. The dose of TBI ranged from 200 – 1575 cGy with the median dose being 1320 cGy (n=64) with 102 participants (88%) receiving doses between 1200–1575 cGy. Only one patient received a TBI dose of 200 cGy given along with myeloablative chemotherapy. Most survivors had a diagnosis of either acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) and 76.8% of all survivors had an allogeneic donor source. Of the 116 survivors who received an allogeneic HCT, 76% had documented acute and/or chronic graph

versus host disease (GVHD) at some point following HCT but this was resolved in all cases and no subjects were receiving any GVHD therapy at the time of study enrollment.

Survivors who received TBI with CNS radiation had a mean adjusted height that was 11.6 cm shorter ($p<0.001$) than sibling controls, and 9.5 cm shorter for TBI alone ($p<0.001$; Table 2). The survivors exposed to TBI + CNS radiation also had a mean adjusted weight that was 13.3 kg less than siblings ($p<0.001$) and for those who had TBI alone 10.8 kg lower than siblings ($p<0.001$). The height and weight of HCT survivors who received chemotherapy without TBI was statistically not different from sibling controls. The mean adjusted BMI between HCT survivors and siblings were not statistically different. Despite similar BMIs among survivors and siblings, survivors in all 3 treatment groups had a higher adjusted percent fat mass that was approximately 5% higher than sibling control (all p-values <0.005). The mean adjusted total lean mass for survivors exposed to TBI + CRT was 13.4 kg lower than sibling controls ($p<0.001$) and for survivors exposed to TBI without CNS radiation 10.9 kg lower than siblings ($p<0.001$).

After adjusting for age, sex, race, and Tanner stage, all 3 HCT treatment groups had 2- to 3-fold higher levels of leptin compared to sibling controls (Table 3, p values for comparisons all ≤ 0.004). After above adjustments, survivors who received TBI with or without CNS radiation had significantly lower adiponectin levels compared to sibling controls ($p<0.001$ for each) but not those treated with chemotherapy alone ($p=0.158$). Hematopoietic cell transplantation survivors who received TBI with or without CNS radiation or those who received chemotherapy alone, all had evidence of a pro-inflammatory state characterized by significant elevations of IL-6 levels (all p-values <0.05) and although while TNF-alpha levels were slightly higher than siblings, this difference did not reach statistical significance.

After adjusting for age, sex, race, Tanner stage and percent fat mass, there was no association found between elevated leptin, IL-6, TNF-α or decreased adiponectin and allogenic and autologous HCT (all p-values >0.35). A similar analysis was performed for acute and/or chronic graft versus host disease, which also did not show any association (all p-values >0.28).

Discussion

The results of this study demonstrate that compared with sibling controls, survivors who underwent HCT for a primary hematologic malignancy at age ≤21 had a similar BMI yet a higher percent fat mass, signifying a lean mass deficit regardless of their treatment group.

These results are consistent with smaller studies which have demonstrated a lean mass deficit and sarcopenic obesity in HCT survivors exposed to TBI (18). Furthermore, survivors in all 3 treatment groups had higher leptin levels and those who received TBI had significantly lower adiponectin levels compared to sibling controls. Finally, survivors in all 3 treatment categories have a low-grade pro-inflammatory state characterized by significant elevations of plasma IL-6 concentrations compared with the sibling controls.

Hematopoietic cell transplantation survivors have a higher than expected prevalence and early mortality from CVD, and data from this study help to provide some insight in regards

to the etiology of increased cardiometabolic conditions and CVD found in this population (19). Cardiovascular atherogenesis is widely recognized as an inflammatory response to a variety of risk factors and the consequences of this response lead to the development of acute coronary syndrome (14). Studies in non-HCT patients have demonstrated that plasma adiponectin and leptin profiles are highly correlated with BMI (20) with lower plasma adiponectin and higher leptin levels observed in overweight and obese individuals. In the obese state, reductions in adipoQ mRNA, impaired post-translational modifications of adiponectin, and alterations in adiponectin molecular chaperones are thought to cause increased clearance of adiponectin from the bloodstream subsequently lowering measurable levels (21). The enlarged adipocytes of obese individuals have been shown to promote inflammation and release adipokines that predispose towards insulin resistance (9). Plasma levels of adiponectin in individuals with T2DM without coronary artery disease (CAD) have been shown to be lower than those in nondiabetic subjects (22). Hematopoietic cell transplantation survivors in our study have adipokine profiles similar to those observed in obese and overweight patients however the HCT survivors on average were not obese as measured by BMI, and their lean mass deficit was only detected by measuring fat mass using DXA imaging to examine body composition.

Childhood HCT survivors are at increased risk for metabolic syndrome which is associated with CVD (7). Metabolic syndrome in HCT survivors is likely multifactorial and the driving pathophysiology may include distinct factors including immune reconstitution, stem cell source, donor/recipient interactions and post-HCT microbiome alterations (23). The number of constituents of metabolic syndrome present in an individual has been shown to be an independent predictor of CAD in patients without T2DM (24) and associated with advanced coronary disease compared to individuals without metabolic syndrome (25). Insulin resistance, a component of metabolic syndrome is commonly observed in pediatric HCT survivors (11). HCT survivors have been shown to have a higher percentage of intramuscular fat measured with abdominal MRI compared to groups of ALL survivors treated with chemotherapy-only and obese, non-leukemic, otherwise healthy young adults (18). Interestingly, ectopic lipid accumulation, particularly intramyocellular lipid content has been implicated in magnetic resonance spectroscopy (MRS) studies of insulin resistance in muscle tissue of non-cancer patients (26,27) and have clarified the role of muscle-specific insulin resistance in promoting atherogenic dyslipidemia (28). Furthermore, inflammation and macrophage-induced lipolysis has been associated with progression from ectopic lipid-induced insulin resistance to impaired glucose tolerance and T2DM (28) which are known CAD risk factors. Interestingly, the inflammatory state we observed in the HCT survivors was not a phenomenon of having had an allogeneic HCT nor having had acute or chronic GHVD. We hypothesize that the inflammatory state and perhaps changes in adipokine levels, are more likely mediated by higher level of adiposity.

While we did not specifically measure growth hormone (GH) in this study, GH deficiency is commonly seen in TBI-exposed HCT survivors and is associated with changes in body composition including increased visceral adiposity (29) and reduced lean body mass (30). This phenotype has been consistently noted in TBI-exposed childhood cancer survivors and is associated with insulin resistance, glucose intolerance and T2DM (18). There is evidence that GH and insulin-like growth factor 1 (IFG-1) are involved in the development and

function of visceral adipose tissue and GH deficiency may be involved in the development of a sarcopenic obese phenotype that is predisposed to metabolic and CVD risks (31). Because IGF-1 acts as an insulin sensitizer (31), it may be worth considering its use in reducing insulin resistance in patients with lipodystrophies and sarcopenic obesity, in low dose, and in combination with other approaches.

Despite our relatively large sample size, it is possible that we lacked sufficient power to detect clinically significant differences for some of the risk factors examined in this study. It should also be noted that DXA is not be the most sensitive method for determining adiposity and MRI-based techniques that can specifically quantify visceral adiposity along with serum adipokine levels will be important in studies to move the field forward. Finally, as this was a cross-sectional study, we are unable to describe the onset that these changes take place in the post-HCT period. Further longitudinal research in this population is needed to elucidate the sequence of events and time frame leading to the abnormalities presented.

This study serves to fill important gaps in knowledge regarding associations between adiposity, adipokines and inflammation and cardiometabolic risk factors among HCT survivors. Although it is not new to find an association between alterations in adipokines, adiposity, inflammation and cardiometabolic risk factors in obese populations, results suggesting that these relationships are stronger in HCT survivors than in controls are of importance, as they suggest that increasing lean body mass may serve as a tangible target in mitigating the already high cardiometabolic risks of many HCT survivors.

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References

1. D’Souza, A., Zhu, X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides [Internet]. HCT Trends and Survival Data. 2017. Available from: http://www.cibmtr.org
2. Armenian SH, Sun C-L, Kawashima T, Arora M, Leisenring W, Sklar CA, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). Blood. 2011 Aug 4; 118(5):1413–20. [PubMed: 21652685]
3. Bhatia S, Francisco L, Carter A, Sun C-L, Baker KS, Gurney JG, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood. 2007 Nov 15; 110(10):3784–92. [PubMed: 17671231]
4. Oeffinger KC, Buchanan GR, Eshelman DA, Denke MA, Andrews TC, Germak JA, et al. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2001 Oct; 23(7):424–30. [PubMed: 11878576]

5. Oeffinger KC, Adams-Huet B, Victor RG, Church TS, Snell PG, Dunn AL, et al. Insulin Resistance and Risk Factors for Cardiovascular Disease in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2009 Aug 1.27(22):3698. [PubMed: 19564534]
6. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study. J Clin Oncol. 2003 Apr 1; 21(7):1359–65. [PubMed: 12663727]
7. Tichelli A, Rovó A, Passweg J, Schwarze CP, Lint MTV, Arat M, et al. Late complications after hematopoietic stem cell transplantation. Expert Rev Hematol. 2009 Oct 1; 2(5):583–601. [PubMed: 21083023]
8. Reusch JEB. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. Am J Cardiol. 2002 Sep 5; 90(5, Supplement 1):19–26. [PubMed: 12088773]
9. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006 Feb; 83(2):461S–465S. [PubMed: 16470013]
10. Skoczen S, Tomasik PJ, Fijorek K, Strojny W, Wieczorek A, Balwierz W, et al. Concentrations of adipokines in children before and after hematopoietic stem cell transplantation. Pediatr Hematol Oncol. 2016 Jan 2; 33(1):21–38. [PubMed: 26901378]
11. Airaghi L, Usardi P, Forti S, Orsatti A, Baldini M, Annaloro C, et al. A comparison between metabolic syndrome post-hematopoietic stem cell transplantation and spontaneously occurring metabolic syndrome. J Endocrinol Invest. 2011 Jan 1; 34(1):e6–11. [PubMed: 20595801]
12. Neville KA, Cohn RJ, Steinbeck KS, Johnston K, Walker JL. Hyperinsulinemia, Impaired Glucose Tolerance, and Diabetes Mellitus in Survivors of Childhood Cancer: Prevalence and Risk Factors. J Clin Endocrinol Metab. 2006 Nov 1; 91(11):4401–7. [PubMed: 16954158]
13. Arvidson J, Lonnerholm G, Tuvemo T, Carlson K, Lannering B, Lonnerholm T. Prepubertal Growth and Growth Hormone Secretion in Children After Treatment for Hematological Malignancies, Including Autologous Bone Marrow Transplantation. Pediatr Hematol Oncol. 2000 Jan 1; 17(4):285–97. [PubMed: 10845227]
14. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of Inflammation and Cardiovascular Disease. Circulation. 2003 Jan 28; 107(3):499–511. [PubMed: 12551878]
15. Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, et al. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Lett. 1989 Jan 2; 242(2):237–9. [PubMed: 2464504]
16. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990 Feb 1; 265(3):621–36. [PubMed: 1689567]
17. Steinberger J, Sinaiko AR, Kelly AS, Leisenring WM, Steffen LM, Goodman P, et al. Cardiovascular Risk and Insulin Resistance in Childhood Cancer Survivors. J Pediatr. 2012 Mar; 160(3):494–9. [PubMed: 21920542]
18. Wei C, Thyagiarajan MS, Hunt LP, Shield JPH, Stevens MCG, Crowne EC. Reduced insulin sensitivity in childhood survivors of haematopoietic stem cell transplantation is associated with lipodystropic and sarcopenic phenotypes. Pediatr Blood Cancer. 2015 Nov 1; 62(11):1992–9. [PubMed: 25989749]
19. Chow EJ, Wong K, Lee SJ, Cushing-Haugen KL, Flowers MED, Friedman DL, et al. Late cardiovascular complications after hematopoietic cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2014 Jun; 20(6):794–800.
20. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. 1999. Biochem Biophys Res Commun. 2012 Aug 31; 425(3):560–4. [PubMed: 22925674]
21. Achari AE, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. Int J Mol Sci. 2017 Jun 21.18(6):1321.
22. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma Concentrations of a Novel, Adipose-Specific Protein, Adiponectin, in Type 2 Diabetic Patients. Arterioscler Thromb Vasc Biol. 2000 Jun 1; 20(6):1595–9. [PubMed: 10845877]

23. Turcotte LM, Yingst A, Verneris MR. Metabolic Syndrome after Hematopoietic Cell Transplantation: At the Intersection of Treatment Toxicity and Immune Dysfunction. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2016 Jul; 22(7):1159–66.
24. Kim J-Y, Choi E-Y, Mun H-S, Min P-K, Yoon Y-W, Lee BK, et al. Usefulness of metabolic syndrome score in the prediction of angiographic coronary artery disease severity according to the presence of diabetes mellitus: relation with inflammatory markers and adipokines. Cardiovasc Diabetol. 2013; 12:140. [PubMed: 24088407]
25. Solymoss BC, Bourassa MG, Lespérance J, Levesque S, Marcil M, Varga S, et al. Incidence and clinical characteristics of the metabolic syndrome in patients with coronary artery disease. Coron Artery Dis. 2003 May; 14(3):207–12. [PubMed: 12702923]
26. Krssak M, Petersen KF, Dresner A, DiPietro L, Vogel SM, Rothman DL, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia. 1999 Jan 1; 42(1):113–6. [PubMed: 10027589]
27. Perseghin G, Scifo P, Cobelli FD, Pagliato E, Battezzati A, Arcelloni C, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes. 1999 Aug 1; 48(8):1600–6. [PubMed: 10426379]
28. Shulman GI. Ectopic Fat in Insulin Resistance, Dyslipidemia, and Cardiometabolic Disease. N Engl J Med. 2014 Sep 18; 371(12):1131–41. [PubMed: 25229917]
29. Attallah H, Friedlander AL, Hoffman AR. Visceral obesity, impaired glucose tolerance, metabolic syndrome, and growth hormone therapy. Growth Horm IGF Res Off J Growth Horm Res Soc Int IGF Res Soc. 2006 Jul; 16(Suppl A):S62–67.
30. Talvensaari KK, Lanning M, Tapanainen P, Knip M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab. 1996 Aug 1; 81(8):3051–5. [PubMed: 8768873]
31. Lewitt MS. The Role of the Growth Hormone/Insulin-Like Growth Factor System in Visceral Adiposity. Biochem Insights. 2017; 10 1178626417703995.

Research Highlights

- Childhood HCT survivors have high leptin and low adiponectin compared to siblings.
- Inflammatory cytokine IL-6 is elevated in HCT survivors compared to siblings.
- Despite similar BMI, HCT survivors have a higher PFM and lower LBM than siblings.
- Total body irradiation exposure is correlated with greater severity of these observations.

Table 1

Characteristics of HCT Survivors and Sibling Controls

Variable	Survivors (n = 151)		Controls (n = 92)	
Category	n (%)	Mean +/− SE	n (%)	Mean +/− SE
Age at study, yr		24 +/− 0.6		24.2 +/− 0.7
Sex				
Male	87 (57.6)		49 (53.6)	
Female	64 (42.4)		43 (46.4)	
Race/Ethnicity				
White non-Hispanic	137 (90.7)		85 (92.4)	
Other	14 (9.3)		7 (7.6)	
Tanner stage				
1	6 (4.3)		2 (2.3)	
2	4 (2.8)		3 (3.5)	
3	10 (7.1)		1 (1.2)	
4	9 (6.4)		9 (10.5)	
5	112 (79.4)		71 (82.6)	
Diagnosis				
ALL	47 (31.1)		NA	
AML	54 (35.7)			
CML	15 (9.9)			
HOD	12 (8.0)			
MDS	13 (8.6)			
Others	10 (6.6)			
Age at most recent HCT, yr		11.2 +/− 0.5	NA	
HCT Preparative Regimen				
TBI + CNS Radiation	31 (20.5)		NA	
TBI without CNS Radiation	85 (56.3)			
Chemotherapy without TBI*	35 (23.2)			
HCT Type				
Allogeneic	116 (76.8)		NA	
Autologous	35 (23.2)			
GVHD**	76 (65.5)		NA	

(ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CNS, Central Nervous System; HOD, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; NA, not applicable; GVHD, Graft versus host disease; TBI, total body irradiation)

*Some survivors received other radiation before or after HCT: mantle/mediastinal (n = 10 for HD), arm, orbit (n = 2 for chloromas), temple (n = 1 with history of sarcoma and HCT for secondary AML), abdominal (n = 1 for non-Hodgkin lymphoma).

**Among the 116 allogeneic HSCT survivors

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Table 2

Height, Weight, BMI, Total Lean Mass and Percent Fat Mass in HCT Survivors and Sibling Controls

Outcome	HCT Survivors									Siblings	
	TBI + CNS Radiation			TBI without CNS Radiation			Chemotherapy without TBI				
	Adjusted Mean	95% CI	P-value	Adjusted Mean	95% CI	P-value	Adjusted Mean	95% CI	P-value	Adjusted Mean	95% CI
Height (cm)	158.3	(154.2, 162.5)	<.001	160.4	(157.0, 163.7)	<.001	167.9	(164.4, 171.4)	0.159	169.9	(166.9, 172.9)
Weight (kg)	58.7	(51.4, 65.9)	<.001	61.2	(54.2, 68.1)	<.001	74.2	(65.3, 83.1)	0.580	72	(64.6, 79.3)
BMI (kg/m2)	23.2	(20.9, 20.5)	0.162	23.4	(121.4, 25.4)	0.05	25.8	(23.3, 28.3)	0.321	24.6	(22.6, 26.7)
Total Lean Mass, kg	34.4	(31.0, 37.7)	<.001	36.9	(34.1, 39.7)	<.001	45.6	(41.2, 50.0)	0.262	47.8	(45.0, 50.5)
Percent Fat Mass	35.2	(32.1, 38.4)	<.001	34.4	(31.4, 37.4)	<.001	34.9	(31.4, 38.4)	0.005	29.6	(26.7, 32.4)

(CNS, Central Nervous System; TBI, total body irradiation)

*Adjusted for age, sex, race, Tanner stages

Table 3

Adipokine and Inflammatory Cytokine Levels in HCT Survivors and Sibling Controls

Adipokine or Inflammatory Cytokine	HCT Survivors									Siblings	
	TBI + CNS Radiation			TBI without CNS Radiation			Chemotherapy without TBI				
	Adjusted Mean*	95% CI	p-value	Adjusted Mean*	95% CI	p-value	Adjusted Mean*	95% CI	p-value	Adjusted Mean	95% CI
Adipokine											
Leptin (ng/ml)	18.4	(12.2, 27.8)	<.001	13.8	(10.0, 19.0)	<.001	12.4	(7.9, 19.4)	0.004	6.3	(45.8, 87.7)
Adiponectin (mcg/ml)	20.6	(16.3, 26.0)	<.001	23.3	(19.1, 28.4)	<.001	30.6	(25.3, 37.2)	0.267	33.2	(28.2, 39.0)
Inflammatory Cytokine											
IL-6 (pg/ml)	5.7	(4.0, 8.2)	0.005	4.5	(3.5, 5.9)	0.002	5.2	(3.4, 7.9)	0.019	3.4	(2.7, 4.3)
TNF-alpha (pg/ml)	1.8	(1.7, 2.0)	0.061	1.8	(1.7, 2.0)	0.056	1.8	(1.7, 2.0)	0.303	1.7	(1.5, 1.8)

(CNS, Central Nervous System; IL-6, Interleukin-6; TNF-alpha, TBI, total body irradiation; Tumor Necrosis Factor alpha)

Model adjusted for age (categorized), sex, race and Tanner stage