Diabetes and Metabolic Syndrome in Survivors of Childhood Cancer

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Abstract

Endocrine complications, including diabetes and metabolic syndrome, are highly prevalent in childhood cancer survivors. These metabolic derangements may contribute to survivors' risk of excess cardiovascular morbidity and premature mortality. This review summarizes existing knowledge on risk of diabetes and metabolic syndrome among childhood cancer survivors, focusing specifically on known risk factors, potential mechanisms, and screening recommendations. Early diagnosis via standardized risk-based screening can improve long-term outcomes in this population. Additional work is needed to elucidate the mechanisms underlying these metabolic complications and to inform the design of risk-reducing interventions and optimize long-term cardiometabolic health among survivors of childhood cancer.

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Introduction

With improvements in cancer-directed therapies and supportive care over the past decades, 5-year survival for childhood cancer now exceeds 80% [1]. Survivors, however, remain at lifelong risk for the development of treatment-related complications, collectively known as “late effects.” Endocrinopathies, which include diabetes mellitus (herein abbreviated as diabetes) and metabolic syndrome, are among the most common late effects [2–4] with approximately 50% of survivors experiencing at least one hormonal derangement during their lifetime [3]. A prolonged latency may exist between treatment exposure and various complications, thus highlighting the need for continued lifelong vigilance for the development of treatment-related complications in long-term childhood cancer survivors.

In the general population, diabetes and metabolic syndrome are associated with an increased risk of cardiovascular morbidity and mortality [5, 6]. In childhood cancer survivors, cardiovascular disease is the second leading cause of late mortality [7]; given this risk, it is imperative to identify cardiovascular risk factors (CVRFs), including diabetes and components of the metabolic syndrome, at an early stage and employ aggressive risk-reduction strategies, such as dietary modification, increased physical ac-

tivity, and early treatment of hypertension and/or dyslipidemia, when possible. The purpose of this review article is to provide an overview of diabetes and metabolic syndrome after cancer therapy during childhood, with an emphasis on potential mechanisms, risk factors, and existing screening recommendations for those at risk for these complications. All screening recommendations listed below originate from the North American Long-Term Follow-Up Guidelines, which are risk-based, exposure-driven screening and surveillance recommendations published by the Children's Oncology Group (COG) and publicly available online at <http://www.survivorship-guidelines.org> [8]. However, it is important to note that a number of other published guidelines are also available and may be better suited for specific practice settings, particularly in resource-limited areas. Guidelines should be adapted accordingly.

Diabetes

Diabetes is a metabolic disorder characterized by hyperglycemia related to insufficient insulin secretion, insulin resistance, or both. Type 1 diabetes results from autoimmune destruction of pancreatic β -cells and leads to insulinopenia, while type 2 diabetes is characterized by an initial period of insulin resistance and compensatory hyperinsulinemia, with progression over time to β -cell failure. Chronic hyperglycemia, which characterizes the disease, results in long-term end-organ damage. Recent data have demonstrated that childhood cancer survivors are at increased risk of developing diabetes [4, 9–11], with risk further increased among individuals treated at a young age [11, 12] and among those exposed to abdominal radiation [9, 12, 13] or total body irradiation (TBI) [4, 9, 14–17]. Given that the prevalence and pathophysiology of diabetes after abdominal radiation and TBI are likely dissimilar, each one is summarized separately in the sections below.

Treatment-Related Risk Factors

Abdominal Radiation

Abdominal radiation is used as a cornerstone of therapy for a variety of solid malignancies, including neuroblastoma, Wilms tumor, and some sarcomas. Historically, infradiaphragmatic radiation was also used to treat some patients with Hodgkin lymphoma. Of note, in an analysis of 8,599 survivors enrolled in the Childhood Cancer Survivor Study (CCSS), and 2,936 randomly selected siblings, survivors exposed to abdominal radiation were at 3.4-fold (95% confidence interval [CI], 2.3–5.0;

$p < 0.001$) increased risk of diabetes when compared to siblings, after adjusting for body mass index (BMI) [9]. When compared to siblings, survivors of neuroblastoma and Wilms tumor treated with abdominal radiation were at 6.9- and 2.1-fold increased risk of diabetes, respectively; individuals in these diagnostic groups who had not been exposed to abdominal radiation were not at increased risk, thus suggesting that risk of diabetes is related to prior treatment rather than disease-specific factors [9]. The French-UK and Dutch cancer survivor cohorts have similarly reported an increased risk of diabetes after abdominal radiation [12, 13].

The pathophysiology of diabetes after abdominal radiation is thought to be related to radiation-induced damage to the tail of the pancreas, resulting in pancreatic insufficiency [12, 13]. The exact nature of the relationship between radiation dose and diabetes risk, however, remains contested. Among 2,520 French-UK survivors of childhood solid cancer or lymphoma, the relative risk of diabetes was 11.5 (95% CI, 3.9–34.0) among survivors who received ≥ 10 Gy to the pancreatic tail; risk increased with increasing dose to the tail of the pancreas through 20–29 Gy with subsequent plateau in risk [12]. In contrast, a more recent analysis of 2,264 Hodgkin lymphoma survivors in the Netherlands found that risk of diabetes significantly increased with higher mean radiation doses to the tail without any evident plateau in risk ($p < 0.001$) [13]. Survivors treated with ≥ 36 Gy to the para-aortic lymph nodes and spleen, which includes the vast majority of the volume of the pancreas, were at highest risk.

Total Body Irradiation

TBI is generally used as preconditioning for individuals with high-risk hematologic malignancies undergoing hematopoietic cell transplantation (HCT) [18, 19]; it may also be used as pre-transplantation cytoreduction for individuals with select high-risk solid malignancies, such as neuroblastoma [20, 21]. Unlike abdominal radiation, TBI entails radiation exposure to the whole body, including the hypothalamic-pituitary axis, and thus places survivors at risk for a range of radiation-related endocrinopathies, such as growth hormone deficiency [22–26]. Survivors are also at risk for thyroid dysfunction and hypogonadism related to radiation-related target organ damage [27–29]. It is well-established that survivors treated with TBI during childhood are also at increased risk for diabetes [4, 9, 14, 16, 17, 30–32], with risk estimated to be 12.6-fold greater than siblings after adjusting for BMI (95% CI, 6.2–25.3, $p < 0.001$) [9]. Hyperinsulinemia and insulin resistance, rather than pancreatic insufficiency, are

thought to be the primary pathophysiologic mechanisms underlying diabetes development after TBI [15, 31, 33, 34], although it is likely that other TBI-associated endocrinopathies also contribute to risk [35].

Recent work has demonstrated that young adult HCT survivors are at risk for adverse cardiometabolic phenotypes consistent with sarcopenic obesity [36–39], which is typically observed in elderly populations at increased risk for adverse health events. Specifically, those treated with TBI demonstrate increased total fat mass and decreased lean body mass and muscle mass, despite similarities in BMI to controls [36, 40]. TBI-exposed survivors also demonstrate an unfavorable profile of inflammation and altered adipokines (higher leptin/lower adiponectin) [40, 41]. Importantly, growth hormone deficiency is associated with reduced lean body mass and increased visceral adiposity in both healthy individuals and childhood cancer survivors [38, 42], and may also contribute to metabolic dysregulation in this cohort. The loss of muscle mass in this cohort may also contribute to diabetes development after TBI; one study of non-human primates exposed to whole-body irradiation suggests that reduced insulin signaling by skeletal muscle plays a central role in the pathophysiology of diabetes after radiation therapy [43]. Further work is needed to clarify the mechanisms leading to diabetes after TBI.

Exogenous Corticosteroids

Survivors exposed to supraphysiologic doses of exogenous corticosteroids, such as those with a history of acute lymphoblastic leukemia (ALL), may be at risk for diabetes and metabolic dysfunction. While steroid-induced transient hyperglycemia in children with cancer often resolves after cessation of therapy [44–46], prolonged hyperglycemia with progression to permanent diabetes has been reported [47]. In a study of diabetes risk among 8,599 childhood cancer survivors, exposure to corticosteroids was associated with an increased prevalence of diabetes in univariate analysis but not in multivariate analysis [9]. Steroid use has also been associated with insulin resistance [48] and obesity [49], which are associated with diabetes development in non-cancer populations [50–52]. More recent data from the Swiss Childhood Cancer Study, however, found no evidence of a dose-response relationship between cumulative glucocorticoid dose and overweight in a cohort of 1,936 long-term childhood cancer survivors [53]. Further work is needed to better delineate the relationship between exogenous glucocorticoid use and diabetes risk in childhood cancer survivors.

Potential Mechanisms Underlying Diabetes Development after Cancer Therapy

While many studies on diabetes risk after cancer therapy presume that survivors are at risk for type 2 diabetes [9, 13], it remains unclear whether this is strictly true according to classic definitions of diabetes. Indeed, type 2 diabetes is characterized by hyperglycemia and insulin resistance, often in the setting of overweight and obesity [54, 55], while type 1 diabetes is distinguished by autoimmune destruction of the pancreatic β -cells with resultant insulin deficiency requiring lifelong insulin treatment [56].

Large studies of diabetes risk in childhood cancer survivors have not generally assessed pancreatic autoantibody status. In a study of autoimmune disease among 20,361 1-year survivors of childhood cancer survivors in Scandinavia, survivors were at 1.6-fold increased risk for hospitalization related to insulin-dependent diabetes, when compared to matched population-based controls, although autoantibody status in survivors was not reported [57]. Similarly, the French-UK cohort reported an increased incidence of both insulin-dependent and non-insulin-dependent diabetes after abdominal radiation in their survivor cohort [12]; information on antibody status again was not available.

Our group recently evaluated pancreatic autoantibody status (glutamic acid decarboxylase [GAD-65], insulin autoantibodies, islet antigen-2) in 40 survivors of childhood cancer exposed to abdominal radiation [58]. While a variety of glucose and insulin derangements were noted in this investigation, none of the participants had more than one positive pancreatic autoantibody, suggesting that autoimmunity is not the underlying etiology of post-therapy diabetes.

In the general population, risk of type 2 diabetes is inextricably linked to obesity; in childhood cancer survivors, however, increased diabetes risk persists after adjustment for BMI [9, 12, 13]. Prior studies have suggested that BMI is not a reliable measurement of adiposity after abdominal radiation or TBI and alternate measurements such as waist circumference are needed to determine total body fat and fat distribution [59], which may explain this discrepancy. Alternatively, we and others have theorized that radiation to the abdomen damages abdominal subcutaneous adipose tissue and leads to preferential lipid deposition in the visceral depots, which is associated with chronic low-grade inflammation and metabolic derangements, including diabetes. Further study is indicated to determine whether radiation-induced adipose tissue dysfunction, rather than obesity per se, plays a key role in contributing to the pathophysiology of diabetes after radiation therapy.

Screening and Management

According to the current COG guidelines, individuals exposed to abdominal radiation or TBI should have a fasting blood glucose or hemoglobin A1c checked every 2 years, or more frequently if clinically indicated [8]. There is some evidence, however, that hemoglobin A1c has poor sensitivity for diagnosing diabetes among HCT survivors [17], and clinicians should thus have a low threshold for performing oral glucose tolerance testing in suspected cases. Furthermore, those with a positive family history of type 2 diabetes may be at increased risk for impaired glucose tolerance and diabetes due to genetic factors; this added background risk likely warrants closer surveillance in these individuals [60]. Patients with evidence of impaired glucose metabolism on routine screening should be referred to an endocrinologist for further evaluation and management. All childhood cancer survivors should be counseled annually on the importance of regular physical activity and a heart-healthy diet. Beyond this, however, evidence-based strategies for prevention or treatment of diabetes specific to childhood cancer survivors are lacking.

Metabolic Syndrome

Metabolic syndrome consists of a constellation of adverse metabolic factors that are associated with increased risk for type 2 diabetes and cardiovascular disease. These risk factors include obesity, elevated blood pressure, glucose intolerance, and dyslipidemia [5, 61, 62]. The most recently proposed criteria emphasize the role of central obesity and the hypothesis that visceral adipose tissue plays a key role in contributing to metabolic syndrome [63]. In the general population, a clear relationship has emerged between fat accumulation in specific depots, chronic inflammation (increased C-reactive protein, tumor necrosis factor- α , and interleukin-6), and metabolic dysfunction [63, 64]. The proposed pathophysiology of metabolic syndrome after childhood cancer therapy is depicted in Figure 1.

Treatment-Related Risk Factors

Prior studies have demonstrated an increased prevalence of metabolic syndrome and its components in childhood cancer survivors [65, 66], with risk estimates varying widely from 7 to 60% [27, 67–71]. In a report of 8,599 childhood cancer survivors enrolled in the CCSS, risk factors for the cardiovascular risk factor (CVRF) cluster, a surrogate for metabolic syndrome, included older at-

tained age (≥ 40 vs. < 30 years of age; odds ratio [OR], 8.2; 95% CI, 3.5–19.9), TBI exposure (OR, 5.5; 95% CI, 1.5–15.8) or radiation to the chest and abdomen (OR, 2.3; 95% CI, 1.2–2.4), and physical inactivity (OR, 1.7; 95% CI, 1.1–2.6) [67]. Various other studies have found that risk of metabolic syndrome is pronounced among those previously exposed to cranial radiation [72–74]. Interestingly, in a study of 532 adult long-term childhood cancer survivors, treatment factors and not genetic variation were found to determine risk of hypertension, increased waist circumference, diabetes, and metabolic syndrome [75].

Metabolic risk in survivors of childhood ALL has been particularly well described [69, 72, 74, 76, 77]. Compared to population controls, ALL survivors have been shown to have a high prevalence of metabolic syndrome, as well as individual CVRFs and obesity [72, 74]; those previously exposed to cranial radiation or TBI are at highest risk. A study of 650 leukemia survivors (mean attained age: 24.2 years) who were not treated with HCT (18% treated with cranial irradiation), found that age-specific cumulative prevalence of metabolic syndrome increases sharply with increasing age; cumulative prevalence at 20, 25, 30, and 35 years of age was 1.3, 6.1, 10.8, and 22.4%, respectively [68]. A more recent study from the French L.E.A. cohort showed that the prevalence of metabolic syndrome was increased among childhood leukemia survivors, relative to controls; risk was greatest, however, among those transplanted with TBI (OR 6.26, 95% CI, 4.17–9.36; $p < 0.001$) followed by those treated with chemotherapy and cranial radiation (OR 2.32, 95% CI, 1.36–3.97; $p = 0.002$), transplantation without radiation (OR 2.18, 95% CI, 0.97–4.86; $p = 0.057$), and chemotherapy alone (OR 1.68, 95% CI, 1.17–2.41; $p = 0.005$). Interestingly, metabolic syndrome presentation differed based on exposure history; when compared to controls, cranial radiation recipients with metabolic syndrome had a *larger* waist circumference relative to controls (109 vs. 99.6 cm; $p = 0.007$), while TBI recipients had a *smaller* waist circumference (91 vs. 99.6 cm; $p = 0.01$) as well as increased triglyceride levels, fasting glucose levels, and systolic blood pressure [78]. These differences likely reflect divergent pathophysiology of metabolic syndrome after different treatment exposures; further work is needed to elucidate the mechanisms underlying these noted discrepancies.

Cranial radiation is often cited as an independent risk factor for both obesity and metabolic syndrome [72–74]. A single-center cohort study of 500 childhood cancer survivors (median attained age: 28 years, range: 6–49 years) found that 13% of participants met the criteria for meta-

Fig. 1. Pathophysiology of metabolic syndrome. TG, triglycerides; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; IGF-1, insulin-like growth factor 1; GH, growth hormone; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; PAI-1, plasminogen activator inhibitor-1; FFA, free fatty acid.

bolic syndrome; those treated with cranial radiation were identified as particularly high risk [71]. As previously discussed, cranial radiation is associated with growth hormone deficiency, which has been shown to be associated with higher fasting insulin, abdominal obesity, and dyslipidemia [79], and may independently contribute to the development of metabolic syndrome in survivors of childhood cancer.

Exposure to TBI has also been identified as an independent risk factor for the development of CVRFs and metabolic syndrome among childhood cancer survivors [34, 41, 80–83]. Importantly, metabolic syndrome after TBI may occur in the absence of obesity. In a large single-institution study of 1,885 1-year HCT survivors (median

age at HCT: 44.4 years; 30.5% treated prior to age 35; 52.7% treated with TBI), the prevalence of CVRFs was significantly higher among HCT survivors when compared to the general population; those treated with TBI-based conditioning regimens were at highest risk for the development of diabetes and dyslipidemia [84]. Importantly, 10-year incidence of cardiovascular disease has been shown to incrementally increase with number of CVRFs (4.7% [none], 7.0% [1 CVRF], 11.2% [≥ 2 CVRFs], $p < 0.01$), including hypertension, diabetes, and dyslipidemia [84]. The pathophysiologic mechanism underlying this increased risk is likely multifactorial and warrants further study; Figure 1 depicts the various factors that likely contribute to risk in survivors exposed to TBI.

Other populations of cancer survivors have been found to be at risk for metabolic syndrome as well. One study of 103 neuroblastoma and Wilms survivors, and 61 controls, found that survivors had more components of metabolic syndrome than controls. Interestingly, when total fat percentage, as assessed by dual energy X-ray absorptiometry, was used as a surrogate marker of adiposity, the metabolic syndrome was three times more frequent in abdominally irradiated survivors (27.5%) than in non-irradiated survivors (9.1%, $p = 0.018$) [59]. These findings require replication in large solid tumor survivor cohorts.

Contribution of Other Endocrinopathies

In the general population, low testosterone and estrogen levels have been associated with visceral obesity, insulin resistance, and dyslipidemia. In childhood cancer survivors, sex hormone deficiencies may be present after direct damage to the gonads due to exposure to high-dose alkylating agents and/or radiotherapy, or due to secondary damage after high-dose cranial radiation (>30 Gy to the hypothalamic-pituitary axis). While the effect of these changes on risk of metabolic syndrome in childhood cancer survivors is poorly characterized, these hormonal abnormalities may contribute to an adverse cardiometabolic phenotype as well.

Lifestyle Factors

Lifestyle factors, such as diet, physical activity, and smoking habits, may impact risk of developing metabolic syndrome among childhood cancer survivors. A recent report of 1,598 adult survivors of childhood cancer (median attained age: 32.7 years) enrolled in the St. Jude Lifetime Cohort Study found that 31.8% met criteria for metabolic syndrome [69]. Among individuals who did not follow World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations for a heart-healthy lifestyle, women were 2.4 times (95% CI, 1.7–3.3) and men were 2.2 times (95% CI, 1.6–3.0) more likely to meet criteria for metabolic syndrome, when compared to those who followed WCRF/AICR guidelines.

Other studies have similarly highlighted the importance of lifestyle factors in mediating metabolic risk in childhood cancer survivors. In a cross-sectional study of 117 adult survivors of childhood ALL, our group found that the odds of having metabolic syndrome fell by 31% for each unit increase in adherence to a Mediterranean diet [74]. Others have similarly demonstrated that increased physical activity is associated with improved car-

diometabolic risk factor status in childhood cancer survivors [85, 86] and in HCT survivors specifically [87]. These studies provide important foundational data for future intervention studies assessing the impact of lifestyle change on metabolic risk in childhood cancer survivors.

Screening and Management

The most recent version of the COG LTFU guidelines (v4.0) removed any specific screening guidelines for metabolic syndrome related to cranial radiation or TBI [8]. Rather, the guidelines suggest that individuals treated with cranial radiation should have their height, weight, and blood pressure checked annually with assessment of nutritional status. Individuals treated with TBI should have a fasting lipid profile and blood glucose (or hemoglobin A1c) checked every 2 years, and as clinically indicated. All survivors should be counseled about the importance of a heart-healthy lifestyle. At this time, specific strategies for prevention or treatment of metabolic syndrome in childhood cancer survivors are lacking.

Importance of Lifelong Risk-Based Screening and Long-Term Follow-Up

Given the high prevalence of metabolic dysfunction in this cohort, it is imperative that survivors receive appropriate lifelong risk-based care. Many of the toxicities described have a prolonged, clinically silent latency period; for instance, a minimum latency of approximately 20 years has been described between abdominal radiation exposure and diabetes development [12]. Thus, appropriate risk-based screening and surveillance can enable early detection of potential treatment-related complications. Often, referral to an endocrinologist for further management and care is appropriate. Endocrine hormone replacement, as clinically indicated, is an important part of the management of metabolic abnormalities in childhood cancer survivors.

In North America, childhood cancer survivorship clinics generally follow the COG guidelines, which are detailed above. Efforts are also underway to harmonize survivorship guidelines worldwide; more information may be found at: www.ighg.org [88]. An international panel of experts is currently developing harmonized guidelines for diabetes and metabolic syndrome screening among childhood cancer survivors, which should be forthcoming in the next year. Once complete, this effort

will establish an integrated strategy for the surveillance of metabolic dysfunction among childhood and young adult cancer survivors worldwide. This work marks the beginning of an international collaboration to improve the long-term health of childhood cancer survivors. Given that many of the existing guidelines are based on expert consensus, ongoing longitudinal data collection and audit are needed to optimize these guidelines to improve outcomes among this cohort of high-risk individuals.

Conclusions

Childhood cancer survivors are at risk of a wide range of treatment-related complications, which may occur many years after therapy, including diabetes and metabolic syndrome. While specific risk factors for metabolic dysfunction, including cranial irradiation, abdominal radiation, and TBI, have been identified, the exact mechanisms underlying these derangements remain unclear. Data are similarly lacking on survivor-specific preventive strategies and treatment recommendations for metabolic dysfunction in this high-risk population. Given that survivors are already at increased risk for premature cardiovascular morbidity and mortality, early initiation of risk-based screening and implementation of risk-reducing strategies are indicated in this high-risk population. Fu-

ture studies are needed to clarify the pathophysiology of these metabolic derangements to inform future therapeutic efforts and preventive strategies and improve the quality and quantity of life of long-term survivors of childhood cancer.

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Author Contributions

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