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A systematic approach to the endocrine care of survivors of pediatric hematopoietic stem cell transplantation

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Abstract
Hematopoietic stem cell transplantation (HSCT) is used in children to treat a variety of malignant and nonmalignant hematologic conditions and certain inborn errors of metabolism. Survivors of HSCT are markedly affected by disease and treatment toxicity. Endocrine complications are among the most commonly reported chronic health conditions in this population. In this review, we summarize the most common endocrine late effects after pediatric HSCT. We also highlight the importance of systematic and longitudinal evaluations to achieve early diagnoses and treatment for these conditions and improve the long-term health outcomes for patients who received HSCT as children.

Keywords Hematopoietic stem cell transplantation · Endocrine care · Late effects · Pediatric cancer

1 Introduction

Hematopoietic stem cell transplantation (HSCT) is used to treat a variety of childhood diseases, including hematologic malignancies, immune system deficiency states, hemoglobinopathies, bone marrow failure syndromes, and inborn errors of metabolism. HSCT is performed by intravenously infusing multipotent hematopoietic stem cells to the transplant recipient. Conditioning for HSCT comprises depletion of the bone marrow before HSCT *via* treating patients with myeloablative agents, such as high-dose chemotherapy and/or total body irradiation (TBI) or total lymphoid irradiation (TLI) [1]. Additional treatment exposures during the immediate post-transplantation period include immunosuppressive agents, such as systemic glucocorticoids, to prevent the rejection of donor cells or to treat graft-*versus*-host disease (GVHD) [2]. Surviving HSCT recipients have a high risk of experiencing chronic health conditions that may appear after a variable latency period and are hence termed late effects [3, 4]. Endocrinopathies are among the most commonly reported late effects [5]. Survivors may benefit from early recognition of endocrinopathies because many are amenable to treatment, whereas the absence of therapy may lead to worsened general health outcomes [3]. Here, we summarize current reports of endocrine late effects resulting from pediatric HSCT, with an emphasis on gaps in knowledge and areas for further investigation and clinical improvement.

1.1 Endocrinopathies in pediatric HSCT survivors

1.1.1 Prevalence and risk factors

Endocrinopathies are among the most frequent late effects associated with pediatric HSCT, with nearly 60% of affected individuals receiving HSCT before 10 years of age [5]. The endocrine organs affected by HSCT include the hypothalamic-pituitary axis, thyroid gland, and gonads. Systems supporting linear growth, bone health, and metabolism may also be affected [6]. The risk factors for endocrine late effects after HSCT include treatment-, transplant-, recipient-, and graft-related variables. High-dose chemotherapy and irradiation before HSCT impose the most considerable risk [7]. TBI is responsible for a large portion of post-transplant endocrinopathies, especially when delivered as a single fraction [8]. In modern protocols, TBI is usually delivered in three to nine fractions, with a total dose ranging from 10 to 16 Gy, to

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decrease the risk of complications [9]. Additional efforts to decrease treatment toxicity include lower-intensity, chemotherapy-alone conditioning regimens. However, long-term follow-up data for these patients are limited [10]. Lasting endocrine deficits may also occur as a consequence of post-transplant complications, such as those requiring prolonged glucocorticoid treatment, including GVHD [11]. These complications may add to the burden of coexisting sequelae of HSCT, such as malnutrition and cardiorespiratory compromise [6, 12]. Patient factors such as young age at HSCT and graft-related issues such as transmission of autoimmune disease may further contribute to the risk of endocrine impairment after HSCT [13].

1.1.2 Linear growth impairment

The prevalence of linear growth impairment ranges from 20 to 84%, a variation largely due to cohort heterogeneity and differences in outcome measures (e.g., the proportion of final adult height in reported data) [14, 15]. Abnormal linear growth patterns in HSCT recipients are frequently multifactorial and may potentially involve hormonal deficits, such as growth hormone (GH) deficiency, disorders of puberty, and thyroid dysfunction. Nonhormonal factors, such as growth plate damage from TBI-impaired spinal growth [9] and/or adverse effects related to glucocorticoids, malnutrition, or vital organ impairment, may further contribute to growth failure in children treated with HSCT. GH deficiency may affect 20 to 40% of transplant recipients [9, 16–18]. Single fraction [19] and higher doses [17] of TBI expose children to a higher risk of GH deficiency than do fractionated TBI and doses less than 8 Gy. Prior exposure to cranial irradiation, a younger age at TBI [6], and time since treatment [18] represent additional risk factors for GH deficiency. Hypothalamic-pituitary dysfunctions other than GH deficiency are uncommon in HSCT survivors in the absence of exposure cranial radiotherapy in addition to TBI. Some reports may have overestimated the risks of central hypothyroidism [20] or adrenal insufficiency [21] in this population because of questionable testing modalities [22].

1.1.3 Thyroid disease

Primary hypothyroidism affects a reported 10 to 50% of HSCT recipients [6, 7, 12, 15, 16, 22–26]. TBI, especially when delivered in a single fraction, represents the main risk factor for thyroid disease [8, 22, 24–26]. Conditioning with chemotherapy alone by using busulfan and cyclophosphamide may expose patients to a higher risk of subclinical and frequently transient hypothyroidism [12, 23, 24]. The transfer of autoimmunity from graft donors may also cause HSCT recipients to experience autoimmune thyroid disease, leading to hypothyroidism or hyperthyroidism [27]. Secondary thyroid cancer has been reported following TBI [28] after a median latency time of 8.5 years, with additional risk factors, including young age at HSCT, female sex, and a history of GVHD [28].

1.1.4 Gonadal disorders

Premature ovarian insufficiency affects more than 75% of female pediatric HSCT recipients [15] due to the gonadotoxic nature of alkylating chemotherapy agents used for conditioning, such as cyclophosphamide and busulfan [29], as well as that of TBI [30, 31]. Older age (> 10 years) at exposure may increase risk or hasten the occurrence of premature ovarian insufficiency [30–32], possibly due to a lower follicular reserve in older patients than in younger individuals at the time of treatment [33]. Gonadal shielding may offer a measure of protection, but long-term follow-up data on efficacy are lacking [34]. Reduced intensity conditioning, using lower doses of chemotherapy and/or radiotherapy, has been observed to be associated with lower rates of female infertility [35]. Female survivors of HSCT who may become pregnant may also have a higher risk of miscarriage [36]. This may be attributed to TBI effects on the uterus or its vasculature [37]. In male patients, germ cell failure (i.e., oligospermia or azoospermia) frequently occurs after HSCT because of the toxic effects of alkylating agents [38] and TBI [39] on germ cells. Testicular shielding may protect a subset of individuals from the effects of TBI [40], but sperm banking should be offered whenever feasible due to the very high risk of infertility associated with HSCT [38]. In contrast, Leydig cell function, which is responsible for testosterone production, is seldom impaired in male HSCT recipients, unless these individuals were also exposed to testicular radiotherapy (e.g., treatment for relapsed leukemia) [21, 23, 29, 41].

1.1.5 Bone mineral density deficit

The prevalence of severe bone mineral density deficit, defined by age- and sex-matched z-scores less than −2, has been reported at 21% in 5-year survivors of pediatric HSCT [42]. The etiology of this deficit is most likely multifactorial. Issues related to primary disease, treatment toxicities, post-transplant complications (e.g., GVHD), hormonal deficits, and lifestyle choices may contribute to bone mineral density deficits to various extents in individuals [43]. Preferential differentiation of mesenchymal stem cells towards adipogenesis, rather than osteogenesis, is a suggested additional mechanism for bone mineral density deficit [44].

1.1.6 Abnormal body composition, impaired glucose metabolism, and dyslipidemia

Survivors of pediatric HSCT reportedly experience insulin resistance, diabetes mellitus, and dyslipidemia at higher than expected rates than in the general population [45–48]. The prevalence of diabetes mellitus was reported at 5% after a median follow-up duration of 11 years [46]. A subset of survivors may experience post-transplant diabetes mellitus because of prolonged treatment with immunosuppressive drugs known to affect beta cell function including glucocorticoids and calcineurin inhibitors such as tacrolimus [49]. Insulin resistance is frequent in HSCT survivors, with a reported prevalence of 52% [45]. Exposure to TBI appears to be the primary risk factor for abnormal glucose metabolism in this population [50–53], and changes in insulin sensitivity in this context may be associated with changes in body composition (i.e., increased body fat and decreased lean mass, termed sarcopenic obesity [53]) rather than with obesity defined by body mass index [50, 52]. Pancreatic islet cell injury from radiotherapy is a suggested mechanism for abnormal glucose metabolism [54, 55]. Low high–density lipoprotein and elevated triglyceride levels are reported in up to 30% of pediatric HSCT recipients [56, 57]. Possible contributors to dyslipidemia include host factors, such as obesity and family history, in addition to TBI and transplant complications (i.e., GVHD, liver disease, and hormonal deficits) [57, 58]. Immune system dysfunction, inflammatory mechanisms, and changes in microbiome composition were recently suggested to contribute to persistent metabolic derangements after HSCT; however, supporting evidence for this is lacking [59].

1.2 Suggested screening and management approaches

A systematic screening approach aiming at early diagnosis and treatment of endocrine complications associated with HSCT has the potential to improve general health outcomes in survivors of pediatric HSCT because of the contribution of hormonal deficits to other health complications, such as frailty [60] and cardiovascular risk [15, 58]. It is reasonable to initiate systematic surveillance in asymptomatic individuals 1 year after transplant given that the latency period between HSCT and the onset of endocrine late effects has been reported between 0.8 and 9.5 years [6, 18]. Table 1 summarizes the recommendations for such screening by the Children's Oncology Group consortium [61]. An effort to harmonize recommendations with other national or regional groups is currently underway [62]. The diagnostic and treatment approaches for endocrine disorders in survivors of childhood HSCT generally follow guidelines that are similar to those applied in non-cancer or other cancer survivor populations, with some adjustments related to specific conditions (highlighted in the following section and summarized in Table 2).

1.2.1 Linear growth impairment

Children experiencing decreased growth velocity for age and pubertal stage should receive an evaluation that includes a thorough clinical examination with pubertal staging and assessment of body proportion (i.e., sitting height or arm span). Laboratory test orders should be guided by patient medical history and clinical findings, but individuals in whom nutritional and other endocrine causes for growth deceleration (e.g., hypothyroidism or pubertal delay) have been ruled out should be further investigated for GH deficiency *via* dynamic testing [63]. Screening for GH deficiency by serum insulin–like growth factor 1 levels is not a reliable approach for childhood cancer survivors exposed to radiotherapy [64]. Assessment of skeletal maturity with a bone age X-ray can help ascertain growth potential. The diagnosis and treatment of GH deficiency in HSCT recipients follows a similar path as in other populations [63]. Medical providers should be aware that individuals treated with TBI may not experience an adequate growth spurt during puberty [9, 17, 19]. Patients and families should thereby be counseled that treatment with GH may not fully mitigate poor final height outcomes in individuals with a considerable burden from disease and treatment exposures [9].

The safety of treatment with GH in childhood cancer survivors has been a subject of debate for decades. Treatment with GH does not appear to increase the risk for cancer recurrence nor mortality in GH-deficient childhood cancer survivors, but uncertainties regarding an association with secondary neoplasia should be discussed with patients and families and balanced with the potential benefits of treatment for height and quality of life [65, 66]. Growth enhancement strategies in non-GH-deficient children with short stature in the non-cancer population have included treatment with GH [67], with or without pubertal suppression and aromatase inhibitors [68]. However, no data pertaining to the safety and efficacy of these approaches are available in non-GH-deficient HSCT survivors with decreased growth velocity and/or markedly short stature [63].

1.2.2 Thyroid disease

Screening of serum levels of free T4 and thyroid-stimulating hormone is recommended at least annually for individuals exposed to TBI or TLI. These values should also be measured as clinically indicated, such as in children experiencing poor growth and individuals experiencing hypothyroidism or hyperthyroidism symptoms, regardless of treatment exposure [61]. The management of thyroid dysfunction in HSCT recipients follows the general approach used in the non-cancer

Table 1 Screening recommendations for endocrine late effects after pediatric hematopoietic stem cell transplantation

Late effect	Treatments associated with highest risk	Population to screen	Screening modality	Frequency
Growth hormone deficiency	TBI Cranial radiotherapy	All survivors who have not attained final adult height	Physical examination: height, weight, BMI, Tanner stage	Every 6 months
Thyroid disease	TBI Neck irradiation	Survivors with neck exposure to irradiation, including TBI	History to elicit signs of hypo or hyperthyroidism Physical examination: palpation of neck[1] Laboratory: serum freeT4 and TSH	Yearly
Gonadal dysfunction	TBI Cranial radiotherapy Alkylating agents Heavy metals	Survivors exposed to TBI, cranial radiotherapy, alkylating agents, or heavy metals	History to elicit abnormal puberty timing or signs of gonadal dysfunction Physical examination: pubertal status Laboratory: Females ≥ 13 years old: estradiol, LH, FSH Males ≥ 14 years old: morning testosterone[2]	Yearly[4]
Bone health	TBI Cranial radiotherapy Corticosteroids Methotrexate Calcineurin inhibitors	All survivors	Bone mineral density evaluation using dual energy X-ray absorptiometry or quantitative computed tomography, starting at 1 year after transplant	Repeat as clinically indicated
Obesity, diabetes, dyslipidemia	TBI Cranial radiotherapy	All survivors	Physical examination: weight, body mass index Laboratory: fasting glucose or hemoglobin A1c, fasting lipids[3]	Clinical: yearly Laboratory: every 2 years

TBI indicates total body irradiation; BMI, body mass index; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone

[1] Initial screening via neck ultrasound is subject to debate.

[2] Semen analysis is most informative for fertility evaluation.

[3] Labs are indicated in individuals exposed to TBI or abdominal radiotherapy.

[4] Not specified by guidelines, suggested by review authors. Table was adapted from Chow EJ et al. (2016) Late Effects Surveillance Recommendations Among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant,* 22:782-95.

population and in other populations of childhood cancer survivors [69]. Measurement of thyroid autoantibodies (e.g., thyroperoxydase and thyroglobulin antibodies) can help differentiate radiation-induced hypothyroidism from autoimmune causes in individuals with abnormal thyroid function tests. However, this is not recommended as a screening modality [69].

It is unclear whether treatment of subclinical forms of primary hypothyroidism (i.e., elevated thyroid-stimulating hormone and normal free T4 values) improves growth outcomes and decreases the risk for secondary thyroid neoplasms [69]. Screening for secondary thyroid neoplasia in individuals exposed to neck radiotherapy, including TBI or TLI, is a subject of controversy. Some, but not all, experts recommend using thyroid ultrasound rather than relying fully on periodic neck palpation [70]. The management of secondary thyroid cancer in HSCT survivors follows the same guidelines used for thyroid neoplasia in children, adolescents, and adults [71, 72]. Given the substantial health burdens experienced by HSCT recipients from disease- and treatment-related late effects, the risks and benefits of treatment with radioactive iodine for thyroid cancer should carefully be balanced and discussed with patients and their families [71].

1.2.3 Gonadal disorders

Survivors of pediatric HSCT exposed to TLI, TBI, cranial radiotherapy, or gonadotoxic chemotherapy should have yearly evaluations of pubertal development and gonadal function [61]. These evaluations include obtaining a pertinent history of pubertal progression and symptoms of hypogonadism (i.e., amenorrhea in females and symptoms of low testosterone, such as erectile dysfunction, in adult males). Physical examinations should be performed with Tanner staging in children and adolescents to assess pubertal delay or arrested pubertal development. Medical providers should be aware that measurement of testicular volume is not reliable in male individuals exposed to testicular radiotherapy and/or gonadotoxic

Table 2 Management of endocrine disorders after a positive screen in survivors of pediatric hematopoietic stem cell transplantation

Late effect	Clinical considerations	Confirmatory labs	General counseling and treatment approaches	Remarks/areas of uncertainty or active investigation
GH deficiency	Measure body proportions (sitting height or arms span) to consider skeletal toxicity of treatment Investigate other causes of decreased linear growth, including nutritional factors, pubertal disorders, and hypothyroidism	GH stimulation test Bone age X-ray	GH replacement in individuals with GH deficiency after discussion of benefit *vs.* risk of treatment Counsel on the risk for short stature despite GH therapy due to direct skeletal toxicity and burden from disease and cancer therapy	Association between GH replacement and risk for secondary neoplasia No known strategy to address impaired growth spurt during puberty No guidance available for non-GH-deficient children with short stature
Hypothyroidism	Causes could include thyroid exposure to radiotherapy but also autoimmune thyroid disease (e.g., Hashimoto thyroiditis)	Serum free T4, TSH Thyroperoxydase and thyroglobulin autoantibodies	Treatment with levothyroxine as in other populations	Association between isolated TSH elevations and thyroid neoplasia and rationale for treating compensated forms
Thyroid cancer	Individuals may present with thyroid nodules or cervical lymph nodes	Thyroid ultrasound Ultrasound-guided fine-needle aspiration biopsy	Similar approach to thyroid cancer in the general population Importance of avoiding unnecessary treatment with radioactive iodine	The place of ultrasound in screening is uncertain
Premature ovarian insufficiency	Assess age at puberty onset (Tanner staging based on breast development), rate of pubertal progression, menstrual history	Serum estradiol, FSH	Sex hormone replacement therapy to allow pubertal development in children and improved bone, cardiac, and psychosexual health in adults Mature oocyte cryopreservation if feasible prior to HSCT	Duration of replacement in adulthood Modification by exogenous estrogen of secondary breast cancer risk in individuals exposed to chest radiotherapy Fertility preservation of prepubertal patients
Male hypogonadism	Assess age at puberty onset, rate of pubertal progression, signs of hypoandrogenemia Do not use testicular volume measurement for Tanner staging because of the effect of gonadotoxic treatments on testicular size	Serum AM testosterone, LH (Leydig cell function) Semen analysis (fertility)	Sex hormone replacement therapy to allow pubertal development in children and improved bone, cardiac, and psychosexual health in adults Sperm banking if feasible prior to HSCT	Fertility preservation of prepubertal patients
Bone mineral density deficit	Assess for suboptimal nutrition/lifestyle and signs of endocrine deficits	Serum vitamin D25	Assess for and treat vitamin D deficiency and other hormone deficits, counsel on improving nutrition and lifestyle factors	Role of bisphosphonates and other pharmacologic agents in improving outcomes long term
Abnormal glucose tolerance and dyslipidemia	Assess body proportions (abdominal obesity *via* waist-to-height ratio) Obtain family history Gather nutritional and lifestyle data	Oral glucose tolerance test Fasting lipids	Counsel on healthy lifestyle and improved dietary choices Dietary management of dyslipidemia	Role of pharmacotherapy in partial states (prediabetes) Treatment approach in children

GH indicates growth hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; HSCT, hematopoietic stem cell transplant

chemotherapy because these individuals may maintain normal testosterone production but have small testes due to germ cell depletion [41]. Ascertaining secondary sex characteristics (e.g., pubic hair, scrotal thinning, and penile size) may reveal gonadal disorders in such instances, but corroboration by laboratory measurements should be obtained.

Annual measurement of serum-luteinizing hormone, follicle-stimulating hormone, estradiol (females), and morning testosterone (males), starting at age 13 years in females or 14 years in males, is recommended for HSCT recipients exposed to cranial radiotherapy and/or gonadotoxic therapies [61]. Sex hormone replacement therapy follows similar guidelines to those used in other populations [73–75]. Estrogen replacement does not appear to increase the risk of secondary breast cancer in women exposed to chest radiation, including TBI, to more than the risk in women without

premature ovarian insufficiency. This is, however, an area of active investigation [76]. Evaluation of male fertility requires semen analyses because of the lack of reliability of surrogate serum markers [77]. If feasible, fertility preservation *via* sperm banking (males) or mature oocyte cryopreservation (females) should be considered before HSCT because of the known toxicity of conditioning regimens [77, 78]. Fertility preservation in prepubertal patients is still considered experimental and may carry additional risks for HSCT recipients treated for hematologic malignancies because of the possibility of reseeding cancer cells should gonadal tissues harvested before treatment be reimplanted in survivors later in life [33]. Dissemination of knowledge related to this field remains necessary; recent data have shown that while 87% of at-risk HSCT survivors were informed of possible gonadal injury from treatment by their oncologists, only 56% of males and 36% of females were referred to fertility specialists [79].

1.2.4 Bone mineral density deficit

The Children's Oncology Group recommends obtaining bone mineral density evaluations *via* dual X-ray absorptiometry (DXA) or quantitative computed tomography at 1 year after HSCT, with repeat testing ordered only if clinically indicated [61]. This recommendation is primarily based on expert opinion; however, evidence for the benefits of and optimal timing for screening is lacking. It is important to note the limitations of single evaluations in patient trajectories and to stress the importance of adjusting DXA values according to patient age and height to ensure accurate interpretation of the results [43]. Recommendations to medical providers caring for HSCT recipients include counseling for adequate nutritional intake of calcium, regular physical activity, and early remediation for vitamin D insufficiency and hormonal deficits [80]. Treatment with bisphosphonates reportedly improved bone mineral density in HSCT recipients in a retrospective study analyzing DXA changes over a median of 377 and 299 days in 18 treated children and 48 children who did not receive these agents, respectively [81]. Gains appeared higher among those with a history of prolonged exposure to glucocorticoids for GVHD [81]. Whether such gains will improve long-term bone health outcomes (e.g., reduced fractures) or override concerns related to the adverse effects associated with bisphosphonates (e.g., atypical fractures and osteonecrosis of the jaw) remains uncertain [82].

1.2.5 Abnormal body composition, impaired glucose metabolism, and dyslipidemia

Although identified as a potential contributor to cardiovascular disease, recommendations specifically addressing screening for and management of sarcopenic obesity in survivors of pediatric HSCT are not available [58]. Current recommendations for abnormal glucose tolerance and dyslipidemia risks include screening HSCT recipients treated with abdominal radiotherapy, including TBI, by measuring body weight at least annually and obtaining fasting glucose or hemoglobin A1c values and lipid values every 2 years [61]. Non-pharmacologic lifestyle modifications remain the first step in the management of metabolic derangements in HSCT survivors [58]. It is unknown whether the use of glucose-lowering medications, such as metformin, can delay progression from prediabetic states to diabetes in this population [58]. Statins appear effective for reducing low-density lipoprotein cholesterol and triglyceride levels in survivors of adult HSCT [83]. Guidance is lacking for the management of dyslipidemia in HSCT survivors treated during childhood and particularly among those who experience lipid disorders as children [58].

2 Conclusions

Recipients of pediatric HSCT are vulnerable to late-onset endocrine effects, which may exacerbate adverse general health outcomes by mechanisms that increase cardiovascular risk factors and decrease quality of life. The importance of systematic and longitudinal follow-up of HSCT survivors cannot be overemphasized given the dramatic opportunity it provides for early diagnosis and management. Many areas of uncertainty persist, especially for disorders that are uncommon in the general pediatric population such as decreased bone mineral density and dyslipidemia. These areas represent opportunities for future research.

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