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CONSENSUS UPDATE

RECOMMENDATIONS FOR SCREENING AND MANAGEMENT OF ENDOCRINOPATHIES AFTER PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Endocrine disorders after pediatric hematopoietic stem cell transplantation result from the interaction between the underlying disease, host characteristics and treatment, including exposure to pre- and peri-transplant agents (chemotherapy and radiotherapy). In addition, post-transplantation factors, including graft-versus-host disease, and its treatment, especially glucocorticoids, also contribute to hormone deficiencies or endocrine disorders. Endocrinological alterations can be divided into six main groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Osteometabolic disorders; 6) Obesity and metabolic syndrome. The purpose of this article is to update screening recommendations and management approaches for the various endocrine diseases, defining populations at risk, recommendations during follow-up, and treatment strategies, with attention to controversial issues.

KEYWORDS: Bone Marrow Transplantation. Graft vs Host Disease. Glucocorticoids. Growth Disorders. Adrenal Insufficiency. Thyroid gland/radiation effects. Gonads/drug effects. Adiposity. Atherosclerosis. Bone and bones/metabolism.

INTRODUCTION

Endocrinological disorders after pediatric hematopoietic stem cell transplantation (HSCT) result from the synergistic interaction between the underlying disease, host characteristics, exposure to pre- and peri-HSCT factors (chemotherapeutic agents, conditioning and radiotherapy regimen, RT) and post-HSCT factors, including graft-versus-host disease (GVHD) and its treatment.[1-4]

Endocrinopathies are the most frequent late effects associated with HSCT, with almost 60% of those affected having had HSCT before 10 years of age, and onset between 0.8 to 9.5 years after HSCT. They are divided into six main groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Osteometabolic disorders; 6) Obesity and metabolic syndrome.[1-4]

The goal of this paper is to present, in Tables 1 and 2 (attached), a summary of the recommendations of the 2020/2021 Consensus[1], with revised aspects, supported by retrospective studies and international guidelines, and/or experience with non-transplanted patients, in order to define populations at risk and management strategies for the follow-up and treatment of endocrinopathies after HSCT, with attention to controversial issues.[4-10]

TABLE 1 - Screening recommendations for endocrinopathies after pediatric hematopoietic stem cell transplantation (HSCT)

Endocrinopathy	Related treatments	Population at risk	How to do the screening?	Frequency
Growth disturbances	Cranial RT TBI Glucocorticoid	Growing phase and exposed to the related treatments	Clinic: height, BMI, growth velocity, target height, Tanner stage Imaging: bone age Laboratory: FT4 and TSH, GH/IGF-1axis	Every 6 months
Thyroid diseases	Cervical RT Cranial and/or craniospinal RT TBI	Exposed to the related treatments	Clinic: thyroid palpation Laboratory: FT4 and TSH Imaging: thyroid US (controversial)	Yearly, start 1 year after HSCT
Gonadal dysfunction	Cranial and/or pelvic/ testicular RT TBI Alkylating drugs Heavy metals	Exposed to the related treatments	Clinic: Tanner stage Laboratory: Female > 12-13 years: E2, LH, FSH Male > 13-14 years: T, LH, FSH Semen analysis (fertility)	Yearly
Adrenal failure	Glucocorticoid Cranial RT	Exposed to high and prolonged glucocorticoid doses (GVHD) Cranial RT (rare)	Clinic: fatigue, anorexia, nausea, vomiting, weight loss, hypotension Laboratory: hyponatremia, hyperkalemia and hypoglycemia	After glucocorticoid therapy discontinuation and cranial RT (yearly)
Osteometabolic disturbances	Cranial RT and/or TBI Glucocorticoid Metotrexate Calcineurin inhibitors	All survivors	Bone mineral density (DXA)	Start 1 year after HSCT Repeat according to detected alteration
Obesity and metabolic syndrome	Cranial RT TBI	All survivors	Clinic: BMI, circumferences and blood pressure Laboratory: glucose, insulin, HOMA1-IR, glycated hemoglobin (HbA1c), lipids	Clinic: yearly Laboratory: every 2 years. If alteration, individualize each case

Abbreviations: RT: radiotherapy; TBI: total body irradiation; BMI: body mass index; FT4: free thyroxin; TSH: thyroid-stimulating hormone; GH: growth hormone; IGF-1: insulin-like growth factor 1; US: ultrasound; E2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone; T: total testosterone; GVHD: graft-versus-host disease; DXA: dual energy x-ray absorciometry; HOMA1-IR: homeostase model assessment-insulin resistance. Adapted from van Iersel et al., 2021; Paetow et al., 2020 and Chow et al., 2016.

TABLE 2 - Management of endocrinopathies after hematopoietic stem cell transplantation (HSCT)

Endocrinopathy	General considerations	Complementary exams	How to treat?	Observations/controversies
GH deficiency	Investigate nutritional and pubertal disorders, or hypothyroidism Spinal RT: measure sitting height Pubertal spurt poor (limited trunk growth)	Bone age FT4 and TSH GH stimulation tests IGF-1	rhGH replacement after discussion of risks and benefits with oncologist and family	Recurrence and second malignancy No strategy improves pubertal growth No recommendation for short stature and non-GH deficient children
Hypothyroidism	Investigate graft donor-related autoimmune disease	FT4 and TSH Antithyroid antibodies	Sodium levothyroxin in overt hypothyroidism (TSH > 10 mIU/L)	There is no recommendation for treatment of borderline TSH (5-10 mIU/L) with normal FT4 Thyroid cancer risk
Thyroid cancer	Thyroid nodules or cervical lymph nodes in a thyroid exposed to RT Therapeutic 131-I-MIBG	US-guided fine needle aspiration (FNA) of suspicious nodule	Equal to thyroid cancer in the general population: thyroidectomy and therapeutic iodine if necessary	US in screening for nodules is controversial
Ovarian failure	Age of onset and progression of puberty, menstrual history, and libido Ovary poorly resistant to drugs and RT (hormonal and germ portions are equally impaired) Precocious menopause	E2, FSH, LH	E2 to induce puberty (adolescents) and improve bone, heart and psychological health in young adults Discuss fertility preservation: specialist services	Hormone replacement: transdermal route if thrombosis No increased risk of relapse or breast cancer Fertility preservation in prepubescent still limited
Male hypogonadism	Age of onset and progression of puberty, signs of hypoandrogenism Testicle is compartmentalized: Leydig is more resistant than Sertoli Alkylating drugs impair testis growth (germ epithelium)	T, LH (Leydig function indicates hormone production) FSH (Sertoli function indicates fertility) Sperm analysis (fertility, if desired)	Many male presents with spontaneous puberty and satisfactory hormone production despite infertility (Leydig function more resistant than Sertoli) Discussion of fertility preservation	T concentration that indicates replacement still controversial, consider if T < 300 ng/dL Fertility preservation in prepubescent still limited
Adrenal failure	Chronic fatigue, weakness, anorexia, nausea, vomiting, weight loss, postural hypotension, hyponatremia, hypokalemia, and hypoglycemia	Cortisol, ACTH and/or ACTH stimulation test	Discontinuation of prolonged high-dose glucocorticoid therapy should be gradual Consider "stress dose" during acute illness	Adrenal function usually recovers once exogenous glucocorticoid therapy is discontinued, but recovery time is variable
Low bone mineral density	Nutritional status and lifestyle Rule out hormone deficiency (hypogonadism and GH deficiency) Effect of medications (glucocorticoid)	25OH vitamin D Calcium, phosphorus, alkaline phosphatase, PTH and renal function DXA	Improve calcium intake and physical activity, encourage sun exposure if possible Vitamin D deficiency and other hormone deficits should be treated	Consider bisphosphonate if: Z-score < -2.0 (child) or T-score < -2.5 (adult), and/or multiple fractures Ideal regimen not yet defined
Obesity and metabolic syndrome	Sarcopenic obesity: assessing body composition and fat distribution Consider atherosclerosis and premature cardiovascular risk (epidemiological) Family history and lifestyle	Blood pressure Glucose, insulin and HOMA1-IR Glycated hemoglobin (HbA1C) Lipids	Healthy lifestyle: food and physical activity	Pharmacotherapy in obesity and insulin resistance Treatment of hypertension and dyslipidemia follows specific consensus

Abbreviations: GH: growth hormone; RT: radiotherapy; FT4: free thyroxin; TSH: thyroid-stimulating hormone; IGF-1: insulin-like growth factor 1; rhGH: recombinant human GH; MIBG: metaiodobenzilguanidine; US: ultrasound; E2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone; T: total testosterone; ACTH: adrenocorticotropic hormone; PTH: parathyroid hormone; DXA: dual energy x-ray absorciometry; HOMA1-IR: homeostase model assessment-insulin resistance. Adapted from van Iersel et al. 2021; Paetow et al., 2020 and Chow et al., 2016.

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