Endocrine dysfunction and surveillance following hematopoietic stem cell transplantation: A clinical practice guideline update

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ABSTRACT

Endocrine disorders are the most common long-term complications after hematopoietic stem cell transplantation (HSCT). They can affect growth, thyroid, adrenal, gonadal function, bone health, and metabolism. In 2021, the Brazilian Society of Bone Marrow Transplantation (SBTMO) published guidelines for endocrine follow-up after HSCT, which were updated in 2023, providing practical support for monitoring and managing transplant survivors. Since then, these guidelines have been reinforced, with the main shift being toward personalized monitoring strategies. In this approach, the intensity and frequency of endocrine surveillance are adjusted according to each survivor's treatment exposures and overall risk, rather than following fixed screening schedules. The scope of follow-up has also expanded to include fertility preservation and transition to adult care. Rather than introducing entirely new recommendations, current practice reflects a refinement of existing approaches. Even so, many recommendations still rely on moderate-quality evidence, underscoring the need for prospective multicenter studies.

Keywords: Hematopoietic stem cell transplantation; Endocrine late effects; Survivorship; Screening; Fertility preservation.

INTRODUCTION

Endocrine disorders are among the most common and clinically important late effects after hematopoietic stem cell transplantation (HSCT). They contribute to increased morbidity, reduced quality of life, and greater healthcare use. Endocrine dysfunction after HSCT can result from several factors, including pre-transplant therapies, conditioning regimens, total body irradiation (TBI), graft-versus-host disease (GVHD), prolonged corticosteroid use, immunosuppressive treatment, genetic susceptibility, and environmental influences. These complications may affect any endocrine gland and can appear months, years, or even decades after transplantation.[1–8]

In 2021, the Brazilian Society of Bone Marrow Transplantation (SBTMO) released a consensus on endocrine complications following HSCT, which was updated in 2023 with detailed guidance on screening, diagnosis, and management of endocrine late effects in survivors.[9,10]. In 2025, the pediatric working group also published current specific recommendations for endocrine follow-up in pediatric HSCT survivors.[11]

Since the 2021 SBTMO consensus, the core principles of endocrine monitoring after HSCT have remained consistent. Instead of major revisions, later international guidelines have refined existing recommendations

and placed greater emphasis on a risk-based approach to long-term follow-up. This approach recognizes that HSCT survivors have different levels of risk for endocrine complications and therefore do not require identical screening schedules. Risk-based monitoring tailors follow-up according to treatment-related factors that influence the likelihood of late endocrine effects, such as cumulative radiation doses (TBI/cranial/cervical), specific conditioning agents (alkylators/busulfan), age at transplantation, sex, the presence of chronic inflammation from GVHD, corticosteroid use, and prior endocrine disorders. These factors help determine which tests should be performed, when they should begin, and how often they should be repeated. Survivors with lower-risk exposures may need less frequent testing, but still require lifelong clinical monitoring.[8–14]

This review summarizes the main updates in endocrine clinical practice following HSCT and highlights areas in which recommendations have been refined. [6–8, 12–14]

ENDOCRINE SURVEILLANCE SINCE THE UPDATED 2023 SBTMO CONSENSUS

Growth and development

Growth hormone deficiency (GHD) occurs in 20-85% of pediatric HSCT survivors. Regular monitoring of growth velocity is essential, especially in children exposed to TBI or high-dose cranial irradiation at a younger age, since GHD may develop years after transplantation. Recombinant human growth hormone may benefit carefully selected cancer survivors once a stable cancer remission is confirmed, although the risk of recurrence and second neoplasm should be discussed.[3,6–8,15]

Thyroid dysfunction and second neoplasm

Annual thyroid function testing is recommended for survivors who have received direct or indirect thyroid irradiation because of the ongoing risk of hypothyroidism and secondary thyroid cancer. Functional hypothyroidism remains the primary defect, with a median onset of 4 years. Overt hypothyroidism is defined as thyroid-stimulating hormone (TSH) > 10 mIU/mL. There is currently no uniform recommendation for treating borderline/subclinical elevations (5< TSH< 10 mIU/mL) with normal free thyroxine (T4), although these patients require more frequent monitoring.[8,12–15]

Rather than routine ultrasound screening for all survivors, a targeted strategy is preferred, focusing on patients with prior neck irradiation, TBI, or suspicious findings on thyroid examination, as irradiated survivors face a 51% risk of nodules and a 30% risk of secondary thyroid malignancy.[8,12–15]

Adrenal function and recovery

Persistent hypothalamic-pituitary-adrenal axis suppression should be identified in survivors receiving prolonged glucocorticoid therapy for GVHD. Systematic assessment of clinical symptoms and signs (anorexia, nausea, weight loss, and postural hypotension) and laboratory markers (hyponatremia, hyperkalemia, and hypoglycemia) is mandatory. Morning cortisol and adrenocorticotropic hormone (ACTH) are the preferred diagnostic modalities.[8,12,15]

Discontinuation of high-dose steroids must be gradual to allow for variable recovery times. In addition, patients should be educated about adrenal crisis and the appropriate use of stress-dose glucocorticoids during acute febrile illness, trauma, or surgery.[8,12,15]

Gonadal function, fertility, and reproductive health

Diagnostic focus has shifted toward biomarkers that distinguish between hormonal production (testosterone and estradiol) and reproductive potential. Male hypogonadism is still controversial when indicating replacement, particularly in the post-HSCT setting, usually defined by total testosterone levels below 300 ng/dL.[3,8,12,15]

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Fertility assessment and preservation have advanced, with inhibin B now recognized as a valuable biomarker alongside semen analysis, which remains the gold standard for evaluating male reproductive function. In females, anti-Müllerian hormone (AMH) is considered the preferred biomarker for assessing ovarian reserve and for detecting premature menopause.[3,8,12,15]

Metabolic health: sarcopenia and metabolic syndrome

The sarcopenic obesity phenotype is a critical concern, characterized by a normal body mass index (BMI) that masks high visceral fat and significantly reduced lean body mass. This is driven by the synergistic effects of TBI and chronic inflammation related to GVHD.[8,12,13]

The screening protocol for metabolic syndrome encompasses yearly clinical assessment (BMI, waist circumference, and blood pressure) and laboratory tests (fasting glucose, insulin, homeostatic model assessment of insulin resistance [HOMA1-IR], glycated hemoglobin, and a full lipid profile), which are repeated every 2 years. If abnormalities are detected occur, assessments must be individualized.[8,12,13]

Bone health and osteometabolic disturbances

Low bone mineral density affects up to 75% of survivors. Surveillance must account for impaired peak bone mass acquisition and the impact of glucocorticoids, calcineurin inhibitors (cyclosporine/tacrolimus), and methotrexate, collectively known as the bone-toxic triad. Bone health assessment now goes beyond measuring bone mineral density alone. Yearly assessment of physical activity, vitamin D status, calcium levels, fracture history, muscle mass, and body composition should be performed since skeletal health after HSCT is influenced by multiple interacting factors. Specialized intervention (e.g., bisphosphonates) should be considered if Z-score < -2.0 (pediatric) or T-score < 2.5 (adult), or in the presence of multiple fragility fractures.[8,12,16]

Structured transition from pediatric to adult care

Transition from pediatric to adult care has become increasingly important. Although the original SBTMO consensus did not directly address this issue, more recent international guidelines emphasize the need for structured transition programs. These programs are designed to reduce loss to follow-up and support lifelong monitoring for endocrine and other late effects. A standardized treatment summary of all cumulative doses of radiation and chemotherapy is a mandatory prerequisite for a safe transition.[8,12,13]

Table 1 summarizes the key current considerations in endocrine surveillance after HSCT, including level of evidence and recommendation grade.[17]

Table 1. Consolidated endocrine clinical guidelines (2024-2026) after HSCT.

Endocrine domain	Screening frequency	Preferred modality marker	Level of evidence	Recommendation grade
Growth (pediatric)	Every 6-12 months until final height	Growth velocity and dynamic testing	2	B
Thyroid function	Yearly Start 1-year post-HSCT	TSH (threshold > 10 mIU/mL) and free T4	2	B
Thyroid cancer	Annual	Clinical palpation Selective ultrasound in irradiated survivors and if palpation abnormal	3	B/C
Adrenal function	Post-steroid discontinuation	Morning cortisol and ACTH	2	B
Gonadal function (both sexes)	Yearly	LH, FSH and total testosterone (T) or estradiol Consider replacement if T < 300 ng/dL, even though controversial in the post-HSCT setting	2-3	B

Continue...

Continuation.

Endocrine domain	Screening frequency	Preferred modality marker	Level of evidence	Recommendation grade
Male fertility	On demand/ pre-conception	Inhibin B but sperm cell count still as the gold standard Sperm cryopreservation as the established standard (post-pubertal); testicular tissue cryopreservation is experimental (prepubertal)	2	B
Female fertility	On demand/ pre-conception	AMH as the preferred marker of ovarian reserve Oocyte or ovarian tissue cryopreservation as the primary options	2	B
Metabolic syndrome	Annual clinical assessment/Laboratory testing every 2 years	BMI/ Blood pressure/ HOMA1-IR/ Lipid profile	1-2	A/B
Bone health	1-year post-HSCT; then risk-based	DXA Z-score < -2.0 (pediatric) / T-score < -2.5 (adult)	2	B

HSCT: hematopoietic stem cell transplantation; TSH: thyroid-stimulating hormone; T4: thyroxine; ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; AMH: anti-Müllerian hormone; BMI: body mass index; HOMA1-IR: homeostatic model assessment of insulin resistance; DXA: dual X-ray absorptiometry. Source: Data adapted from Lee *et al.*, (2025)[8]; Siviero-Miachon *et al.*, (2021; 2023)[9,10]; and Rotz *et al.*, (2024)[12]. Level of evidence and recommendation grade according to Arcuri *et al.*, (2021)[17].

CONCLUSION

- Endocrine complications remain among the most common late effects after HSCT and require lifelong follow-up.
- The core principles outlined in the SBTMO consensus are still relevant.
- Endocrine evaluation has evolved toward risk-adapted follow-up, tailored to treatment exposures and individual patient characteristics rather than uniform screening schedules for all survivors.
- Fertility preservation, metabolic health, and structured transition to adult care are now increasingly recognized as essential components of comprehensive survivorship care.
- Despite these advances, much of the available evidence remains observational, reinforcing the need for prospective multicenter studies to strengthen future recommendations.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

AUTHOR'S CONTRIBUTIONS

Conception: Siviero-Miachon AA, Alves-Junior PAG; **Investigation:** Siviero-Miachon AA, Alves-Junior PAG; **Methodology:** Siviero-Miachon AA, Alves-Junior PAG; **Formal Analysis:** Siviero-Miachon AA, Alves-Junior PAG; **Data Curation:** Siviero-Miachon AA, Alves-Junior PAG; **Project Administration:** Siviero-Miachon AA, Alves-Junior PAG, Fraietta R, Spinola-Castro AM, Bordallo MAN; **Writing:** Siviero-Miachon AA, Alves-Junior PAG, Fraietta R, Spinola-Castro AM, Bordallo MAN; **Supervision:** Siviero-Miachon AA, Alves-Junior PAG, Fraietta R, Spinola-Castro AM, Bordallo MAN; **Final Approval:** Siviero-Miachon AA.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

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