Clinical Hematology International
Vol. **1(4)**, December 2019, *pp.* 180–188
DOI: https://doi.org/10.2991/chi.d.190917.001; eISSN: 2590-0048
https://www.atlantis-press.com/journals/chi/

Review

Managing Endocrine Disorders in Adults After Hematopoietic Stem Cell Transplantation

Juliana Matthews[1,*], Dwight Eplin[2], Bipin Savani[3], Barbara Gisella Carranza Leon[1], Leslee Matheny[1]

[1]*Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt University Medical Center, Nashville, TN*
[2]*Division of Stem Cell Transplant, Veterans Affairs Medical Center, Nashville, TN*
[3]*Division of Hematology and Oncology, Vanderbilt University Medical Center & Veterans Affairs Medical Center, Nashville, TN*

ARTICLE INFO

Article History
Received 14 Jun 2019
Accepted 26 Aug 2019

Keywords
Stem cell transplant
Endocrine complications
Post-transplant diabetes
Transplant complications
Transplant survivorship

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) has become a potentially curative therapy for an increasing number of malignant and non-malignant conditions. As survival rates continue to improve, the focus of patient care has shifted from managing not only immediate but also long-term complications. Endocrine disorders are among the most prevalent late effects following HSCT. Detecting and treating such conditions offer new challenges, as well as opportunities to reduce preventable morbidity and mortality associated with HSCT. Our objective is to summarize recent literature and describe practical approaches to screening for and managing endocrine-related late effects. We focus on dyslipidemia, diabetes, thyroid disorders, osteoporosis, and hypogonadism. Mechanisms, monitoring, and management recommendations for each disorder are outlined. Growing data on these disorders in the post-transplant setting highlight the need for future study and evidence-based guidelines.

1. INTRODUCTION

Worldwide, more than 50,000 people undergo hematopoietic stem cell transplantation (HSCT) each year [1]. This number continues to rise, with projections that by 2020 there may be half a million long-term survivors [2]. Technological advances have led to progressive improvements in long-term survival of recipients. Broader indications for transplantation, newer graft sources, and transplantation of older patients using less intense conditioning regimens have also contributed to an increasing number of HSCT recipients. With enhanced therapies for immediate complications, we face new challenges in managing these survivors long-term.

Despite improvements in peri-transplant survival, life expectancy for those who survive more than five years post-transplant is around 30% lower than the general population [3]. This excess mortality has been attributed to the various long-term complications of HSCT, including chronic graft-versus-host disease (GVHD), infections, and end-organ dysfunction [4]. Although HSCT recipients generally enjoy good health, for some cure of the underlying disease is not accompanied by full restoration of health [5].

Growing data highlight the prevalence of endocrine complications which can impair quality of life and contribute to late morbidity and mortality for these patients [2,6]. Chemotherapy, radiation, and transplantation can all cause hormonal dysfunction. Moreover, recent studies suggest that immunosuppressive treatment and immune system derangement play an important role in the development of endocrine disorders after allografting [7,8].

While most complications discussed are particularly related to allogeneic HSCT, autologous recipients are also at risk. Providers should be attentive to these late effects in all post-transplant patients, as both groups can experience various toxicities and immune impairment due to exposure to corticosteroids or other drugs that may cause prolonged lymphopenia [1].

Transplant patients require a lifelong, multidisciplinary approach to manage endocrine dysfunction. This article summarizes updated findings and recommendations on the detection, prevention, and treatment of endocrinopathies in HSCT survivors. As there are limited published guidelines and randomized trials on managing late effects in this population, we offer suggested approaches based on expert opinion, general medicine studies, and literature review (Table 1).

2. DYSLIPIDEMIA

Dyslipidemia and cardiovascular disease (CVD) are common occurrences post-HSCT that cause significant morbidity and mortality [9,10]. Data indicate that these complications are not only frequent, but occur much earlier than expected compared to their appearance within the general population [11]. Furthermore, there is growing evidence that lipid-lowering medications—statins in particular—may have a role in modulating GVHD [11].

Corresponding author. Email: Juliana.j.matthews@vumc.org
Peer review is under responsibility of the International Academy for Clinical Hematology

Table 1 | Summary of management strategies in HSCT recipients.

Endocrine Disorder	Monitoring	Management
Dyslipidemia	*Fasting lipid panel* • Pre-transplant • Around day 100 post-HSCT • Annually if on stable Immunosuppresive therapy (IST) regimen • Repeat if IST regimen change or GVHD • Check 2–3 months after changes in lipid-lowering therapy • If off IST or on stable IST regimen with a normal lipid profile, then testing frequency may revert to general population guidelines	• Refer to ACC/AHA 2018 Cholesterol Guidelines to determine who is a candidate for therapy. • Consider treating all allogeneic HSCT patients at high risk for CVD. • Consider GVHD a "Risk Enhancer" under ACC/AHA guidelines. • Refer to registered dietician. • Start **pravastatin** at low dose if no contraindications. • If higher intensity statin needed, prefer **rosuvastatin**. • Refer to lipid specialist if inadequate control on above. • Encourage lifestyle measures including exercise and dietary modifications.
Diabetes mellitus	*Fasting blood glucose* • Weekly post-transplant, then at 3, 6, and 12 months; annually thereafter • Repeat testing if GVHD or adjusting steroids or IST.	• Insulin preferred inpatient. • Refer to endocrinologist for insulin regimen and/or consideration of oral agents if no contraindications.
Thyroid dysfunction	*TSH, free thyroxine (T4)* • annually, or more frequently if concerning symptoms Annual physical exam to evaluate for thyroid nodules.	• Levothyroxine for overt hypothyroidism, with weight-based dosing. • Refer to endocrinologist for hyperthyroidism treatment.
Osteoporosis	*DEXA* • within one year of transplantation • If normal BMD post-HSCT, repeat DEXA at 2 or more years, with consideration of ongoing risk factors (i.e. steroids, IST).	• Ensure adequate vitamin D and calcium intake. Encourage weight-bearing exercise as tolerated. • Refer to endocrinologist or osteoporosis specialist for treatment.
Hypogonadism	• Men should be tested for hypogonadism if suggestive symptoms including low libido, erectile dysfunction, fatigue, or bone loss. • Women should be tested if pre- or post-HSCT regimen includes agents known to affect gonadal function.	• Refer to endocrinologist or fertility specialist as indicated.

Chronic GVHD along with the use of drugs such as glucocorticoids, sirolimus, and calcineurin inhibitors have all been associated with the substantial incidence of post-HSCT dyslipidemia. A retrospective chart review of 761 patients who survived >100 days post-allogeneic HSCT found that 73.4% of patients developed dyslipidemia [9]. More recently, a 2018 retrospective study of 1196 patients found the prevalence of dyslipidemia before transplantation was 36% and 28% in the autologous and allogeneic groups, respectively; at three months after HSCT, the prevalence rose to 62% and 74%, and at 25 years, it was 67% and 89% [10].

Among HSCT survivors, CVD is one of the leading causes of non-relapse mortality [12]. Post-HSCT dyslipidemia has been found to be a significant risk factor for premature CVD [13,14]. When adjusting for age, allogeneic HSCT patients have an almost 7-fold increase in the risk of a cardiovascular event. Moreover, the median age at first cardiovascular event is 53 years old, notably lower than that observed in the general population (67 years) [12,15].

While lowering of cardiovascular risk is the primary goal of lipid-lowering therapy in transplant patients, several of these agents possess unique immunomodulatory effects that require further investigation [11]. Data suggest that statin use post-transplant may reduce chronic GVHD by affecting pathogenic T-cells through multiple mechanisms [11,16]. Phase II trials are currently underway to determine the effect of statins on GVHD, both as donor pre-treatment and recipient GVHD prophylaxis. Due primarily to the benefits of statins with regard to CVD, these agents should be strongly considered in patients undergoing allogeneic HSCT.

Management of dyslipidemias includes both a non-pharmacologic and a pharmacologic approach. Dietary counseling should be tailored to the patient's cholesterol disorder. We recommend that all patients with a dyslipidemia meet with a registered dietitian. Patients with hypercholesterolemia should be counseled to follow a low-fat diet. We recommend that they limit their fat intake to less than 30% of their total calories per day, which is about 30 to 35 grams of total fat per day for women and 50 to 55 grams for men. Patients with hypertriglyceridemia need to limit their simple carbohydrate intake (avoid white bread, white rice, cookies, cakes, regular soda, juices, etc.) and should avoid alcohol. Patients with mixed hyperlipidemia will need to limit both their fat and simple carbohydrate intake.

Drug–drug interactions, side effects, and relative efficacy must be considered. Of the anti-hyperlipidemia medications, the best evidence is on statins to safely manage dyslipidemia in the HSCT population. Data from a 2015 review indicate that, as allogeneic HSCT patients are at significantly greater risk of CVD, they could potentially benefit from statin therapy, regardless of calculated risk based on age and traditional risk factors.

2.1. Monitoring

1. Fasting lipid panel should be checked prior to transplant to identify non-transplant related dyslipidemia. Reviewing these results is an opportunity to discuss patient education including dietary modifications for prevention of dyslipidemia, given its high prevalence post-HSCT.
2. Fasting lipid levels should be checked around day 100 post-HSCT.
3. If patients are on a stable immunosuppressive regimen, repeat lipid panel in one year.
   - If repeat testing is normal and no changes to Immunosuppresive therapy (IST) are planned, testing frequency may revert to the guidelines for the general population.
   - If IST regimen changes or patient develops GVHD, recheck lipid panel.
4. After initiating or adjusting lipid-lowering therapy, repeat lipid panel in 2–3 months to assess the efficacy of treatment
5. While on lipid-lowering therapy, check a lipid panel annually to monitor efficacy.

2.2. Management

Candidates for therapy

- We recommend adhering to the most recent American College of Cardiology (ACC)/American Heart Association (AHA) 2018 Cholesterol Guidelines to determine who is a candidate for therapy.
  - We recommend considering GVHD as a "Risk Enhancer" under these guidelines as an "inflammatory disease" (although the authors only note "especially rheumatoid arthritis, psoriasis, HIV" as specific conditions) [17].
- Based on the significantly increased age-adjusted risk for CVD, some experts advocate treatment of all *allogeneic* HSCT patients able to tolerate moderate- to high-intensity statin therapy based on guidelines for targeting high-risk patients.
- Although strict diet and exercise regimens may be difficult in some HSCT recipients, appropriate dietary and exercise counseling should be provided as part of treatment.

Hyperlipidemia

- We recommend statins as first-line therapy for hyperlipidemia, as they have the strongest evidence for reduction in cardiovascular complications, as well as the most potent effects on low density lipoprotein cholesterol (LDL-C). Other agents are reasonable choices in the case of severe isolated hypertriglyceridemia (fibrates, cholesterol absorption inhibitors), statin intolerance, or contraindications (drug–drug interaction).
  - Care should be taken to avoid drug–drug interactions that may increase statin myopathy risk or affect immunosuppression levels, as cyclosporine and tacrolimus are both heavily metabolized by CYP3A4.
- *Pravastatin* is the recommended first-line statin, as it has the least interaction with CYP3A4 as only a minor substrate.
  - We recommend starting at a low dose (10–20 mg daily) and up-titrating to 40 mg, if needed, while monitoring for any adverse effects such as myalgias.
- If a higher intensity statin is indicated, we recommend *rosuvastatin*, as it is also only a minor substrate of CYP3A4.

- We advise starting at a lower dose (5–10 mg) and titrating as needed.
- If the patient is taking cyclosporine, the maximum dose is 5 mg.

- We recommend avoiding *simvastatin, lovastatin*, and *atorvastatin* while on IST, as these are major substrates of CYP3A4 and have increased risk of drug–drug interactions with related toxicity.
  - *Simvastatin* and *lovastatin* are contraindicated in patients taking cyclosporine.

Hypertriglyceridemia

- Triglycerides (TG) of more than 500 mg/dL should be treated to prevent pancreatitis. Fenofibrate is recommended as first-line, as gemfibrozil has increased myopathy risk when used in conjunction with statins and is a CYP3A4 substrate, potentially interacting with calcineurin inhibitors. Omega-3-fatty acids have no significant drug interactions and can lower triglycerides by 35% to 45% at high doses.
- Patients need to follow a low-fat, low-carbohydrate diet. Recommend referral to a nutritionist to discuss dietary changes avoiding simple carbohydrates.

Newer agents

- The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as *evolocumab* (Repatha) and *alirocumab* (Praluent) have been approved by for the treatment of individuals with familial hypercholesterolemia or patients with clinical cardiovascular disease whose reduction of LDL cholesterol is not achieved with statin therapy. These agents can lower LDL by 40%–60%. Clinical benefits include reduced rates of myocardial infarction and stroke [18].
  - While PCSK9 inhibitors have not been studied specifically in HSCT recipients, if a patient is believed to be a candidate for this medication, he/she should be referred to a lipid specialist to discuss this option.
  - There are no known interactions between PSCK9 inhibitors and IST.

3. DIABETES MELLITUS

Post-transplantation diabetes mellitus (PTDM) is an important complication because of its negative impact on cardiovascular health, microvascular sequelae, and quality of life [19]. Allogeneic HSCT recipients are at greater risk for PTDM compared to autologous transplants, with reported prevalence of 30% in the former [20]. Several studies have shown increased mortality risk in patients with PTDM, up to 3-fold in a recent report [8,20,21].

PTDM physiology remains poorly understood. While current dogma suggests PTDM is mainly related to diabetogenic immunosuppressive medications, other mechanisms may contribute to impaired insulin sensitivity. Glucocorticoids primarily increase insulin resistance, while cyclosporine and tacrolimus seem to impair insulin secretion [20]. Additional risk factors for PTDM include older age, total body irradiation (TBI), and chronic GVHD [20,22].

Despite the clinical burden of PTDM, limited data are available on anti-hyperglycemic agents for this population. Thus, treatment decisions must consider safety, efficacy, and tolerability in the context of each patient's transplant-related medications and comorbidities [20]. Intensive management of diabetes with goals similar to those for non-transplant patients could reduce long-term complications in HSCT survivors.

3.1. Monitoring

- International consensus guidelines based on *solid organ* transplantation data recommend monitoring for diabetes by measuring fasting glucose levels weekly for 4 weeks post-transplantation; then at 3, 6, and 12 months thereafter.
  - This is a reasonable approach, although we recommend continuing more frequent monitoring (every 6 months) in patients on immunosuppressive agents with potential impact on glucose control.
- While some patients may have resolution of hyperglycemia when tapered off of IST, they continue to have a lifelong increased risk of developing diabetes.
  - Thus, we recommend monitoring fasting blood glucose or hemoglobin A1C levels annually.
- We recommend referral to an endocrinologist for comprehensive diabetes care if the diagnosis is established with any of the following criteria:
  - Fasting blood glucose (BG) ≥ 126 mg/dL
  - Hemoglobin A1C ≥ 6.5%
  - Random BG ≥ 200 in the presence of hyperglycemic symptoms (thirst, polyuria, weight loss, blurry vision)
  - Two-hour BG ≥ 200 during an oral glucose tolerance test (OGTT)

3.2. Management

- A glycated hemoglobin (A1C) goal of less than 7.0% with minimal hypoglycemia is an appropriate target in most patients. A more liberal A1C goal (< 8.0%–8.5%) may be reasonable in those with certain comorbidities.
  - The appropriate target for A1C should be individualized based on overall health and life expectancy, as per discussion between the patient and endocrinologist.
  - It is important to note that measurement of A1C may not be accurate in several situations seen frequently in post-HSCT patients (recent transfusions or acute illnesses, chronic kidney or liver disease).
- Self-glucose monitoring is important for any transplant recipient using insulin or any agent that stimulates insulin secretion, with frequency based on his/her regimen.
- Although strict diet and exercise regimens may be difficult in some HSCT recipients, appropriate dietary and exercise counseling should be provided as part of treatment.

Insulin

- Insulin is the preferred agent in patients with clinically unstable, severe hyperglycemia, or on high-dose.
- Insulin lacks drug interactions, is safe in renal and hepatic failure, and can be readily adjusted in the setting of steroid changes or other factors.

Non-insulin oral and injectable agents

- No large randomized controlled trials have confirmed the safety of oral hypoglycemic specifically in HSCT patients. Still, oral therapies may be considered if there is no major contraindication. There are more data on PTDM solid organ transplant recipients (particularly kidney) that can help guide decision-making [23].
- **Metformin**
  - May be appropriate if normal kidney function and no need for frequent iodinated contrast.
  - Used commonly, but often has to be withdrawn due to IST-related nephrotoxicity
  - Recommend starting low dose (500 mg daily) and monitoring for gastrointestinal side effects (diarrhea) which may be minimized if extended-release formula used and taken with a meal.
  - Given frequency of renal insufficiency as well as other causes of diarrhea seen in the post-transplant period (infectious causes, GVHD of the gut, mycophenolate-induced), in practice it is often difficult to use metformin in this population.
- **Sulfonylureas *(glipizide, glimepiride)***
  - Avoid glyburide given potential interaction with IST which increases risk of hypoglycemia.
  - Can be used, but with caution if renal disease or inconsistent oral intake, given the risk of hypoglycemia. Start with low dose and up-titrate.
- **Meglitinides *(repaglinide, nateglinide)***
  - Used infrequently, but can be considered, given benefits of shorter duration of action and lack of renal clearance.
  - Metabolized by cytochrome P (CYP) enzymes, thus sensitive to CYP inhibition (as seen with cyclosporine and some antifungal agents) which can increase the hypoglycemia risk with these agents.
- **Dipeptidyl-peptidase-4 (DPP4) inhibitors *(sitagliptin, saxagliptin, linagliptin, alogliptin)***
  - Benefits include relatively low risk of hypoglycemia, weight neutral, and can be used safely in patients who have only mild reductions in kidney function or if the dose is adjusted appropriately with more significant chronic kidney disease [23].
  - All except linagliptin require dose reduction for reduced glomerular filtration rate (GFR).
  - These factors, along with evidence that they do not affect immunosuppressant levels, has led to an increased use of DPP-4 inhibitors for PTDM without significant safety concerns being identified [23].
  - Retrospective and small random controlled trials of kidney transplant recipients show safety and efficacy of several DPP-4 inhibitors [23].
  - These agents have low efficacy for glucose control, with only modest improvement in hemoglobin A1C. Reasonable to use if only mild hyperglycemia is present.
- **Glucagon-like-peptide-1 (GLP-1) agonists *(liraglutide, exenatide, dulaglutide, semaglutide)***
  - These agents include daily or weekly injections, with a potential benefit of weight loss as well as improved cardiovascular outcomes in those with known ASCVD, which may be an appealing option, given the incidence of CVD in HSCT recipients. However, there are less data and greater concern about the use of GLP-1 agonists, which can cause nausea and impact gastric emptying [23]. These effects raise concerns about whether these agents might impact transplant outcomes by changing IST absorption and warrant further study.
  - Can consider using with caution in patients off IST if no contraindications.
- **Sodium-glucose cotransporter 2 (SGLT-2) inhibitors *(dapagliflozin, canagliflozin)***
  - Given the risk of genitourinary infections, one should avoid the use of these agents in transplant recipients until further safety studies are performed [23].
  - Can consider using with caution in patients off IST if no contraindications.

4. THYROID DISORDERS

Thyroid dysfunction is a well-recognized late complication after allogeneic HSCT, with the long-term prevalence of hypothyroidism ranging from 20% to 50% [7,24–26]. Survivors of childhood HSCT are at increased risk. Findings from a 2012 retrospective analysis suggest that the cumulative incidence of thyroid disorders in HSCT recipients may be higher than expected, and that this risk persists long after transplant [27]. These data reinforce the current recommendations for sustained long-term monitoring of thyroid function tests in HSCT survivors.

In addition to affecting quality of life, untreated thyroid disorders can have cardiac and metabolic sequelae. Moreover, a few studies have linked thyroid dysfunction to chronic GVHD [7,25]. Proposed mechanisms for thyroid disorders in transplant patients vary. Hypothyroidism has been linked to TBI, radiation, immune suppression, and autoimmune antibodies [2,27]. Hyperthyroidism is less common in HSCT recipients but has been described as a possible autoimmune transfer phenomenon [28].

Thyroid adenomas and carcinomas may occur at higher rates in adults post-HSCT, although large scale data are limited [29]. As survivorship years increase, we anticipate more data will be

available to help assess this risk in adults. Prior TBI, female gender, age <20 years at HSCT, and chronic GVHD increase the risk of secondary thyroid cancer after allogenic HSCT [30]. Screening for thyroid nodules may be useful for survivors treated with TBI and allogeneic HSCT; however, the interval at which these scans should be performed in adult survivors is not currently known [29]. Malignancy should be considered in patients who have a rapidly enlarging thyroid mass, exposure to ionizing or external beam radiation, family history of thyroid cancer, suspicious ultrasound characteristics, or who have focal thyroid abnormality on FDG-PET imaging [29].

4.1. Monitoring

- Transplant survivorship guidelines recommend checking thyroid function tests (thyroid-stimulating hormone [TSH] and free thyroxine [FT4]) annually or sooner if there are concerning symptoms.
- Screening for thyroid cancer should include annual physical exam with palpation for nodules, which should prompt further investigation with thyroid ultrasound. We recommend heightened awareness if recipients were <20 years old at HSCT, received TBI, or developed chronic GVHD. Suspicious features on ultrasound should prompt referral to the endocrine team to determine the need for fine-needle aspiration biopsy (FNAB).

4.2. Management

- Treatment should be initiated in cases of overt primary or central hypothyroidism. Therapeutic replacement dosing is approximately 1.6 μg of levothyroxine per kilogram of body weight; however, a lower initial dose may be used (25–50 μg daily).
- For subclinical hypothyroidism with mild thyroid-stimulating hormone elevation (e.g., < 10 IU/mL), it is reasonable to repeat the tests in 2 to 3 months before starting treatment, because such elevations may be transient, as in the case of non-thyroidal illness.
- TSH and FT4 should be checked 6 to 8 weeks after dose initiation or changes, and replacement titrated to keep TSH within normal limits of lab assay.

5. OSTEOPOROSIS

Transplant recipients are at heightened risk of decreased bone density, which begins early [2,15]. The incidence of osteoporosis is estimated to approach 20% at 2 years [31,32]. Ultimately, more than half of long-term allogeneic HSCT survivors assessed with dual-energy x-ray absorptiometry (DEXA) develop osteopenia or osteoporosis [33–36]. This increases the risk of non-traumatic fractures in HSCT recipients, resulting in significant impairment of quality of life.

Risk factors for reduced bone density include glucocorticoid exposure, calcineurin inhibitors, chronic GVHD, physical inactivity, hypogonadism, and vitamin D deficiency [15,36]. HSCT may also directly damage the marrow by affecting osteoprogenitor cells. Inability to regenerate a normal number of osteoblastic precursors in the stromal stem cell compartment may contribute to severe long-lasting loss of bone mass post-transplant [36,37]. In addition to reduced bone density, low vitamin D levels have been independently linked to increased risk for GVHD and infectious complications after HSCT, due to its immunoregulatory properties [38–40].

The most effective method to prevent and treat bone loss in this population has not been determined. While therapeutic interventions such as bisphosphonates may prove beneficial, long-term follow-up data are not available [6,41]. Further studies on these and other agents such as denosumab are paramount.

5.1. Monitoring

- Transplantation survivorship guidelines recommend checking bone mineral densitometry (BMD) with DEXA within one year of transplantation, especially in those receiving allogeneic HSCT and/or patients treated with prolonged corticosteroids and calcineurin inhibitors [42].
- If normal BMD is documented after transplantation in patients without ongoing exposure to risk factors, then a repeat densitometry at 2 or more years is suggested.
- We recommend measuring 25-hydroxyvitamin D levels pre-transplant, at days 30 and 100 in HSCT recipients.

5.2. Management

- For prophylaxis, elemental calcium intake of 1000 to 1200 mg/day in divided doses as well as vitamin D at 800–1000 IU/day should be initiated in all patients at the time of transplant.
- Gastrointestinal GVHD may interfere with absorption of supplements. Calcium should be given with food to maximize absorption, and calcium citrate should be used in patients on antacids or proton-pump inhibitors.
- In patients with vitamin D level <30 ng/mL pre- or post-transplant, we recommend repletion with cholecalciferol 2000–4000 IU daily.
- Weight-bearing exercise should be encouraged as tolerated.
- Bisphosphonates are the mainstay of treatment for established osteoporosis. If present, endocrinology referral may be indicated. There is insufficient evidence to recommend denosumab for this patient population.
- In patients on treatment for osteoporosis or osteopenia, monitoring with DXA every 1 to 2 years is recommended. The duration of bisphosphonate therapy remains an area of uncertainty—a ”drug holiday” may be considered after approximately 5 years of therapy.

6. HYPOGONADISM

Hypogonadism is common after HSCT, with rates as high as 92% for males and 99% for females [1,43]. The degree of dysfunction is dependent on age, gender, pre-transplant therapy, and conditioning regimen [44]. Almost all women will have some gonadal

dysfunction after high-intensity conditioning. Major indications for treatment of adult hypogonadism include maintenance of bone density and prevention of associated symptoms.

Male and female HSCT survivors are at risk of infertility due to pre-transplant and transplant-related treatment exposures [42]. Natural pregnancies following gonadal recovery in women or in partners of male HSCT recipients have been reported, but the estimated incidence is less than 15% [45]. Pregnancy outcomes after transplant are generally good; however these women should be managed as a high-risk pregnancy, given the increased risk of maternal and fetal complications [42,45].

6.1. Males

- Men should be tested for hypogonadism if they have suggestive symptoms, including low libido, erectile dysfunction, fatigue, or bone loss. Some centers routinely measure testosterone at one year after transplantation, particularly if men are receiving steroids.
- A morning, fasting, total testosterone is the recommended initial test, followed by a morning total and free testosterone if total testosterone is abnormal. Gonadotropins (luteinizing hormone [LH] or follicile-stimulating hormone) measurement will help determine primary versus secondary/central hypogonadism.
- We recommend referral to the endocrinologist for testosterone replacement therapy. The choice of agent (transdermal gel, patch, or intramuscular injections) should be based on patient preference, after discussion of the risks and benefits of each. The goal of therapy is improved symptoms and a testosterone level within the normal range (usually between 350 and 600 ng/dL). The most common side effect of testosterone therapy is erythrocytosis, thus hematocrit must be monitored regularly. The possibility of increased thrombosis and cardiovascular risk must be also considered and discussed with patients when counseling on risks and benefits of treatment.

6.2. Females

- Women with amenorrhea should be evaluated for primary ovarian insufficiency. Consider referral to the endocrine team or reproductive endocrinologist for further evaluation.
- Estrogen-progesterone therapy is contraindicated in patients with history of stroke, venous thromboembolism, severe hypertriglyceridemia, active liver disease, undiagnosed abnormal uterine bleeding, or estrogen-dependent tumors such as breast cancer [2].
- For physiologic replacement in pre-menopausal aged females, 100 μg/day estradiol by transdermal patch can often achieve levels of serum estradiol in the normal range. Transdermal estrogen may carry a lower risk of venous thromboembolism.
- Women with an intact uterus should have cyclic progesterone added (i.e., medroxyprogesterone acetate at 10 mg/day for 12 days of each menstrual cycle) to induce menstruation and prevent endometrial hyperplasia. Combination oral contraceptives may also be used.

6.3. Fertility

- Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving. This usually occurs prior to initial chemotherapy in this population.
- Although infertility is common, patients should be counseled regarding birth control post-transplantation, with particular attention to risks and benefits of various contraception options.

7. CONCLUSION

Endocrine complications are increasingly prevalent following HSCT as long-term survival improves. These patients require life-long, multidisciplinary attention to manage endocrine dysfunction and optimize their quality of life. Evidence-based guidelines are needed to assist the practicing community and improve the care for the rapidly growing number of transplant recipients. Further studies to investigate the pathogenesis, management, and long-term impact of these disorders will enhance the growing number of years experienced by HSCT survivors.

CONFLICTS OF INTEREST

None to disclose.

AUTHORS' CONTRIBUTIONS

All authors have approved the final article. J.M., wrote the manuscript with support from the remaining authors.

Funding Statement

None.

ACKNOWLEDGMENTS

None.

REFERENCES

[1] Majhail, NS, Rizzo, JD. Surviving the cure: long term followup of hematopoietic cell transplant recipients. Bone Marrow Transplant 2013;48;1145–51.
[2] Savani, BN, Griffith, ML, Jagasia, S, Lee, SJ. How I treat late effects in adults after allogeneic stem cell transplantation. Blood 2011;117;3002–9.
[3] Martin, PJ, Counts Jr, GW, Appelbaum, FR, *et al.* Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol 2010;28;1011–16.
[4] Mohty, M, Apperley, JF. Long-term physiological side effects after allogeneic bone marrow transplantation. Hematol Am Soc Hematol Educ Program 2010;2010;229–36.
[5] Mohty, B, Mohty, M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. Blood Cancer J 2011;1;e16.

[6] Chemaitilly, W, Sklar, CA. Endocrine complications of hematopoietic stem cell transplantation. Endocrinol Metab Clin North Am 2007;36;983–98; ix.
[7] Tauchmanova, L, Selleri, C, Rosa, GD, *et al.* High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. Cancer 2002;95;1076–84.
[8] Engelhardt, BG, Savani, U, Jung, DK, *et al.* New-onset post-transplant diabetes mellitus after allogeneic hematopoietic cell transplant is initiated by insulin resistance, not immunosuppressive medications. Biol Blood Marrow Transplant 2019;25;1225–31.
[9] Blaser, BW, Kim, HT, Alyea 3rd, EP, *et al.* Hyperlipidemia and statin use after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2012;18;575–83.
[10] Premstaller, M, Perren, M, Kocack, K, *et al.* Dyslipidemia and lipid-lowering treatment in a hematopoietic stem cell transplant cohort: 25 years of follow-up data. J Clin Lipidol 2018;12;464–80 e463.
[11] Marini, BL, Choi, SW, Byersdorfer, CA, Cronin, S, Frame, DG. Treatment of dyslipidemia in allogeneic hematopoietic stem cell transplant patients. Biol Blood Marrow Transplant 2015;21;809–20.
[12] Armenian, SH, Sun, CL, Mills, G, *et al.* Predictors of late cardiovascular complications in survivors of hematopoietic cell transplantation. Biol Blood Marrow Transplant 2010;16;1138–44.
[13] Tichelli, A, Bucher, C, Rovo, A, *et al.* Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. Blood 2007;110;3463–71.
[14] Tichelli, A, Passweg, J, Wojcik, D, *et al.* Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the late effects working party of the European group for blood and marrow transplantation. Haematologica 2008;93;1203–10.
[15] Bhatia, S, Armenian, SH, Landier, W. How I monitor long-term and late effects after blood or marrow transplantation. Blood 2017;130;1302–14.
[16] Rotta, M, Storer, BE, Storb, R, *et al.* Impact of recipient statin treatment on graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2010;16;1463–66.
[17] Grundy, SM, Stone, NJ, Bailey, AL, *et al.* AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American college of cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;73;3168–209.
[18] McKenney, JM, Koren, MJ, Kereiakes, DJ, Hanotin, C, Ferrand, AC, Stein, EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol 2012;59;2344–53.
[19] Griffith, ML, Jagasia, MH, Misfeldt, AA, *et al.* Pretransplantation C-peptide level predicts early posttransplantation diabetes mellitus and has an impact on survival after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2011;17;86–92.
[20] Griffith, ML, Jagasia, M, Jagasia, SM. Diabetes mellitus after hematopoietic stem cell transplantation. Endocr Pract 2010;16;699–706.
[21] Hammer, MJ, Casper, C, Gooley, TA, O'Donnell, PV, Boeckh, M, Hirsch, IB. The contribution of malglycemia to mortality among allogeneic hematopoietic cell transplant recipients. Biol Blood Marrow Transplant 2009;15;344–51.
[22] Baker, KS, Ness, KK, Steinberger, J, *et al.* Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood 2007;109;1765–72.
[23] Shivaswamy, V, Boerner, B, Larsen, J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr Rev 2016;37;37–61.
[24] Sanders, JE, Hoffmeister, PA, Woolfrey, AE, *et al.* Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood 2009;113;306–8.
[25] Savani, BN, Koklanaris, EK, Le, Q, Shenoy, A, Goodman, S, Barrett, AJ. Prolonged chronic graft-versus-host disease is a risk factor for thyroid failure in long-term survivors after matched sibling donor stem cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant 2009;15;377–81.
[26] Somali, M, Mpatakoias, V, Avramides, A, *et al.* Thyroid dysfunction in adult long-term survivors after hemapoeitic stem-cell transplantation (HSCT). Horm Metab Res 2005;37;494–99.
[27] Sanchez-Ortega, I, Canals, C, Peralta, T, *et al.* Thyroid dysfunction in adult patients late after autologous and allogeneic blood and marrow transplantation. Bone Marrow Transplant 2012;47;296–98.
[28] Cohen, A, Bekassy, AN, Gaiero, A, *et al.* Endocrinological late complications after hematopoietic SCT in children. Bone Marrow Transplant 2008;41;S43–S48.
[29] Savani, BN. Blood and marrow transplantation long-term management: prevention and complications. John Wiley & Sons; Chichester, UK 2013.
[30] Cohen, A, Rovelli, A, Merlo, DF, *et al.* Risk for secondary thyroid carcinoma after hematopoietic stem-cell transplantation: an EBMT late effects working party study. J Clin Oncol 2007;25;2449–54.
[31] Schimmer, AD, Mah, K, Bordeleau, L, *et al.* Decreased bone mineral density is common after autologous blood or marrow transplantation. Bone Marrow Transplant 2001;28;387–91.
[32] Stern, JM, Sullivan, KM, Ott, SM, *et al.* Bone density loss after allogeneic hematopoietic stem cell transplantation: a prospective study. Biol Blood Marrow Transplant 2001;7;257–64.
[33] Yao, S, McCarthy, PL, Dunford, LM, *et al.* High prevalence of early-onset osteopenia/osteoporosis after allogeneic stem cell transplantation and improvement after bisphosphonate therapy. Bone Marrow Transplant 2008;41;393–98.
[34] Ebeling, PR. Approach to the patient with transplantation-related bone loss. J Clin Endocrinol Metab 2009;94;1483–90.
[35] Savani, BN, Donohue, T, Kozanas, E, *et al.* Increased risk of bone loss without fracture risk in long-term survivors after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2007;13;517–20.
[36] Weilbaecher, KN. Mechanisms of osteoporosis after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2000;6;165–74.
[37] Tauchmanovà, L, Serio, B, Del Puente, A, *et al.* Long-lasting bone damage detected by dual-energy x-ray absorptiometry, phalangeal osteosonogrammetry, and in vitro growth of marrow stromal cells after allogeneic stem cell transplantation. J Clin Endocrinol Metab 2002;87;5058–65.

[38] Glotzbecker, B, Ho, VT, Aldridge, J, *et al*. Low levels of 25-hydroxyvitamin D before allogeneic hematopoietic SCT correlate with the development of chronic GVHD. Bone Marrow Transplant 2013;48;593–97.

[39] Hansson, ME, Norlin, AC, Omazic, B, *et al*. Vitamin d levels affect outcome in pediatric hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2014;20;1537–43.

[40] von Bahr, L, Blennow, O, Alm, J, *et al*. Increased incidence of chronic GvHD and CMV disease in patients with vitamin D deficiency before allogeneic stem cell transplantation. Bone Marrow Transplant 2015;50;1217–23.

[41] Pundole, X, Cheema, HI, Petitto, GS, Lopez-Olivo, MA, Suarez-Almazor, ME, Lu, H. Prevention and treatment of bone loss and fractures in patients undergoing a hematopoietic stem cell transplant: a systematic review and meta-analysis. Bone Marrow Transplant 2017;52;663–70.

[42] Majhail, NS, Rizzo, JD, Lee, SJ, *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Hematol Oncol Stem Cell Ther 2012;5;1–30.

[43] Cornillon, J, Vantyghem, MC, Couturier, MA, *et al*. Management of endocrine dysfunctions after allogeneic hematopoietic stem cell transplantation: a report of the SFGM-TC on dyslipidemia and thyroid disorders. Pathol Biol (Paris) 2013;61;168–70.

[44] Ranke, MB, Schwarze, CP, Dopfer, R, *et al.* Late effects after stem cell transplantation (SCT) in children–growth and hormones. Bone Marrow Transplant 2005;35;S77–S81.

[45] Salooja, N, Szydlo, RM, Socie, G, *et al.* Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet 2001;358;271–76.