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REVIEW ARTICLE

Endocrine Late Effects in Childhood Cancer Survivors

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A B S T R A C T

Endocrine complications are highly prevalent in childhood cancer survivors. Approximately 50% of survivors will experience at least one hormonal disorder over the course of their lives. Endocrine complications often are observed in survivors previously treated with radiation to the head, neck, or pelvis. We provide an overview the most common endocrine late effects seen in survivors, including hypothalamic-pituitary dysfunction, primary thyroid dysfunction, obesity, diabetes mellitus, metabolic syndrome, and decreased bone mineral density. Primary gonadal injury is discussed elsewhere in this series. Given a variable latency interval, a systematic approach where individuals are periodically screened on the basis of their risk factors can help to improve health outcomes by prompt diagnosis and treatment of evolving endocrinopathies. These recommendations must be revised in the future given changes and improvements in cancer treatment over time.

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INTRODUCTION

Endocrine complications are prevalent in childhood cancer survivors (CCSs), with 50% experiencing at least one hormonal disorder over the course of their lives.[1] Endocrine deficits frequently appear as late effects in the years after cancer treatment.[2] Long-term follow-up data demonstrate that endocrine late effects continue to appear in adulthood[3] at a significantly higher rate than in siblings[4] and the general population.[5] Additional data have revealed frequent delays in the diagnosis and treatment of endocrine late effects,[2] with potential repercussions on general health.[3]

We provide an overview of the most common endocrine late effects, including hypothalamic-pituitary (HP) dysfunction, primary thyroid dysfunction, obesity, diabetes mellitus (DM), metabolic syndrome, and decreased bone mineral density (BMD). Sex hormone deficits related to primary gonadal injury are reviewed in the articles dedicated to reproductive late effects in this series. Data that pertain to risk factors, screening, and management strategies are listed in Table 1. Screening recommendations were derived from the most current version of the regularly updated Children's Oncology Group long-term follow-up guidelines.[6]

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HP DYSFUNCTION

HP injury can result from the following conditions: growth hormone (GH) deficiency, central precocious puberty (CPP), luteinizing hormone/follicle-stimulating hormone (LH/FSH) deficiency (hypogonadotropic hypogonadism), thyroid-stimulating hormone (TSH) deficiency (central hypothyroidism), and adrenocorticotropic hormone (ACTH) deficiency (central adrenal insufficiency). Central diabetes insipidus typically is caused by HP damage from tumor growth and/or surgical resection and is seen in the first weeks after intervention. Central diabetes insipidus is not discussed in this review because it does not occur as a late effect.[15]

The occurrence of HP dysfunction as a late effect is primarily a result of radiotherapy.[15,16] In contrast to injury from tumor growth or surgery, where patients frequently present with HP disorders from the onset, radiation-induced HP disorders tend to appear sequentially in a dose-dependent manner months to several decades after radiation.[3,15,16] At least one HP deficit after cranial radiotherapy was reported in 51% of a cohort followed long term[3] (Fig 1). Efforts to eliminate unnecessary exposures, such as with the abandonment of prophylactic CNS irradiation in acute lymphoblastic leukemia (ALL), or to reduce scatter to normal tissue, such as with the use of protons instead of photons, are likely

Table 1. Risk Factors and Management of Endocrine Late Effects of Childhood Cancers

Late Effect	Risk Factor	History/Physical*	Blood Test Screen*	Subsequent Test	Treatment
GHD	Young age at diagnosis HP tumor or surgery HP RT ≥ 18 Gy† TBI ≥ 10 Gy one fraction TBI ≥ 12 Gy multifractions TKI, anti–CTLA-4 mAb	Interval growth Height, weight Growth rate Sitting height or arm span (spinal RT) Tanner stage	No laboratory tests; clinical parameters used for screening	GH stimulation test	GH replacement
CPP	Young age at diagnosis Tumor near HP region Optic pathway glioma Hydrocephalus HP RT ≥ 18 Gy	Interval growth and puberty changes Height, weight Growth velocity Tanner stage	Morning testosterone‡	Bone age x-ray Pelvic US (females)§ GnRH or GnRHa test	GnRHa
LH/FSHD	HP tumor or surgery HP RT ≥ 30 Gy† Anti–CTLA-4 mAb	Puberty, sexual function, menses Height, weight Growth velocity Tanner stage	LH, FSH Estradiol (females) Morning testosterone (males)	Bone age x-ray Pelvic US (females)§	Sex hormone replacement
TSHD	HP tumor or surgery HP ≥ 30 Gy† Anti–CTLA-4 mAb	Hypothyroidism symptoms Height, weight Growth rate	TSH‖, free T4	—	Levothyroxine¶
ACTHD	HP tumor or surgery HP ≥ 30 Gy† Anti–CTLA-4 mAb	Failure to thrive Anorexia, lethargy Dehydration, hypotension	8:00 AM cortisol	ACTH stimulation test	Hydrocortisone¶ Glucocorticoid stress dose teaching
Hyperprolactinemia	HP tumor or surgery HP ≥ 40 Gy	Galactorrhea, menses Tanner stage	Prolactin	—	Antidopaminergics
Primary hypothyroidism	Surgical resection Thyroid RT ≥ 10 Gy Allogeneic HSCT TKI Anti–CTLA-4 mAb, interferon Radioactive iodine, I-MIBG	Hypothyroidism symptoms Height, weight Growth rate Tanner stage	TSH, free T4	—	Levothyroxine¶
Autoimmune thyroid disease	Allogeneic HSCT Anti–CTLA-4 mAb, interferon	Hypothyroidism or hyperthyroidism symptoms	TSH, free T4	Thyroperoxidase, thyroglobulin Ab TSH receptor Ab#	Depending on consequence (hyper or hypo)
Hyperthyroidism	Allogeneic HSCT Thyroid RT ≥ 30 Gy Anti–CTLA-4 mAb, interferon	Hyperthyroidism symptoms Height, weight	TSH, free T4	TSH receptor Ab	β-blockers Antithyroid agents
Obesity	HP tumor or surgery HP RT > 20 Gy Glucocorticoids	Diet, physical activity Height, weight BMI	No laboratory tests; clinical parameters used for screening	Fasting lipids, glucose	Diet, exercise
DM	HSCT TBI or abdominal RT Glucocorticoids	Polyuria, polydipsia Height, weight BMI	Fasting glucose HbA_{1c}	Oral glucose tolerance test	Diet, exercise Medications as needed
Low BMD	Young age at diagnosis Leukemia HSCT ± TBI Cranial RT Glucocorticoids	Diet, physical activity Bone, skeletal pain Fracture history Height, weight	DXA	25-Hydroxy vitamin D	Diet/calcium, vitamin D, exercise

NOTE. Recommendations were based on the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers Version 4.0[6] and additional resources.[7-14]

Abbreviations: Ab, antibody; ACTHD, adrenocorticotropic hormone deficiency; BMD, bone mineral density; BMI, body mass index; CPP, central precocious puberty; DM, diabetes mellitus; DXA, duel-energy x-ray absorptiometry; GHD, growth hormone deficiency; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist; HP, hypothalamic-pituitary; HbA_{1c}, hemoglobin A_{1c}; HSCT, hematopoietic stem-cell transplantation; I-MIBG, ^{131}I-metaiodobenzylguanidine; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; mAb, monoclonal antibody; RT, radiotherapy; T4, thyroxine; TBI, total body irradiation; TKI, tyrosine kinase inhibitor; TSHD, thyroid-stimulating hormone deficiency; US, ultrasound.

*Clinical and laboratory screening should be conducted at least every 6 months during childhood and then yearly or more frequently if clinically indicated.

†Condition may appear at a lower dose of RT with longer follow-up.

‡Males exposed to direct testicular radiotherapy and/or gonadotoxic chemotherapy.

§To measure uterine height in girls with discrepant clinical and laboratory data.

‖TSH not useful for follow-up.

¶Evaluation for and treatment of ACTHD should always precede that of hypothyroidism in patients at risk for both conditions.

#In case of hyperthyroidism.

to modify the prevalence of HP dysfunction in survivors treated more recently.[17] Conventional chemotherapy agents have not been shown consistently to cause HP dysfunction.[18] HP deficits have been reported in patients treated with the newer targeted chemotherapy agents such as imatinib, a tyrosine kinase inhibitor (TKI),[7] and immune system modulators.[8] Whether the deleterious

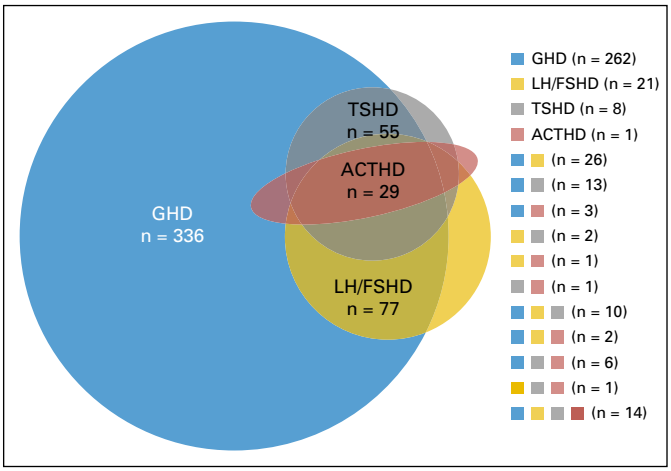

Fig 1. Overlap among anterior pituitary deficiencies after cranial radiotherapy. ACTHD, adrenocorticotropic hormone deficiency; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; TSHD, thyroid-stimulating hormone deficiency. Reproduced with permission.[3] Copyright © 2015 American Society of Clinical Oncology.

effects of these newer targeted agents are reversible after their discontinuation has yet to be fully elucidated.

GH Deficiency

GH deficiency is the most common pituitary hormone deficit in CCSs with a reported prevalence of 12.5% overall[15] and 46.5% after HP radiotherapy.[3] An increased likelihood and earlier development of GH deficiency are directly related to radiation dose and inversely related to the number of fractions.[19] GH deficiency frequently develops after HP radiotherapy doses ≥ 30 Gy[3,20] but can develop after 18 to 24 Gy, doses that have been used to treat ALL and lymphoma.[21] GH deficiency also is reported after lower doses with a single fraction of 10 Gy and fractionated doses of 12 to 18 Gy when administered as total body irradiation (TBI) in the context of hematopoietic stem cell transplantation (HSCT).[22] Although the development of GH deficiency after chemotherapy alone[18] is controversial, autoimmune hypophysitis that results in GH deficiency is increasingly recognized with the use of the immune checkpoint inhibitor ipilimumab (an anti–CTLA-4 monoclonal antibody).[8] Imatinib mesylate, a TKI used in the treatment of children with certain forms of leukemia, impairs growth, but whether the mechanism is through GH deficiency, GH resistance,[23] or skeletal toxicity is unclear.[24]

GH deficiency should be suspected when linear growth failure (height trajectory that crosses to lower percentile lines) or lack of growth acceleration during puberty are seen after ruling out hypogonadism, hypothyroidism, inadequate nutritional intake, or excess glucocorticoid exposure. Measuring the sitting height or determining the ratio of upper to lower segment are helpful to rule out poor spinal growth after radiation.[25] Insulin-like growth factor I levels are not always low in the context of radiation-induced GH deficiency and should not be used to screen patients at risk.[26] When GH deficiency is suspected, a referral to a pediatric endocrinologist is indicated for additional evaluation with stimulation testing.

Replacement with recombinant human GH (hGH) results in a significant improvement in height in children with GH deficiency, but patients may not achieve their genetic potential because of other factors, such as spinal[25] irradiation, TBI,[27] scoliosis, or direct growth plate injury from agents such as *cis*-retinoic acid.[28] Treatment with hGH may improve cardiovascular risk factors, such as dyslipidemia, and quality of life in adult CCSs similar to the non-CCS population, but studies are lacking in children, and results are variable and limited.[29,30] Long-term data from the Childhood Cancer Survivor Study have suggested no significant association between hGH and recurrence of the primary cancer.[31] Data on the association between hGH and secondary neoplasia are conflicting,[31,32] and more studies are needed.

CPP

CPP is the onset of puberty before 8 years (girls) or 9 years (boys) of age as a result of the activation of the HP-gonadal axis.[33] Left untreated, CPP may result in psychosocial dysfunction and short stature.[34] Up to 15.2% of CNS tumor survivors have been reported to experience CPP.[15,34] The prevalence is even higher (30%) in children with a history of tumors near the HP region.[34,35] Other risk factors include the exposure of the HP region to radiotherapy at doses of 18 to 50 Gy and increased intracranial pressure.[15,34-36]

The diagnosis of CPP follows the same steps as in the non-CCS population,[9,33] with two exceptions. First, the clinical diagnosis of puberty in boys treated with gonadotoxic modalities (eg, direct testicular radiotherapy, alkylating agent chemotherapy) should rely on findings other than testicular volume (eg, phallic enlargement, pubarche, scrotal thinning) because patients may have inappropriately small testes as a result of germ cell and Sertoli cell depletion and yet still be able to produce testosterone.[37] Additional confirmation should be sought by measuring morning plasma testosterone levels. Second, CPP and GH deficiency have been shown to co-occur frequently in CCSs; thus, growth velocity assessment should be interpreted with this association in mind because delays in the diagnosis and treatment of either condition can result in irreversible losses in final height.[34] The first line of therapy is a gonadotropin-releasing hormone agonist. The timing of discontinuation of pubertal suppression needs to be individualized, but treatment after 12 years of age rarely is indicated.[9]

LH/FSH Deficiency

Patients with LH/FSH deficiency experience a lack of gonadal sex hormones (estrogen, progesterone in females; testosterone in males) because of lack of stimulation of the gonads by the HP axis. Children and adolescents may present with pubertal delay (absence of pubertal development past the ages of 13 [girls] or 14 [boys] years).[10] Later in life, manifestations include arrested puberty, primary or secondary amenorrhea, or symptoms related to low testosterone or estrogen levels. The prevalence of LH/FSH deficiency was reported at 6.5% in CCSs overall[38] and 11% after HP radiotherapy.[3] The main risk factors of LH/FSH deficiency are HP tumor, surgery, or radiotherapy at doses ≥ 30 Gy within or near the HP region.[3,39] Association with doses of 20 to 29 Gy was reported in cohorts with an extended duration of follow-up.[3,34]

The diagnosis of LH/FSH deficiency in CCSs follows the same guidelines as in the non-CCS population.[10,11] Lower-than-normal

levels of sex hormones that coincide with low or inappropriately normal levels of LH and/or FSH are generally suggestive of LH/FSH deficiency.[10,11] Hyperprolactinemia, a known complication of high-dose HP irradiation, should be ruled out as a possible cause.[39] Treatment relies on sex hormone replacement therapy.[10,11] Although hypogonadism is known to decrease the risk of secondary breast cancer in female CCSs treated with chest irradiation, recent reports have shown that full replacement with estrogen and progesterone either had no effect[40] or resulted in a moderately increased risk that nevertheless remained lower (hazard ratio, 0.47; 95% CI, 0.23 to 0.94) than that of CCSs without hypogonadism who underwent chest irradiation.[41] Prescribers should be aware of drug interactions between estrogen and antiepileptic drugs as well as other hormone replacement therapies (GH, levothyroxine) and plan appropriately for monitoring and dosage adjustment.[11] Adult CCSs with hypogonadism should be encouraged to consult with fertility specialists with regard to reproductive options.[12,13]

TSH Deficiency

Individuals with TSH deficiency experience hypothyroidism because of lack of stimulation of the thyroid by the HP axis. Presentation may include fatigue, slow linear growth, and/or abnormal weight gain. Rates of TSH deficiency have been reported at 7.5% to 9.2% in survivors of childhood brain tumors and those exposed to HP radiotherapy.[1,3,15] Risk factors include tumors or surgery in the HP region and HP radiation doses ≥ 30 Gy.[3,15,16] Longer time since treatment and the presence of other central endocrinopathies increase the likelihood of TSH deficiency.[3,35]

Low, normal, or marginally elevated plasma TSH levels in association with low free thyroxine (T4) levels generally suggest TSH deficiency.[11] Treatment with levothyroxine should target free T4 levels in the mid to upper half of the normal range for age, and TSH values should not be used to adjust doses.[11,14] The addition of antiepileptic drugs, estrogens, and/or glucocorticoids may require adjustments in levothyroxine doses.[11] The adrenal axis should be evaluated in patients at risk for central endocrinopathies before beginning thyroid hormone replacement lest the thyroid supplementation precipitate adrenal insufficiency.[11]

ACTH Deficiency

Individuals with ACTH deficiency have insufficient cortisol secretion because of inadequate stimulation of the adrenal cortex by the HP axis. Aldosterone production typically is preserved. Presentation may include fatigue, weight loss, and/or low blood glucose levels. Patients are at risk for adrenal crisis in times of significant physical illness.[11] Estimates of the prevalence of ACTH deficiency in CCSs have varied widely partly because of the use of different testing modalities. The 5-year cumulative incidence of ACTH deficiency has been reported at 2.9% in a cohort of CNS tumor survivors.[15] Risk factors for ACTH deficiency include tumor growth and/or surgery that involved the HP region as well as HP radiation doses ≥ 30 Gy.[3] Longer time since treatment and the presence of other central endocrinopathies increase the likelihood of ACTH deficiency.[3,42] Subclinical forms of ACTH deficiency have been reported in individuals treated with imatinib, but the clinical implications of this observation are unclear.[7]

At-risk patients should be screened by assessing their symptoms and with annual measurement of an 8:00 AM plasma cortisol level. Values < 83 nmol/L (3 μg/dL) suggest ACTH deficiency, whereas values > 413 nmol/L (15 μg/dL) indicate normal ACTH-adrenal function.[11] Confirmatory testing may include low- (1 μg) or high- (250 μg) dose ACTH stimulation or insulin tolerance testing.[11,42] Treatment of ACTH deficiency includes daily replacement of glucocorticoids to mimic normal physiologic production, additional oral steroids at times of mild to moderate illness, and parenteral steroids during severe illness. Medical alert identification information should be carried or worn to notify emergency personnel of the need for rapid steroid treatment.[11]

PRIMARY THYROID DYSFUNCTION

Thyroid disorders are among the most common endocrine sequelae after treatment of childhood cancer.[4] CCSs are at risk for the development of hypothyroidism and hyperthyroidism as well as for thyroid neoplasia (reviewed elsewhere in this series).

Primary hypothyroidism is one of the most frequently observed late effects in CCSs; its prevalence has been reported at 13.8% to 20.8% in the overall population of survivors (Fig 2).[1,2,4,43] The highest incidence was reported in survivors of Hodgkin lymphoma after neck irradiation > 45 Gy, with up to 50% diagnosed after 20 years of follow-up.[43] Patients treated with craniospinal radiotherapy represent another high-risk population.[16] Treatment with ^{131}I-metaiodobenzylguanidine can cause primary hypothyroidism because of radionuclide uptake in the thyroid gland. Thyroid protection through potassium iodide; perchlorate; or the combination of potassium iodide, T4, and a thiamazole decreases but does not entirely eliminate the risk of ^{131}I-metaiodobenzylguanidine–induced hypothyroidism.[44] Conventional chemotherapy agents, especially busulphan and cyclophosphamide, are associated with transient and often mild forms of hypothyroidism.[18] More recently, hypothyroidism has been recognized as among the most common adverse effects of TKIs, especially sorafenib, sunitinib, and imatinib.[7] The precise mechanism of TKI-induced hypothyroidism is unknown. A subset of CCSs may experience hypothyroidism as a consequence of autoimmune thyroid disease, which has been reported after HSCT and likely is due to the transfer of autoimmunity from the graft donor.[45] It may occur as an adverse effect of treatment with immune system modulators, such as interferon and anti–CTLA-4 monoclonal antibodies (ipilimumab, tremelimumab, nivolumab, and pembrolizumab).[8] Hyperthyroidism is significantly less common than hypothyroidism in CCSs; it can present after neck or craniospinal irradiation (Fig 2) and in patients with autoimmune thyroid disease.[4,43]

Patients at risk for primary thyroid dysfunction should be screened by assessing their symptoms and measuring plasma free T4 and TSH levels at least yearly (Table 1). Screening with thyroid autoantibody titers is not advised because the development of hypothyroidism or hyperthyroidism cannot be predicted on the basis of the presence or absence of these antibodies. However, these can be used to investigate the etiology of hypo- or hyperthyroidism further. Patients administered targeted therapies should be screened

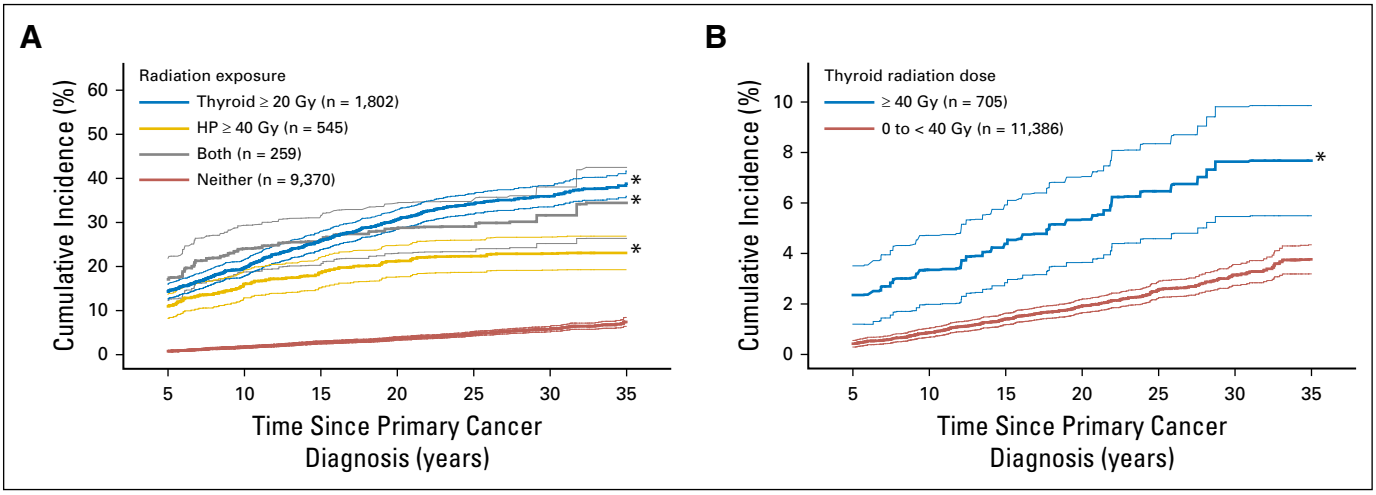

Fig 2. Cumulative incidence of thyroid disorders. (A) Underactive thyroid and (B) overactive thyroid in survivors stratified by treatment exposure. Thin lines represent 95% CIs. *$P < .01$ for comparison versus the non–high-risk exposure group. HP, hypothalamic pituitary. Reproduced with permission.[4] Copyright © 2016 American Society of Clinical Oncology.

per their treatment protocols.[7] Treatment of hypothyroidism with levothyroxine is indicated for lowered free T4 values in combination with elevated TSH values, after evaluation of the adrenal axis in patients who also are at risk for adrenal insufficiency.[11] The benefit of treatment of compensated (subclinical) hypothyroidism (ie, elevated TSH accompanied by normal free T4 values) remains controversial; normalization of TSH may decrease the growth of thyroid nodules in at-risk patients, although data are inconsistent.[46] Management of persistent and symptomatic hyperthyroidism follows similar steps as with hyperthyroidism as a result of Graves disease, with the understanding that it is frequently transient.[45]

OBESITY, DM, AND METABOLIC SYNDROME

The risks of obesity and DM are significantly higher in CCSs than in their siblings.[4] Metabolic syndrome, a constellation of cardiovascular (hypertension) and metabolic (obesity, abnormal glucose metabolism, and dyslipidemia) abnormalities associated with cardiovascular mortality, also has been shown to affect a sizeable proportion of CCSs (31.8%) and at a higher rate than in the general population of adults younger than 40 years of age (18.3%).[47,48]

Patients with hypothalamic injury as a result of tumor or surgical resection are at the highest risk for obesity, which can be severe (hypothalamic obesity).[49] Survivors of childhood ALL represent another high-risk group because of treatment with cranial radiation and high-dose glucocorticoids. Up to 46% of ALL survivors have been reported to be obese at 10 years of follow-up.[50] Patients treated with HSCT have higher-than-expected rates of abnormal glucose metabolism, independently from obesity.[51] The prevalence of insulin resistance and DM in HSCT recipients has been reported at 52%[52] and 5%,[53] respectively. Treatment with TBI, decreased lean mass (sarcopenia),[54,55] and atypical body fat distribution may explain the prevalence of abnormal glucose metabolism after HSCT.[56] Longitudinal follow-up data from young HSCT survivors have suggested an increase in the prevalence of metabolic syndrome/cardiovascular risk over time (10.6% at 5 years of follow-up to 28.4% at 10 years), especially among those treated with cranial radiotherapy in addition to TBI.[57] Abdominal radiotherapy also has been associated with an increased risk of glucose intolerance and DM in survivors of solid tumors.[58,59]

Annual screening for overweight and obesity is recommended by using height, weight, and body mass index measurements. Fasting blood glucose or hemoglobin A_{1c} at least every 2 years is recommended to screen for DM in CCSs treated with abdominal radiotherapy or TBI, regardless of body mass index.[59] Treatments of hypothalamic obesity have included octreotide,[49] diazoxide,[60] amphetamine derivatives,[61] glucagon-like peptide 1 receptor agonists,[62] and bariatric surgery,[63] but data on long-term efficacy are lacking. Physical activity may prevent additional deterioration of metabolic control[55]; the risk/benefit ratio of pharmacotherapy (eg, metformin) is unknown in CCSs.[64]

LOW BMD

The prevalence of low BMD has been reported at 9% to 18% in general cohorts of CCSs.[1,2] High-risk groups include survivors of pediatric ALL, CNS tumors, and HSCT.[65-67] Several factors contribute to poor bone acquisition and alterations in bone resorption in CCSs, including the following: the direct impact of cancer diagnosis (eg, leukemia) on the skeleton, glucocorticoid treatment, osteotoxic chemotherapy, and radiation as well as comorbid conditions such as treatment-induced endocrine deficits (eg, GH deficiency, hypogonadism), malnutrition, physical impairment, and reduced muscle strength.[66,67] Adverse skeletal growth outcomes have more recently been reported in individuals treated with retinoid derivatives[28] and with TKIs such as imatinib, sunitinib, dasatinib, and vandetanib[7]; additional data are needed to better understand and address the detrimental effects of these agents on the developing skeleton.

Dual-energy x-ray absorptiometry (DXA) is recommended for bone health assessment after childhood cancer therapy.[68] The BMD of shorter individuals and those with pubertal delay may be

underestimated by DXA.[69] A single DXA measurement alone is insufficient to dictate the initiation of specific therapeutic interventions, and emphasis should be placed on fracture history, risk factors, and BMD changes over time.[70] Treatment for low BMD includes prompt recognition and treatment of hormonal deficiencies, repletion of vitamin D insufficiency/deficiency, and supplementation of poor calcium intake. Furthermore, CCSs should be counseled about the benefits of regular physical activity on bone remodeling and the deleterious effects of smoking and alcohol consumption.[71]

In conclusion, endocrine complications are among the most common late effects in CCSs. Given a variable latency interval, a systematic approach where individuals are periodically screened on the basis of their risk factors can help to improve health outcomes by prompt diagnosis and treatment of evolving endocrinopathies. Changes and improvements in cancer treatments over time will necessitate future revisions of these recommendations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Endocrine Late Effects in Childhood Cancer Survivors

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