

Hypothyroidism—Etiologies, Evaluation, and Emergency Care



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KEYWORDS

- Hypothyroidism • Myxedema coma • Autoimmune thyroiditis
- Congenital hypothyroidism • Thyroid emergencies • Emergency medicine

KEY POINTS

- Hypothyroidism is a common endocrinopathy that affects patients of all ages.
- Hypothyroidism can be the result of thyroid gland dysfunction, dietary insufficiencies, genetic factors, medication side effects, or abnormalities in the hypothalamus–pituitary–thyroid axis.
- Decompensated hypothyroidism and myxedema coma are endocrine emergencies, requiring hospitalization and emergent treatment with parenteral thyroid hormone.

INTRODUCTION

Although often not a primary emergency department (ED) diagnosis, hypothyroidism is one of the most prevalent endocrinology disorders among the general population. Due to the various effects of thyroid hormone on metabolism, coexisting thyroid disorder must be considered during the management of other ED complaints. The degree of morbidity from hypothyroidism can vary widely between only mild symptoms and at its worst, myxedema coma, a sometimes fatal manifestation of severe hypothyroidism. Emergency physicians must understand the function of the thyroid gland as well as the pathophysiology and management of thyroid disorders.

EPIDEMIOLOGY

Clinical primary hypothyroidism is defined as thyroid-stimulating hormone (TSH) concentrations above the reference range in conjunction with free thyroxine (FT₄)

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concentrations below the reference range. Comparatively, subclinical hypothyroidism may serve as a marker of early thyroid dysfunction and is defined by TSH concentration above the reference range but normal free thyroxine concentration.¹ The prevalence of overt hypothyroidism in the general population varies between 0% to 3% worldwide and 3% to 7% in the United States.¹ The primary etiology of hypothyroidism in developing nations is low dietary iodine intake. In developed countries that supplement salts with iodine, the most common etiology of hypothyroidism is autoimmune thyroiditis, or Hashimoto's disease.² There is a greater incidence of hypothyroidism among certain demographics including women, individuals older than 65, and Caucasians. Hypothyroidism is found more frequently in patients with autoimmune diseases including type 1 diabetes, celiac disease, and other autoimmune endocrinopathies.¹ Genetic conditions including Down syndrome or Turner syndrome also carry an increased risk of hypothyroidism.³ Tobacco smoking and moderate alcohol intake are associated with a decreased risk of hypothyroidism.^{4,5}

PHYSIOLOGY

A review of thyroid physiology is necessary to understand the effects of thyroid hormone dysregulation and the mechanisms of available therapies. Thyroid hormone is regulated by the hypothalamic–pituitary–thyroid (HPT) axis. Thyrotropin-releasing hormone (TRH) is excreted from the periventricular nucleus of the hypothalamus. TRH then enters the hypophyseal portal circulation where it travels to the anterior pituitary gland, triggering the synthesis of thyroid-stimulating hormone (TSH).⁶

TSH in turn binds to the thyroid-stimulating hormone receptor (TSH-R) on thyroid follicular cells, signaling the release of tetraiodothyronine (T_4) and triiodothyronine (T_3) through the process detailed in [Fig. 1](#).⁶ Malfunctions at any step of this process as well as the overall HPT axis can give rise to symptomatic hypothyroidism.

Once in the systemic circulation, thyroid hormone binds to transporter proteins including thyroxine-binding globulin, transthyretin, and albumin.⁶ At the cellular level, T_3 and T_4 enter the cytoplasm through the monocarboxylate transporter 8 thyroid hormone transporter. T_4 undergoes deiodination by 2 5'-deiodinase (DII) to form T_3 , or by 3 5-deiodinase (DIII) to form the inactive hormone reverse T_3 (rT_3). T_3 enters the nucleus directly where it binds to thyroid receptors bound to DNA to promote gene transcription.⁷

PRIMARY THYROID DISORDERS

Iodine Deficiency

Iodine, absorbed through the small intestine, is a naturally occurring trace element found in seafood, seaweed, vegetables, and supplemented in table salt. Iodine deficiency remains a leading worldwide cause of hypothyroidism. The World Health Organization (WHO) recommends a target intake of 150 $\mu\text{g}/\text{day}$ for adults greater than 12.⁸ As of 2021, a survey of urinary iodine concentrations in 189 countries found that at least 26 countries report inadequate iodine intake.⁹ Areas with iodine-deficient soils such as the goiter belt of the Midwestern United States carry a higher incidence of local iodine deficiency due to the limited availability of iodine in local produce.¹⁰ Additionally, excess dietary iodine intake may also be detrimental. A Danish study demonstrated that TSH concentrations among a population measured before and after mandatory iodization of salt were 16% higher compared to areas that did not implement iodization.¹¹ One proposed mechanism is that an excess iodine intake can lead to the formation of iodopeptides that inhibit thyroid peroxidase (TPO) mRNA. Normally, excess iodine intake initiates a self-regulatory phenomenon coined the "Wolff–

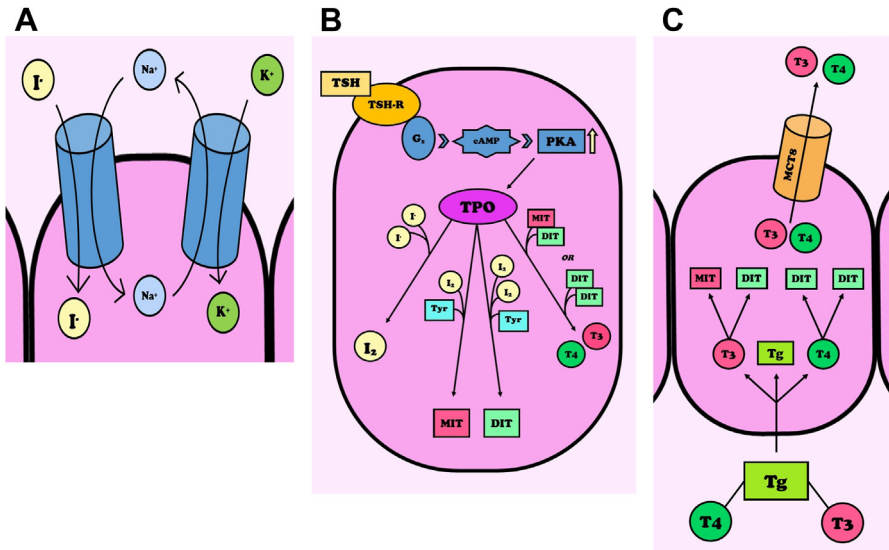


Fig. 1. (A). Iodide ions (I^-) are brought into thyrocytes from systemic circulation through a sodium iodide (Na^+/I^-) symporter driven by an adenosine triphosphate (ATP)-dependent sodium-potassium (Na^+/K^+) pump.⁶ (B). Stimulation of the $G_{\alpha s}$ protein by thyroid-stimulating hormone (TSH) binding to its receptor leads to an increase in cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). PKA in turn phosphorylates thyroid peroxidase (TPO), a catalyst of 3 reactions: oxidation, organification, and a coupling reaction. TPO utilizes hydrogen peroxide to oxidize iodide (I^-) to iodine (I_2). TPO then combines a tyrosine residue (Tyr) with 1 iodine molecule to produce monoiodotyrosine (MIT). Alternatively, it can combine 2 iodine molecules with Tyr to produce diiodotyrosine (DIT). Finally, TPO mediates either the coupling of MIT and DIT to make T_3 or 2 DIT molecules to make T_4 .⁶ (C). Thyrocytes produce thyroglobulin (Tg), an inactive protein stored in the lumen of thyroid follicles. Tg binds T_3 and T_4 for storage in thyroid follicles. Thyrocytes uptake the bound T_3 and T_4 complex, which then undergoes lysosomal cleavage into its components: MIT, DIT, T_3 , and T_4 . T_3 and T_4 are released into systemic circulation through the monocarboxylate transporter 8 thyroid hormone transporter.⁶

Chaikoff effect," leading to the downregulation of the Na^+/I^- symporter over the course of several weeks until baseline intrathyroidal iodine levels are achieved.¹²

Autoimmune Thyroiditis

Hashimoto disease or chronic autoimmune thyroiditis is the most common autoimmune thyroid disorder (AITD), causing symptomatic hypothyroidism in approximately 20% to 30% of affected patients.¹³ Risk factors include female sex and increasing age. This condition is caused by the development of autoimmune antibodies selective for several antigens including thyroglobulin (Tg) and TPO. Anti-TPO antibodies are present in 80% to 90% patients with AITD, and the detection of these antibodies within systemic circulation has a 90% sensitivity for the diagnosis of AITD.¹³ Ultimately, these antibodies cause lymphocytic infiltration of the thyroid and fibrosis of thyrocytes. This cytologic abnormality is seen in both extreme cases of Hashimoto thyroiditis, as well as a distinct condition known as fibrous atrophic thyroiditis, or Ord disease. This condition is characterized by the development of atrophic thyroiditis without the goiter associated with cases of Hashimoto disease.¹⁴ There is also a component of

genetic susceptibility that predisposes patients to developing autoimmune thyroiditis.¹³

Medication Induced

Several medications have been associated with hypothyroidism including thionamides, iodinated contrast agents, amiodarone, lithium, tetracyclines, and some antineoplastic agents.¹⁵ Thionamides include methimazole, carbimazole, and propylthiouracil, which inhibit TPO function, thus causing a clinically desirable effect when used in the treatment of hyperthyroidism. Iodinated contrast agents as well as excessive dietary iodine intake can inhibit thyroid function through the Wolff–Chaikoff effect discussed earlier. In euthyroid patients, this effect is transient, however, the effect is impaired in patients with pre-existing thyroid disorders leading to dysregulation of iodine concentration within the thyroid.¹⁵ Amiodarone is a complex molecule with multiple pharmacologic properties and is made of approximately 37% iodine by weight. Two hundred mg of oral amiodarone daily corresponds to approximately 75 mg of dietary iodine intake, far exceeding the recommended daily intake of 150 µg, which can inhibit thyroid function. Additionally, amiodarone inhibits the deiodination activity of DI and DII, limiting peripheral conversion of T₄ to T₃, which in turn leads to uncontested DIII activity that produces greater amounts of inactive rT₃.¹⁶ Lithium has a 3 to 4 times greater concentration in the thyroid than plasma, where it can inhibit iodotyrosine coupling and block release of thyroid hormone. Thyroid function testing should be obtained before starting treatment with lithium and repeated at 6 to 12-month intervals.¹⁷ Lastly, patients initiating beta blocker therapy should be monitored for signs of hypothyroidism as beta blockers may inhibit deiodination of T₄ to T₃ and increase conversion to inactive rT₃.¹⁸

Antineoplastics

Similarly, several antineoplastic agents have been associated with hypothyroidism. Interferon alpha, a medication used to treat cancer and hepatitis, was associated with the onset of AITD with pre-existing TPO antibody levels.¹⁹ Tyrosine kinase inhibitors are an important etiology of hypothyroidism, causing ischemic thyroiditis due to blockage of vascular endothelial growth factor and thyroid capillary regression.¹⁵ Additionally, this class of medication can induce DIII function, leading to the peripheral inactivation of thyroid hormone to rT₃. Bexarotene, a synthetic retinoid used in the treatment of cutaneous T-cell lymphoma, can cause central hypothyroidism by suppressing the gene promoter of the TSH beta subunit and by increasing peripheral metabolism of thyroid hormone.¹⁵ Alemtuzumab is a monoclonal antibody that promotes selective cell destruction by targeting CD52 on lymphocytes. During the T-cell recovery phase, self-reactive clones can develop, predisposing patients to both hypothyroidism and hyperthyroidism.²⁰

Congenital Hypothyroidism

Congenital hypothyroidism (CH) is another etiology characterized by defective formation of the thyroid gland, known as dysgenesis, or abnormal synthesis of thyroid hormone called dys hormonogenesis. Thyroid dysgenesis encompasses 3 phenotypes: Complete agenesis, ectopic gland, or hypoplastic thyroid. The incidence of this condition has been increasing in the United States at an estimated 3% per year.²¹ Although previously thought to be less common, universal newborn screenings and a change in laboratory cutoffs for diagnosis to identify less severe cases has led to an increase in diagnoses of CH. Newborn screening is required in all 50 states and usually occurs between days 2 to 4 of life. There are 2 methods for screening,

either Primary TSH with backup T_4 or Primary T_4 with backup TSH.²² Early detection of CH is important as prompt treatment can prevent severe neurocognitive deficits. Preterm infants and children with trisomy 21 are at highest risk for CH. Untreated CH can cause delays in motor development, verbal skills, attention, and memory.²³

Iatrogenic

Both total and partial thyroidectomies are important iatrogenic causes of primary hypothyroidism in post-surgical patients. In addition to typical hypothyroidism symptoms, post-thyroidectomy patients will also exhibit hypocalcemia due to destruction of parafollicular T cells and a resultant reduction in calcitonin secretion.²⁴ A meta-analysis of 32 studies revealed a 20% overall risk of hypothyroidism after a hemithyroidectomy. Based on aggregate data from 4 studies, risk can be further stratified into a 12% risk of SH and 4% risk of clinical hypothyroidism.²⁵ Irradiation of the thyroid gland during treatment of head and neck cancers may also produce symptomatic hypothyroidism, with Caucasian race and female gender associated with a higher risk.²⁶

Subclinical Hypothyroidism

SH is a biochemical diagnosis defined as elevated TSH levels with normal levels of free T_4 . It is most often caused by autoimmune disease and can affect up to 10% of the US population. This condition creates a risk for later development of overt hypothyroidism, with an increased risk if TPO antibodies are present. Patients with TSH levels less than 10 mU/L had a 2% to 4% risk of developing clinical hypothyroidism, 40% risk with TSH 10 to 14.9 mU/L, and 85% risk with TSH 15 to 19.9 mU/L.²⁷ Typically, quality of life is not affected by SH, but some studies demonstrate an association with cardiovascular risks including diastolic heart dysfunction and hyperlipidemia as well as minor cognitive impairment.²⁷

Non-Thyroidal Illness Syndrome

Illness and starvation states can lead to an initial decrease in serum T_3 levels followed by a decrease in T_4 as well, known as sick euthyroid syndrome (SES) or non-thyroidal illness syndrome (NTIS). In many cases, but not all, there is an increase in reverse T_3 (rT_3), the biologically inactive form of T_3 .²⁸ Excluding cases of acute medication-induced hypothyroidism, laboratories in NTIS may show a low to normal TSH with low T_3 and T_4 . Critical illness can also lead to reduced food intake, hypothalamic adaptations, pituitary adaptations, and maladaptive intra-thyroidal changes, which additionally contribute to NTIS.²⁸

CENTRAL HYPOTHYROIDISM

Central hypothyroidism, less common than primary hypothyroidism, stems from pituitary and hypothalamic disorders. It is usually characterized by low to normal TSH concentrations as well as low free thyroxine concentrations.²⁹ This highlights an important pitfall of false-negative results when using reflex TSH testing strategies without T_4 levels to rule out hypothyroidism. However, in select cases, TSH may be mildly elevated, especially in hypothalamic disorders with intact pituitary function.²⁹ Suspicion for central hypothyroidism should be present in the context of several etiologies including compressive pituitary lesions, trauma, vascular accidents, autoimmune disease, infiltrative lesions, iatrogenic factors, infection, or inherited disorders.

Anterior Pituitary Dysfunction

Secondary hypothyroidism refers to etiologies arising specifically from the anterior pituitary gland. Intrapituitary etiologies include pituitary macroadenomas, and craniopharyngiomas. Pituitary macroadenomas account for approximately 50% of all cases of central hypothyroidism. These lesions can cause destruction of thyrotropes within the anterior pituitary itself or result from the compression of the pituitary stalk and hypothalamus.³⁰ Pituitary dysfunction can also be caused by other compressive conditions including meningiomas, Rathke cleft cysts, empty sella syndrome, and carotid aneurysms.³¹ Increased intracranial pressure in the setting of traumatic brain injury, subarachnoid hemorrhage, or particularly traumatic childbirth may also lead to compressive dysfunction of the pituitary. Similarly, cranial surgery or irradiation to the pituitary gland can give rise to central hypothyroidism.³¹

Autoimmune Disorders

Autoimmune hypophysitis can manifest as a disturbance in multiple pituitary gland functions. The thyrotropin axis is the second most commonly affected axis after the corticotrope axis.³⁰ This condition encompasses several histologic variants of anterior pituitary inflammation, the most common of which is lymphocytic infiltration. These variants lead to compression of the sella and parasellar structures, including anterior pituitary thyrotropes.³² Sarcoidosis is a multisystem disease, which can manifest as neurologic symptoms in 5% to 13% of patients. Of this subset, 2.5% of patients have involvement of the hypothalamic–pituitary region, resulting in pituitary hormone abnormalities.³³

Inherited Disorders

Secondary hypothyroidism can arise from genetic mutations in genes encoding the TSH-B subunit, TRH receptor, and most commonly immunoglobulin superfamily member 1, a membrane-bound protein involved in regulation of TRH receptors.³⁴ In patients with thalassemias, frequent transfusion therapy is indicated for treatment of the disorder but can lead to iron overload, which causes generation of free hydroxyl radicals and oxidative damage to tissues.³⁵ Interestingly, in hereditary hemochromatosis, while iron has been documented to deposit in both the anterior pituitary gland and thyroid gland, the prevalence of clinical hypothyroidism does not differ between patients with hemochromatosis and those without.³⁶

Miscellaneous

Other miscellaneous etiologies include pituitary apoplexy, an acute pituitary hemorrhage, as well as Sheehan syndrome, an ischemic injury to the pituitary caused by intrapartum blood loss. The mechanism of this condition stems from pregnancy-related pituitary hyperplasia causing increased oxygen demand followed by hypoperfusion to anterior pituitary cell lines including thyrotrophs after significant hemorrhage and systemic hypovolemia.³⁷ Patients with these acute processes may initially present with normal TSH levels, although a portion of this TSH may be biologically inactive.^{29,30} Glucocorticoids are also a notable cause of central hypothyroidism given their widespread use in treating other conditions. Hydrocortisone has an inverse relationship with TSH, suggesting fluctuating cortisol levels may underlie the known diurnal variation of lower TSH levels in the morning and higher levels at night. High-dose glucocorticoids can suppress TSH release acutely, however, long-term glucocorticoid administration or Cushing syndrome do not appear to cause clinically evident central hypothyroidism.³⁸ Infectious causes of central hypothyroidism include

tuberculosis (TB), syphilis, and viral and fungal infections.³¹ While exceedingly rare, sellar tuberculomas have been reported in developing countries where there is a high prevalence of TB. Radiological MRI findings may mimic pituitary adenomas, however, histologic analysis reveals necrotizing granulomas in the anterior pituitary that can inhibit thyrotrope activity.³⁹

CLINICAL FEATURES BY SYSTEM

General Symptoms

Thyroid receptors (TR) are expressed in many tissues throughout the body, but the degree of expression of TR isoforms can differ. This gives rise to the varying effects of thyroid hormone on different organs.⁴⁰ If a malfunction occurs at any step of the HPT axis from hypothalamic signaling down to the thyroid hormone receptor binding in individual tissues, the effects of thyroid hormone deficiency can manifest clinically. Central or primary hypothyroidism beginning in the brain or at the thyroid gland may cause global dysfunction. Clinically, hypothyroidism may present with a variety of vague complaints of unclear chronicity including cold intolerance, weight gain, concentration difficulty, depression, and voice changes.⁴¹ Depending on the time course and degree of hypothyroidism, symptom severity can vary greatly as well.

Cardiovascular

The effects of thyroid dysfunction on the cardiovascular system can manifest as pericardial effusion, bradycardia, diastolic hypertension, increased systemic vascular resistance, atherosclerosis, and even heart failure with reduced cardiac output in severe cases. Even SH has been associated with ischemic heart disease and increased cardiovascular mortality.⁴² Physical examination may reveal muffled heart sounds, pericardial rub, and jugular venous distention.⁴¹ Bedside echocardiography can provide real-time confirmation of the presence of pericardial effusion and assess cardiac contractility. Case reports suggest that the effusion can progress to hypothyroidism-induced cardiac tamponade if left untreated.⁴³

Respiratory

Patients may have reduced breath sounds secondary to hypoventilation or pleural effusions.⁴¹ Hypoventilation may occur secondary to altered nerve function and myopathies, which decrease respiratory muscle strength.⁴⁴ The degree of hypothyroidism correlates well with respiratory muscle function and variables such as vital capacity and forced expiratory volume in 1 second. These measures can be improved after thyroxine replacement therapy.⁴⁵

Gastrointestinal

Hypothyroidism leads to delayed gastrointestinal transport, predisposing to constipation and ileus. These can present with hypoactive bowel sounds on auscultation as well as diffuse abdominal tenderness. Consistent with other signs of hypothyroid-induced volume overload, patients can present with abdominal ascites, however, this is a rare complication occurring only in 4% of patients with thyroid disease.⁴¹

Renal

Epidemiologic data demonstrate a positive relationship between the prevalence of hypothyroidism and increasing severity of chronic kidney disease (CKD). The prevalence of hypothyroidism in dialysis patients ranges from 13% to 25%.⁴⁶ Animal

studies have revealed that hypothyroidism affects both kidney size and structure, resulting in reduced renal mass. At the microscopic level, thickening of the glomerular basement membrane (GBM) was observed as well as loss of GBM permselectivity, leading to proteinuria.^{46,47} Elevated TSH levels among CKD patients has also been associated with increased all-cause mortality compared to euthyroid CKD patients.⁴⁶ Hypothyroidism is also associated with hyponatremia through renally mediated mechanisms, most notably through syndrome of inappropriate antidiuretic hormone secretion. Hypothyroidism reduces heart rate and in turn cardiac output, leading to baroreceptor stimulation and release of antidiuretic hormone. This promotes fluid retention at the level of the collecting duct and dilutional hyponatremia. Comorbid renal disease can exacerbate this fluid retention as a preexisting reduced GFR limits delivery of excess water to the diluting segments of the nephron.⁴⁸

Musculoskeletal

Thyroid hormone is essential for skeletal development, with deficiencies during childhood causing delayed skeletal development, reduced linear growth, and impaired bone mineralization. This can present as delayed closure of the fontanelles, patent skull sutures, scoliosis, congenital hip dislocation, and slipped capital femoral epiphysis. On X-ray imaging, epiphyseal dysgenesis may be detected as a stippled appearance of the epiphyses.^{49,50} In adults, an interruption of the direct activity of thyroid hormone on osteoblast function and indirect regulation of osteoclast function result in prolonged bone remodeling. This results in a net increase in bone mineralization without a change in bone volume.⁵¹

Dermatologic

Hypothyroidism may present as non-pitting edema. This represents deposition of glycosaminoglycans, causing a fluffy appearance to the skin, called myxedema. Additionally, patients may present with pallor, secondary to underlying anemia. The skin will often appear dry and coarse with brittle nails. Hair is also coarse with areas of thinning. Facial edema including periorbital edema can develop.⁴¹ It is important to recognize the distinction of exclusive facial swelling that separates it from the exophthalmos observed with hyperthyroidism.

Neurologic

Neurologic effects of hypothyroidism primarily manifest as cognitive dysfunction, including alterations in orientation, memory, and higher order thoughts. Peripherally, patients exhibit proximal muscle weakness, increased fatigability of strength, and delayed reflexes. Additionally, nerve entrapment syndromes such as carpal tunnel may occur due to localized edema.⁴¹ Hypothyroid patients may also exhibit global gait abnormalities, base of support alterations, and reduced velocity compared to euthyroid individuals, increasing their fall risk.⁵¹

Psychiatric

Hypothyroidism can lead to depression and mood changes. Patients may present with a slow, flat affect. A severe condition known as myxedema madness has been described in which patients display signs of psychosis with responses to internal stimuli.⁴¹ Affective and cognitive dysfunction caused by overt hypothyroidism may be reversible with treatment. SH is not associated with major neuropsychiatric deficits but may cause small deficits in memory and executive function.⁵²

CLINICAL CONSIDERATIONS FOR SPECIAL POPULATIONS

Pediatrics

Although less common in children than adults, the prevalence of hypothyroidism in the pediatric population may be as high as 1.7% to 9.5% and can be divided into 2 categories, congenital or acquired.⁵³ Although most children with CH will be diagnosed via universal newborn screening, some infants with CH may be undiagnosed. Any infants presenting to the ED with poor feeding, hypothermia, bradycardia, edema, prolonged jaundice, poor growth, or developmental delay should be evaluated for CH.⁵⁴ On examination, a goiter, large fontanelle, macroglossia, or an umbilical hernia may offer additional clues for diagnosis.

Hashimoto thyroiditis is the most common cause of acquired hypothyroidism in children in iodine-sufficient areas, with an estimated prevalence of 3%.⁵³ Hypothyroidism is more frequent in children with autoimmune diseases who will also have a higher incidence of hypothyroidism due to shared genetic predisposition. There is a well-documented association between type 1 diabetes and Hashimoto thyroiditis in pediatric patients.⁵⁵ Children who acquire hypothyroidism may show signs of cognitive dysfunction, delayed developmental milestones, lower *intelligence quotient* scores, and balance and gait issues secondary to cerebellar effects, in addition to the other organ system symptoms commonly seen in adults.⁵⁵

Pregnancy

The most common thyroid disorder during pregnancy is hypothyroidism.⁵⁶ In pregnancy, trimester-specific TSH cutoffs are used to make the diagnosis of overt hypothyroidism (2.5 mIU/L for the first trimester, 3.0 mIU/L for the second, and 3.0–3.5 mIU/L for the third).⁵⁶ SH may also be diagnosed during pregnancy, but contradictory studies debate the benefit in fetal or maternal outcomes with levothyroxine treatment in SH. In an attempt to prevent hypothyroidism, a 50% increase in dietary iodine intake is recommended during pregnancy even in iodine-sufficient regions.^{57,58} The WHO recommends 250 µg of iodine/day during pregnancy to reduce the incidence of congenital and infantile hypothyroidism.⁵⁷ Pregnant people with hypothyroidism will need higher doses of levothyroxine, especially in the first trimester, because of an increased demand for thyroid hormone. If a pregnant person with hypothyroidism is not appropriately treated, they are at increased risk for miscarriage. If the pregnancy does continue, the fetus is at risk for preterm delivery, low birth weight, and intellectual delays.⁵⁶

Older Adults

Hypothyroidism affects 5% to 20% of older women and 3% to 8% of older men.⁵⁹ The symptoms of hypothyroidism in older adults can be vague and the diagnosis can be elusive. Psychiatric symptoms, such as depression and mood disturbance, are common in older adults with hypothyroidism.⁶⁰ Hyperlipidemia can be a symptom of hypothyroidism in older adults and should prompt TSH screening.⁶¹ Hypothyroidism leads to a reduction of blood volume, cardiac dysfunction, and bradycardia, all of which contribute to heart failure.⁶¹ Although clinicians have long suspected a relationship between hypothyroidism and cognitive decline/dementia, most studies have not shown a definitive link between the 2 conditions in older adults. Similarly, research does not support the hypothesis that treating hypothyroidism can reverse cognitive decline.⁶²

EMERGENCY MANAGEMENT

Hypothyroidism can progress to myxedema coma, a life-threatening emergency. Myxedema coma occurs in patients with severe, decompensated hypothyroidism.

This disease carries an estimated mortality rate of approximately 30% to 60%.⁶³ The most common cause for worsening hypothyroidism is non-compliance with maintenance medications, but more than a third of patients that present to the ED with advanced hypothyroidism will have no known history of thyroid disease.⁶⁴ Myxedema coma is usually triggered by a combination of uncontrolled hypothyroidism and a precipitating event. Common precipitating events include infections or new medications: specifically amiodarone, lithium, and beta blockers. Despite the name of this disease process, most patients do not present to the ED in a comatose state. Patients may present to the ED with altered mental status, hypothermia, hypoventilation, hypotension, or bradycardia. Hypothermia is the most common vital sign abnormality and is present in ~90% of patients with myxedema coma.⁶⁵

When examining patients with suspected myxedema coma, ED clinicians should start the evaluation with an airway, breathing, circulation, disability, exposure (ABCDE) primary assessment. A patient with an altered level of consciousness may not be able to protect his airway and may require intubation. Intubation of these patients may be complicated by an enlarged tongue or the presence of a goiter. These patients may also have hypoxemia and lower physiologic reserves, putting them at risk for decompensation during intubation.

Patients with suspected myxedema coma should be continuously monitored and require IV access. Hypoglycemia must be considered and treated expediently with dextrose. Patients with myxedema coma may present with hypotension. Vasopressors should be started after thyroid hormone is administered. Hypotension will often be refractory to vasopressors if the hypothyroidism remains untreated.⁶⁶ Physicians should perform a bedside ultrasound to screen for a pericardial effusion or cardiac tamponade in hypotensive patients with suspected decompensated hypothyroidism.

ED clinicians should assess skin condition and reflexes. Patients with advanced hypothyroidism will have dry skin and delayed deep-tendon reflexes. Non-pitting edema of the extremities may be present. A surgical scar from a prior thyroidectomy may be present and provide a clue to the diagnosis. Extremities may be cool to touch and passive rewarming with blankets is indicated. Active rewarming may worsen hemodynamic instability as cold-induced peripheral vasoconstriction and circulatory centralization are reversed.⁶⁷

If the diagnosis of decompensated hypothyroidism is suspected, treatment should be started immediately. While laboratory studies can contribute to making the diagnosis, waiting for these results can delay treatment and worsen outcomes.

DIAGNOSTIC WORKUP

There are several diagnostic tests available to assess thyroid function, however, a stepwise approach is recommended for best resource utilization. Asymptomatic patients should not be screened for hypothyroidism. If hypothyroidism is on the ED differential, initial testing can be limited to a TSH level only. If the TSH is abnormal, this should prompt free T_4 testing to distinguish between subclinical and clinical hypothyroidism. However, if there is reason to suspect a hypothalamic or pituitary cause, a free T_4 level should be included in the initial testing as TSH cannot rise appropriately in response to free T_4 decline and may appear normal.⁶⁸ A diagnosis of clinical hypothyroidism in turn should prompt an outpatient autoimmune work-up including TPO antibodies and thyroglobulin antibodies. TSH concentrations can also occur in cases of primary adrenal insufficiency, prompting further workup of this etiology.⁶⁸

It is important to note that free T_4 testing is recommended as the "free" form of thyroid hormone is the active form while 98% to 99% is inactive and bound to plasma

proteins including thyroxine-binding globulin. Additionally, the thyroid gland secretes 80% T_4 and 20% T_3 , making T_4 the superior marker for thyroid gland function.⁶ Therefore, routine testing of total T_4 , total T_3 , free T_3 , or reverse T_3 levels of ED patients is not indicated.⁶⁸ In chronically ill patients or malnourished patients, this advanced testing can aid in the diagnosis of non-thyroidal illness syndrome.

If SH is suspected in the ED from an isolated, elevated TSH level, the patient should be referred to outpatient follow-up for confirmatory TSH and free T_4 testing within 1 to 3 months. If the initial TSH is greater than or equal to 15, follow-up should occur within 1 to 2 weeks. After confirmation of persistently elevated TSH levels, the patient should be tested for TPO antibodies and can be started on low-dose levothyroxine (25–75 μg daily) based on the categories listed in the following paragraph.²⁷ If treatment is initiated, repeat TSH level should be obtained in 6 weeks and levothyroxine dose adjusted accordingly. Once target TSH level is reached, patients can be monitored with annual TSH testing.²⁷

1. TSH between 4.5 and 6.9 mU/L: Patient should be referred to primary care for testing of TPO antibodies. In patients younger than 65 years, consider treatment with levothyroxine if patient demonstrates multiple symptoms of hypothyroidism, positive TPO antibodies, progressively increasing thyrotropin levels, plan for pregnancy, or goiter.²⁶
2. TSH between 7.0 and 9.9 mU/L: Initiate levothyroxine in patients less than 65 but consider treatment in older age groups to reduce risks of strokes or coronary heart disease.²⁶
3. TSH greater than 10.0 mU/L: Initiate levothyroxine in all ages to reduce progression to overt hypothyroidism.²⁶

THERAPEUTIC CONSIDERATIONS

When treating uncomplicated hypothyroidism, patients can be referred to their primary doctor or an endocrinologist. Older adults should be started at lower doses and slowly uptitrated to prevent cardiac dysrhythmias. Pregnant women and children with hypothyroidism should be treated in consultation with an endocrinologist as their higher metabolic rates will likely demand higher dosing of levothyroxine.

Patients with myxedema coma or decompensated hypothyroidism should be treated with IV thyroid hormone. Clinicians can use levothyroxine (T_4) 300 to 500 μg IV bolus or liothyronine (T_3) 25 to 50 μg IV or a combination of both medications at the lowest doses. Concomitant adrenal insufficiency is common and clinicians should consider prescribing stress dose steroids (hydrocortisone 100 mg IV). Liothyronine is the active thyroid hormone, T_3 . It has a fast onset and it crosses the blood–brain barrier, which may improve altered mental status more quickly than levothyroxine. T_3 should be used cautiously because it can cause hemodynamic instability and arrhythmias. T_4 is safer to administer, especially in patients with cardiac history or risk factors, but the onset of action is slower than T_3 .⁶⁵ No studies have proven one treatment better than the other.

Patients that develop myxedema coma are usually triggered from a state of hypothyroidism to decompensated hypothyroidism by an inciting event such as sepsis, trauma, myocardial infarction, or stroke. Clinicians should be thorough in their assessment of potential triggers for myxedema coma and consider empiric treatment with antibiotics as sepsis is a common cause.⁶⁴ Patients with myxedema crisis may be hypotensive and require volume resuscitation. Hyponatremia, also seen in decompensated hypothyroidism and adrenal insufficiency, can complicate fluid management in these patients.

DISPOSITION

Patients with mild hypothyroidism can be started on levothyroxine in the outpatient setting by their primary doctor or by an endocrinologist. Patients with myxedema coma or decompensated hypothyroidism should be admitted to the intensive care unit as they are at high risk for respiratory, cardiovascular, and neurologic decompensation.

DISCUSSION

Proper function of the thyroid gland is required for normal development and metabolism. While most cases of hypothyroidism in iodine-sufficient countries arise from a dysfunctional thyroid gland, some causes of hypothyroidism originate outside of the thyroid. Secondary causes related to the hypothalamus, pituitary gland, or external factors, such as medication exposure, must be considered. Hypothyroidism can affect all age groups, including neonates, pregnant women, and geriatric patients. A low level of thyroid hormone can impact all organ systems. Symptoms may be mild, such as skin and hair changes, or can advance to a life-threatening condition—myxedema crisis. When a patient with decompensated hypothyroidism presents to the ED, clinicians should assess the patient's airway, breathing, and circulation. If myxedema coma is suspected, the patient should be empirically treated with parenteral thyroid hormone while awaiting the diagnostic tests of TSH and free T₄. Adrenal insufficiency may also be present and can complicate the management of hypothyroidism.

CLINICS CARE POINTS

Pearls:

1. Thyroid dysfunction may occur when starting treatment with any of the following medications: thionamides, iodinated contrast agents, amiodarone, lithium, tetracyclines, and antineoplastic agents.
2. Older adults, women, and Caucasian patients are at highest risk for hypothyroidism.
3. Thyroid hormone affects all body systems and hypothyroidism can manifest with a variety of constitutional or vague symptoms.

Pitfalls:

1. If a patient is diagnosed with pituitary dysfunction, hypothyroidism must also be considered. A screening TSH test may not be sufficient to exclude hypothyroidism and a free T₄ test may be required to make the diagnosis.
2. Most infants will be diagnosed with CH via newborn screening, but the diagnosis should be considered in infants that present to the ED with poor feeding, developmental delays, and hypotonia.
3. Emergency physicians must recognize and empirically treat myxedema coma (decompensated hypothyroidism) even if confirmatory laboratory studies are not yet available to decrease morbidity and mortality.

DISCLOSURE

Drs. N. Cimino-Fiallos and B. Hurt have no financial interests to disclose.

REFERENCES

1. Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. *Lancet* 2017;390(10101):1550–62.
2. Chiovato L, Magri F, Carlé A. Hypothyroidism in Context: Where We've Been and Where We're Going. *Adv Ther* 2019;36(Suppl 2):47–58.

3. Panicker V, Wilson SG, Spector TD, et al. Heritability of serum TSH, free T4 and free T3 concentrations: a study of a large UK twin cohort. *Clin Endocrinol* 2008; 68(4):652–9.
4. Carlé A, Pedersen IB, Knudsen N, et al. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. *Eur J Endocrinol* 2012;167(4):483–90.
5. Asvold BO, Bjørø T, Nilsen TI, et al. Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med* 2007;167(13):1428–32.
6. Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. 2023 Jun 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29763182.
7. Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest* 2012;122(9):3035–43.
8. WHO, UN Children's Fund, International Council for the Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 3rd edition. Geneva: World Health Organization; 2007.
9. Website of the Iodine Global Network (IGN). Available at: <https://www.ign.org>. Accessed December 14, 2022.
10. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol* 2015;3(4):286–95.
11. Carlé A, Laurberg P, Pedersen IB, et al. Epidemiology of subtypes of hypothyroidism in Denmark. *Eur J Endocrinol* 2006;154:21–8.
12. Markou K, Georgopoulos N, Kyriazopoulou V, et al. Iodine-Induced hypothyroidism. *Thyroid* 2001;11(5):501–10.
13. Ragusa F, Fallahi P, Elia G, et al. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab* 2019;33(6):101367.
14. Fröhlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. *Front Immunol* 2017;8:521.
15. Rizzo LFL, Mana DL, Serra HA. Drug-induced hypothyroidism. *Medicina (B Aires)* 2017;77(5):394–404. Review.
16. Jabrocka-Hybel A, Bednarczuk T, Bartalena L, et al. Amiodarone and the thyroid. *Endokrynol Pol* 2015;66(2):176–86.
17. Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23(6):723–33.
18. Perrild H, Hansen JM, Skovsted L, et al. Different effects of propranolol, alprenolol, sotalol, atenolol and metoprolol on serum T3 and serum rT3 in hyperthyroidism. *Clin Endocrinol* 1983;18(2):139–42.
19. Tomer Y, Menconi F. Interferon induced thyroiditis. *Best Pract Res Clin Endocrinol Metab* 2009;23(6):703–12.
20. Effraïmidis G, Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. *Eur J Endocrinol* 2014;170(6):R241–52.
21. Hinton CF, Harris KB, Borgfeld L, et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. *Pediatrics* 2010;125(Suppl 2):S37–47.
22. US Preventive Services Task Force. Screening for congenital hypothyroidism: US Preventive Services Task Force reaffirmation recommendation. *Ann Fam Med* 2008;6(2):166 [Erratum in: *Ann Fam Med*. 2008;6(3):274].
23. Wassner AJ. Congenital Hypothyroidism. *Clin Perinatol* 2018;45(1):1–18.

24. Christou N, Mathonnet M. Complications after total thyroidectomy. *J Visc Surg* 2013;150(4):249–56.
25. Verloop H, Louwerens M, Schoones JW, et al. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. *J Clin Endocrinol Metab* 2012;97(7):2243–55.
26. Vogelius IR, Bentzen SM, Maraldo MV, et al. Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. *Cancer* 2011;117(23):5250–60.
27. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. *JAMA* 2019;322(2):153–60.
28. Fliers E, Boelen A. An update on non-thyroidal illness syndrome. *J Endocrinol Invest* 2021;44(8):1597–607.
29. Persani L, Ferretti E, Borgato S, et al. Circulating thyrotropin bioactivity in sporadic central hypothyroidism. *J Clin Endocrinol Metab* 2000;85(10):3631–5.
30. Grunenwald S, Caron P. Central hypothyroidism in adults: better understanding for better care. *Pituitary* 2015;18(1):169–75.
31. Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab* 2012;97(9):3068–78.
32. Prete A, Salvatori R. Hypophysitis. In: Feingold KR, Anawalt B, Boyce A, et al, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2021. p. 2000.
33. Anthony J, Esper GJ, Ioachimescu A. Hypothalamic-pituitary sarcoidosis with vision loss and hypopituitarism: case series and literature review. *Pituitary* 2016;19(1):19–29.
34. Persani L, Bonomi M. The multiple genetic causes of central hypothyroidism. *Best Pract Res Clin Endocrinol Metab* 2017;31(2):255–63.
35. Mantovani G, Elli FM, Corbetta S. Hypothyroidism associated with parathyroid disorders. *Best Pract Res Clin Endocrinol Metab* 2017;31(2):161–73.
36. Barton JC, Leiendecker-Foster C, Reboussin DM, et al. Hemochromatosis and Iron Overload Screening Study Research Investigators. Thyroid-stimulating hormone and free thyroxine levels in persons with HFE C282Y homozygosity, a common hemochromatosis genotype: the HEIRS study. *Thyroid* 2008;18(8):831–8.
37. Laway BA, Baba MS. Sheehan syndrome. *J Pak Med Assoc* 2021;71(4):1282–12568.
38. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab* 2009;23(6):793–800.
39. Majumdar K, Barnard M, Ramachandra S, et al. Tuberculosis in the pituitary fossa: a common pathology in an uncommon site. *Endocrinol Diabetes Metab Case Rep* 2014;2014:140091.
40. Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001;81(3):1097–142.
41. Dubbs SB, Spangler R. Hypothyroidism: causes, killers, and life-saving treatments. *Emerg Med Clin North Am* 2014;32(2):303–17.
42. Udovcic M, Pena RH, Patham B, et al. Hypothyroidism and the Heart. *Methodist Debaque Cardiovasc J* 2017;13(2):55–9.
43. Kaur H, Chakwop Ngassa H, Elmenawi KA, et al. Hypothyroidism-Related Cardiac Tamponade. *Cureus* 2021;13(10):e18611.
44. Schlenker EH. Effects of hypothyroidism on the respiratory system and control of breathing: Human studies and animal models. *Respir Physiol Neurobiol* 2012;181(2):123–31.

45. Siafakas NM, Salesiotou V, Filaditaki V, et al. Respiratory muscle strength in hypothyroidism. *Chest* 1992;102(1):189–94.
46. Rhee CM. The interaction between thyroid and kidney disease: an overview of the evidence. *Curr Opin Endocrinol Diabetes Obes* 2016;23(5):407–15.
47. Suh JH, Miner JH. The glomerular basement membrane as a barrier to albumin. *Nat Rev Nephrol* 2013;9(8):470–7.
48. Liamis G, Filippatos TD, Lontos A, et al. MANAGEMENT OF ENDOCRINE DISEASE: Hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. *Eur J Endocrinol* 2017;176(1):R15–20.
49. Moyer J, Jacks L, Hunter JD, et al. Slipped capital femoral epiphysis and associated hypothyroidism. A review of the literature with two classic case examples. *J Pediatr Endocrinol Metab* 2016;29(4):427–34.
50. Williams GR, Bassett JHD. Thyroid diseases and bone health. *J Endocrinol Invest* 2018;41(1):99–109.
51. Bano A, Chaker L, Darweesh SK, et al. Gait patterns associated with thyroid function: The Rotterdam Study. *Sci Rep* 2016;6:38912.
52. Samuels MH. Psychiatric and cognitive manifestations of hypothyroidism. *Curr Opin Endocrinol Diabetes Obes* 2014;21(5):377–83.
53. Rodriguez L, Dinauer C, Francis G. Treatment of hypothyroidism in infants, children and adolescents. *Trends Endocrinol Metab* 2022;33(7):522–32.
54. Wassner AJ. Pediatric Hypothyroidism: Diagnosis and Treatment. *Paediatr Drugs* 2017;19(4):291–301.
55. Nandi-Munshi D, Taplin CE. Thyroid-related neurological disorders and complications in children. *Pediatr Neurol* 2015;52(4):373–82.
56. Teng W, Shan Z, Patil-Sisodia K, et al. Hypothyroidism in pregnancy. *Lancet Diabetes Endocrinol* 2013;1(3):228–37.
57. Stagnaro-Green A, Abalovich M, Alexander E, et al. and the American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081–125.
58. Skeaff SA. Iodine deficiency in pregnancy: the effect on neurodevelopment in the child. *Nutrients* 2011;3(2):265–73.
59. Laurberg P, Andersen S, Bülow Pedersen I, et al. Hypothyroidism in the elderly: pathophysiology, diagnosis and treatment. *Drugs Aging* 2005;22(1):23–38.
60. Wildisen L, Feller M, Del Giovane C, et al. Effect of Levothyroxine Therapy on the Development of Depressive Symptoms in Older Adults With Subclinical Hypothyroidism: An Ancillary Study of a Randomized Clinical Trial. *JAMA Netw Open* 2021;4(2):e2036645.
61. Duntas LH, Yen PM. Diagnosis and treatment of hypothyroidism in the elderly. *Endocrine* 2019;66(1):63–9.
62. Parsaik AK, Singh B, Roberts RO, et al. Hypothyroidism and risk of mild cognitive impairment in elderly persons: a population-based study. *JAMA Neurol* 2014;71(2):201–7.
63. Rodríguez I, Fluiters E, Pérez-Méndez LF, et al. Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. *J Endocrinol* 2004;180(2):347–50.
64. Dutta P, Bhansali A, Masoodi S, et al. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. *Crit Care* 2008;12(1):R1.
65. Mathew V, Misgar RA, Ghosh S, et al. Myxedema coma: a new look into an old crisis. *J Thyroid Res* 2011;2011:493462.

66. Bridwell RE, Willis GC, Gottlieb M, et al. Decompensated hypothyroidism: A review for the emergency clinician. *Am J Emerg Med* 2021;39:207–12.
67. Paal P, Pasquier M, Darocha T, et al. Accidental Hypothermia: 2021 Update. *Int J Environ Res Public Health* 2022;19(1):501.
68. Wilson SA, Stem LA, Bruehlman RD. Hypothyroidism: Diagnosis and Treatment. *Am Fam Physician* 2021;103(10):605–13.