JAMA | Review

Hypothyroidism
A Review

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IMPORTANCE Hypothyroidism is a disease of thyroid hormone deficiency. The prevalence ranges from 0.3% to 12% worldwide, depending on iodine intake, and it is more common in women and older adults. Untreated hypothyroidism can cause serious health complications such as heart failure and myxedema coma.

OBSERVATIONS Hashimoto thyroiditis (an autoimmune disease) is the cause of primary hypothyroidism in up to 85% of patients with hypothyroidism living in areas with adequate nutritional iodine levels. The risk of developing hypothyroidism is associated with genetic factors (having a first-degree relative with hypothyroidism), environmental factors (iodine deficiency), undergoing neck surgery or receiving radiation therapy, pregnancy in the setting of underlying autoimmune thyroid disease, and with the use of certain medications (eg, immune checkpoint inhibitors and amiodarone). Patients with hypothyroidism may have nonspecific symptoms due to metabolic slowing, including fatigue (68%-83%), weight gain (24%-59%), cognitive issues (45%-48%) such as memory loss and difficulty concentrating, and menstrual irregularities (approximately 23%) such as oligomenorrhea and menorrhagia. Hypothyroidism can cause insulin resistance and hyperglycemia in patients with diabetes, increase the risk for cardiovascular events, such as heart failure, and negatively affect female reproductive health, causing disrupted ovulation, infertility, and increased risk of miscarriage. Untreated hypothyroidism may progress to severe hypothyroidism with decompensation (myxedema coma), which is a condition associated with hypothermia, hypotension, and altered mental status that requires treatment in an intensive care unit and has a mortality rate of up to 30%. Hypothyroidism is diagnosed based on biochemical testing; a high thyrotropin (TSH) level and a low free thyroxine (T_4) level indicate overt primary hypothyroidism. Screening for hypothyroidism is not recommended for asymptomatic individuals. Targeted testing is recommended for patients who are considered high risk (eg, patients with type 1 diabetes). First-line treatment for hypothyroidism is synthetic levothyroxine to normalize thyrotropin levels. Initial dosages should be tailored to patient-specific factors. Lower starting doses should be used for older patients or those with atrial fibrillation and coronary artery disease. Thyrotropin monitoring should be performed 6 to 8 weeks after initiating levothyroxine treatment, or when changing the dose, and then annually once the thyrotropin level is at goal to avoid overtreatment or undertreatment, both of which are associated with cardiovascular health risks.

CONCLUSIONS AND RELEVANCE Hypothyroidism may be associated with fatigue, weight gain, memory loss, difficulty concentrating, cardiovascular disease such as heart failure, menstrual irregularities, infertility, and increased risk of miscarriage. Levothyroxine is the first-line treatment to normalize the thyrotropin level and improve clinical manifestations due to hypothyroidism.

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Hypothyroidism is characterized by insufficient production of thyroid hormones. Overt primary hypothyroidism is defined as a thyrotropin (TSH) level greater than the upper limit of the reference range and a free thyroxine (T_4) level less than the lower limit of the reference range. Subclinical hypothyroidism is defined by a thyrotropin level greater than the upper limit of the reference range and a free thyroxine level within the reference range.[1,2] Hypothyroidism is common, particularly in women and older adults. The prevalence in North America and Europe ranges from 0.3% to 2%,[3-5] but may affect up to 12% of the population, primarily as subclinical hypothyroidism, with higher prevalence in areas with inadequate nutritional iodine levels.[2,6]

Clinical features vary, but common symptoms include fatigue, weight gain, constipation, dry skin, and cold intolerance.[7] Untreated hypothyroidism is associated with complications such as cardiovascular disease, impaired cognitive function (including concentration and memory deficits), and, in severe cases, myxedema coma. The first-line treatment is levothyroxine. This treatment is required throughout the patient's life in those with overt hypothyroidism. This Review summarizes current evidence regarding the epidemiology, pathophysiology, clinical presentation, and treatment of primary overt hypothyroidism in nonpregnant adults.

Methods

We searched MEDLINE (including PubMed) and Embase for articles published in the English language from database inception (from 1946 for MEDLINE and from 1974 for Embase) through June 6, 2025 (eMethods in the Supplement). Overall, 6319 articles were retrieved. We prioritized the inclusion of studies published in the past 5 years but also included older seminal articles. We selected articles based on the quality and rigor of their study designs and methods and their relevance to clinical practice.

A total of 87 studies were included. There were 5 randomized clinical trials; 11 narrative reviews; 9 systematic reviews and/or meta-analyses; 13 retrospective observational studies; 14 prospective observational studies; 10 guidelines, consensus statements, and recommendations; 24 cross-sectional studies (including mendelian randomization studies assessing causality of associations); and 1 case series.

Epidemiology and Risk Factors

Hypothyroidism is classified as primary (defined as inability to produce sufficient thyroid hormone or absence of the thyroid gland), central (defined as secondary due to an underactive pituitary gland or tertiary due to an underactive hypothalamus), or peripheral (extrathyroidal hypothyroidism caused by genetic variants affecting the hormone receptors or the hormone transport or affecting thyroid hormone metabolism). Primary and central hypothyroidism can be acquired or congenital.[8]

More than 99% of cases of hypothyroidism are classified as primary hypothyroidism. Hashimoto thyroiditis (an autoimmune disease) is the cause of primary hypothyroidism in up to 85% of patients with hypothyroidism living in areas with adequate nutritional iodine levels.[9] Other causes of primary hypothyroidism include iodine deficiency, thyroidectomy, thyroiditis (including subacute, postpartum, and silent thyroiditis), radiation therapy, and use of certain medications (**Table 1**). Secondary, tertiary, and peripheral hypothyroidism are rare and account for less than 1% of prevalent hypothyroidism cases.

The prevalence of primary hypothyroidism varies depending on the nutritional iodine levels in the region (ie, insufficient, adequate, or excess iodine intake). Iodine, a key nutrient for thyroid hormone synthesis, is a natural element in soil and seawater that can be supplemented in foods (eg, iodized salt). In populations with adequate nutritional iodine levels, such as the UK, the prevalence of spontaneous hypothyroidism (ie, primary hypothyroidism that is not iatrogenic, such as after thyroidectomy) is 1% to 2% of the general population.[4] The most recent US data (from 1988 to 2012) indicated a prevalence of overt hypothyroidism of 0.3%.[10] The prevalence of undiagnosed overt hypothyroidism in Europe is estimated at 0.65%.[5] In areas of Asia with inadequate nutritional iodine levels, overt hypothyroidism may affect up to 11% of the population.[11]

Primary hypothyroidism has a female:male ratio of approximately 5:1.[3] Autoimmune hypothyroidism may be present with other autoimmune diseases, such as type 1 diabetes (9.8%) and rheumatoid arthritis (5%-26.2%), reflecting an underlying immune dysregulation and shared genetic factors.[12-15] Prevalence of hypothyroidism is increased among patients with Down syndrome (31%-65%) and Turner syndrome (12.7%).[16-18] In individuals with a history of infertility or recurrent miscarriages, the prevalence of overt hypothyroidism is approximately 0.2% and the prevalence of subclinical hypothyroidism is 2.4%,[19] which is similar to the general population of women of childbearing age.[20] Hypothyroidism is more frequent in Asian and White individuals compared with Black individuals,[21,22] which may be due to environmental factors (eg, areas with inadequate nutritional iodine levels), genetic factors, or both (**Box**).[22-25]

Hypothyroidism can develop after thyroid surgery or radiation therapy. Approximately 25% to 34% of patients require treatment with levothyroxine after hemithyroidectomy, and up to 42% develop hypothyroidism over a span of 7 years after radiation therapy for head and neck cancer.[26,27] Drug-induced hypothyroidism is caused by medications such as amiodarone, lithium, and immune checkpoint inhibitors (**Figure 1**).[28,29]

Screening

In 2015, the US Preventive Services Task Force concluded there was insufficient evidence to recommend either screening or no screening for primary hypothyroidism in asymptomatic, nonpregnant adults.[30] However, the 2012 guideline[31] from the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists recommended screening based on serum thyrotropin level for certain high-risk groups, including individuals with autoimmune diseases (such as type 1 diabetes, primary adrenal insufficiency, pernicious anemia, and vitiligo), individuals with a history of thyroid disease in a first-degree relative, and individuals exposed to head and neck radiation. Based on the American Academy of Pediatrics guidelines, individuals with Down syndrome and Turner syndrome should undergo thyrotropin screening annually.[16,32-34] The 2020 guideline from the American College of

Table 1. Epidemiology and Causes of Hypothyroidism

Types of hypothyroidism	Pathophysiology	Prevalence, %[a]	Age of onset	Risk factors
Primary		0.3-2.0		
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	Immune-mediated destruction of thyroid cells		Typically 30-50 y	Age, genetic predisposition, environmental triggers (eg, smoking, stress), female sex
Congenital	Reduced thyroid hormone production		Birth	Thyroid agenesis, dysgenesis, or dysmorphogenesis (abnormal thyroid development)
Iatrogenic	Thyroid tissue destruction		Any age	Thyroidectomy, radioactive iodine, radiation
Iodine deficiency	Insufficient thyroid hormone production		Any age	Environmental, dietary
Iodine excess	Inhibition of iodide uptake		Any age	Environmental, dietary
Infiltrative disease (eg, sarcoidosis)	Thyroid tissue destruction		Any age	
Transient				
Postpartum, silent, or subacute thyroiditis	Thyroid gland inflammation (thyroiditis)		Childbearing age	Postpartum
Postprocedural	Iatrogenic		Any age	Inadequate radioactive iodine ablation for Graves disease, subtotal thyroidectomy
Medications			Any age	
Amiodarone or lithium	Inhibition of thyroid hormone synthesis, release, or both			
Interferon alfa or interleukin 2	Immune dysregulation			
Tyrosine kinase inhibitors	Destructive thyroiditis, increased type 3 deiodination			
Immune checkpoint inhibitors	Immune dysregulation by targeting proteins (eg, PD-1, PD-L1, CTLA-4)			
Secondary	Decreased thyrotropin production by the pituitary	<1	Any age	Pituitary disorders (eg, tumor, infiltrative disease, Sheehan syndrome), medications (eg, dopamine, somatostatin), congenital
Tertiary	Decreased thyrotropin-releasing hormone secretion from the hypothalamus	<1	Any age	Disorders damaging the hypothalamus or interfering with blood flow in the hypothalamic-pituitary portal
Peripheral	Aberrant expression of the deiodinase 3 enzyme in tumor tissues (consumptive)	<1	Any age	Genetic predisposition
	Tissue-specific hypothyroidism due to reduced sensitivity to thyroid hormone (resistance to thyroid hormone)			

[a] Prevalence is higher in populations with inadequate nutritional iodine levels. Recent epidemiological data were not available to report incidence.

Obstetricians and Gynecologists[35] does not recommend universal screening for thyroid disease in all pregnant individuals, but does recommend screening in pregnant individuals who have a personal or family history of thyroid disease, type 1 diabetes, or symptoms suggestive of thyroid disease.

Pathophysiology

The thyroid hormones (thyroxine and triiodothyronine [T_3]) regulate metabolism, growth, and development. Thyroxine and triiodothyronine are produced by the thyroid gland in a 14:1 ratio through the iodination of tyrosine residues on thyroglobulin, which is a process that requires iodine and the thyroid peroxidase enzyme.[36] Triiodothyronine and, to a lesser extent, thyroxine modulate gene expression by binding to nuclear receptors in nearly all organ systems and tissues, influencing processes such as energy production, heart rate, and protein synthesis.

More than 99.95% of thyroxine and more than 99.5% of triiodothyronine are transported in the bloodstream while bound to proteins such as thyroxine-binding globulin, transthyretin, albumin, and lipoproteins. Tissue availability is dependent on the free (ie, unbound) fraction of thyroid hormones.[37] Thyroxine, the main hormone produced and released by the thyroid gland, is converted to the active hormone triiodothyronine by deiodinase enzymes in a tissue-specific manner (ie, different types of deiodinase enzymes are expressed in different tissues and are involved in the peripheral conversion of thyroxine to triiodothyronine through deiodination).

Hashimoto thyroiditis is an autoimmune disease characterized by lymphocytic infiltration and autoimmune-mediated thyroid gland destruction, leading to apoptosis of thyroid epithelial cells.[30,36] Thyroid tissue B cells are activated, leading to the secretion of antithyroid antibodies such as antithyroid peroxidase and antithyroglobulin antibodies, which, coupled with T-cell–mediated and cytokine-mediated apoptosis, result in thyroid gland injury.[38]

Secondary hypothyroidism is due to reduced secretion of thyrotropin by the pituitary, which leads to decreased thyroid hormone production. Immune checkpoint inhibitors, especially combination therapy involving anti-PD-1, anti-PD-L1, and anti-CTLA-4 drugs, can cause hypophysitis (inflammation of the pituitary gland) that may result in panhypopituitarism.[39] In individuals with tertiary hypothyroidism, decreased secretion of thyrotropin-releasing hormone by

Box. Frequently Asked Questions About Hypothyroidism

What are the risk factors for primary hypothyroidism?
Female sex, genetic predisposition, presence of other autoimmune diseases, and environmental factors (such as iodine intake) are the main risk factors for autoimmune thyroid disease (Hashimoto thyroiditis), which is the most common cause of primary hypothyroidism in the US. Thyroid surgery, pregnancy, radiation therapy, and certain medications (such as amiodarone and immune checkpoint inhibitors) are also associated with an increased risk of primary hypothyroidism.

What is an appropriate initial treatment dose for patients with primary hypothyroidism and how should patients be monitored?
A levothyroxine dose of 1.6 µg/kg/d is considered the full thyroid hormone treatment dose for nonpregnant adults with primary hypothyroidism. However, to avoid overtreatment, lower doses (eg, 25-50 µg/d) are typically prescribed for older adults and patients with cardiovascular disease (eg, atrial fibrillation, coronary artery disease). Thyrotropin levels are typically checked 6 to 8 weeks after initiating therapy or after switching the dose or preparation and annually after the thyrotropin level has normalized. Serum thyrotropin level should also be checked after a change in weight of 4.5 kg or greater, if the patient is experiencing new symptoms of hypothyroidism, or if there is initiation of a medication such as amiodarone that may affect thyroid function.

When should patients with hypothyroidism be referred for consultation with an endocrinologist?
A consultation with an endocrinologist should be considered for patients with hypothyroidism if they (1) are pregnant or planning conception, (2) have a cardiovascular disease (eg, atrial fibrillation, coronary artery disease) or other endocrine disorders (eg, adrenal and pituitary disease, primary or secondary adrenal insufficiency), (3) have medication-induced hypothyroidism, (4) have a history of thyroid cancer, and (5) are being treated with levothyroxine but have difficulty maintaining a euthyroid state.

the hypothalamus reduces thyrotropin secretion. In peripheral hypothyroidism, thyroid hormone production is intact but tissue-specific hypothyroidism occurs due to genetic variants affecting the hormone receptors or the hormone transport, or due to alterations in thyroid hormone metabolism (consumptive hypothyroidism).

Clinical Presentation

Thyroid hormones affect numerous organ systems, including the cardiovascular, musculoskeletal, and nervous systems (**Table 2**). Patients with hypothyroidism may present with a variety of clinical symptoms and signs[7,40] that are often related to metabolic slowing due to insufficient thyroid hormone production (Table 2). Common symptoms include fatigue (74%-86%), weight gain (24%-59%), cold intolerance (35%-65%), bradycardia (12%-19%), constipation (33%-41%), and cognitive impairment (45%-48%), including memory loss and difficulty concentrating.[41,42] Patients aged 70 years or older may have fewer symptoms or signs and are less likely to exhibit some classic signs such as cold intolerance and weight gain compared with younger individuals (aged ≤55 years).[41]

The presence of symptoms is more indicative of overt hypothyroidism in men compared with women, with fatigue being the most common symptom.[43] Patients with hypothyroidism and preexisting comorbidities (such as cardiovascular disease) have reduced health-related quality of life.[44] In a prospective, population-based cohort study of 147 201 adults in the Netherlands, of the 4537 people receiving thyroid hormone therapy, 70% had a score below the age- and sex-specific cutoff values for the RAND 36-Item Short Form Health Survey (a quality-of-life measure) in the mental health domain of the general health dimension compared with 50% of people not receiving thyroid hormone therapy ($P < .001$).[44]

Hypothyroidism can exacerbate cardiovascular risk factors (such as dyslipidemia) by increasing cholesterol levels, particularly low-density lipoprotein cholesterol, and is associated with diastolic hypertension, increasing the likelihood of cardiovascular disease, particularly in patients with diabetes.[45,46] For patients with diabetes, untreated or undertreated hypothyroidism can decrease insulin sensitivity and impair glucose disposal (ie, movement of glucose from the bloodstream into cells for energy or storage), making glucose control difficult.[47]

In women, hypothyroidism can cause menstrual irregularities such as oligomenorrhea or menorrhagia (23%),[48] anovulation, and infertility. The guidelines[31] from 2012 recommend evaluation of serum thyrotropin level in all women being evaluated for infertility and among those with a history of miscarriage.

In men, hypothyroidism may cause low libido, erectile dysfunction, and reduced sperm motility and may contribute to male hypogonadism.[49] However, evidence is limited because most studies were performed before 1990 and included small sample sizes. A recent mendelian randomization study supports a causal association between hypothyroidism and decreased sex hormone–binding globulin and testosterone levels.[50]

Signs of severe hypothyroidism may include bradycardia, coarse and dry skin, delayed relaxation of tendon reflexes (particularly in the ankles), loss of lateral eyebrows, and goiter.

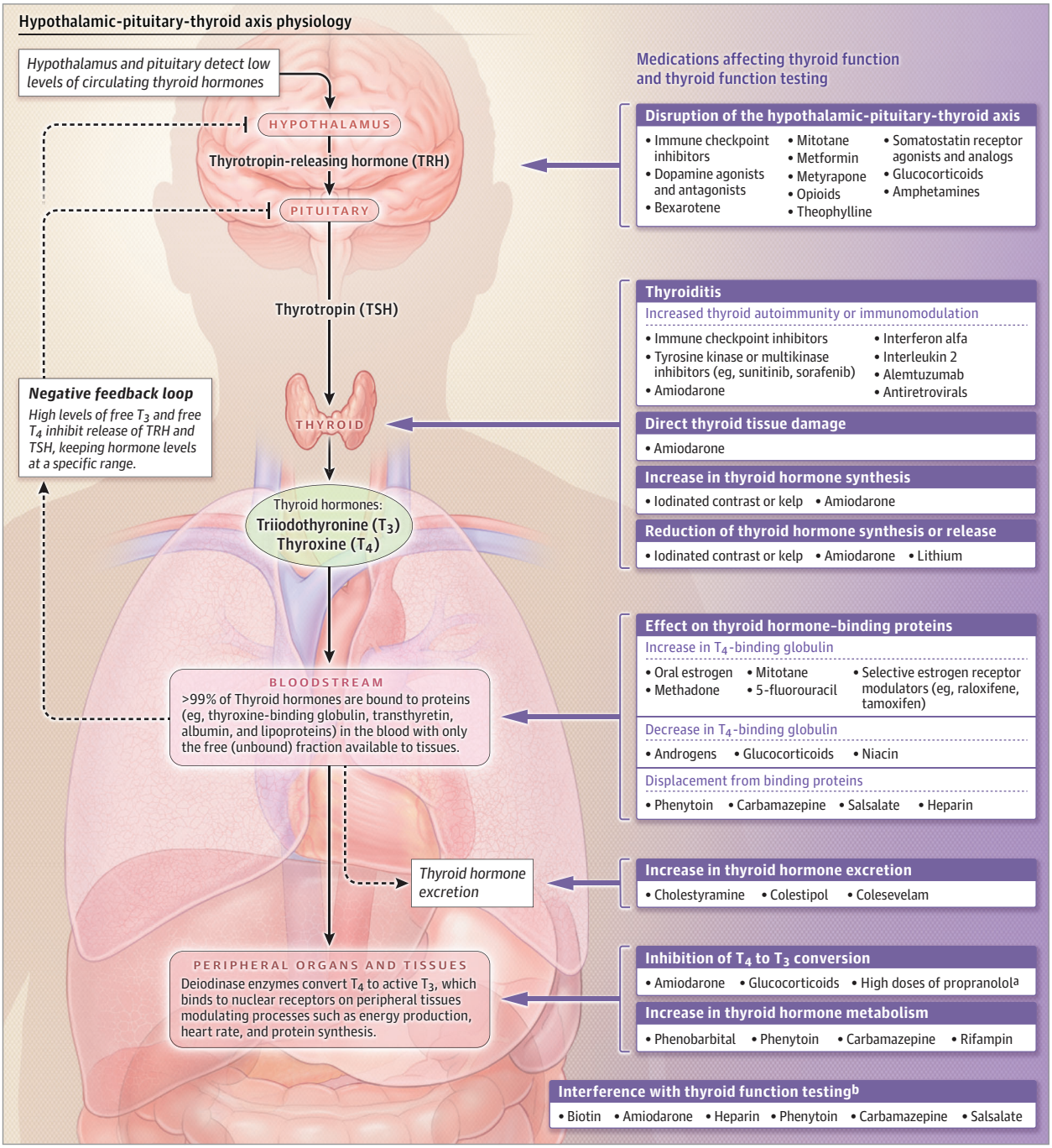
Myxedema Coma

If left untreated, severe hypothyroidism can progress to myxedema coma; the estimated incidence rate is 2.56 cases per 1 million US persons per year.[51] Myxedema coma is a life-threatening condition characterized by hypothermia, decreased mental status, hypoventilation, metabolic derangements (hyponatremia, hypoglycemia, lactic acidosis), bradycardia, decreased cardiac contractility, and hypotension. A study analyzing data from the US National Inpatient Sample between 2016 and 2018 reported that 13.4% of 18 635 patients hospitalized for hypothyroidism were diagnosed with myxedema coma, which was associated with a mortality rate of 6.8%.[51] However, an in-hospital mortality rate of up to 30% also has been reported; a difference in the estimates may depend on the definition of myxedema coma, the study design, and the geographic location.[52]

Assessment and Diagnosis

Hypothyroidism is diagnosed based on serum thyrotropin testing in patients (1) with symptoms such as fatigue, cold intolerance, or dry skin or (2) being evaluated for other conditions such as dyslipidemia,

Figure 1. Medications Affecting Thyroid Function or Interfering With Thyroid Function Testing



[a]A dose greater than 160 mg/d inhibits conversion of T_4 to active T_3 via deiodinase type 1 (dose-dependent action).

[b]Clinicians should be aware of medication interference and adjust the dose of levothyroxine accordingly to achieve a euthyroid status. Medications do not need to be held or discontinued. High doses of biotin (>5000 µg/d) can interfere with certain thyroid function tests that rely on the biotin × streptavidin interaction and may lead to inaccurate results.

heart failure, or infertility. The diagnosis is more likely among patients with a higher number of symptoms of hypothyroidism. In a US case-control study[53] that assessed 17 self-reported hypothyroid symptoms, 76 patients with overt hypothyroidism reported a higher mean percentage of positive hypothyroid symptom responses (30.2%) compared with 147 matched controls (16.5%; $P < .001$). A population-based, case-control study[54] reported the hypothyroidism symptom score, which was defined as the number of hypothyroidism-associated symptoms (score range, 0-13), had a good discriminative ability to identify hypothyroidism in younger patients (aged <60 years; area under the receiver operating characteristic curve [AUROC] of 0.91) but not in older patients (aged ≥60 years; AUROC of 0.64).

Table 2. Clinical Presentation of Hypothyroidism[a]

Description or organ system	Symptoms and signs (prevalence[b])	Consequences (prevalence[b])
Appearance	• Dry and coarse skin (55%-70%) • Puffy face • Loss of eyebrows • Hair loss (24%-36%) • Brittle nails	• Periorbital edema • Macroglossia • Generalized edema
Cardiovascular	• Shortness of breath on exertion (44%-59%) • Reduced exercise capacity • Bradycardia (12%-19%)	• Endothelial dysfunction • Diastolic hypertension • Hypotension • Dyslipidemia • Hyperhomocysteinemia • Pericardial effusion
Gastrointestinal	• Dyspepsia • Bloating • Constipation (33%-41%)	• Esophageal dysmotility • Delayed gastric emptying • Reduced gut motility • Bacterial overgrowth in small intestine • Metabolic dysfunction–associated steatotic liver disease • Ascites (rare)
General metabolic process	• Weight gain (24%-59%) • Fatigue and weakness (74%-86%) • Cold intolerance (35%-65%)	• Low metabolic rate • Higher body mass index • Hypothermia • Myxedema coma (<0.0001%)
Hematologic	• Fatigue • Paleness	• Hypocoagulable state • Increased risk of bleeding • Anemia
Musculoskeletal	• Muscle weakness and cramps • Joint pain • Delayed relaxation of tendon reflexes (75%)	• Myopathy (30%-80%)
Neurological or psychological	• Paresthesias • Cognitive impairment (45%-48%) (eg, slowed mentation, slowed speech, short-term memory impairment) • Depression	• Carpal tunnel syndrome • Peripheral neuropathy • Cognitive impairment • Encephalopathy (rare)
Neurosensory	• Hearing loss • Tinnitus • Voice hoarseness	• Conductive and sensorineural hearing impairment • Dysphonia
Reproductive	• Irregular menstrual cycles (23%) • Decreased libido • Galactorrhea • Erectile dysfunction	• Sexual dysfunction • Infertility • Hyperprolactinemia • Pituitary hyperplasia (rare)
Respiratory	• Shortness of breath on exertion (44%-59%) • Reduced exercise capacity	• Sleep apnea • Pleural effusions

[a] Clinical manifestations are highly variable depending on the age of onset and the duration and severity of hypothyroidism.

[b] Recent epidemiological data were not available to report incidence.

Diagnostic assessment for hypothyroidism is based on serum thyrotropin level, and, if abnormal, serum free thyroxine (free T_4) level (**Figure 2**). Serum thyrotropin is recommended as the initial diagnostic test because it is the most reliable indicator of thyroid status in outpatients without clinically suspected pituitary or hypothalamic disease who are not taking medications that affect thyrotropin secretion, such as glucocorticoids or lithium. Serum thyrotropin sensitivity is approximately 98% and specificity is 92% for identifying overt thyroid dysfunction.[30] Clinicians should suspect pituitary or hypothalamic disease in patients with hypothyroid symptoms and other signs of pituitary or hypothalamic dysfunction, such as adrenal insufficiency, low libido, or menstrual irregularities. If thyrotropin level is high, free thyroxine should be measured or repeat thyrotropin testing should be performed. There is no role for triiodothyronine testing in the diagnosis of hypothyroidism.

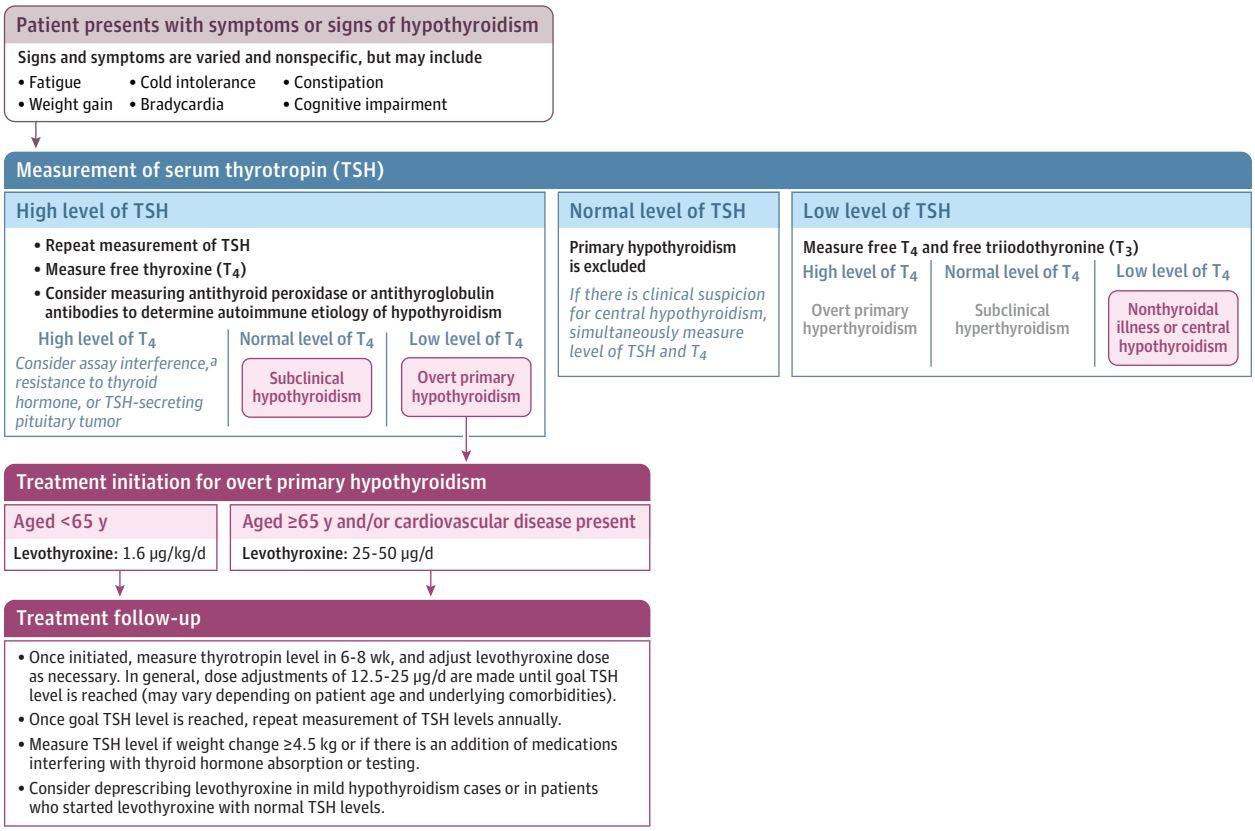
Measuring thyroid peroxidase or antithyroglobulin antibodies is not recommended for the diagnosis of primary hypothyroidism because the prevalence of thyroid antibody test positivity ranges from 5% to 20% in individuals without hypothyroidism.[55,56] For patients with hypothyroidism, use of ultrasonography in the absence of goiter or thyroid nodules is not recommended by endocrine societies.[57]

Treatment

The first-line thyroid hormone treatment for patients with hypothyroidism is synthetic levothyroxine.[1] Levothyroxine is administered orally and should be taken on an empty stomach 30 to 60 minutes before breakfast with water; taking levothyroxine in the evening at least 2 hours after eating food is also acceptable.[58] For patients who are fasting (eg, during Ramadan), levothyroxine can be taken at bedtime with a minimum 2-hour interval since the last meal.[59-61] Patients should be instructed to avoid taking levothyroxine within 4 hours of ingesting calcium or iron supplements or other medications that can interfere with absorption (such as proton pump inhibitors and phosphate binders).

The full adult thyroid hormone replacement dosage with levothyroxine is 1.6 µg/kg/d of actual body weight, but the initial dose should be individualized. Lower doses should be prescribed for older

Figure 2. Assessment of Hypothyroidism and the Therapeutic Approach to the Management of Hypothyroidism in Nonpregnant Adults



[a]Assay interference (eg, heterophile antibodies) could lead to inaccurate results, potentially resulting in misdiagnosis and inappropriate treatment (ie, the laboratory results do not align with the patient's clinical presentation). Thyroid function testing should be repeated with alternative assays that use different antibody types to help confirm or rule out interference.

patients and for those with specific comorbidities (Figure 2). Higher doses should be prescribed during pregnancy. Oral levothyroxine is available as a tablet, gel capsule, or liquid. The 2012 ATA guidelines[31] recommended an initial levothyroxine dose of 25 µg/d to 50 µg/d for patients with cardiovascular disease. Levothyroxine-treated women of childbearing age should be informed that dose requirements increase during pregnancy. For patients with hypothyroidism, the 2017 ATA pregnancy guidelines[62] recommend increasing the levothyroxine dose by 30% (1 extra pill twice per week) once the pregnancy is confirmed and then continue with the increased dose until delivery; serum thyrotropin level should be measured approximately every 4 weeks until midgestation and at least once near 30 weeks' gestation.

It is unclear if repeat thyrotropin testing should be performed after switching levothyroxine preparations. The 2014 ATA guidelines[1] for the treatment of hypothyroidism advised avoiding switches between levothyroxine products because of potential variations in the administered dose (weak recommendation based on low-quality evidence). A cohort study[63] of levothyroxine brand switching using 2 Dutch registries with 59 787 patients taking levothyroxine reported that in patients maintaining a euthyroid state, switching to a different brand at an equivalent dose led to biochemical signs of overreplacement (reflected as a thyrotropin level below the reference range) in up to 63% of cases. However, in 2 comparative effectiveness studies,[64,65] switching was not associated with clinically significant changes in thyrotropin level; one of the studies included a comparison of generic vs brand-name levothyroxine among 17 598 US adults and the other study included switching among different generic levothyroxine products in 15 829 US adults.

For primary hypothyroidism, regular thyrotropin monitoring after dose adjustments is important to ensure optimal treatment. Thyrotropin levels are typically checked 6 to 8 weeks after initiating therapy, or after switching the dose or preparation, and annually after the thyrotropin level has normalized. Serum thyrotropin level should also be checked after a change in weight of 4.5 kg or greater, if the patient is experiencing new symptoms of hypothyroidism, or if there is initiation of a medication such as amiodarone that may affect thyroid function. Treatment targets include normalization of thyrotropin, improvement in clinical manifestations of hypothyroidism, and avoidance of adverse events such as atrial fibrillation and heart failure due to over- or undertreatment.[1] For patients with central hypothyroidism, free thyroxine level should be checked to monitor the adequacy of the levothyroxine dose; the target level of free thyroxine should be in the upper half of the reference range.[31]

Overtreatment and Undertreatment

Overtreatment with levothyroxine, characterized by thyrotropin levels below the lower limit of the reference range (typically serum thyrotropin level <0.5 mIU/L), and undertreatment, characterized by thyrotropin levels above the upper limit of the reference range, may occur. A population-based retrospective study[66] reported that one-third of women with hypothyroidism (n = 6141) in Spain had a measured thyrotropin level higher than (ie, overtreated) or lower than the reference range (ie, undertreated) 1 year before pregnancy. Among patients with hypothyroidism taking levothyroxine, studies[67-70] have reported a cumulative incidence of low thyrotropin levels in 5% to 41% and high thyrotropin levels in approximately 5% to 21%, with varying incidence depending on the population, clinical setting, and criteria used to define abnormal thyrotropin levels. In a recent retrospective cohort study[71] that included 20 724 older primary care patients taking levothyroxine, 34% had thyrotropin levels below the reference range, which was more frequent in women than in men (36.7% vs 23.9%, respectively). In addition, 25% of patients had a thyrotropin level that was 10 mU/L or greater at least once, which was more common among men than women (23.8% vs 28.7%, respectively).[71]

Serum thyrotropin levels below or above the reference range while taking levothyroxine have been associated with increased risk of adverse cardiovascular events.[72-75] In a retrospective cohort study[75] including 705 307 US veterans who received thyroid hormone treatment, 10.8% died of cardiovascular causes over a median follow-up of 4 years. After adjusting for age, sex, traditional cardiovascular risk factors (including hypertension, smoking, and previous cardiovascular disease or arrhythmia), and when analyzing thyrotropin and free thyroxine levels as time-varying covariates, the patients with thyrotropin levels less than 0.1 mIU/L had an increased risk of cardiovascular mortality (adjusted hazard ratio [HR], 1.39 [95% CI, 1.32-1.47]) as did the patients with free thyroxine levels greater than 1.9 ng/dL (adjusted HR, 1.29 [95% CI, 1.20-1.40]) compared with patients maintaining a euthyroid state.[75] Patients with thyrotropin levels greater than 20 mIU/L (adjusted HR, 2.67 [95% CI, 2.55-2.80]) and free thyroxine levels less than 0.7 ng/dL (adjusted HR, 1.56 [95% CI, 1.50-1.63]) had an increased risk of cardiovascular mortality compared with patients maintaining a euthyroid state.[75]

In another retrospective cohort study[74] including 733 208 US veterans receiving thyroid hormone treatment, 11.1% developed atrial fibrillation and 6.3% had a stroke over a median follow-up of 59 months. Thyrotropin levels less than 0.1 mIU/L (adjusted odds ratio [OR], 1.33 [95% CI, 1.24-1.43]) and free thyroxine levels greater than 1.9 ng/dL (adjusted OR, 1.17 [95% CI, 1.06-1.30]) were associated with an increased incidence of stroke compared with levels in the euthyroid range, even after adjusting for several covariates including age, sex, smoking, and prior history of atrial fibrillation. In addition, thyrotropin levels greater than 5.5 mIU/L (adjusted OR, 1.29 [95% CI, 1.26-1.33]) and free thyroxine levels less than 0.7 ng/dL (adjusted OR, 1.29 [95% CI, 1.22-1.35]) were associated with increased incidence of stroke compared with levels in the euthyroid range.

In a population-based study,[73] patients receiving long-term thyroid hormone treatment with levothyroxine (N = 17 684) had an increased incidence of fractures when either overtreated (4.3% in overtreated patients vs 2.6% in patients in euthyroid range; adjusted OR, 2.02 [95% CI, 1.55-2.62]) or undertreated (3.8% in undertreated patients vs 2.6% in patients in the euthyroid range; adjusted OR, 1.83 [95% CI, 1.41-2.37]). Patients with thyrotoxicosis, including due to overtreatment with thyroid hormone therapy, had an increased incidence of cognitive disorders compared with those without thyrotoxicosis (11% v 6.4%, respectively) (N = 65 931; adjusted HR, 1.34 [95% CI, 1.10-1.63]).[76] Recent studies[68,77] have suggested that 18% to 30% of patients receiving thyroid hormone treatment with levothyroxine had normal thyrotropin concentrations prior to initiation of the medication; this practice can lead to overtreatment and patient harm.

Treatment of Myxedema Coma

The first-line therapy for myxedema coma is empiric glucocorticoids followed by administration of intravenous levothyroxine. Empiric glucocorticoids are given to treat possible concomitant adrenal insufficiency (100 mg of hydrocortisone administered intravenously every 8 hours initially, with subsequent tapering and discontinuation after adrenal insufficiency is ruled out).[1] Concomitant intravenous liothyronine (a synthetic form of triiodothyronine) may be given, if available, because thyroxine conversion to triiodothyronine may be decreased. Patients with myxedema coma should be closely monitored for arrhythmias and cardiac ischemia and receive supportive care and treatment of hypothermia, respiratory failure, and electrolyte imbalances. Early diagnosis and management of myxedema coma in an intensive care unit setting are important to improve survival. Clinical and biochemical improvements typically occur within 1 week with prompt intravenous administration of thyroid hormone treatment, and then patients can be switched to oral medications.

Practical Considerations

Patients taking levothyroxine may not achieve target thyrotropin levels due to several factors, including low initial levothyroxine dosing, dose adjustments not made based on thyrotropin levels, medication nonadherence, and not taking the medication consistently on an empty stomach, which can reduce its absorption.

Gastrointestinal conditions, such as celiac disease or *Helicobacter pylori* infection, can impair levothyroxine absorption, leading to higher than anticipated dose requirements. Liquid and softgel formulations are better absorbed and may be helpful in patients with diagnosed malabsorption.[78] A systematic review of 13 studies (5 randomized clinical trials, 7 prospective nonrandomized studies, and 1 cross-sectional study) that included 1697 patients reported that liquid and softgel levothyroxine formulations had the same amount of absorption (based on patients' serum thyrotropin levels) whether taken at breakfast, with other meals, or with other drugs.[79] Chronic kidney disease and cirrhosis can affect thyroid hormone metabolism and excretion, leading to lower levothyroxine dose requirements.[80,81]

Alternative thyroid hormone preparations to levothyroxine include liothyronine and desiccated thyroid extract, which is derived

from the thyroid glands of pigs and contains both thyroxine and triiodothyronine. Current guidelines[1,82] do not recommend routine use of desiccated thyroid extract or combination therapy with synthetic triiodothyronine and thyroxine. In view of conflicting evidence[83-85] regarding the use of vitamin D and selenium as adjunctive treatment for hypothyroidism, current guidelines[1,31] do not recommend vitamin D or selenium for the treatment of hypothyroidism.

Both iodine deficiency and excessive iodine intake can induce hypothyroidism, particularly in patients with underlying autoimmune thyroid disease. The World Health Organization and the ATA recommend an intake of 150 µg/d of iodine in adults and adolescents, with a higher intake of 250 µg/d during pregnancy and lactation. Recommended levels of iodine intake are generally obtained through diet in nonpregnant individuals living in areas with adequate nutritional iodine levels and also can be achieved by taking prenatal vitamins during pregnancy and lactation.[86]

Either discontinuation or dose reduction (deprescribing) of levothyroxine should be considered for patients maintaining a euthyroid state and who were started on the medication for nonspecific symptoms, and for those with low serum thyrotropin while taking levothyroxine. Low-quality evidence suggests that up to 11.8% of patients with a prior diagnosis of overt hypothyroidism continue to maintain a euthyroid state for up to a median follow-up of 60 months after discontinuation of levothyroxine.[87] Deprescribing involves gradually tapering the dose, typically by 25 µg every 6 to 8 weeks, while monitoring symptoms and testing thyroid function every 6 to 8 weeks.

An endocrinologist should be consulted for individuals with hypothyroidism who are pregnant or trying to conceive; patients with cardiovascular, pituitary, or adrenal disease; patients with medication-induced hypothyroidism; patients with a history of thyroid cancer; and patients with frequent fluctuations on their thyroid function test results (ie, for thyrotropin and free thyroxine) or when the test results are difficult to interpret (Box).

Limitations

This review has limitations. First, this was not a systematic review and some relevant articles were probably omitted. Second, a formal quality assessment of the literature was not conducted. Third, high-quality data are lacking for some treatment outcomes.

Conclusions

Hypothyroidism may be associated with fatigue, weight gain, memory loss, difficulty concentrating, cardiovascular disease such as heart failure, menstrual irregularities, infertility, and increased risk of miscarriage. Levothyroxine is the first-line treatment to normalize the thyrotropin level and improve clinical manifestations due to hypothyroidism.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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