INTRODUCTION AND EPIDEMIOLOGY

Hypothyroidism is a clinical syndrome caused by insufficient thyroid hormone production, which slows cell metabolism. The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the United States, and between 0.2% and 5.3% in Europe. The prevalence of hypothyroidism increases with age (>65 years) and is higher among white individuals and women. The disorder is nearly 10 times more common in females than in males. On the other hand, subclinical hypothyroidism is more prevalent than overt hypothyroidism in all age groups and can be seen in 4% to 15% of women, especially the elderly. Myxedema coma mortality rates with current treatments are between 30% and 60%.

PATHOPHYSIOLOGY

Thyroxine (T4) and triiodothyronine (T3) are the thyroid hormones. The ratio of thyroxine T4 to triiodothyronine T3 released in the blood is about 10:1. Peripherally, thyroxine T4 is converted to the active triiodothyronine T3, which is three to four times more potent than thyroxine T4. The half-life of thyroxine T4 is 7 days, and the half-life of triiodothyronine T3 is about 1 day.

Primary hypothyroidism is caused by the intrinsic dysfunction of the thyroid gland. The most common cause is Hashimoto's thyroiditis. Primary hypothyroidism is also caused by surgical removal or radioactive ablation and can be a result of some drug effects. Drugs such as lithium, α-interferon, interleukin, and tyrosine kinase inhibitors (e.g., sunitinib) can cause hypothyroidism. Amiodarone can cause hypothyroidism in up to 14% of patients.

Secondary hypothyroidism is caused by a deficiency of thyroid-stimulating hormone (TSH) from the pituitary gland or deficiency of thyrotropin-releasing hormone from the hypothalamus. Some literature specifically refers to hypothalamic causes as tertiary hypothyroidism. Nevertheless, both are central causes of hypothyroidism involving the hypothalamic-pituitary axis and shall be referred to as secondary hypothyroidism in this chapter.
**Euthyroid sick syndrome** is associated with low triiodothyronine $T_3$ or thyroxine $T_4$ levels and a normal or low TSH level in a patient who is clinically euthyroid. This condition is found in critically ill patients or those with severe systemic illness.

**Table 228-1** lists common causes of hypothyroidism.

<table>
<thead>
<tr>
<th>Common Causes Primary and Secondary of Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Hypothyroidism (disorders of thyroid gland)</strong></td>
</tr>
<tr>
<td>Autoimmune disease (e.g., Hashimoto’s thyroiditis)</td>
</tr>
<tr>
<td>Thyroiditis</td>
</tr>
<tr>
<td>Iodine deficiency</td>
</tr>
<tr>
<td>After ablation (surgery, radioiodine)</td>
</tr>
<tr>
<td>Infiltrative thyroid disease (lymphoma, sarcoid, tuberculosis)</td>
</tr>
<tr>
<td>Drugs directly affecting thyroid function</td>
</tr>
<tr>
<td>• Valproate</td>
</tr>
<tr>
<td>• Potassium perchlorate</td>
</tr>
<tr>
<td>• Iodine</td>
</tr>
<tr>
<td>• α-Interferon</td>
</tr>
<tr>
<td>• Interleukin-2</td>
</tr>
<tr>
<td>• Amiodarone</td>
</tr>
<tr>
<td>• Lithium</td>
</tr>
<tr>
<td>• <strong>Sunitinib</strong></td>
</tr>
<tr>
<td>• Antituberculosis drugs (ethionamide and para-aminosalicylic acid [PAS])</td>
</tr>
<tr>
<td>• Retroviral agents</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES OF HYPOTHYROIDISM**

The common clinical features of hypothyroidism are listed in Figure 228-1. Additional cardiopulmonary findings include angina, bradycardia, distant heart sounds from pericardial effusion, low voltage on the ECG, pleural effusions, cardiomyopathy, or hypoventilation. Figure 228-2 shows an example of severe pretibial myxedema. **Table 228-2** describes the clinical differences between primary and secondary hypothyroidism.
Signs and symptoms of hypothyroidism.

**Signs**
- Periorbital puffiness
- Loss of outer third of eyebrow
- Pallor
- Macroglossia
- Hoarseness
- Bradycardia
- Hypoventilation
- Absent or decreased bowel sounds
- Nonpitting edema
- Delayed relaxation of ankle jerks
- Peripheral neuropathy
- Cool, rough, dry skin
- Hypothermia

**Symptoms**
- Hair loss
- Fatigue
- Depression
- Shortness of breath
- Weight gain
- Constipation
- Menstrual irregularities
- Infertility
- Muscle cramps
- Joint pain
- Cold intolerance


FIGURE 228-2.

Mysedema (non-pitting edema) in a patient with hypothyroidism. (Image courtesy of Dr. Zanariah Hussein.)
**TABLE 228-2**  
Clinical Differentiation of Primary and Secondary Hypothyroidism

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Hypothyroidism</th>
<th>Secondary Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous thyroid operation</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Obese</td>
<td>More obese</td>
<td>Less obese</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Voice</td>
<td>Coarse</td>
<td>Less coarse</td>
</tr>
<tr>
<td>Pubic hair</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Skin</td>
<td>Dry and coarse</td>
<td>Fine and soft</td>
</tr>
<tr>
<td>Heart size</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Menses and lactation</td>
<td>Normal</td>
<td>No lactation, amenorrhea</td>
</tr>
<tr>
<td>Sella turcica size</td>
<td>Normal</td>
<td>May be increased</td>
</tr>
<tr>
<td>Serum TSH</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Plasma cortisol</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Response to TSH</td>
<td>None</td>
<td>Good</td>
</tr>
<tr>
<td>Response to levothyroxine without steroids</td>
<td>Good</td>
<td>Poor response</td>
</tr>
</tbody>
</table>

*Abbreviation: TSH = thyroid-stimulating hormone.*

**CLINICAL FEATURES OF MYXEDEMA CRISIS**

Myxedema crisis is a state of metabolic and multiorgan decompensation characterized by uncorrected hypothyroidism, mental status changes or coma, and hypothermia (usually <35.5°C [95.9°F]). In hypothyroid patients, myxedema crisis can be precipitated by a number of conditions, including infection, anesthetic agents, cold exposure, trauma, myocardial infarction or congestive heart failure, stroke, GI hemorrhage,
surgery, burns, medications (e.g., β-blockers, sedatives, narcotics, phenothiazine, amiodarone), or thyroid medication noncompliance.

The characteristic hypothyroid habitus is evident (Figure 228-1), as well as bradycardia, hypotension, hypothermia, hypoventilation, and altered mental status or coma. Blood pressure is quite variable, but of patients in full myxedema crisis, half initially exhibit clinical shock with systolic blood pressure <100 mm Hg. The capillaries are “leaky,” and this may contribute to hypotension. Infection may be present even though fever, tachycardia and sweating may not be evident, because bradycardia and hypothermia mask these signs. Altered mental status can result from CO₂ narcosis or hypoglycemia. Pleural effusions are frequently demonstrable. Other potential respiratory problems include upper airway obstruction from glottic edema, vocal cord edema, and macroglossia. Metabolism of tranquilizers, sedatives, and anesthetics is reduced in hypothyroidism, and the exaggerated effects of such medications can also contribute to altered mental status. Hypothermia is so common in myxedema crisis that a normal temperature should suggest an underlying infection. Hypothyroid habitus, absence of shivering, and pseudomyotonic reflexes (prolonged relaxation phase of deep tendon reflexes—at least twice as long as the contraction phase) may help distinguish myxedema crisis from accidental hypothermia.

**DIAGNOSIS**

The diagnosis of hypothyroidism is based on laboratory testing. The diagnosis of myxedema crisis is clinical. The differential diagnoses include sepsis, depression, adrenal crisis, congestive heart failure, hypoglycemia, stroke, hypothermia, drug overdose, and meningitis.

**LABORATORY EVALUATION AND IMAGING**

Obtain baseline levels of TSH, thyroxine T4, triiodothyronine T3, and cortisol before initiating treatment. This facilitates eventual diagnosis as well as response to treatment.

High TSH, with low total or free thyroxine T4 and triiodothyronine T3, confirm primary hypothyroidism. Low TSH with low total or free thyroxine T4 and triiodothyronine T3 points toward secondary hypothyroidism (hypothalamic–pituitary etiology). The assays of free thyroxine T4 and triiodothyronine T3 are preferable to total thyroxine T4 and triiodothyronine T3, as results are more accurate and not affected by protein binding.

Thyroid hormone levels may also be altered as a result of drug interactions (Table 228-1), but thyroid function usually normalizes after discontinuation of these drugs. Ideally, thyroid function tests should be obtained before initiating therapy with these agents and periodically thereafter.

Menorrhagia can be a sign of hypothyroidism, and if menorrhagia is severe, microcytic anemia due to iron loss can develop. Hyponatremia due to increased antidiuretic hormone and impaired free water clearance is common. Hypoglycemia may be present due to decreased gluconeogenesis, decreased insulin clearance, and concomitant adrenal insufficiency or growth hormone deficiency. Arterial blood gases typically show
hypoxemia, hypercapnia, metabolic acidosis from tissue hypoxia, and respiratory acidosis from hypoventilation due to muscle weakness.

Further laboratory assessment depends on the differential diagnosis, comorbidities, and search for precipitating factors. Obtain an ECG to identify myocardial infarction or heart block. Chest radiograph is needed to identify pneumonia, pleural effusion, or cardiomegaly. Bedside ultrasound can detect pericardial and pleural effusions.

**TREATMENT OF SYMPTOMATIC HYPOTHYROIDISM**

If a hypothyroid patient has symptoms of hypothyroidism and has been noncompliant with thyroid medication, or a newly diagnosed hypothyroid patient is confirmed by thyroid function tests done in the ED, oral levothyroxine may be started. The average starting dose for healthy adults younger than age 50 is 50 micrograms of oral levothyroxine once a day.\(^\text{14}\) For those older than 50 years or with cardiac disease, the initial dose is lower, 12.5 to 25 micrograms once a day. For all adults, the dose is adjusted by 12.5- to 25-microgram increments at 4- to 6-week intervals. Instruct the patient to follow up with the primary care physician or endocrinologist for monitoring and further dose adjustments in a month.

**TREATMENT OF MYXEDEMA CRISIS**

Myxedema crisis treatment consists of supportive care, thyroid hormone replacement (supplementing with thyroxine T\(_4\), triiodothyronine T\(_3\), or a combination of both), and identification and treatment of precipitating factors (Table 228-3).
### Supportive care

- Airway, breathing, and circulation: airway control, oxygen, IV access, and cardiac monitoring
- IV therapy: dextrose for hypoglycemia; water restriction for hyponatremia
- Vasopressors: if indicated (ineffective without thyroid hormone replacement)
- Hypothermia: treated with passive rewarming
- Steroids: hydrocortisone (due to increased metabolic stress; start with 100–200 milligrams IV)

### Thyroid replacement therapy

(see discussion of thyroid hormone replacement in text)

- IV thyroxine (levothyroxine) at 4 micrograms/kg (typically between 200 and 400 micrograms as initial dose), followed in 24 h by 100 micrograms IV, then 50 micrograms IV until oral medication is tolerated. **Starting dose of thyroxine in the elderly is 100 micrograms IV.**
  - OR

- IV triiodothyronine (liothyronine) at a dose of 20 micrograms IV followed by 10 micrograms IV every 8 h until the patient is conscious. **Start with no more than 10 micrograms IV for the elderly or those with coronary artery disease.** (Triiodothyronine is less preferred in patients with cardiac disease, as its potency could precipitate cardiac arrhythmias or infarction.)

  Note: Start with IV levothyroxine first. IV liothyronine can be added if treatment with IV levothyroxine alone is not effective or in patients with persistent hemodynamic instability or poor respiratory effort.

### Identify and treat precipitating and comorbid factors

- Infections
- Sedatives
- Cold exposure
- Trauma
- Myocardial infarction or congestive heart failure
- Cerebrovascular accident
- GI hemorrhage
- Hypoxia
- Hypercapnia
- Hyponatremia
- Hypoglycemia
Administer thyroid hormone upon clinical suspicion of myxedema crisis, as confirmatory laboratory thyroid hormone levels will not be available initially. IV thyroxine (T4) in the form of levothyroxine should be started as replacement. Alternatively, IV triiodothyronine (T3) in the form of liothyronine (synthetic triiodothyronine T3) can be given if it is available, but should be cautiously used in the elderly or those with cardiac disease as it is more potent. IV thyroxine T4 and IV triiodothyronine T3 can be given together if the patient has persistent hemodynamic instability or poor respiratory effort.

Thyroid hormone replacement should initially be given IV because severe or even mild hypothyroidism results in decreased intestinal motility and GI absorption. Once intestinal motility recovers, oral medication can be given.

**Replacement with Intravenous Thyroxine (Levothyroxine)**

Levothyroxine is the synthetic form of thyroxine. The initial dose for myxedema crisis is 4 micrograms/kg IV, with the usual starting dose from 200 to 400 micrograms IV.\(^\text{15}\) This is followed in 24 hours by 100 micrograms IV, then 50 micrograms IV until oral medication is tolerated. **Starting dose in the elderly is lower at 100 micrograms IV.** The advantages of levothyroxine are smooth, slow, and steady onset of action and its widespread availability. Disadvantages include the fact that extrathyroidal conversion of thyroxine T4 to triiodothyronine T3 may be reduced in myxedema crisis. The onset of action of thyroxine T4 is longer than that of triiodothyronine T3.

**Replacement with Intravenous Triiodothyronine (Liothyronine)**

Liothyronine is the synthetic form of triiodothyronine T3. In myxedema crisis, the loading dose of 20 micrograms can be given, followed by a maintenance dose of 10 micrograms every 8 hours until oral medication can be given.\(^\text{15}\) The advantage of triiodothyronine T3 over thyroxine T4 is that the deiodinase conversion of thyroxine T4 to the active hormone triiodothyronine T3 is reduced in myxedema crisis. IV triiodothyronine T3 also has a rapid onset of action, between 2 and 4 hours. triiodothyronine T3 crosses the blood–brain barrier more readily than thyroxine T4. However, the disadvantages of IV triiodothyronine T3 are its more potent effect and fluctuating serum levels and its potency, which can cause cardiac arrhythmias or myocardial ischemia, especially in the elderly or those with cardiac disease. If IV triiodothyronine T3 is given, provide continuous cardiac monitoring and obtain interval ECGs to identify myocardial ischemia.

**Supportive Management**

Supportive measures should be directed at treating hypothermia, hypoventilation, and hyponatremia, volume depletion, and hypoglycemia. For myxedema crisis, give a stress dose of hydrocortisone (100 to 200
milligrams IV) at the start of therapy. Obtain serum cortisol levels prior to initiation of therapy, but it is not necessary to wait for results. If sepsis is possible or likely, give empiric broad-spectrum antibiotics.\textsuperscript{15,16}

**DISPOSITION AND FOLLOW-UP**

Myxedema crisis carries a high mortality rate, ranging from 30\% to 60\% depending on comorbid diseases.\textsuperscript{6} Factors such as advanced age, bradycardia, and persistent hypotension suggest a poor prognosis. All patients with myxedema crisis require intensive care unit admission. Milder hypothyroidism patients may only be discharged with a clear plan of management with follow-up by either an endocrinologist or primary care physician.

**SPECIAL SITUATIONS**

**PREGNANT WOMEN**

Overt hypothyroidism is seen in about 1\% to 2\% of pregnant women.\textsuperscript{17} Subclinical hypothyroidism is seen in another 2.5\%.\textsuperscript{18}

Pregnancy increases the requirement of thyroid hormone because of the increased rate of metabolism in the mother and the transplacental transport of thyroid hormone, which is essential for the development and maturation of the different organs of the fetus. For women who are being treated for hypothyroidism, the dose of thyroxine $T_4$ should be increased by approximately 30\% as soon as the pregnancy is confirmed.\textsuperscript{19} The thyroid function should be checked every 8 weeks. Thyroid function test results during pregnancy may be difficult to interpret. This is because pregnant women may have a higher production of thyroid hormone from stimulation of the thyroid gland by human chorionic gonadotropin, which has a similar structure to that of TSH. In addition, increased estrogen during pregnancy results in higher levels of thyroid-binding globulin, which transports thyroid hormone in the blood. Therefore, a normal thyroid hormone level in a pregnant woman may not mean the patient is euthyroid, especially if the patient has symptoms of hypothyroidism. Thyroid hormone replacement may still be required in such a case.

Hypothyroidism is diagnosed in pregnancy if patients have symptoms and, in general, have high levels of TSH and low free thyroxine $T_4$. Subclinical hypothyroidism in pregnancy can be identified if the test results show high levels of TSH and normal free thyroxine $T_4$. Subclinical hypothyroidism should be treated to ensure a healthy pregnancy.

In myxedema crisis, IV levothyroxine is used for pregnant women. It is safe for the fetus.

**ELDERLY/CARDIAC PATIENTS**
Age and the presence of cardiac comorbidities are associated with a poor outcome in myxedema crisis. Standard doses of thyroxine $T_4$, and especially of triiodothyronine $T_3$, can precipitate cardiac arrhythmias. When required, start with no more than half the recommended dose of thyroxine $T_4$ or triiodothyronine $T_3$ for elderly patients.

**THE ASYMPTOMATIC PATIENT WITH A PALPABLE NODULE IDENTIFIED IN THE ED**

Solitary thyroid nodules are a common physical finding in the general population. Although most are benign colloid nodules that will disappear over time, a small percentage of solitary nodules are thyroid carcinomas. Refer for fine-needle aspiration biopsy.

**THYROXINE HORMONE OVERDOSE**

Levothyroxine is the most widely used agent for thyroid replacement. When taken in overdose, symptoms do not occur until 24 hours later as a result of metabolic conversion of thyroxine $T_4$ to triiodothyronine $T_3$. The symptoms may present earlier if triiodothyronine $T_3$ is ingested. Treatment is not standardized. For acute ingestion, activated charcoal can be given. Cholestyramine can increase fecal elimination, and propranolol can control tachycardia and anxiety.

**REFERENCES**


