status during treatment, and obtain a stat head CT if mental deterioration develops during treatment. While there are no evidence-based treatments for cerebral edema, mannitol as an osmotic agent remains the most practical option.

More common complications, such as hypoglycemia, hypokalemia, and pulmonary edema, are generally associated with overzealous resuscitation and inadequate monitoring.

DISPOSITION AND FOLLOW UP

When considering the patient population predisposed to developing HHS (debilitated patients with multiple comorbidities), intensive care unit monitoring for the initial 24 hours of care is usually the most appropriate ED disposition. Patients without significant comorbid conditions and who demonstrate a good response to initial therapy as evidenced by documented improvement in vital signs, urine output, electrolyte balance, and mentation may be considered for step-down admission.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 228

Hypothyroidism

Alzamani Mohammad Idrose

INTRODUCTION AND EPIDEMIOLOGY

Hypothyroidism is a clinical syndrome caused by insufficient thyroid hormone production, which slows cell metabolism. Hypothyroidism is common in areas where iodine deficiency is common, particularly inland areas where there is no access to marine foods. In iodine-sufficient areas, chronic autoimmune destruction of thyroid gland (e.g., Hashimoto's thyroiditis) and iatrogenic causes from treatment of Graves' disease are the leading causes of hypothyroidism (after thyroidectomy or radioactive iodine ablation). The prevalence of hypothyroidism increases with age, and the disorder is nearly 10 times more common in females than in males.[1] 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.[2,3]

Hypothyroidism occurs in 1% to 32% of patients taking amiodarone.[1]

PATHOPHYSIOLOGY

Primary hypothyroidism is caused by the intrinsic dysfunction of the thyroid gland, and this is the most common type. **Secondary hypothyroidism** is caused by a deficiency of thyroid-stimulating hormone from the pituitary gland or deficiency of thyrotropin-releasing hormone from the hypothalamus. **Table 228-1** lists common causes of hypothyroidism. **Euthyroid sick syndrome or low thyroxine syndrome**, also called nonthyroidal illness, is the term used for patients with low triiodothyronine and thyroxine levels and a normal or low thyroid-stimulating hormone level, but who are clinically euthyroid. This condition is found in critically ill patients or those with severe systemic illness.

Triiodothyronine is the major form of thyroid hormone. The ratio of triiodothyronine to thyroxine released in the blood is about 10:1. Peripherally, triiodothyronine is converted to the active **thyroxine**, which is three to four times more potent than triiodothyronine. The half-life of triiodothyronine is 7 days, and the half-life of thyroxine is about 1 day.

TABLE 228-1 Common Causes of Hypothyroidism

Primary Hypothyroidism (disorders of thyroid gland)	Secondary Hypothyroidism (disorders at hypothalamic-pituitary axis)
Autoimmune etiologies (Hashimoto's)	Panhypopituitarism
Thyroiditis (subacute, silent, postpartum)*	Pituitary adenoma
Iodine deficiency	Infiltrative causes (e.g., hemochromatosis, sarcoidosis)
After ablation (surgical, radioiodine)	
After external radiation	Tumors impinging on the hypothalamus
Infiltrative disease (lymphoma, sarcoid, amyloidosis, tuberculosis)	History of brain irradiation Infection (e.g., tuberculosis of the brain)
Other Causes	
Congenital	
Drugs affecting thyroid gland function	
Amiodarone	
Lithium	
Potassium perchlorate	
Iodine (in patients with preexisting autoimmune disease)	
α-Interferon	
Interleukin-2	
Idiopathic	

*Self-limiting etiologies, often preceded by hyperthyroid phase before getting into hypothyroid phase.

CLINICAL FEATURES OF HYPOTHYROIDISM

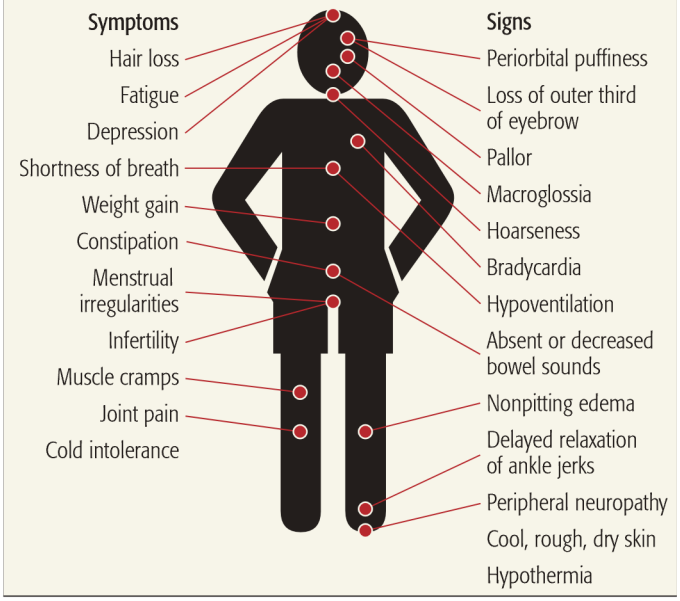
Symptoms can manifest in all organ systems and range in severity based on the degree of hormone deficiency (**Table 228-2**).

The common clinical features of hypothyroidism are listed in **Table 228-2**. Additional cardiopulmonary findings include angina, bradycardia, distant heart sounds from pericardial effusion, low voltage on the electrocardiogram, pleural effusions, cardiomyopathy, or hypoventilation.

Figures 228-1 and **228-2** show some characteristic findings of myxedema.

Table 228-3 describes the differences between primary and secondary hypothyroidism.

TABLE 228-2 Symptoms and Signs of Hypothyroidism



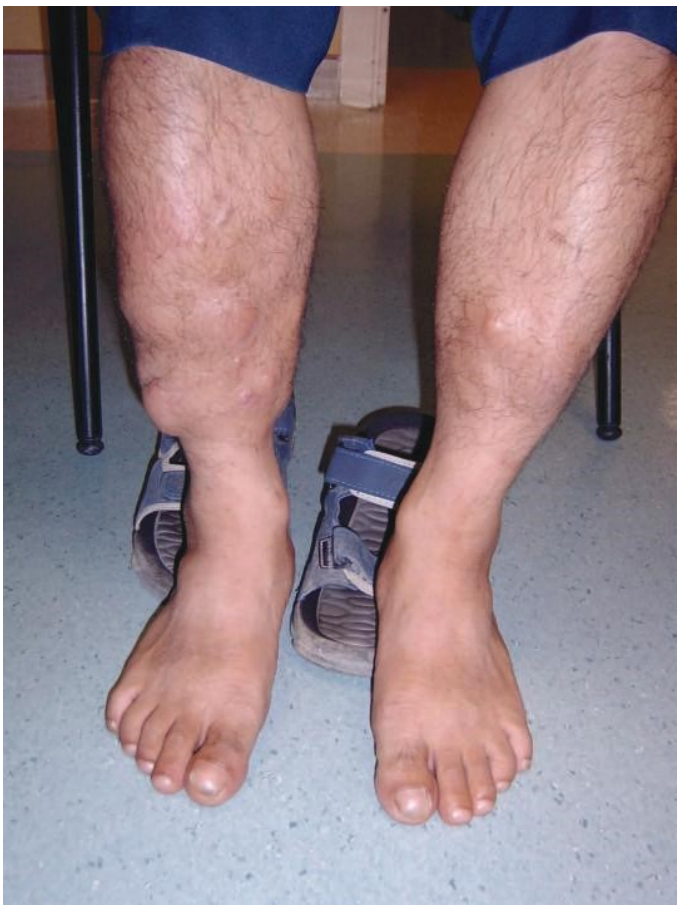


FIGURE 228-1. Myxedema (non-pitting edema) in a patient with hypothyroidism. [Image used with permission of Dr. Zanariah Hussein.]

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]).[1] In hypothyroid patients, myxedema coma can be precipitated by a number of conditions, including infection, anesthetic agents, cold exposure, trauma, myocardial infarction or congestive heart failure, cerebrovascular accident, GI hemorrhage, metabolic conditions, hypoxia, hypercapnia, hyponatremia, hypoglycemia, surgery, burns, medications (e.g., β-blockers, sedatives, narcotics, phenothiazine, amiodarone), or thyroid medication noncompliance.

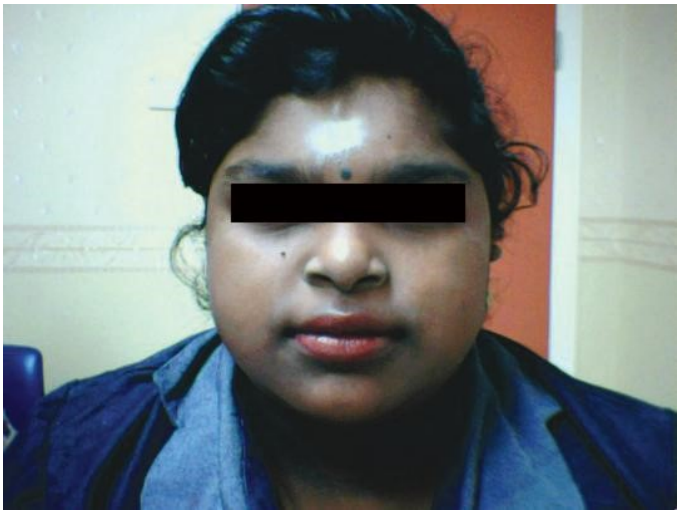


FIGURE 228-2. Hypothyroidism patient with facial swelling. [Image used with permission of Dr. Zanariah Hussein.]

TABLE 228-3 Differentiation of Primary and Secondary Hypothyroidism

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

Abbreviation: TSH = thyroid-stimulating hormone.

The characteristic hypothyroid habitus is evident, as well as bradycardia, hypotension, hypothermia, hypoventilation, and altered mental status or coma. Blood pressure is quite variable, but of patients in full myxedema coma, half initially exhibit clinical shock with systolic pressure <100 mm Hg.[4,5] The capillaries are "leaky," and this may contribute to hypotension. Infection may be present even though fever, tachycardia, sweating, and leukocytosis may not be evident, because bradycardia and hypothermia mask these signs. Respiratory insufficiency and altered mental status can result from carbon dioxide narcosis. 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 that a normal temperature should suggest an underlying infection.** Hypothyroid habitus, absence of shivering, and pseudomyotonic reflexes (prolonged relaxation phase of deep tendon reflex—at least twice as long as the contraction phase) may help distinguish myxedematous 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, cerebrovascular accidents, hypothermia, drug overdose, and meningitis.

LABORATORY EVALUATION AND IMAGING

The baseline levels of thyroid-stimulating hormone, thyroxine, triiodothyronine, and cortisol levels should be drawn before initiating treatment. This facilitates eventual diagnosis as well as response to treatment.

High thyroid-stimulating hormone, with low total or free thyroxine and triiodothyronine, confirms primary hypothyroidism (thyroid gland etiology). Low thyroid-stimulating hormone with low total or free thyroxine and triiodothyronine points toward secondary hypothyroidism (hypothalamic–pituitary etiology). The assay of free thyroxine and triiodothyronine is preferable, as the result is more accurate and is not affected by protein binding.

Thyroid hormone levels may also be altered as a result of interactions with drugs such as amiodarone, lithium, ethionamide, α-interferon, and interleukin-2. Nevertheless, 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.

Hypothyroidism may be associated with pernicious anemia, and thus macrocytic anemia may be evident. However, if menorrhagia after hypothyroidism is severe, anemia may be microcytic from iron deficiency. **Hyponatremia** due to increased antidiuretic hormone and impaired free water clearance is common. **Hypoglycemia** is common because of 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. Electrocardiogram is necessary to identify myocardial infarction or bradyarrhythmias or heart block. Chest radiograph is needed to identify pneumonia, pleural effusion, or cardiomegaly.

TREATMENT OF SYMPTOMATIC HYPOTHYROIDISM

If a patient has symptoms of hypothyroidism or has been noncompliant with thyroid medication, and hypothyroidism can be confirmed by thyroid function tests done in the ED, oral levothyroxine may be started. Full replacement dose for patients without cardiac disease is 1.6 micrograms/kg.[6] The average starting dose for healthy adults younger than 50 is 50 micrograms of oral levothyroxine once a day. 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 for monitoring and further dose adjustments in a month.

TREATMENT OF MYXEDEMA CRISIS

Management of myxedema crisis is shown in **Table 228-4**. **The treatment includes supportive care, thyroid hormone replacement (supplementing with thyroxine, triiodothyronine, or combination of both), and identification and treatment of precipitating factors.**

THYROID HORMONE REPLACEMENT FOR MYXEDEMA CRISIS

Administer thyroid hormone upon clinical suspicion of myxedema crisis, as confirmatory laboratory thyroid hormone levels will not be available initially. Thyroxine is the usual replacement. Triiodothyronine alone can be given if it is available, but should be avoided in the elderly or those with cardiac disease. Triiodothyronine and thyroxine together can be given if the patient has persistent hemodynamic instability or poor respiratory effort. Because myxedema crisis is such a rare condition, there are no clear recommendations for the use of thyroxine alone, combined thyroxine and triiodothyronine, or triiodothyronine alone.

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

Thyroxin (Levothyroxine) The dose is 4 micrograms/kg IV, with the usual dose from 200 micrograms to a maximum of 500 micrograms IV. The onset of action for IV thyroxine is between 6 and 8 hours. The advantages of thyroxine are a smooth, slow, and steady onset of action and its widespread availability. Disadvantages include the fact that extrathyroidal conversion of thyroxine to triiodothyronine may be reduced in myxedema coma. The onset of action of thyroxine is longer than that of triiodothyronine.

Triiodothyronine (Liothyronine) For triiodothyronine (liothyronine), start at 20 micrograms IV followed by 10 micrograms IV every 8 hours until oral medication can be given. The advantage of triiodothyronine over thyroxine is the fact that deiodinase conversion of thyroxine to the active hormone triiodothyronine is reduced in myxedema crisis. IV triiodothyronine also has a rapid onset of action, between 2 and 4 hours. In a primate study, triiodothyronine crossed the blood–brain barrier more readily than thyroxine.[7] However, the disadvantages of triiodothyronine are a more potent effect, fluctuating serum levels, and the fact that triiodothyronine is more likely to cause cardiac arrhythmias or myocardial infarction than thyroxine. Avoid replacement with triiodothyronine in patients with cardiac disease. If triiodothyronine is given, provide continuous cardiac monitoring and obtain interval electrocardiograms to identify myocardial ischemia.

TABLE 228-4 ED Treatment for Myxedema Crisis

Supportive care

Airway, breathing, and circulation support: ensure airway control, oxygen, IV access, and cardiac monitor

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; 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 500 micrograms as initial dose), followed in 24 h by 100 micrograms IV, then 50 micrograms IV until oral medication is tolerated. **Thyroxine is readily available. Thyroxine is preferred in the elderly and those with cardiac disease. Starting dose 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: *Either thyroxine or triiodothyronine alone can be used, but in patients with persistent hemodynamic instability or poor respiratory effort, both can be given simultaneously. When used together, the dose of thyroxine is 200 micrograms IV and triiodothyronine is 20 micrograms IV.*

↓

Identify and treat precipitating and comorbid factors

- Infections
- Sedatives
- Cold exposure
- Trauma
- Myocardial infarction or congestive heart failure
- Cerebrovascular accident
- Gastrointestinal hemorrhage
- Hypoxia
- Hypercapnia
- Hyponatremia
- Hypoglycemia

DISPOSITION AND FOLLOW-UP

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

SPECIAL POPULATIONS

PREGNANT WOMEN

Overt hypothyroidism is seen in about 1% to 2% of pregnant women.[8] Subclinical hypothyroidism is seen in another 2.5%.[9]

Most cases of hypothyroidism during pregnancy have the same cause as in hypothyroidism in general. 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 should be increased approximately by 30% as soon as the pregnancy is confirmed.[10]

Thyroid function test results during pregnancy may be difficult to interpret. This is because pregnant patients may have a higher production of thyroid hormone from stimulation of the gland by human chorionic gonadotropin, which has a similar structure to that of thyroid-stimulating hormone. On top of that, 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 this case.

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

Synthetic thyroxine, which is identical to the thyroxine made by the thyroid gland, is used for pregnant women. It is safe for the fetus. Pregnant women with existing hypothyroidism require an increased dose of thyroxine during pregnancy, and the thyroid function is usually checked every 8 weeks.

ELDERLY PATIENTS

Age, the presence of cardiac comorbidities, and a high dose of thyroxine are associated with a poor outcome in myxedema crisis.[10] Standard doses of thyroxine, and especially of triiodothyronine, can precipitate cardiac arrhythmias. Start with no more than half the recommended dose of thyroxine or triiodothyronine for elderly patients.

PATIENTS WITH CARDIAC DISEASE

Thyroxine has fewer cardiac effects than triiodothyronine. Thyroxine is the preferred choice for thyroid hormone replacement in patients with heart disease.

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. Biopsy results identify 70% of nodules to be benign, 5% to be malignant, and the remainder to be cytologically indeterminate.[11] Therefore, referral for fine-needle aspiration biopsy is indicated for all patients with palpable nodules.

LEVOTHYROXINE OVERDOSE

Synthetic levothyroxine is the most widely used agent for thyroid replacement. Deaths from overdose have not been reported. When taken in overdose, symptoms do not occur until 24 hours later as a result of metabolic conversion of thyroxine to triiodothyronine. Treatment is not standardized. For acute ingestion, activated charcoal can be given. Cholestyramine can decrease fecal elimination, and propranolol can control tachycardia and anxiety. Contact your local poison control center for specific treatment recommendations.

Acknowledgment: The author gratefully acknowledges the contributions of Horace K. Liang, the author of this chapter in the previous edition.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 229

Hyperthyroidism

Alzamani Mohammad Idrose

INTRODUCTION AND EPIDEMIOLOGY

Thyroid hormone affects all organ systems and is responsible for increasing metabolic rate, heart rate, and ventricle contractility, as well as muscle and central nervous system excitability. Two major types of thyroid hormones are thyroxine and triiodothyronine. Thyroxine is the major form of thyroid hormone. The ratio of thyroxine to triiodothyronine released in the blood is 20:1. Peripherally, thyroxine is converted to the active triiodothyronine, which is three to four times more potent than thyroxine.

Hyperthyroidism refers to excess circulating hormone resulting only from thyroid gland hyperfunction, whereas thyrotoxicosis refers to excess circulating thyroid hormone originating from any cause (including thyroid hormone overdose).

Thyroid storm is the extreme manifestation of thyrotoxicosis. This is an acute, severe, life-threatening hypermetabolic state of thyrotoxicosis caused either by excessive release of thyroid hormones causing adrenergic hyperactivity or altered peripheral response to thyroid hormone following the presence of one or more precipitants.

The mortality of thyroid storm without treatment is between 80% and 100%, and with treatment, it is between 15% and 50%.

Primary hyperthyroidism is caused by the excess production of thyroid hormones from the thyroid glands. Secondary hyperthyroidism is caused by the excess production of thyroid-releasing hormones or thyroid-stimulating hormones in the hypothalamus and pituitary, respectively (**Tables 229-1** and **229-2**).

In the case of thyroid storm, the most common underlying cause of hyperthyroidism is Graves' disease (85% of all hyperthyroidism cases in the United States). It is caused by the thyrotropin receptor antibodies that stimulate excess and uncontrolled thyroidal synthesis and secretion of thyroid hormones. It occurs most frequently in young women (10 times more common in women compared with men) at any age group.[1]

PATHOPHYSIOLOGY

The pathophysiologic mechanisms underlying the shift from uncomplicated thyrotoxicosis to thyroid storm are not entirely clear. However, they involve adrenergic hyperactivity either by increased release of thyroid hormones (with or without increased synthesis) or increased receptor sensitivity. Many of the signs and symptoms are related to adrenergic hyperactivity. Patients with thyroid storm reportedly have relatively higher levels of free thyroid hormones as opposed to those with uncomplicated thyrotoxicosis. The total thyroid hormone level may or may not be increased in these patients.

When there is excess of thyroid hormones, circulating thyroxin and triiodothyronine are taken into the cytoplasm of cells. Thyroxin is converted to its active form, triiodothyronine. Within the cytoplasm, the triiodothyronine then exerts its effect by passing into the nucleus and binding to thyroid hormone receptors or thyroid hormone–responsive elements to induce gene activation and transcription.[2] The receptors receiving the hormone will stimulate changes specific to the tissue.