Hypothyroidism: Management Across the Continuum

Case Study and Commentary, *Leo Tchong, MD, Colleen Veloski, MD, and Elias S. Siraj, MD*

Abstract

- *Objective:* To review the diagnosis and treatment of hypothyroidism.
- *Methods:* Review of the literature.
- *Results:* Hypothyroidism is a common endocrine disorder that occurs more commonly in women, the elderly, and those with autoimmune disorders. Symptoms are gradual in onset and include fatigue, cold intolerance, dry skin, and weight gain. Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of primary hypothyroidism; other causes include surgical removal or radioiodine ablation of the thyroid and drugs that cause a suppression of normal thyroid gland function. Commonly used medications can also cause a hypothyroid state. Treatment of hypothyroidism is thyroid hormone replacement with levothyroxine. If left untreated, hypothyroidism in its most severe form can lead to myxedema coma, an endocrine emergency associated with a high mortality rate.
- *Conclusion:* Physicians should have a low threshold for screening for hypothyroidism in patients with symptoms suggestive of the disease.

Hypothyroidism is a common endocrine disorder involving a deficiency in thyroid hormone function. It is more common in women, the elderly, and those with autoimmune disorders. Subclinical hypothyroidism is a condition in which the thyroid-stimulating hormone (TSH) level is elevated, but the free thyroxine (FT4) level remains within normal range. If adequately treated with thyroid hormone replacement, hypothyroidism is a benign disorder. If left untreated, however, hypothyroidism in its most severe form can lead to myxedema coma, an endocrine emergency associated with a high mortality rate. This article presents a clinical overview of hypothyroidism, focusing on clinical features, pertinent diagnostic testing, and management applications.

CASE STUDY

Initial Presentation

A 55-year-old woman presents to her primary care physician complaining of increased fatigue and a 10-lb weight gain over a period of 6 months. She is otherwise healthy and takes no medications. Laboratory testing reveals an elevated serum TSH level of 8.8 mIU/L (normal range, 0.40–4.50 mIU/L). Further laboratory testing reveals normal free FT4 and free triiodothyronine (T3) levels.

- **How is subclinical hypothyroidism diagnosed and treated?**

Subclinical Hypothyroidism

Subclinical hypothyroidism is a designation for patients who have an elevated TSH level in conjunction with normal levels of FT4 and free T3. The prevalence of subclinical hypothyroidism increases with age and is more common in women. It is a condition of mild thyroid failure, yet it is common for patients with subclinical hypothyroidism to be relatively asymptomatic. Subclinical hypothyroidism has been associated with higher total cholesterol and low-density lipoprotein (LDL) cholesterol levels compared with euthyroid subjects [1,2]. It has also been associated with an increased risk for congestive heart failure and atherosclerosis [3,4].

Since the evidence ascertaining the risks of subclinical hypothyroidism is limited primarily to cross-sectional and case-control studies, controversy exists as to whether screening and treatment is warranted. Nevertheless, general guidelines exist pertaining to the management of subclinical hypothyroidism (**Figure**). In general, patients with subclinical hypothyroidism are divided into those with a TSH level of 4.5 to 10 mIU/L and those with a TSH level greater than 10 mIU/L [5]. Treatment with levothyroxine should be considered when the TSH level is greater than 10 mIU/L [6,7]. Patients who meet this criterion tend to have a higher risk for their disease to progress to overt hypothyroidism. If the TSH level is less than 10 mIU/L, the risk of progression to overt hypothyroidism tends to be low, and patients with

From the Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism, Temple University School of Medicine, Philadelphia, PA.

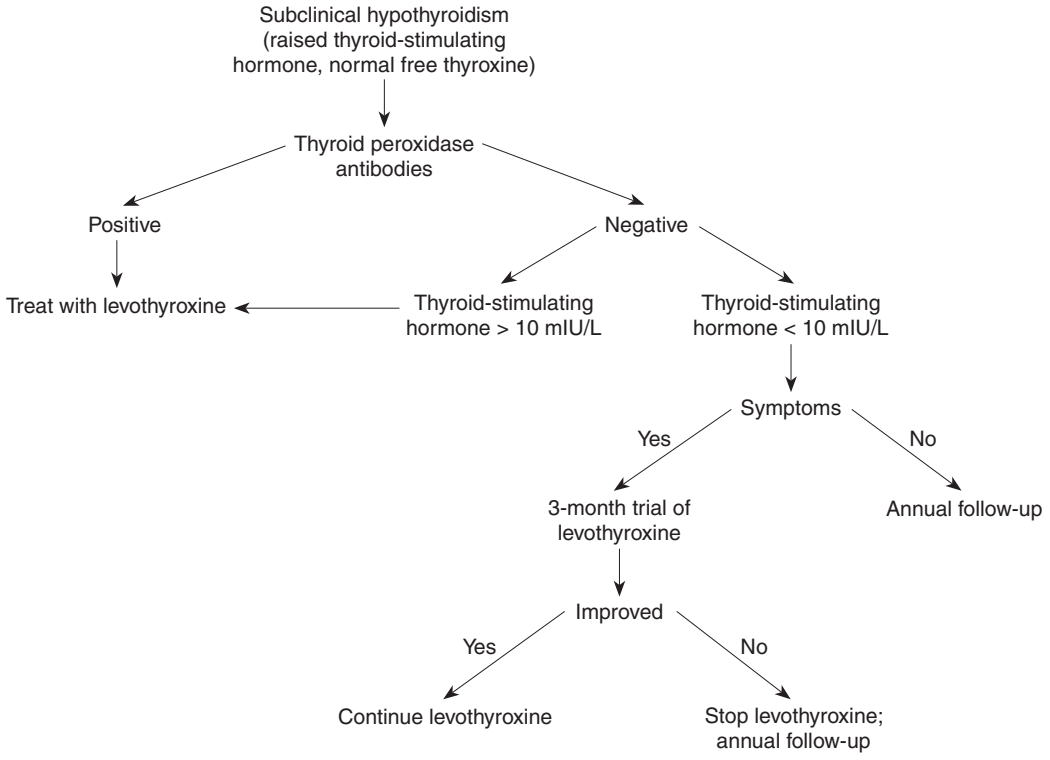

Figure. Algorithm for managing non-iatrogenic subclinical hypothyroidism. (Adapted with permission from Weetman AP. Fortnightly review: hypothyroidism: screening and subclinical disease. BMJ 1997;314:1175.)

such TSH levels can be observed and monitored as clinically indicated [8]. Despite these guidelines, the decision to medically treat versus clinically observe subclinical hypothyroidism should be considered on a patient-by-patient basis, taking into account the degree of symptoms and the coexistence of comorbidities in which levothyroxine treatment is relatively contraindicated.

- **Is there a role for checking thyroid peroxidase (TPO) antibodies in the evaluation of subclinical hypothyroidism?**

TPO is a protein expressed in the thyroid follicular cells that liberates iodine for addition to tyrosine residues on thyroglobulin for the production of T3 and T4. Antibodies to TPO are present in most patients with Hashimoto's thyroiditis. Typically, if TPO antibodies are positive in a patient with subclinical hypothyroidism, most recommendations suggest initiation of levothyroxine replacement therapy. In a patient with subclinical hypothyroidism and positive TPO antibodies, it can be safely presumed that overt hypothyroidism secondary to Hashimoto's thyroiditis will eventually manifest itself [9]. Such reasoning supports the notion that treatment with levothyroxine in this situation is warranted.

Case Continued

The primary care physician decides not to initiate levothyroxine therapy in the patient. After 5 years, the patient reports worsening fatigue, more weight gain, and dry skin. Thyroid function tests reveal an elevated TSH level of 20.1 mIU/L and a low FT4 level.

- **What are the causes of primary hypothyroidism?**

Primary Hypothyroidism

The most common causes of primary hypothyroidism are summarized in **Table 1**. Chronic autoimmune thyroiditis, also known as Hashimoto's thyroiditis, is the most common cause of primary hypothyroidism. It is characterized by chronic lymphocytic infiltration and destruction of the thyroid gland, mediated by the presence of TPO antibodies. TPO

Table 1. Causes of Hypothyroidism

Chronic autoimmune thyroiditis
Radioactive iodine therapy
Subtotal thyroidectomy
Antithyroid drugs
Head and neck surgery
Radiation therapy to the head, neck, or chest
Iodine deficiency
Medications: lithium, iodine, amiodarone
Secondary hypothyroidism (hypopituitarism)
Idiopathic
Congenital

Adapted with permission from Adlin V. Subclinical hypothyroidism: deciding when to treat. Am Fam Physician 1998;57:776–80.

antibody is present in greater than 90% of cases of chronic autoimmune thyroiditis and thus serves as an important marker for the disease [10]. Other causes of hypothyroidism include surgical removal or radioiodine ablation of the thyroid or drugs that cause a suppression of normal thyroid gland function. Numerous commonly used medications can cause a hypothyroid state (**Table 2**). Amiodarone is a medication with high iodine content that can cause hyper- or hypothyroidism in various patients.

- **What are the features of hypothyroidism?**

The onset of hypothyroid symptoms is gradual and cumulative. Symptoms include fatigue, cold intolerance, dry skin, and weight gain (**Table 3**). Such clinical and physical manifestations of hypothyroidism tend to be nonspecific and can often be overlooked and ignored. Due to the vague nature of individual signs and symptoms of hypothyroidism, clinicians should maintain a low threshold for screening in those patients with any signs suggestive of hypothyroidism.

- **How is hypothyroidism treated?**

The treatment for hypothyroidism is thyroid hormone replacement with levothyroxine. The average maintenance dose of levothyroxine is 1.6 μg/kg/day. For adults, this is equivalent to approximately 100 to 150 μg/day. Typically, the starting dose could be much less than the ultimate maintenance dose. The dose is then adjusted until a normal TSH level is achieved. In elderly patients or those with coronary artery disease or a history of cardiac arrhythmias, the initial dose should be 25 μg/day [11]. Levothyroxine dose adjustments should be based on TSH levels checked at 6- to 8- week intervals. Once a stable dose is achieved, the surveillance of serum TSH levels can be performed annually.

Table 2. Drugs that Cause Hypothyroidism in Patients Not Taking Levothyroxine

Amiodarone	Iodide
Aminoglutethimide	Lithium
Bexarotene	Sunitinib
Ethionamide	Sorafenib
Imatinib	Thalidomide
Interleukin-2	

- **Should hypothyroidism be routinely screened for?**

The question of routine or population screening for hypothyroidism is a controversial issue [6,12–13]. Some organizations favor routine screening [14], while others have found insufficient evidence to recommend routine screening [12,15]. In contrast, case finding, or using TSH testing in patients with clinical signs or symptoms that could be attributable to thyroid disease, is an appropriate management option, with aggressive case finding recommended for pregnant women, women older than 60 years, and others at high risk for thyroid dysfunction [6,15]. Overall, given the inconclusive nature of the evidence, it is left to the individual clinician to make a clinical judgement as to which approach to use.

Case Continued

The primary care physician prescribes levothyroxine 75 μg daily, and the patient is instructed to return in 2 months with a repeat TSH level. The patient is lost to follow-up, missing her doctor's appointments for the next 2 years. She is emergently transported to the local hospital emergency department via ambulance after a neighbor noticed her to be increasingly lethargic and confused. Vital signs include a temperature of 93.2°F, a heart rate of 53 bpm, and a blood pressure of 78/40 mm Hg. Physical examination reveals minimal responsiveness, dry skin, thin scalp hair, macroglossia, and significant periorbital edema. Laboratory evaluation reveals a serum sodium level of 125 mEq/L, an elevated TSH level of 211 mIU/L, and a very low FT4 level. The patient becomes increasingly obtunded and is intubated for airway protection. A transthoracic echocardiogram demonstrates a moderately sized pericardial effusion. The patient is admitted to the medical intensive care unit for ventilatory support and intravenous medications.

Table 3. Signs and Symptoms of Hypothyroidism

Bradycardia
Coarse hair, hair loss
Cold intolerance
Constipation
Muscle cramps
Delayed return phase of reflexes (eg, ankle, knee jerk)
Dry skin
Facial, eyelid edema
Lethargy, fatigue
Menorrhagia
Nonpitting lower extremity edema
Voice hoarseness
Weight gain

- **What are the common precipitating factors of myxedema coma?**

Myxedema Coma: An Endocrine Emergency

Myxedema coma is a serious form of untreated hypothyroidism that carries a high mortality rate, reported to be as high as 50% or more if diagnosed late [16]. Because of improved health care, myxedema coma has become a rare occurrence. Nevertheless, it is important to diagnose and treat myxedema coma quickly because of its high mortality rate. Myxedema coma is most commonly associated with the cessation of thyroid hormone therapy and may be precipitated by a concurrent illness such as cerebrovascular accident, myocardial infarction, or infection [17]. Other precipitating factors include acute trauma and narcotic overdose [17]. History from the patient may be inadequate, and further information from family members or previous medical records may reveal that the patient had previously received thyroid hormone treatment, or that the patient has had thyroid surgery or radioiodine treatment in the past.

- **What are the principal features of myxedema coma?**

The findings of myxedema coma are generalized and nonspecific. Physical findings include altered consciousness leading to a semicomatose or comatose state, dry skin, thinning hair, macroglossia, generalized edema, and slow reflex relaxation phase. It is a condition that can affect multiple organ systems such as pulmonary (hypoventilation leading to hypercapneic respiratory failure), cardiac (bradycardia, hypotension, reduced cardiac output, pericardial effusion), gastrointestinal (ileus), and renal (rhabdomyolysis and decreased renal perfusion due to water retention and increased vascular permeability) [18]. Hypothermia, which can be severe, can mask a fever due to infection [19]. Other features may include hypoglycemia, constipation, and urinary retention.

- **Which diagnostic tests should be performed in the evaluation of myxedema coma?**

The key laboratory tests are a TSH level, which is generally markedly elevated in myxedema coma, and a FT4 level, which is generally very low. The TSH level may not be as elevated as predicted due to concomitant sick euthyroid syndrome. One should consider central hypothyroidism if the FT4 level is low and the TSH level is low-normal. Electrolytes should be checked, as excessive volume retention can lead to hyponatremia [20]. Renal function should be assessed by measuring the creatinine level. Arterial blood gas, an electrocardiogram, and a chest radiograph should be performed to assess cardiopulmonary status. Before initiating treatment, if feasible, a baseline cortisol level or an adrenocorticotropic hormone (ACTH) stimulation test should be checked to evaluate for the possibility of adrenal insufficiency due to hypopituitarism or an associated autoimmune polyglandular failure.

- **How should myxedema coma be managed?**

Since myxedema coma is a severe illness, patients are usually admitted to the medical intensive care unit for ventilatory support and intravenous medications. Because most patients with myxedema coma have some degree of ileus, all medications should be given intravenously until the patient becomes medically stable. Most recommendations suggest using a loading dose of 200 to 400 μg of levothyroxine given intravenously and subsequently maintained on 50 to 100 μg of levothyroxine intravenously daily. Occasionally, a patient's clinical presentation may benefit from small doses of liothyronine (T3) in the amount of 10 μg intravenously every 8 hours for the first 48 hours [18]. Intravenous fluid administration may be needed for the underlying medical condition. Fluid overload should be avoided.

Water should be restricted if hyponatremia exists. Initially, glucocorticoids in the form of intravenous hydrocortisone 50 to 100 mg every 6 to 8 hours for the first 48 hours should be administered to prevent adrenal crisis in patients with possible adrenal insufficiency due to hypopituitarism

or autoimmune polyglandular syndrome. A baseline serum cortisol level greater than 30 µg/dL or a normal cosyntropin stimulation test suggests an adequate adrenal response to physiologic stress, and thus glucocorticoids are generally not necessary [18]. When a pericardial effusion is present, thyroid hormone replacement therapy generally resolves the effusion. If a patient's cardiopulmonary status is severely compromised, however, an emergent pericardiocentesis may be indicated.

Conclusion

Hypothyroidism is a very treatable endocrine disorder. Levothyroxine replacement therapy can be prescribed for most patients, and the dose can be titrated to attain a TSH level in the normal range. Since hypothyroidism is easily managed with thyroid hormone replacement therapy, physicians should have a low threshold for screening patients with symptoms suggestive of hypothyroidism. Screening guidelines are not concrete and are a subject of debate among practicing physicians. More research is required to help determine the utility of routine screening for hypothyroidism.

Corresponding author: Elias S. Siraj, MD, Temple Univ. Hospital, 3322 N. Broad St., Philadelphia, PA 19140.

Financial disclosures: None.

Author contributions: conception and design, LT, ESS; analysis and interpretation of data, LT; drafting of article, LT, ESS; critical revision of the article, LT, CV, ESS; administrative or technical support, ESS; collection and assembly of data, LT.

References

1. Bauer DC, Ettinger B, Browner WS. Thyroid functions and serum lipids in older women: a population-based study. Am J Med 1998;104:546–51.
2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160: 526–34.
3. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 2005;165:2460–6.
4. Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000;132:270–8.
5. Woolever DR, Beutler AI. Hypothyroidism: a review of the evaluation and management. Fam Pract Recert 2007;29:45–52.
6. Gharib H, Tuttle RM, Baskin HJ, et al. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol 2005;90:581–5.
7. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and managment. JAMA 2004;291:228–38.
8. Weetman AP. Hypothyroidism: screening and subclinical disease. BMJ 1997;314:1175–8.
9. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43: 55–68.
10. Laurberg P, Pedersen KM, Vittinghus E, Ekelund S. Sensitive enzyme-linked immunosorbent assay for measurement of autoantibodies to human thyroid peroxidase. Scand J Clin Lab Invest 1992;52:663–9.
11. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hypothyroidism. Standards of Care Committee. American Thyroid Association. JAMA 1995;273:808–12.
12. U.S. Preventive Services Task Force. Screening for thyroid disease: recommendation statement. Ann Intern Med 2004;140: 125–7.
13. McDermott MT. Serum TSH testing is necessary for primary hypothyroidism case finding. J Postgrad Med 2004;50:11.
14. Ladenson PW, Singer PA, Ain KB, et al. America Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160:1573–5.
15. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.
16. Greco LK. Hypothyroid emergencies. Endocrine emergencies. Top Emerg Med 2001;23:44–50.
17. Ringel MD. Management of hypothyroidism and hyperthyroidism in the intensive care unit. Crit Care Clin 2001;17:59–74.
18. Gardner GG. Endocrine emergencies. In: Gardner GG, Shoback D, editors. Greenspan's basic and clinical endocrinology. 8th ed. New York: McGraw-Hill 2007:869–70.
19. Devdhar M, Ousman YH, Burman KD. Hypothyroidism. Endocrinol Metab Clin North Am 2007;36:595–615.
20. Guha B, Krishnaswamy G, Peiris A. The diagnosis and management of hypothyroidism. South Med J 2002;95:475–80.