Review Article

Hypothyroidism - A New View On An Old Disease

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Abstract

Hypothyroidism is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. Underactivity of thyroid is usually primary, from disease of thyroid, but may be secondary to hypothalamic-pituitary disease (reduced TSH drive). Untreated hypothyroidism can cause a number of health problems, such as obesity, hypertension, dyslipidaemia, infertility. The prevalence increases with age, and is higher in females than in males. Autoimmune thyroid disease is the most common aetiology of hypothyroidism. Clinical symptoms of hypothyroidism are nonspecific and may be subtle, especially in older persons. TSH and FT_4 measurement are the laboratory examinations necessary for the diagnosis of hypothyroidism as well as the differential diagnosis between primary (clinical or subclinical) and secondary one. In the majority of patients, alleviation of symptoms can be accomplished through oral administration of synthetic levothyroxine, and most patients will require lifelong therapy.

Introduction

Hypothyroidism is defined as failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body. Untreated hypothyroidism can contribute to obesity, hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction. The prevalence increases with age, and is higher in females than in males[1].

Hypothyroidism may occur as a result of primary thyroid gland failure (primary hypothyroidism) or insufficient thyroid gland stimulation by the hypothalamus or pituitary gland (secondary hypothyroidism). Primary gland failure can result from congenital abnormalities, autoimmune destruction (Hashimoto disease), iodine deficiency, and infiltrative diseases. Autoimmune thyroid disease is the most common aetiology of hypothyroidism[2]. Iatrogenic forms of hypothyroidism occur after thyroid surgery, radioiodine therapy, and neck irradiation[3]. Disorders generally associated with transient hypothyroidism include postpartum thyroiditis, subacute thyroiditis, silent thyroiditis, and thyroiditis associated with thyroid-stimulating hormone (TSH) receptor-blocking antibodies[3].

Central causes of hypothyroidism typically present with other manifestations of hypothalamic or pituitary

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dysfunction, and are characterized by inappropriately normal or low levels of TSH relative to insufficient thyroid hormone. Drugs classically associated with thyroid dysfunction include lithium, amiodarone, interferon alfa, interleukin-2, and tyrosine kinase inhibitors[4,5].

Clinical presentation

The clinical presentation depends on duration and severity of hypothyroidism. Symptoms commonly associated with hypothyroidism are often nonspecific (Table I). These include weight gain, fatigue, poor concentration, depression, diffuse muscle pain, and menstrual irregularities. Symptoms with high specificity for hypothyroidism include constipation, cold intolerance, dry skin, proximal muscle weakness, and hair thinning or loss[6].

Table I: Common symptoms of hypothyroidism

Arthralgias
Cold intolerance
Constipation
Depression
Difficulty concentrating
Menorrhagia
Myalgias
Weakness
Weight gain
Dry skin
Fatigue
Hair thinning/hair loss
Memory impairment

Symptoms of hypothyroidism may vary with age and sex. In older patients, cognitive decline may be the sole manifestation. Women who have hypothyroidism may present with menstrual irregularities and infertility. Examination findings associated with hypothyroidism include but are not limited to goitre, delayed relaxation phase of deep tendon reflexes, thin or brittle hair, dry skin, and peripheral oedema (Table II). Common electrocardiography findings include bradycardia, flattened T waves, and low voltage. Patients with severe hypothyroidism may present with pericardial effusion, pleural effusion, megacolon, haemodynamic instability, and coma. The clinical presentation is often confused with septic shock. Laboratory findings in hypothyroidism may include hyponatraemia, hypercapnia, hypoxia, normocytic anaemia, elevated creatine kinase, hyperprolactinaemia, and hyperlipidaemia[7].

Table II: Clinical signs of hypothyroidism with non-specific laboratory abnormalities

Bradycardia
Coarse facies
Cognitive impairment
Delayed relaxation phase of deep tendon reflexes
Diastolic hypertension
Oedema
Goitre
Hypothermia
Lateral eyebrow thinning
Macroglossia
Periorbital oedema
Pleural and pericardial effusion
Low-voltage electrocardiography
Laboratory results
• Elevated C-reactive protein
• Hyperprolactinaemia
• Hyponatraemia
• Increased creatine kinase
• Increased low-density lipoprotein cholesterol
• Increased triglycerides
• Normocytic anaemia
• Proteinuria

Screening and diagnosis

Physicians should evaluate for thyroid dysfunction in all patients with symptoms of hypothyroidism. Screening of asymptomatic patients may be considered in those with risk factors for hypothyroidism, such as a history of autoimmune disease, history of head or neck irradiation, previous radioactive iodine therapy, presence of a goitre, family history of thyroid disease, or treatment with drugs known to influence thyroid function.The best laboratory assessment of thyroid function, and the preferred test for diagnosing primary hypothyroidism, is a serum TSH test[8]. If the serum TSH level is elevated, testing should be repeated with a serum free thyroxine (T_4) measurement (Figure 1[9-11]). Measurements of serum T_3 are unhelpful since they do not discriminate reliably between euthyroidism and hypothyroidism[12]. Overt primary hypothyroidism is indicated with an elevated serum TSH level and a low serum free T_4 level. An elevated serum TSH level with a normal range serum free T_4 level is consistent with subclinical hypothyroidism.

A low serum free T_4 level with a low, or inappropriately normal, serum TSH level is consistent with secondary hypothyroidism and will usually be associated with further evidence of hypothalamic-pituitary insufficiency.

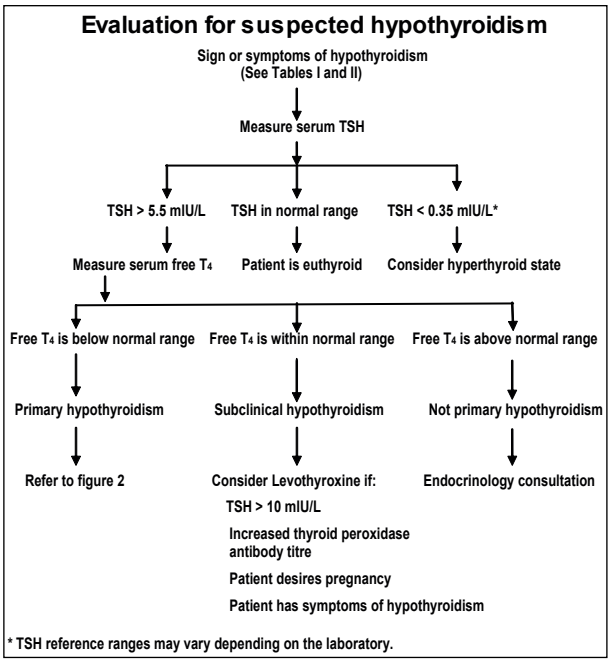

Figure 1: Algorithm for evaluating suspected hypothyroidism

Management

Most patients with hypothyroidism will require lifelong thyroid hormone therapy (Figure 2[9,13-18]). The normal thyroid gland makes two thyroid hormones: thyroxine (T_4) and triiodothyronine (T_3). Although T_4 is produced in greater amounts, T_3 is the biologically active form. Approximately 80% of T_3 is derived from the peripheral conversion of T_4 by deiodinase enzymes. However, because T_3 preparations have short biologic half-lives, hypothyroidism is treated almost exclusively with synthetic thyroxine preparations. Once absorbed, synthetic thyroxine, like endogenous thyroxine, undergoes deiodination to the more biologically active T_3.

The starting dosage of levothyroxine in young, healthy adults for complete replacement is 1.6 µg/kg/day. (Table III [13-15,19]). Thyroid hormone is generally taken in the morning, 30 minutes before eating. Calcium and iron supplements should not be taken within four hours of taking levothyroxine, because these supplements may decrease thyroid hormone absorption. Poor adherence to levothyroxine therapy is the most common cause of persistently elevated TSH levels in patients on adequate doses of thyroid hormone. Levothyroxine has a half-life of 7 days so it should always be taken as a single daily dose and at least 6 weeks should pass before repeating thyroid function tests and adjusting the dose, usually by 25 µg per day. Patients feel better within 2-3 weeks. Reduction in weight and periorbital puffiness occurs quickly, but the restoration of skin and hair texture and resolution of any effusions may take 3-6 months[12]. The dose of levothyroxine should be adjusted to maintain serum TSH within the reference range. To achieve this, serum T_4 often needs to be in the upper part of the reference range or even slightly raised, because the T_3 required for receptor activation is derived exclusively from conversion of T_4 within the target tissues, without the usual contribution from thyroid secretion[12]. Patients who have difficulty with morning levothyroxine dosing may find bedtime dosing an effective alternative. In a well-designed study conducted in the Netherlands, bedtime dosing of levothyroxine resulted in lower TSH and higher free T_4 levels, but no difference in quality of life[20]. Alternatively, patients with marked difficulty in adhering to a once-daily levothyroxine regimen can safely take their entire week's dosage of levothyroxine once weekly[21]. It is important to measure thyroid function every 1-2 years once the dose of levothyroxine is stabilised[12].

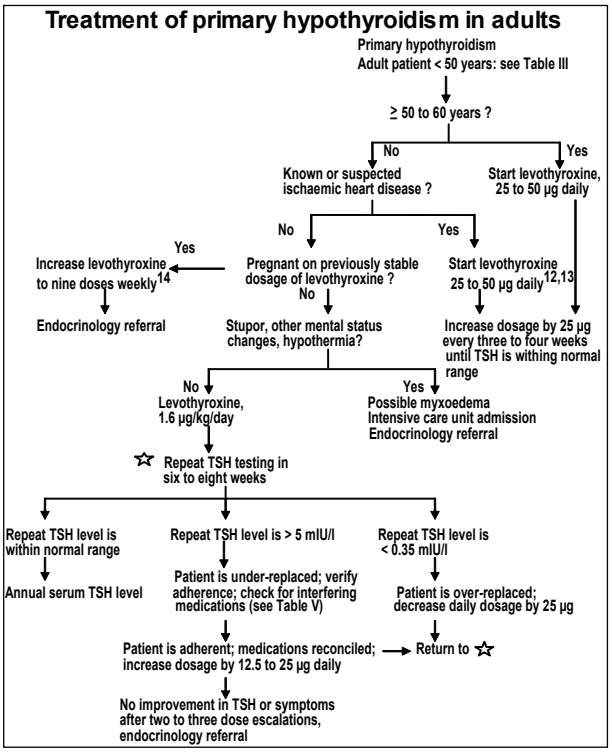

Figure 2: Algorithm for the treatment of primary hypothyroidism

Special populations

Six populations deserve special consideration:

1. Older patients;
2. Patients with known or suspected ischaemic heart disease;
3. Pregnant women;
4. Patients with persistent symptoms of hypothyroidism despite taking adequate doses of levothyroxine;
5. Patients with subclinical hypothyroidism; and
6. Patients suspected of having myxoedema coma.

Table III: Levothyroxine dosing guidelines for hypothyroidism in adults

Population	Dosing
Nonpregnant patients	1.6 µg/kg/day initial dosage[19]
Older patients; patients with known or suspected cardiac disease	25 or 50 µg daily starting dosage; increase by 25 µg every three to four weeks until full replacement dosage reached[13,14]
Pregnant patients	Increase to nine doses weekly (one extra dose on two days of the week) at earliest knowledge of pregnancy; refer to endocrinologist[15]
Patient with subclinical Hypothyroidism	TSH < 10 mIU/l: 50 µg daily, increase by 25 µg daily every six weeks until TSH = 0.35 to 5.5 mIU/l TSH 10 mIU/l: 1.6 µg/kg/day[19]

Older patients and patients with ischaemic heart disease

In older patients and in patients with coronary artery disease, the initial dosage is generally 25 µg or 50 µg daily, with the dosage increased by 25 µg every three to four weeks until the estimated full replacement dose is reached[13,14]. Thyroid hormone increases heart rate and contractility, and therefore increases myocardial oxygen demand[16]. Consequently, starting at higher doses may precipitate acute coronary syndrome or an arrhythmia. However, there are no high quality studies that show that lower starting doses and slow titration result in fewer adverse effects than full-dose levothyroxine replacement in older patients and patients with ischaemic heart disease[17].

Pregnancy

Thyroid hormone requirements increase during pregnancy. In one prospective study, 85% of pregnant patients required a median increase of 47% in their thyroid hormone requirements[15]. These increases in levothyroxine dosing were required as early as the fifth week of pregnancy in some patients, which is before the first scheduled prenatal care visit. It is recommended that women on fixed doses of levothyroxine take nine doses each week (one extra dose on two days of the week), instead of the usual seven, as soon as pregnancy is confirmed[15]. Repeat thyroid function tests should be obtained five weeks after the increase in dosage. The increase in thyroid hormone requirement lasts throughout pregnancy.

Patients with persistent symptoms

A small number of patients with hypothyroidism, mostly women, treated with an adequate dose of levothyroxine will report persistent symptoms such as fatigue, depressed mood, and weight gain despite having a TSH level in the lower half of the normal range. Some patients may have an alternative cause for their symptoms; in these patients, a limited laboratory and clinical investigation is reasonable (Table IV). Combination T_3/T_4 therapy, in the form of desiccated thyroid hormone preparations or levothyroxine plus liothyronine, is sometimes prescribed for patients with persistent symptoms of hypothyroidism.

Table IV: Alternative causes of persistent symptoms in patients with normal-range thyroid-stimulating hormone levels

- Adrenal insufficiency (rare)
- Anaemia
  - --B12 deficiency
  - --Iron deficiency
- Chronic kidney disease
- Depression, anxiety disorder, and/or somatoform disorders
- Liver disease
- Obstructive sleep apnoea
- Viral infection (e.g. mononucleosis, Lyme disease, human immunodeficiency virus/AIDS)
- Vitamin D deficiency

Desiccated thyroid hormone preparations are not recommended by the American Association of Clinical Endocrinologists for the treatment of hypothyroidism, and a meta-analysis of 11 randomised controlled trials of combination T_3/T_4 therapy versus T_4 monotherapy showed no improvements in bodily pain, depression, or quality of life[22]. A subsequent study showed that a small subset of patients who have a specific type 2 deiodinase polymorphism may benefit from combination therapy[23]. However, there is insufficient evidence to recommend the use of combination T_3/T_4 therapy in the treatment of primary hypothyroidism. Numerous medications can affect thyroid hormone levels in patients taking levothyroxine (Table V[24,25]). Patients on a stable dose of levothyroxine who are then started on a selective serotonin reuptake inhibitor, in particular sertraline,

may show a rise in their TSH level and require an increase in their thyroid hormone dose[25].

Table V: Common reasons for abnormal TSH levels on a previously stable dosage of thyroid hormone

•Patient nonadherent to thyroid hormone regimen (missing doses)
• Decreased absorption of thyroid hormone
--Patient is now taking thyroid hormone with food
--Patient takes thyroid hormone within four hours of calcium, iron, soy products, or aluminum-containing antacids
--Patient is prescribed medication that decreases absorption of thyroid hormone, such as cholestyramine, colestipol, orlistat, or sucralfate
• Patient is now pregnant or recently started or stopped oestrogen-containing oral contraceptive or hormone therapy
• Generic substitution for brand name or vice versa, or substitution of one generic formulation for another
• Patient started on sertraline, another selective serotonin reuptake inhibitor, or a tricyclic antidepressant
• Patient started on carbamazepine or phenytoin

Subclinical hypothyroidism

Subclinical hypothyroidism is a biochemical diagnosis defined by a normal-range free T_4 level and an elevated TSH level. Patients may or may not have symptoms attributable to hypothyroidism. On repeat testing, TSH levels may spontaneously normalise in many patients. However, in a prospective study of 107 patients older than 55 years, an initial TSH level greater than 10 to 15 mIU/l was the variable most strongly associated with progression to overt hypothyroidism[26]. Elevated thyroid peroxidase antibody titres also increase the risk of progressing to frank thyroid gland failure, even when the TSH level is less than 10 mIU/l. Treatment with levothyroxine should be considered for patients with initial TSH levels greater than 10 mIU/l, patients with elevated thyroid peroxidase antibody titres, patients with symptoms suggestive of hypothyroidism and TSH levels between 5 and 10 mIU/l, and for patients who are pregnant or are attempting to conceive[11].

Myxoedema coma

Myxoedema coma is a rare but extremely severe manifestation of hypothyroidism. Mental status changes including lethargy, cognitive dysfunction, and even psychosis, and hypothermia are the hallmark features of myxoedema coma[27]. Hyponatraemia, hypoventilation, and bradycardia can also occur. Because myxoedema coma is a medical emergency with a high mortality rate, even with appropriate treatment, patients should be managed in the intensive care unit where proper ventilatory, electrolyte, and haemodynamic support can be given. Corticosteroids may also be needed. A search for precipitating causes such as infection, cardiac disease, metabolic disturbances, or drug use is critical[27]. Endocrinology referral is recommended for all patients with suspected myxoedema coma and other indications listed in Table VI.[10]

Table VI: Reasons for endocrinology consultation in patients with hypothyroidism

• Age younger than 18 years
• Cardiac disease
• Co-existing endocrine diseases
• Myxoedema coma suspected
• Pregnancy
• Presence of goitre, nodule, or other structural thyroid gland abnormality
• Unresponsive to therapy

SORT: The Strength-of-Recommendation Taxonomy; A: Consistent, good-quality patient-oriented evidence; B: Inconsistent or limited-quality patient-oriented evidence; C: Consensus, disease- oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

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