DISEASE MANAGEMENT

Treat hypothyroidism in all patients with overt disease, as well as some patients with subclinical disease

Hypothyroidism is a common chronic disorder that is usually treated with levothyroxine sodium. All patients with overt hypothyroidism and subclinical hypothyroidism with serum thyroid-stimulating hormone levels >10 mIU/L should receive thyroid hormone replacement therapy, as should women who are pregnant or contemplating pregnancy. Treatment of other cases of subclinical hypothyroidism may be considered in the presence of symptoms, infertility, goitre or positive anti-thyroid peroxidase antibodies.

Primary hypothyroidism most common

Hypothyroidism is associated with insufficient production of thyroid hormone by the thyroid gland,[1] and is one of the most common chronic disorders in Western countries.[2] Hypothyroidism is classified as primary or central disease based on the cause of the insufficiency; primary disease is caused by an abnormality in the thyroid gland itself, and central disease is the result of pituitary or hypothalamic disease (table I).[1]

In developed countries, the most common cause of hypothyroidism is autoimmune thyroiditis, which may involve either a goitre (Hashimoto's thyroiditis) or thyroid atrophy, with equal frequency.[2] Other important causes of hypothyroidism include radioiodine ablation or surgical thyroidectomy (for treating hyperthyroidism or thyroid cancer), adverse drug reaction, pituitary or hypothalamus disorders or congenital disorders (e.g. thyroid aplasia or hypoplasia). Iodine deficiency is frequent in some countries, resulting in developmental deficits and hypothyroidism.[2]

This article provides an overview of the treatment of hypothyroidism, as reviewed by Khandelwal and Tandon.[1] A treatment algorithm of patients with primary hypothyroidism, as suggested by these authors, is presented in the *Patient care guidelines*.

To treat or not to treat?

Overt hypothyroidism is permanent in most cases (exceptions include recovery from thyroiditis or drug-induced hypothyroidism), and requires lifelong treatment, regardless of the presence of symptoms.[1] In addition, there is general agreement that all patients with subclinical hypothyroidism and serum thyroid-stimulating hormone (TSH) levels >10 mIU/L should be treated.[1-3]

The management of patients with subclinical hypothyroidism and TSH levels ≤10 mIU/L, however, is less straightforward and remains controversial.[1,4] Some authors believe that these patients should not be treated,[3] but others believe that these patients should be considered for treatment on an individual basis.[1,2,5] This is because although subclinical disease may progress to overt disease, and serum TSH levels >10 mIU/L are associated with a decline in lipid profiles, there is insufficient evidence to demonstrate a link between adverse cardiac events, cardiac dysfunction, neuropsychiatric symptoms or systemic hypothyroidism symptoms and TSH levels ≤10 mIU/L.[3]

Levothyroxine is standard of care

The treatment of choice in patients with primary or central hypothyroidism is levothyroxine (levothyroxine

Table I. Types of hypothyroidism[1]

Primary
Accounts for the vast majority (≈99%) of cases
Incidence increases with age (especially after middle age)
Failure of the thyroid gland results in reduced serum thyroid hormone levels and subsequent increased secretion of TSH
Measurement of serum TSH level is the single best test for diagnosis
Overt
Occurs in 1–2% of the population
Ten times more common in women than in men
Patients have elevated serum TSH levels in the presence of low serum free T4 levels
Subclinical
Occurs in ≈8% of women and 3% of men
Patients have elevated serum TSH levels in the presence of normal serum T4 and T3 levels
≈2–5% of cases progress to overt disease (more commonly in patients with both high serum TSH and anti-thyroid antibody levels than in those with only one of these indicators)
Central
Caused by insufficient stimulation of a structurally normal thyroid gland
Not always possible to distinguish between secondary (results from reduced TSH release from the pituitary) and tertiary (results from reduced TRH release from the hypothalamus) disease
Clinical manifestations are generally similar to those of primary hypothyroidism, but manifestations might be modified by symptoms of other coexisting pituitary hormone deficiencies
Best test for diagnosis is serum free T4 levels, as patients have low serum T4 levels but varying levels of serum TSH

T3 = tri-iodotyronine; **T4** = thyroxine; **TRH** = thyrotropin-releasing hormone; **TSH** = thyroid-stimulating hormone.

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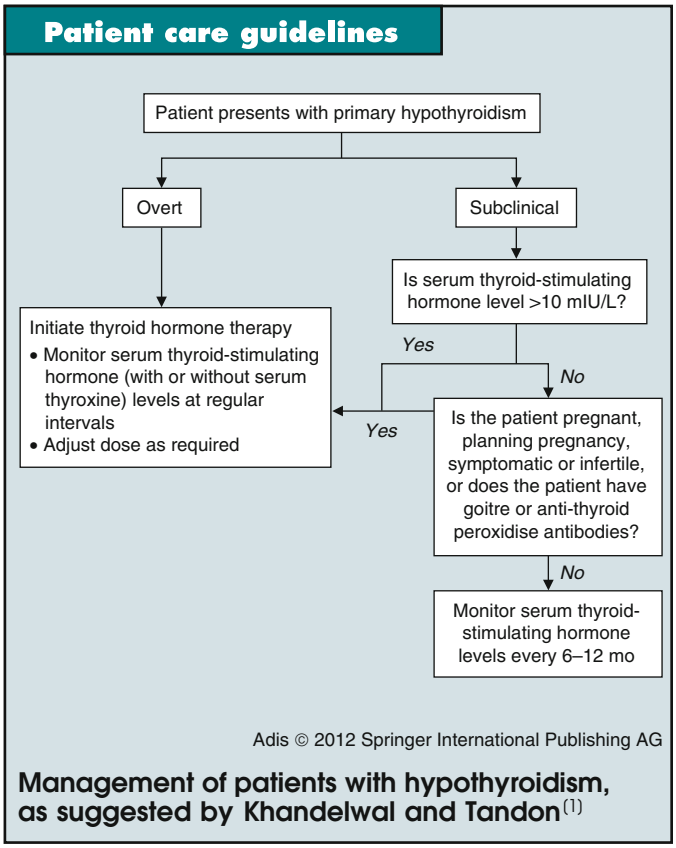

Management of patients with hypothyroidism, as suggested by Khandelwal and Tandon[1]

sodium, L-thyroxine sodium) on the basis of its clinical advantages (table II).[1] Aside from liothyronine (L-triiodothyronin), which may be more appropriate than levothyroxine in some patients (table II), there is a lack of support for the use of combination therapy with levothyroxine plus liothyronine, or desiccated thyroid.[1]

One starting dosage does not fit all

Levothyroxine is usually taken once daily in the fasting state, ≥30 minutes prior to breakfast.[1] Administration at bedtime is an alternative in patients who have their last food intake of the day at 4–5 hours before bedtime.[1] In patients taking concurrent drugs that are known to affect levothyroxine absorption (table III), levothyroxine should be taken at least 4–6 hours apart.[7]

In patients aged <60 years who are otherwise healthy, the levothyroxine dosage should be 1.6–1.8 µg/kg ideal weight (the complete replacement dosage).[8] Patients who are elderly or those with coronary artery disease or long-standing severe hypothyroidism should receive a low starting dose (25–50 µg/day) that is titrated slowly. Patients without any functioning thyroid tissue should receive levothyroxine 100–150 µg/day (women) or 125–200 µg/day (men). Patients with residual functioning thyroid tissue generally require a lower dosage; in those with subclinical disease, 25–50 µg/day may be sufficient. In patients with primary hypothyroidism, pretreatment serum TSH levels may be an indicator of the most appropriate levothyroxine dosage.[8]

Table II. Overview of advantages and disadvantages of commonly used thyroid hormones[1]

Advantages	Disadvantages
Levothyroxine (levothyroxine sodium, L-thyroxine sodium)	
The preferred agent, as its administration mimics glandular secretion of T4, with the body regulating the conversion to T3 (for a steady and adequate supply) Long elimination half-life (7 d) allows once-daily administration, resulting in small serum concentration fluctuations between doses; a missed dose has little clinical relevance Multiple tablet strengths simplifies dose titration	Has a narrow therapeutic index Excessive treatment has significant clinical consequences, including increased risks of bone loss (especially in postmenopausal women) and atrial fibrillation Soon after initiation of treatment, a syndrome of hyperandrenergic state (which can be a result of anaemia) or transient scalp hair loss may occur It is not advisable to change formulations during long-term therapy (generic and brand-name formulations are mostly bioequivalent, but some differences in bioavailability have been reported)
Liothyronine (L-triiodothyronin)	
Substitution of liothyronine for equivalent doses of levothyroxine reduced body weight and improved lipid profiles without appreciable adverse effect in a recent crossover trial;[6] however, the study was limited by its sample size (n = 14) and three-times-daily administration of study drugs As patients can be withdrawn from liothyronine for shorter periods than from levothyroxine, liothyronine may be of benefit prior to radioactive iodine (^{131}I) therapy for thyroid cancer May be considered in rare cases of maldigestion or malabsorption of levothyroxine, or in patients with documented inhibition of conversion from T4 to T3	Half-life ≈1 d, thus requiring multiple daily administration During the absorption phase, serum concentration may be 250–600% of normal, resulting in adverse events, especially palpitations In general, should not be considered for sole maintenance therapy

T3 = tri-iodothyronine; **T4** = thyroxine.

Table III. Situations requiring adjustment in the maintenance dosage of levothyroxine (levothyroxine sodium, L-thyroxine sodium)[1,7]

Situation	Cause of situation
Dosage increase	
Increased need for levothyroxine	Pregnancy, concomitant use of estrogen or selective estrogen receptor modulators, weight gain, nephrotic syndrome
Decreased absorption of levothyroxine	Malabsorption/medical conditions (e.g. coeliac disease, inflammatory bowel disease, *Helicobacter pylori* infection) or concomitant use of dietary fibre supplements, soy supplements, coffee or certain drugs (e.g. sucralfate, ferrous sulfate, bile acid sequestrants, aluminium hydroxide, calcium products, raloxifene, sevelamer, lanthanum carbonate, proton pump inhibitors, chromium picolinate)
Increased metabolism of levothyroxine	Concomitant use of rifampicin (rifamycin), phenytoin, phenobarbital, carbamazepine
Blockade of deiodinase synthesis	Cirrhosis, selenium deficiency
Other (mechanism unknown)	Concomitant use of sertraline, lovastatin
Dosage decrease	
Decreased need for levothyroxine	Loss of lean body mass, androgen therapy in women
Decreased clearance of levothyroxine	Aging, age ≥65 y

Ongoing adjustments may be required

Once levothyroxine therapy has begun, serum TSH should be re-checked after ≥2 months to allow the pituitary-thyroid axis enough time to re-set.[1] The dosage should be adjusted to maintain serum TSH within 0.5–2.0 mIU/L (lower half of normal range), with small adjustments of 12.5 or 25 µg and checking serum TSH again in 2 months. Even smaller dosage adjustments can be made by adding or withdrawing a tablet once or twice a week, because of the long half-life of the drug. Minor changes in serum TSH should be checked again in 2–3 months, instead of adjusting the levothyroxine dosage right away.[1]

Once a biochemical euthyroid state is achieved, TSH should be monitored after 6 months, and annually after a stable levothyroxine dosage has been achieved.[1] Of note, patients with post-ablative hypothyroidism may have a continually declining thyroid reserve, and may require 6-monthly or annual dosage changes until the effects of radioactive iodine therapy are stabilized; this gradual decline may also be present in patients with Grave's disease who have had a sub-total thyroidectomy.[1]

Other situations may also require a change in the levothyroxine maintenance dosage, such as persistently elevated serum TSH levels despite adequate levothyroxine (which may be a result of malabsorption, drug interactions [table III] or poor patient compliance). Coeliac disease should be excluded in these patients, as it may coexist because of its autoimmune nature.[1] Serum heterophil antibodies may interfere with laboratory testing, leading to falsely elevated TSH levels.[1]

In patients with central hypothyroidism, monitoring of serum total or free T4 may help to guide levothyroxine dosage.[1] Of note, the blood sample must be taken prior to that day's levothyroxine dose. Serum TSH levels in the mid to low normal range should be associated with mid to high normal range serum T4 levels.[1]

Compliance may be problematic

Elevated TSH and high or elevated serum free T4 levels, despite an adequate levothyroxine dosage, may be seen in non-compliant patients who take several tablets in the few days prior to testing.[1] In this situation, the levothyroxine dosage should not be altered, but further emphasis should be placed on compliance with repeat testing in 3–4 weeks. Although not ideal, it is acceptable to treat patients who are habitually non-compliant with weekly dosages[9] or who take end-of-week catch-up dosages (i.e. take all the missed doses of each week on the last day of that week). However, weekly administration should be avoided in patients with coronary artery disease.[1]

Be wary of adverse events

Over-treatment occurs in ≈20% of levothyroxine recipients, although under-treatment is also an issue.[1] Aside from the adverse events described in table II, rare reports of allergic reactions to levothyroxine have been reported, usually secondary to the dye component. This is generally overcome by switching to brands with a different dye. In children in the early phase of levothyroxine therapy, acute transient psychosis and benign intracranial hypertension are rare occurrences.[1]

Base decisions on patient needs

Hypothyroidism is usually managed by general practitioners.[2] However, patients whose symptoms do not re-

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Table IV. Management of special populations with primary hypothyroidism[1]

Patients who are pregnant or planning pregnancy
Both overt and subclinical disease may adversely affect the mother and/or the offspring
Although excess thyroid hormone can lead to fetal loss, maternal over-treatment is generally considered to be of low fetal risk
Adjust levothyroxine dosage to reach serum TSH ≤2.5 mIU/L prior to pregnancy, with increases of 25–50% (in steps of 25–50 μg/d) to maintain serum TSH <2.5 mIU/L in the first trimester and <3 mIU/L thereafter (assess serum TSH and T4 levels every 4–6 wk)[12]
If patient is already pregnant, initiate levothyroxine treatment as soon as possible; the dosage should be 2.0–2.4 μg/kg body weight/d (give 2–3 times the estimated final dosage in the first few days) and re-assess after 30–40 d[12]
Iron and calcium supplements may interfere with levothyroxine efficacy, and should be taken 4–6 h apart
Immediately after delivery, reduce levothyroxine to the pre-pregnancy dosage, and re-assess TSH after 6 wk
If hypothyroidism is subclinical, continue thyroid hormone replacement after delivery only in women who are planning a subsequent pregnancy; stop replacement therapy after delivery in all other women (monitor thyroid function every 6–12 mo)
Patients with coronary artery disease
Treatment will reduce peripheral vascular resistance, but will increase the need for oxygen in the myocardium
Treat with caution to avoid angina pectoris, acute myocardial infarction, ventricular arrhythmias or congestive heart failure (also angina in patients with coronary atherosclerosis)
If possible, treat lesions of the coronary arteries prior to initiating levothyroxine (starting dose of ≤25 μg/d, with increases no sooner than 4 wk); in the case of angina, reduce to the highest tolerated dosage and increase only after 4 wk
Elderly patients
Normal starting dosage is ≈1 μg/kg/d for 4–6 wk (lower if the patient has heart disease), with adjustments thereafter according to TSH response and clinical state, but focusing on potential cardiac adverse effects
Some evidence suggests that treatment of subclinical disease in patients aged >85 y does not appear to be beneficial[13]
Patients with congenital hypothyroidism
Treatment is needed to ensure normal growth and development (including cognitive outcome), by maintaining serum T4 levels in the upper half of the age-adjusted normal range (e.g. serum T4 10–16 μg/dL, serum free T4 1.4–2.3 ng/dL, serum TSH <5 mIU/L in the first year)
Initial levothyroxine dosage should be 10–15 μg/kg/d, usually 37.5 or 50 μg/d[14]
Monitoring frequency ranges from 2 and 4 wk after levothyroxine initiation to 6–12 mo with increasing age, but more often with dosage adjustments, compliance issues or abnormal test results[14]
Administer only levothyroxine tablets (not thyroid suspensions), crushed and suspended in a few mL of formula, breast milk or water; repeat if vomiting occurs within 1 h
Avoid concomitant administration of soy, fibre or iron supplements
Paediatric patients
Progression from subclinical to overt disease is uncommon, while recovery of thyroid function is common
Patients with co-morbid type 1 diabetes mellitus have a significantly higher risk of hypoglycaemia, which can be reduced with levothyroxine therapy
Recommended dosages are: 6–10 μg/kg/d (3–12 mo), 4–6 μg/kg/d (1–3 y), 3–5 μg/kg/d (3–10 y), 2–4 μg/kg/d (10–16 y)[15]
Monitor serum free T4 and TSH levels every 3–6 mo

T4 = thyroxine; **TSH** = thyroid-stimulating hormone.

spond or worsen after treatment, those whose serum TSH levels are persistently high even on a full dosage of levothyroxine, those who are pregnant and those with co-morbidities or complications (e.g. active and unstable ischaemic heart disease) should be referred to a specialist.[2]

In patients with concurrent glucocorticoid and thyroid hormone deficiency, the deficiency in glucocorticoid hormones should addressed prior to starting levothyroxine to avoid the likelihood of an adrenal crisis.[1] In patients who have had a thyroidectomy for differentiated thyroid cancer, levothyroxine is required to minimize potential TSH stimulation of tumour growth, and the target serum TSH levels range from <0.1 to 1.0 mIU/L, based on risk and disease state.[10,11]

Table IV provides a summary of the management of other special patient populations with primary hypothyroidism.[1]

Consider co-morbid conditions when treating central hypothyroidism

Central hypothyroidism (table I) accounts for a small proportion of cases of hypothyroidism.[1] In theory, thyrotropin-releasing hormone and TSH are ideal treatments, but levothyroxine is the standard of therapy because of its low cost, high availability and ease of administration. Serum free T4 levels should be maintained in the upper half of the normal age-adjusted range. If there are no alterations in binding proteins, it is acceptable to monitor total T4 levels.[16] It is important to assess pituitary and adrenal function and, if present, secondary adrenal insufficiency should be treated prior to initiation of levothyroxine therapy.[1]

The required dosage of levothyroxine may be affected by the treatment of other pituitary hormone deficiencies. Central hypothyroidism may be masked by growth hormone deficiency and may not become evident until after replacement

of growth hormone.[17] As concomitant estrogen replacement in women increases thyroxine-binding globulin levels, a significant increase in the dosage of levothyroxine is required.[18]

Myxoedema coma requires immediate treatment

Myxoedema coma is a decompensated state of severe untreated hypothyroidism that can be fatal if it is not recognized and treated in a timely manner.[1] It usually occurs in elderly patients with long-standing hypothyroidism, particularly during winter months. Treatment should be initiated as soon as possible (while awaiting laboratory results) and includes the use of supportive measures (especially haemodynamic support, including the use of steroids), thyroid hormone replacement and concomitant management of comorbid conditions (most importantly infections).

The type (levothyroxine, liothyronine or both) and route (oral, nasogastric or intravenous) of thyroid hormone therapy is controversial because of the rarity of cases of myxoedema coma. Generally, intravenous levothyroxine (loading doses of 200–500 μg with maintenance dosages of 20–100 μg/day) is the favoured treatment.[1] When oral intake and bowel motility are adequate, the patient can be switched to an oral thyroid hormone. Although some experts recommend the concomitant use of intravenous liothyronine in all patients with myxoedema coma, other experts suggest that it should be used only in comatose patients, and others suggest that is has no utility.[1]

Disclosure

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