Research Review™
EDUCATIONAL SERIES

Primary hypothyroidism in adults

About the Reviewer

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- Diabetes — all aspects of management and complications.
- Thyroid disease — especially thyrotoxicosis and hypothyroidism.
- Osteoporosis.
- Pituitary and adrenal disorders.
- Male hypogonadism.
- Polycystic ovarian syndrome.
- Hyperlipidaemia and hypertension.

Abbreviations used in this review

BDI	Beck Depression Inventory
BMI	Body mass index
CI	Confidence interval
FMD	Flow-mediated dilation
SMD	Standardised mean difference
T_3	Tri-iodothyronine
T_4	Thyroxine
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone

This education series provides detailed insight into disease-background and disease-management issues in primary (i.e. subclinical or overt) hypothyroidism. Subclinical hypothyroidism is essentially a biochemical classification (**Table 1**). Overt hypothyroidism is particularly common in women aged 30-65 years and is easy to diagnose and treat. However, it typically has a slow onset, and patients frequently have prolonged periods of reduced quality of life before the disorder is diagnosed and treatment started. This education series outlines that treatment of overt hypothyroidism is straightforward — levothyroxine for life. However, problems may exist with delayed diagnosis; under- or over-treatment; and poor responses to treatment, in part because of poor patient adherence. This review addresses these issues, with expert commentary provided by Dr Rick Cutfield, Waitemata District Health Board, Auckland.

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Introduction

Primary (i.e. subclinical or overt) hypothyroidism is one of the most frequent endocrine conditions.[1] It has a gradual onset and is associated with various non-specific symptoms, yet with considerable morbidity.[2] Biochemically, it is initially characterised by increased serum levels of thyroid-stimulating hormone (TSH; thyrotropin), but with normal serum levels of free thyroxine (T_4) and tri-iodothyronine (T_3). This is referred to as subclinical hypothyroidism. Subsequently, T_4 levels decrease and most patients develop noticeable symptoms. This is referred to as overt hypothyroidism (**Table 1**).[2,3]

Table 1. **Biochemical classification of hypothyroidism**

	Normal range	Subclinical	Overt
Thyroid-stimulating hormone, TSH	0.3–4.0 mIU/L	≥4 mIU/L	>10 mIU/L
Free thyroxine, T_4	10–20 pmol/L	10–20 pmol/L	<10 pmol/L
Free tri-iodothyronine, T_3	3.0-6.5 pmol/L*	3.0-6.5 pmol/L*	3.0-6.5 pmol/L*

* In adults.

Prevalence of hypothyroidism

Hypothyroidism is frequently encountered by primary care physicians, but its incidence and prevalence vary. In New Zealand, it is estimated that conditions of the thyroid gland affect 5% of women and 1% of men.[4] A retrospective review of primary care health records in Hamilton revealed an overall prevalence of overt hypothyroidism of 2.5%.[5] In the US, approximately 1 in every 300 people have the condition; however, almost 13 million people may have undiagnosed disease.[6] In the UK, the annual incidence of hypothyroidism is reported as 4 cases per 1,000 in women, with prevalence in the general population documented as approximately 4–5%.[7]

In Australia, the Busselton thyroid study reported the prevalence of overt hypothyroidism as 5.4 cases per 1,000.[8] However, a cross-sectional survey of more than 3,500 individuals aged ≥49 years in the Blue Mountains revealed a 10% prevalence of recognised thyroid disease (i.e. a self-reported history of thyroid disease, or current levothyroxine therapy). A further 3.6% of individuals surveyed had unrecognised thyroid disease (i.e. abnormal TSH levels). Somewhat surprisingly, 25% of people taking levothyroxine had an abnormal TSH level.[9] This suggests that many patients with hypothyroidism experience problems because of:

- Poor adherence to treatment.
- Reduced levothyroxine absorption, potentially because of drug–drug interactions.
- Inefficient levothyroxine dosing, potentially because of poor bioequivalence and interchangeability if patients switch from one levothyroxine preparation to another.

The prevalence of hypothyroidism increases with age, and the disorder is up to 10 times more common in women than men.[2] The condition is particularly common in women aged 30–65 years, as about 10% of women in this age group are positive for antithyroid antibodies.[10]

Causes of hypothyroidism

In western countries, the most common cause of hypothyroidism is chronic autoimmune lymphocytic thyroiditis.[1,2] Worldwide, iodine deficiency is the most frequent cause of hypothyroidism. Other causes and clinical aspects of the condition are listed in **Table 2**.[1]

Table 2. **Causes and clinical aspects of hypothyroidism**
(adapted from So et al.[1])

Causes:	Clinical aspects to determine:
Autoimmune lymphocytic thyroiditis • Hashimoto thyroiditis • Atrophic thyroiditis	Previous patient or family history of autoimmune disorders. Physical examination reveals evidence of specific autoimmune conditions such as vitiligo.
After ablative therapy or surgery • Radioiodine therapy • Thyroidectomy	Previous radioiodine therapy or thyroid surgery. Physical examination reveals surgical scar, or skin changes indicating previous external neck irradiation.
Transient causes • Subacute thyroiditis • Silent thyroiditis • Postpartum thyroiditis • Early after ablative therapy	Previous history of pregnancy, radioiodine therapy, or viral infection. Physical examination reveals an enlarged, tender thyroid gland (subacute thyroiditis).
Iodine-related causes • Iodine deficiency • Iodine-induced disease	Elicit patient history of dietary iodine intake.
Drug-induced causes • Amiodarone • Carbimazole • Interferons • Iodine • Lithium • Propylthiouracil • Rifampicin • Sunitinib • Thalidomide	Carefully document patient medication history.
Infiltrative causes • Amyloid disease • Haemochromatosis • Infections (e.g. tuberculosis) • Riedel (fibrous) thyroiditis • Scleroderma	Elicit patient history, or additional systemic features, of an infiltrative condition.
Congenital/neonatal causes • Genetic disorders influencing synthesis of T_3 and T_4 • Thyroid agenesis/ectopia • Transplacental transfer of TSH receptor-blocking antibody	Document family history of hypothyroidism/ thyroid disease. Record maternal medication use during pregnancy.
Rare causes • Abnormal laboratory results for TSH (e.g. due to heterophile antibodies) • Secondary (i.e. hypothalamic or pituitary disease) • Thyroid hormone resistance syndrome	Look for clinical signs of pituitary deficiency

T_3, tri-iodothyronine; **T_4**, thyroxine; **TSH**, thyroid-stimulating hormone.

Diagnosis and testing

Making a diagnosis: symptoms, signs and tests

The key clinical symptoms of overt hypothyroidism include: cold intolerance, constipation, fatigue, unexpected weight gain, heavy menstruation, infertility, mental slowing, mood changes, muscle pains, puffy face, and occasional carpal tunnel syndrome. Signs detected on physical examination include: bradycardia, sometimes with hypertension; deep voice; hair loss; pale, cold, dry and doughy skin; periorbital puffiness; and, occasionally, peripheral neuropathy and thyroid enlargement. Laboratory test alterations in overt hypothyroidism include raised serum TSH and reduced serum T_4 and, occasionally, raised serum creatine kinase and serum cholesterol, and hyponatraemia.[3,6] Indeed, hyponatraemia is not commonly found unless hypothyroidism is severe.

Importantly, the symptoms of primary hypothyroidism are often non-specific and, initially, mild; they typically progress gradually and are often attributed to other factors such as life stresses, workload, etc. Most of the signs and symptoms listed above, and in **Table 3**, are associated with significant hypothyroidism.[3,6]

Table 3. **Key clinical signs and symptoms of hypothyroidism** (adapted from So et al.[1])

Appearance	• Puffy, pale face • Dry, brittle hair • Scant eyebrows • Dry, cool skin • Brittle and thickened nails • Myxoedema — non-pitting oedema in the tissues, particularly in the face and shins
Cardiovascular	• Bradycardia • Reduced exercise tolerance • Diastolic hypertension • Pericardial effusion
Cognitive/psychiatric	• Depression • Impaired memory • Reduced attention span
Energy and nutrient metabolism	• Cold intolerance • Fatigue • Weight gain
Gastrointestinal	• Anorexia • Constipation
Musculoskeletal	• Arthralgia • Myalgia
Nervous system	• Altered deep tendon reflexes • Carpal tunnel syndrome (and other paraesthesias) • Cerebellar ataxia • Headache
Reproductive system	• Irregular or heavy menstruation • Infertility

Diagnosis is based mainly on biochemical findings of raised serum TSH with normal free T_4 (subclinical hypothyroidism) or low free T_4 and raised TSH (overt hypothyroidism) with or without classic symptoms.[2] A physical examination of the patient's neck should be conducted to look for goitre or thyroid nodules. Other possible causes should also be looked for, including physical evidence of a thyroidectomy scar, or skin changes indicating previous external neck irradiation, or autoimmune conditions such as vitiligo (**Table 2**). The clinical presentation may vary in severity from subclinical disease to myxoedema coma; the latter condition is rare, but is an endocrine emergency.[1]

If serum TSH level is raised at the initial biochemical investigation, it should be re-measured within 2–8 weeks; the serum level of free T_4 should also be measured to endorse the diagnosis. Additional investigations should be performed for hypercholesterolaemia, hyponatraemia, mild anaemia, and raised serum creatine kinase level; patients with inexplicable raised serum cholesterol levels may have undiagnosed hypothyroidism. However, statin therapy should be avoided in patients with hypothyroidism, since it increases the risk of rhabdomyolysis. A low serum level of T_4, without associated elevation of serum TSH, suggests secondary hypothyroidism due to hypothalamic or pituitary pathology and would prompt other tests for pituitary insufficiency, including possible MRI of the pituitary (**Figure 1**).[1]

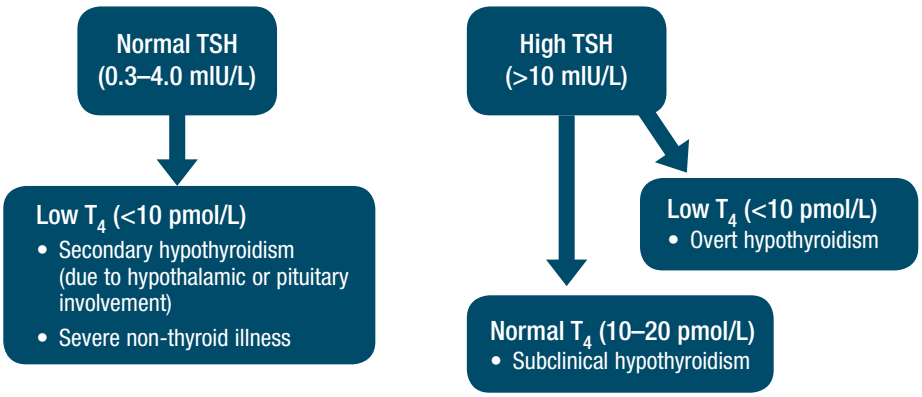

Figure 1. **TSH test result interpretation** (adapted from So et al.[1]).
Cases of suspected secondary or tertiary hypothyroidism should be referred to a specialist.

To confirm a diagnosis of autoimmune thyroiditis — the most common cause of hypothyroidism — testing for thyroid peroxidase (TPO) antibodies is all that is needed.[1] Anti-TPO or antithyroglobulin antibodies are detectable in almost all patients (95%) with autoimmune thyroiditis. Approximately 10–15% of the general population is TPO antibody-positive, but this is not an indication for levothyroxine therapy if biochemical thyroid function is normal. Interestingly, some evidence suggests that TSH rises slightly as we age and that 'mild' TSH elevation in the elderly may be associated with increased longevity.[11] Thyroid ultrasound is needed only if structural abnormalities of the thyroid are suspected. There is no place for thyroid radionuclide scanning in the initial patient work-up for primary hypothyroidism.[1]

Treatment of primary hypothyroidism

The key goals of treatment for overt hypothyroidism are to re-establish physical and psychological well-being, to maintain serum TSH levels within the standard laboratory reference range (0.3–4.0 mIU/L), and relieve symptoms (if present).[1,2] In patients with persistent symptoms, titration of levothyroxine dosage is appropriate to maintain serum TSH level in the lower end of its range (0.3–2.0 mIU/L). In elderly patients, maintaining a serum TSH level in the upper-normal range or even slightly higher (2.5-5.0 mIU/L) is appropriate. However, lower TSH targets may be needed in pregnant women and those with thyroid cancer. Referral to a specialist is required in these situations, and in patients: aged <18 years; unresponsive to treatment; with cardiac disease; with goitre, nodules, or other structural thyroid changes; or with other endocrine conditions.[1]

In most patients with overt hypothyroidism, the key goals of treatment are attained with lifelong replacement of T_4 via oral levothyroxine therapy (1.6 µg/kg of lean bodyweight daily). However, if hypothyroidism is transient or drug-induced, levothyroxine therapy may not be required, or may be needed for only short-term treatment.[1,6]

Levothyroxine dosage

In patients with hypothyroidism who are elderly, frail and/or have symptomatic angina, serious thought should be given to starting the levothyroxine dosage at less than 1.6 µg/kg/day. Indeed, levothyroxine increases myocardial oxygen demand and may increase the risks of an angina attack or myocardial infarct. In healthy elderly patients, a suitable initial dosage is 50 µg per day, whereas in the very frail or those with symptomatic angina, an appropriate starting dosage is 12.5–25 µg per day.[1]

Usually, levothyroxine is taken every day, in the morning, 30 minutes before food. Calcium or iron supplements should not be taken within 4 hours of levothyroxine administration, as these can reduce levothyroxine absorption. If poor patient adherence to levothyroxine therapy becomes an issue, the drug can be administered once weekly; it has a half-life of about 1 week.[1,6]

Avoid under- or over-treatment

Clinical and biochemical evaluation of the sufficiency of levothyroxine therapy are needed to ensure that under- and over-treatment are avoided. Inadequate thyroid hormone replenishment can lead to adverse effects on serum lipid profiles, and to cardiovascular disease progression.[2] Conversely, excessive thyroid hormone replenishment can lead to thyrotoxicosis, and symptoms of diarrhoea, fatigue, increased appetite, insomnia, nervousness, palpitations, and tremors. Such symptoms require repeat measurement of TSH, and if levels are suppressed, the levothyroxine dosage should be reduced.[1] Potentially more serious consequences of over-treatment with levothyroxine include osteoporosis and atrial fibrillation. Such over-treatment, and serum TSH levels <0.1 mIU/L, should be avoided, particularly in postmenopausal women and elderly patients.[2]

Ongoing monitoring

After starting levothyroxine, patients' TSH levels should be monitored every 6–8 weeks; this interval permits attainment of steady-state levothyroxine levels. The levothyroxine dosage should be adjusted (usually upwards in increments of 12.5–25 µg/day) until elevated TSH levels become normal and stable.[1,2] Subsequently, TSH levels should be checked every 4–6 months, and then annually, unless situations altering levothyroxine requirements manifest: for example, marked weight gain; commencement of an oral contraceptive or proton-pump inhibitor; or planned pregnancy.[1]

Avoidance of the need to cut levothyroxine tablets is important. In practice, the drug can be administered every other day, or its dose altered depending on day of the week (e.g. 100 µg on Monday–Friday; 200 µg on Saturday and Sunday).[1]

Levothyroxine availability in NZ

Three different levothyroxine preparations are fully funded on the Pharmaceutical Schedule:
Eltroxin® (Healthcare Logistics, Auckland) 50 µg and 100 µg tablets.
Levothyroxine (Mercury Pharma, Auckland) 50 µg and 100 µg tablets.
Synthroid® (BGP Products, Auckland) 25 µg, 50 µg and 100 µg tablets.

The advantage of 25 µg tablets is that they may help daily drug dosing in some patients.

For most patients treated with levothyroxine, specific prescribing of a particular branded product or generic medicine is usually unnecessary.[2] However, it is prudent to exercise caution and not assume bioequivalence or interchangeability of levothyroxine preparations.[6] If a prescriber does decide to switch from one levothyroxine formulation to another, a plan should be in place for monitoring TSH levels. Prescribers should also be aware that dosage adjustment may be needed.

Overall, levothyroxine is a sensible, simplified, and safe strategy for T_4 replenishment in patients with primary hypothyroidism. Patient outcomes can be improved by approaches designed to:[2]

- Optimise drug delivery.
- Standardise thyroid-hormone preparations administered.
- Enhance patient adherence to treatment.

Products to avoid

Serum levels of T_3 should not be used as a clinical target in the treatment of hypothyroidism, as there is no definitive evidence to indicate that this is worthwhile. Thus, there is no resounding evidence to support routine use of the following in patients with primary hypothyroidism:[2]

- Monotherapy with levo-tri-iodothyronine.
- Combination therapy with levothyroxine and levo-tri-iodothyronine.
- Thyroid extracts.
- Compounded thyroid hormones.
- Iodine-containing products.
- Dietary supplements.
- Over-the-counter products.

Management of poor responses to treatment

In primary care, poor responses to seemingly appropriate dosages of levothyroxine may result from reduced levothyroxine absorption, poor patient adherence to treatment, and/or drug–drug interactions.[1] In such situations, repeat TSH measurement is needed to confirm the inadequacy of levothyroxine therapy.

Reduced levothyroxine absorption

Various malabsorptive disorders, such as coeliac disease, inflammatory bowel disease, and lactose intolerance, may reduce the efficiency of gastrointestinal absorption. As such, the proportion of levothyroxine absorbed from an ingested dose may decrease, with a consequent increase in thyroid hormone requirements.[1] In addition, chronic gastritis due to *Helicobacter pylori* infection may reduce levothyroxine absorption, although this situation can be corrected with relevant combination therapy for *H. pylori* eradication.[12]

Poor patient adherence

Despite administration of apparently appropriate-dosage levothyroxine therapy, some patients with primary hypothyroidism fail to attain normal thyroid function.[1] Indeed, in some settings, the prevalence of continued elevation of TSH levels during levothyroxine therapy has been reported to be as high as 25%.[9] Poor patient adherence to treatment is one of the most common reasons for such continued TSH elevation.[13]

Sometimes, if a patient has not adhered to the levothyroxine schedule for a prolonged period, s/he might take a large levothyroxine dose before a thyroid-function test.[1] Characteristic features of the test result may then include raised TSH, but with a T_4 level in the upper-normal or elevated range.[14] If this situation arises, the pattern of tablet taking should be elicited from the patient, and the importance of adherence to levothyroxine therapy should be emphasised.[13]

Drug–drug interactions

Several potential drug–drug interactions may reduce levothyroxine absorption or increase levothyroxine metabolism (**Table 4**). Appropriate alteration of levothyroxine dosage will then be needed. Women with primary hypothyroidism should also be told to take their levothyroxine dose on an empty stomach, at least half an hour before other medicines and espresso coffee.[1,2,15]

Table 4. **Potential drug–drug interactions with levothyroxine**[1,6]

Drugs reducing levothyroxine absorption	Drugs increasing levothyroxine metabolism
Calcium carbonate	Antidepressants (e.g. sertraline, tricyclic antidepressants)
Cholestyramine	Anti-epileptic drugs (e.g. carbamazepine, phenytoin)
Ferrous sulphate	Oral contraceptives
Multivitamins	Rifampicin
Orlistat	Tyrosine kinase inhibitors (e.g. imatinib)
Phosphate binders	
Proton-pump inhibitors	
Sucralfate	

Management of primary hypothyroidism in special populations

Subclinical hypothyroidism

This condition is characterised biochemically by an increased serum TSH level (≥4.0 mIU/L), yet normal T_4 level (10–20 pmol/L). Patients may be symptomatic or asymptomatic. With repeat TSH testing, the elevated TSH level may resolve spontaneously.[1,2,6] Such resolution is more common within the first 2 years of diagnosis, in patients negative for antithyroid antibodies, and in patients with serum TSH <10 mIU/L.[2]

Subclinical hypothyroidism occurs in about 5–10% of the general population, and is particularly common in women aged >60 years (prevalence approximately 15–20%).[1,2] Progression to overt hypothyroidism occurs in about 5–20% of patients each year, and an increased risk of such progression is associated with:[1]

- Antithyroid antibodies (2-fold risk increase).
- Goitre.
- Greater degree of TSH elevation.
- History of radioablative external radiation and/or chronic lithium treatment.

Much controversy has surrounded the issue of whether or not to treat subclinical hypothyroidism. Possible risks of non-treatment were considered to comprise progression to overt hypothyroidism, dyslipidaemia, and cardiovascular and neuropsychiatric effects.[1] A Cochrane review reported that levothyroxine in subclinical hypothyroidism failed to ameliorate cardiovascular morbidity, health-related quality of life, or overall survival, although it did improve indices of cardiovascular disease such as left ventricular function, lipid profile, and vascular compliance.[16]

A more recent consensus from guidelines and systematic reviews is that there has been no consistent evidence of benefit for levothyroxine in randomised controlled trials in subclinical hypothyroidism.[2,17] Generally, these trials *'… have been too small to detect any clinically relevant improvements in outcomes.'*[3]

That said, in patients who are clearly symptomatic, and with a serum TSH level of 4–9 mIU/L, a therapeutic trial of levothyroxine may be justified to keep TSH within the standard reference range. This is especially true in individuals aged <60 years. If symptoms improve, levothyroxine should be continued.

In neonates, children, and women who are pregnant or trying to conceive, a mildly increased serum TSH level should be treated.

Patients with persistent symptoms

Some patients treated with levothyroxine continue to have symptoms of hypothyroidism, despite having a normal serum TSH level.[2,7] In such situations, consideration should be given to possible other causes (**Table 5**).[2,6]

Table 5. **Possible causes of persistent symptoms of hypothyroidism in levothyroxine-treated patients with normal serum TSH** (adapted from Okosieme et al.[2])

Drugs	• β-blockers • Opiates • Statins
Endocrine/ autoimmune	• Adrenal insufficiency • Coeliac disease • Diabetes mellitus • Hypopituitarism • Pernicious anaemia
End-organ damage	• Chronic kidney disease • Chronic liver disease • Congestive heart failure
Haematological	• Anaemia • Multiple myeloma
Lifestyle	• Excess alcohol consumption • Poor sleep hygiene • Stress and exhaustion
Metabolic	• Electrolyte imbalance • Hypercalcaemia • Obesity
Nutritional	• Folate deficiency • Iron deficiency • Vitamin B_{12} deficiency • Vitamin D deficiency
Other	• Anxiety • Carbon monoxide poisoning • Chronic fatigue syndrome • Depression • Fibromyalgia • Obstructive sleep apnoea • Polymyalgia rheumatica • Viral and postviral syndromes

Levothyroxine dosage adjustments can be made to try to reduce serum TSH to the lower end of its reference range (~1 mIU/L).[1] That said, increasing levothyroxine doses were administered in a Western Australian study with serum TSH targets of 0.3, 1.0 and 2.8 mIU/L. No major differences between patients were noted regarding indices of well-being and quality of life.[18] However, TSH levels <0.4 mIU/L are associated with increased risks of atrial fibrillation and loss of bone density in individuals aged >60 years.[1]

In patients with persistent symptoms, desiccated thyroid or thyroid hormone extracts, which are impure products and which have quality control issues, should not be used as thyroid replacement therapy.[1] The same applies to the combination of levothyroxine with tri-iodothyronine, since a large meta-analysis of 11 randomised trials involving more than 1,000 patients revealed no major benefit for the combination.[19]

Hypothyroidism during pregnancy

All women with hypothyroidism who are planning a pregnancy should receive iodine supplementation (150 µg/day), unless this is contraindicated. During pregnancy, maternal thyroid function is markedly altered because of increased metabolic needs of the foetus.[1] It has been estimated that 85% of pregnant women with hypothyroidism have a median increase in thyroid hormone requirements of 47%.[6] β-Human chorionic gonadotrophin also has direct thyrotropic activity, such that serum TSH levels are considerably reduced during the first trimester.[1] Endocrine societies therefore advocate altered laboratory reference ranges for TSH according to trimester of pregnancy: first trimester 0.4–2.5 mIU/L; and second and third trimesters 0.4–3.0 mIU/L.[2]

Generally, specialist involvement is needed for the treatment of elevated TSH levels in pregnancy.[1] Thyroid-function testing is recommended every 4 weeks, up to 20 weeks' gestation, with less frequent testing thereafter.[20] In pregnant women with overt hypothyroidism (TSH >2.5 mIU/L with reduced T_4; or TSH >10 mIU/L, regardless of T_4 level), levothyroxine therapy is recommended and can be started (e.g. 50–100 µg/day) while patients are waiting for specialist review. In pregnant women with subclinical hypothyroidism (TSH 2.5–10 mIU/L with normal T_4), management options comprise: starting levothyroxine therapy, or monitoring TSH levels every 4 weeks; and ordering a TPO antibody test while patients wait for specialist review. In pregnant women with a known history of hypothyroidism, levothyroxine dosage should be adjusted when pregnancy is confirmed, or even in women who are planning to conceive. An appropriate TSH target is <2.5 mIU/L, the levothyroxine dosage can be increased by two tablets per week (i.e. +25–30%), and thyroid-function testing should be conducted every 4 weeks.[1,20] Combination therapy with levothyroxine plus levo-tri-iodothyronine is not recommended during pregnancy.[2]

Myxoedema coma

This condition is rare, yet particularly severe. It occurs most often in elderly women with a history of hypothyroidism. Characteristic features comprise cognitive dysfunction, hypothermia, lethargy, and psychosis; bradycardia, hyponatraemia, and hypoventilation may also occur. Immediate referral to hospital is recommended for all patients with suspected myxoedema coma, as the condition is a medical emergency that has a high mortality rate, even with relevant intervention.[6]

TAKE-HOME MESSAGES

- Primary hypothyroidism is a common condition in women aged 30–65 years and is frequently encountered by primary care physicians.
- Overt hypothyroidism is characterised by a raised TSH level (>10 mIU/L) with a low level of free T_4 (<10 pmol/L). Most patients will also have physical signs and symptoms.
- In western countries, the most common cause is chronic autoimmune lymphocytic thyroiditis, which can be identified by a TPO antibody test.
- The key goals of treatment are to re-establish physical and psychological well-being, to maintain serum TSH levels within the standard laboratory reference range (0.3–4.0 mIU/L), and relieve symptoms (if present).
- In most patients, these goals are attained with lifelong replacement of T_4 via oral levothyroxine therapy (1.6 µg/kg/day).
- Usually, levothyroxine is taken every day, in the morning, 30 minutes before food. Avoidance of the need to cut levothyroxine tablets is important.
- Bioequivalence and interchangeability of levothyroxine preparations should not be assumed, and care should be exercised to avoid under- or over-treatment and to encourage appropriate patient adherence to treatment.
- There is no convincing evidence, in the routine management of primary hypothyroidism, that the use of levo-tri-iodothyronine, combination levothyroxine + levo-tri-iodothyronine, desiccated thyroid or thyroid hormone extracts, iodine-containing products, dietary supplements, or over-the-counter products adds anything to benefit patients. In some cases, these interventions may be harmful.

Expert's comments

Most GPs will have patients in their practice with primary hypothyroidism, usually caused by Hashimoto's thyroiditis, or after thyroidectomy or ^{131}I therapy. It is important to adjust thyroxine replacement therapy to keep serum TSH level in the normal range, the low-normal range in some situations, such as pregnancy or some thyroid cancers, or in the high-normal range in the elderly. Reasons for not achieving these targets are multiple, but mostly related to adherence or absorption issues. Treating subclinical hypothyroidism in individuals with a serum TSH level of 4–9 mIU/L is usually unnecessary in non-pregnant women and the elderly.

Care should be taken to avoid overtreating overweight patients. Some cases of hypothyroidism are due to pituitary disease and, in these cases, T_4 rather than TSH should be monitored; the aim should be to keep serum T_4 level in the mid-normal range. Some cases of hypothyroidism are transitory: for example, as may occur after hyperthyroidism in postpartum thyroiditis or subacute thyroiditis.

While stabilising patients on levothyroxine, it is important to consider drugs that might interfere with absorption. It is also important to emphasise the need to take tablets 30 minutes before food, or occasionally at bedtime, if more convenient, but never with food. Adjustments to the levothyroxine dosage can be made every 6–8 weeks and, when TSH is normalised and stable, then every 6–12 months.

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