Hypothyroidism: a definitive diagnosis guides treatment

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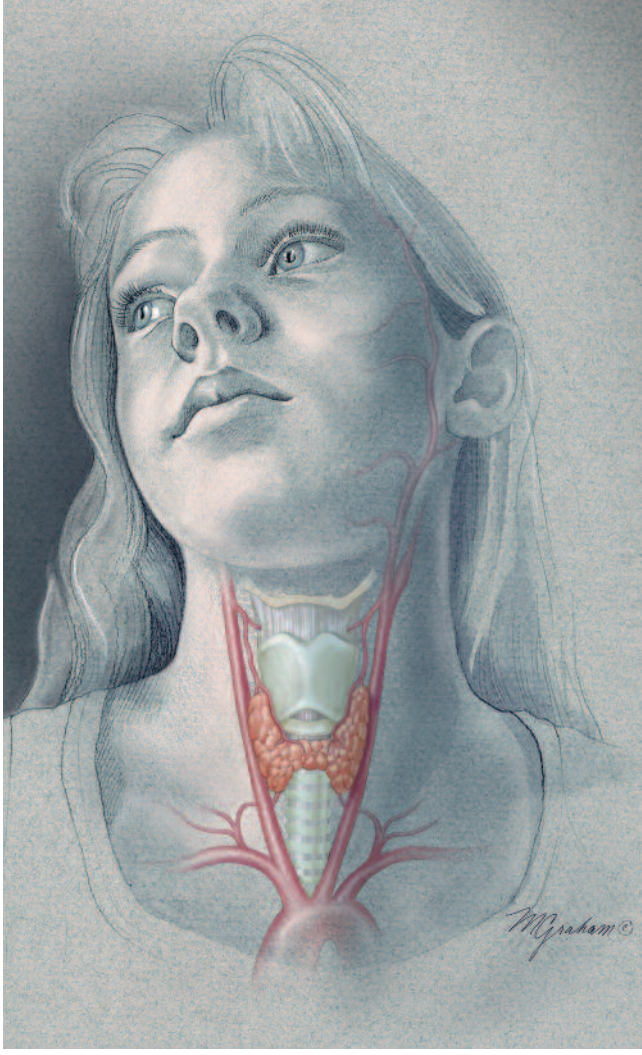
Hypothyroidism may be obvious clinically but it has a wide spectrum of severity and can be very subtle. Many people with a normal thyroid function may present to GPs with complaints of mild symptoms suggestive of hypothyroidism. Therefore, biochemical confirmation of true hypothyroidism is mandatory. There is no evidence that thyroxine treatment of suggestive symptoms is beneficial when tests are normal.



Hypothyroidism is a common condition that affects almost 5% of the population. Subclinical hypothyroidism is most common but less than 0.5% of the population have clinically apparent disease.[1] Severe hypothyroidism (myxoedema), although usually easy to recognise clinically, is uncommon. Most cases of hypothyroidism are diagnosed on suspicion based on one or more milder symptoms and signs that are not pathognomonic. The most common cause of hypothyroidism in our community is autoimmune disease of the thyroid gland and this is more common in women than in men.

This article aims to provide information to guide diagnosis and optimal treatment in the range of commonly encountered forms of hypothyroidism.

What is the cause?

Deficiency of thyroid hormone is usually due to damage to the thyroid gland itself (primary hypothyroidism), but can also result from impairment of pituitary function with diminished thyroid-stimulating hormone (TSH, also know as thyrotropin) drive to the thyroid gland. In this circumstance, either the pituitary gland itself is damaged (secondary hypothyroidism) or there is a loss of hypothalamic signal to the pituitary (thyrotropin-releasing hormone [TRH]) due to hypothalamic disease (tertiary hypothyroidism). As secondary and tertiary hypothyroidism are often difficult to distinguish they may together be termed central hypothyroidism. The box on page 20 lists the different causes of hypothyroidism.

Key points

- **Hypothyroidism is a common condition, with most patients having subclinical hypothyroidism.**
- **The most common cause of hypothyroidism in Australia is autoimmune disease of the thyroid gland.**
- **A clinical diagnosis of hypothyroidism should be considered in the presence of one or more of its classic symptoms and signs.**
- **People with normal thyroid function may complain of mild symptoms that suggest the possibility of hypothyroidism so that biochemical confirmation is mandatory.**
- **Synthetic thyroxine is the best standard replacement therapy for patients with hypothyroidism.**

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Causes of hypothyroidism

- Autoimmune thyroid disease: nongoitrous/atrophic; goitrous/Hashimoto's thyroiditis
- After thyroid ablative therapy for hyperthyroidism
- Transient: during the course of subacute thyroiditis, postpartum thyroiditis, after radioiodine therapy
- Drug induced: lithium, amiodarone, thionamide, interferon; interference with thyroxine therapy in treated hypothyroidism (iron, calcium, cholestyramine, sucralfate)
- Iodine associated: iodine deficiency, iodine induced
- Neonatal/congenital: thyroid agenesis, genetic thyroid disorders, transient thyroid-stimulating hormone receptor blockage from maternal antibody
- Secondary: pituitary or hypothalamic disease (e.g. tumour, trauma)
- Other causes: thyroid hormone resistance

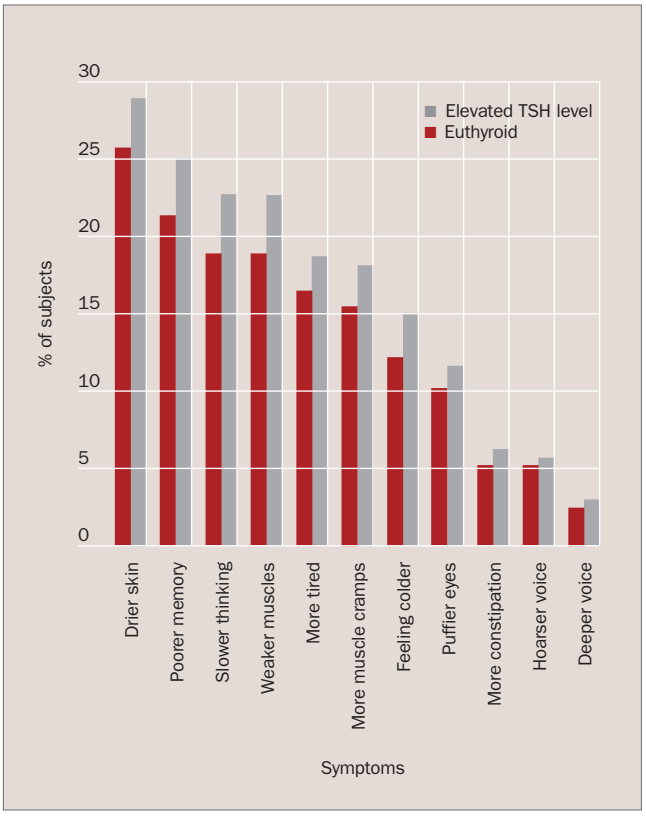

Figure 1. A comparison of euthyroid subjects compared with those with an elevated thyroid-stimulating hormone (TSH) level who reported symptoms of hypothyroidism. Although showing a higher rate of characteristic symptoms of hypothyroidism in patients with raised TSH levels, a high rate in the euthyroid group is also shown, indicating the low specificity of these symptoms.
Adapted from: Canaris GJ, et al. Arch Int Med 2000; 160: 526-534.[2]

How to diagnose

Clinical diagnosis

A clinical diagnosis of hypothyroidism should be considered in the presence of one or more of its classic symptoms and signs, including chronic tiredness, poor mental concentration, depression, weight gain, constipation, myalgia, dry skin and hair, facial puffiness and husky low-pitched voice. Hypothyroidism should be excluded in patients with psychosis and in those with apparent dementia.

Hypothyroidism may be obvious clinically but has a wide spectrum of severity and can be very subtle. Conversely, many people with normal thyroid function complain of mild symptoms that suggest the possibility of hypothyroidism (Figure 1),[2,3] so that biochemical confirmation is mandatory.

Biochemical diagnosis

Primary hypothyroidism is characterised by a raised serum TSH level with a low free thyroxine (T_4) level. Subclinical hypothyroidism (also know as mild thyroid failure)[4] is defined by raised TSH levels but free T_4 within the normal range (Table).[5] These definitions raise the question of the true reference ranges particularly for TSH. The upper limit of the normal range of TSH is usually described as 4 to 5 mIU/L but a lower limit of around 3 mIU/L has been advocated. However, without evidence of benefit of treatment for borderline TSH, an upper limit of about 4 to 5 mIU/L is still generally recommended.[6] Indeed in extreme old age (older than 85 years) the TSH normal range may be extended up to about 7 mIU/L and one epidemiological study has even suggested a survival benefit for higher TSH levels.[7]

Secondary hypothyroidism is characterised by a low free T_4 level with a normal or low TSH level. However, milder forms should be suspected in the appropriate clinical context when the free T_4 level is low-normal.

In the individual person the free T_4 range is more tightly regulated than the population normal range.[8] A low to normal value may therefore occasionally raise concern about hypothyroidism but, when the TSH level is normal, this should not be interpreted as primary hypothyroidism, and only as secondary hypothyroidism when there is other evidence to support hypothalamo-pituitary disease.

As autoimmune thyroid disease is the most common cause of primary hypothyroidism, measurement of serum thyroid autoantibodies can be a useful diagnostic test. The most sensitive test is that for antithyroid peroxidase antibodies (aTPO). Antithyroglobulin antibodies (aTg) are often also measured. Low levels of aTg, in the absence of aTPO, should be interpreted with caution, and the only clear remaining place for aTg is to validate the measurement of serum thyroglobulin as a thyroid cancer marker after thyroid ablation. Serial measurement of aTPO is unnecessary because changes in levels have no clinical correlate.

There is no routine role for thyroid imaging in the diagnosis or management of hypothyroidism. Imaging should only be performed for specific reasons (e.g. in the assessment of a specific nodule). Hashimoto's thyroiditis is typically nodular when advanced (Figure 2) and a nodular biopsy, when the diagnosis has been made

Table. A matrix for interpreting thyroid function tests*

	High TSH level	Normal TSH level	Low TSH level
High T_4 level	*In vivo* or *in vitro* artefact Pituitary hyperthyroidism (TSHoma) Thyroid hormone resistance	Same as box to left Sampling within 6 hours of thyroxine dose	Hyperthyroidism (for this diagnosis, TSH must be suppressed rather than just low)
Normal T_4 level	Mild thyroid failure (primary) (also termed subclinical hypothyroidism and diminished thyroid reserve)	Normal (in patients taking thyroxine, TSH levels above 3 mIU/L may indicate subtle under-replacement)	Subclinical hyperthyroidism Subtle thyroxine over-replacement Thyroid autonomy (multinodular goitre or autonomous functioning thyroid nodule) Nonthyroidal illness
Low T_4 level	Primary hypothyroidism	Pituitary or hypothalamic hypothyroidism Severe nonthyroidal illness	Pituitary or hypothalamic hypothyroidism Severe nonthyroidal illness

* Medicare Australia restricts financial reimbursement to serum TSH alone, except in specified clinical circumstances, when additional measurements of free T_4 and free triiodothyronine (T_3) are sanctioned. We suggest that practitioners routinely request 'thyroid function tests' and provide clear clinical information to enable the laboratory to perform additional tests if justified. The information should include the suspected condition (especially if hypopituitarism) and medications (e.g. thyroxine, carbimazole or propylthiouracil, amiodarone or phenytoin).
Abbreviations: T_4 = serum free thyroxine; TSH = thyroid-stimulating hormone.

serologically, is usually not necessary. However, thyroid lymphoma, although a rare disease, has a high relative risk when autoimmune thyroid disease is present. Therefore, an enlarging nodule despite thyroid hormone treatment may require cytological examination (i.e. ultrasound-guided fine needle biopsy).

Types of hypothyroidism

Severe hypothyroidism/myxoedema coma

The clinical manifestation of severe hypothyroidism is termed myxoedema because of the marked generalised puffiness of non-pitting oedema. Muscle aching is common and because creatine kinase clearance is reduced with elevated creatine kinase levels, an incorrect diagnosis of myositis may be made.[9] Intestinal pseudo-obstruction can occur.

If symptomatic ischaemic heart disease occurs in the presence of severe hypothyroidism it may be impossible to correct hypothyroidism with thyroxine therapy despite cautious dose increment. In this case, coronary artery bypass may have to be conducted with the patient remaining hypothyroid, which requires dose reduction of all drugs and use of anaesthetic agents and fluid therapy. Surgery can, however, be conducted successfully.

Severe hypothyroidism can be precipitated into myxoedema coma by intercurrent illness or cold exposure. In myxoedema coma, there is obtundation, hypoventilation, hypothermia, hypotension and hyponatraemia.[10] This life-threatening condition may require assisted ventilation and general intensive support with strict attention to fluid and electrolyte balance. Thyroid hormone replacement usually using parenteral liothyronine is required with supportive glucocorticoid therapy.

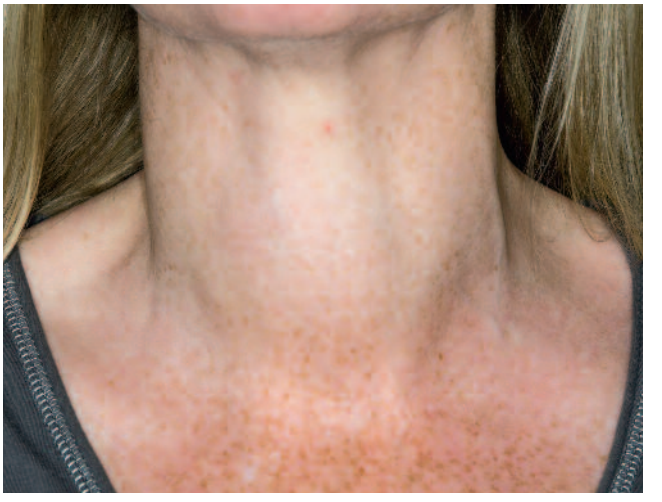

Figure 2. A 47-year-old woman with a goitre.

Transient hypothyroidism

Early in the course of Hashimoto's thyroiditis, thyroid status can vary spontaneously and mild hypothyroidism can remit. After radioiodine therapy for Graves' hyperthyroidism, hypothyroidism occurring within the next six months can remit. Subacute thyroiditis typically has a transient hyperthyroid phase then a hypothyroid phase, with subsequent re-establishment of the euthyroid state. In the absence of major symptoms it is reasonable to continue monitoring without institution of replacement therapy until stable thyroid function, either hypothyroid or euthyroid, is apparent.

Subclinical hypothyroidism

Subclinical hypothyroidism is defined biochemically as raised TSH levels with normal free T_4 levels, although the occasional patient is in fact symptomatic. The free T_4 value is usually toward the low end of the normal range, and symptoms are presumed to arise if the free T_4 is sufficiently lower than the individual free T_4 set point.

In general, unless the TSH value is more than 10 mIU/L no clinical benefit results from thyroxine treatment.[11] Comorbidities, such as dyslipidaemia and clinical assessment of likely progression, for example, with concomitant presence of aTPO (which predicts progression to overt hypothyroidism at about 5% per year),[12] are factors prompting treatment rather than monitoring alone. If the patient is intending to conceive or is already pregnant, treatment to reduce TSH levels to less than 2.5 mIU/L is indicated.[13]

Pregnancy-associated hypothyroidism

In women with established hypothyroidism it is important to optimise the replacement thyroxine dose preconception and to increase the dose during pregnancy to maintain optimal replacement (see below). Fetal thyroid function does not develop until the 12th to 18th week of gestation, so before then the fetus requires maternal thyroxine, particularly for neurological development. A raised maternal TSH level in pregnancy has been associated with a loss of IQ points in the offspring.[14]

The change in immune state in pregnancy can cause induction of thyroid autoimmunity and either hypo- or hyperthyroidism. It is still debated whether assessment of thyroid function should be routine at diagnosis of pregnancy but certainly it should be performed if there is a personal or close family history of thyroid dysfunction or any relevant symptoms. If hypothyroidism is detected then aggressive thyroxine replacement therapy at full dose (2 to 2.4 µg/kg/day) should be immediately instituted to optimise fetal thyroxine supply. In patients with severe hypothyroidism a few days of double-dose therapy can be given.

Congenital hypothyroidism

One in 3500 live births is associated with congenital hypothyroidism usually due to athyreosis and occasionally to lingual thyroid – that is, failure of normal fetal thyroid tissue migration. Failure to institute prompt thyroxine replacement leads to permanent neurological deficit. For this reason thyroid function assessment is part of the universal newborn screening program by heel-prick blood testing, with the aim of therapy by no later than the 10th postnatal day. Thyroxine dosing needs to be carefully and progressively adjusted for age to prevent over- and under-treatment.[15] Early treatment results in an excellent outcome.

Iodine-induced hypothyroidism

Iodine is an essential trace element for thyroid function. The recommended intake is about 150 µg/day, and 200 to 250 µg/day in women during pregnancy and when breastfeeding. This is less than a 5 g requirement over an average life-time. Iodine is only stored in the body within the thyroid. Measurement of urinary iodine concentration is not a useful test for individual diagnosis but is a fundamental tool in community-based public health surveillance.

Despite iodine being essential, excessive iodine intake can provoke thyroid dysfunction in the already diseased thyroid.[16] The mechanisms of thyroid hormone synthesis are chronically inhibited by excessive iodine, and quiescent autoimmunity may be activated. An intake of iodine of more than the recommended daily dose should therefore be discouraged. During pregnancy, excessive iodine intake can promote fetal goitre. Use of Lugol's iodine should absolutely be confined to specialist use before thyroidectomy in patients with Graves' disease, despite its irrational advocation by various fringe practitioners and websites of dubious veracity. Similarly, use of kelp tablets should also be discouraged.

Amiodarone-induced hypothyroidism

The anti-arrhythmic drug amiodarone that is 37.2% iodine liberates about 9 mg/day of iodine per 200 mg tablet and can therefore cause iodine-induced hypothyroidism. The organic metabolite desmethylamiodarone is also toxic to the thyroid. Amiodarone-induced hypothyroidism tends to occur in the already diseased thyroid so that predose thyroid function tests to detect subclinical hypothyroidism and the presence of thyroid autoantibodies is useful, with routine monitoring every six months thereafter.[17] Thyroxine replacement therapy is usually straightforward and amiodarone, which may be necessary to treat a life-threatening arrhythmia, can be continued.

Associated conditions

Other autoimmune conditions are associated with Hashimoto's thyroiditis. In more than 14% of cases of Hashimoto's thyroiditis there may be one or more associated conditions, including pernicious anaemia/atrophic gastritis (so-called thyrogastric cluster), Addison's disease, coeliac disease, vitiligo and rheumatoid arthritis.[18] Patients should be clinically assessed at diagnosis and yearly thereafter, with serological and other laboratory assessment of any clinical manifestations. An increase in requirement for thyroid hormone replacement should be investigated by exclusion of coeliac disease.

Nonthyroidal illness

Measurement of serum thyroid hormone levels is not an infallible guide to thyroid status. Profound alterations in thyroid hormone economy can occur in diseases not directly affecting the thyroid gland itself, leading to changes in thyroid hormone levels and diagnostic uncertainty. Overt hypothyroidism or hyperthyroidism can, however, be confidently diagnosed. As a general rule it is best to repeat testing in four to six weeks when changes due to nonthyroidal illness will usually have resolved.[19]

In mild nonthyroidal illness, such as a bacterial infection, serum triiodothyronine (T_3) levels can fall quickly, usually accompanied by a rise in reverse T_3. Some fringe practitioners suggest that reverse T_3 measurement is useful clinically, but there is no good evidence to support this practice. Severe nonthyroidal illness, causing a fall in free T_4 levels, is more diagnostically challenging. This commonly occurs in patients with severe trauma and burns and suggests the possibility of hypothyroidism. However, TSH levels are not elevated acutely, so that in the absence of head trauma and possible pituitary damage, hypothyroidism can be discounted.

Synthetic thyroxine is the best standard replacement therapy for patients with hypothyroidism. However, there is no evidence that thyroxine treatment of suggestive symptoms is beneficial when tests are normal.

How to treat

Thyroxine therapy

Synthetic thyroxine (available in 50, 75, 100 and 200 µg tablets) is the best standard replacement therapy for patients with hypothyroidism.[20] The dose best relates to lean body mass (1.5 to 3.0 µg/kg/day), but in routine clinical care the usual adult dose is 100 to 150 µg/day. In otherwise healthy adults an initial dose of 50 to 100 µg/day can be increased after a minimum of four to six weeks (three to five half-lives) as necessary, targeting a serum TSH level of 0.5 to 2 mIU/L. In the presence of ischaemic heart disease or increased risk of arrhythmia, the TSH target should be less than 5 mIU/L. This can be achieved by commencing thyroxine at 25 to 50 µg/day increasing by 25 µg/day after a minimum of every four weeks.[21] An initially very high TSH level may take months to normalise so that, for up to six months, the achievement of a satisfactory free T_4 level in the mid to normal range and a clinical response should be accepted over TSH normalisation. There is no evidence that thyroxine treatment of suggestive symptoms is beneficial when tests are normal.[22,23]

During early pregnancy and before conception a TSH target of less than 2.5 mIU/L and up to 3 mIU/L in the second and third trimesters is recommended.[24] The increased metabolism of thyroxine in pregnancy requires a prompt adjustment of thyroxine dose by 30 to 50% once pregnancy is confirmed. A simple initial adjustment is two daily doses per week extra, and further adjustment by monthly thyroid function testing during pregnancy. The preconception dose can be resumed postpartum.

In secondary hypothyroidism, TSH level cannot be used as target and a mid to high-normal free T_4 value regardless of the TSH level is the aim. Dose selection and adjustment frequency is the same. Consideration should be given to the adequacy of other pituitary hormonal axes, in particular adrenal function. Thyroxine replacement can render borderline hypoadrenalism overt due to increased steroid hormone clearance.

Thyroxine should be ingested on an empty stomach usually in the morning avoiding concomitant medications, especially calcium or iron supplements. Thyroxine should be stored at 2 to 8°C but tablets for immediate ingestion can be kept at room temperature if sealed and protected from direct sunlight.

Liothyronine therapy

Liothyronine therapy is usually confined to transient use (at 20 to 40 µg/day) replacing thyroxine before whole-body radioiodine scanning in the follow up of patients with thyroid cancer. Genuine intolerance or allergic reactions to synthetic thyroxine are rare and unresponsiveness is rarer still, therefore, chronic use of liothyronine alone is rarely necessary.

Liothyronine therapy is difficult to manage because T_3 levels vary markedly throughout the day in relation to time of ingestion (liothyronine has a half-life of 24 hours), and T_4 levels will be low and not indicative of thyroid status. TSH level is the best biochemical index to use, but it is unclear if the nonphysiological variation of T_3 levels from high to low throughout the day is without risk.

Combined therapy

Combined use of thyroxine and liothyronine therapy has been examined in many small trials in patients dissatisfied with thyroxine replacement alone and, when adequate blinding has been conducted, no clear clinical benefit has been identified.[25] Combination therapy should never be routine and, if trialled clinically, a liothyronine dose of 10 to 20 µg/day is generally used with monitoring using TSH measurement to regulate the dose and avoid TSH suppression.

Thyroid extract, which contains both thyroxine and liothyronine,

is supplied by compounding pharmacists and is often advocated by fringe practitioners. For 50 years, thyroid extract was the routine form used until synthetic thyroxine with a more precise dosage became available. Thyroid extract has no evidence of better efficacy, the relative T_4 to T_3 content is difficult to standardise leading to variable under- or over-dosage and it is an animal source product with the potential for prion infectivity. Thyroid extract is generally discouraged if a pure synthetic form is available because it has not been assessed for efficacy or safety by regulatory agencies and its use cannot therefore be recommended. Should it nevertheless be used, monitoring using TSH levels is essential.

Monitoring

In general, once the correct dose of thyroxine has been achieved, the required dose remains stable and only yearly thyroid function test monitoring is routinely required. With the decrease of lean body mass in advanced age, a decrease in dose may be required.

Not infrequently there is no available documentation of hypothyroidism in a person taking thyroxine therapy. If it is appropriate to re-establish the need for thyroxine therapy then it can be ceased for five weeks and then if the TSH level is elevated, primary hypothyroidism is confirmed.[26]

Role of the GP

GPs are in an excellent position to suspect, diagnose, treat and monitor patients with hypothyroidism. Although the development of hypothyroidism can be subtle and insidious, sometimes rendering the new medical observer at an advantage to the regularly seen doctor, a high index of suspicion for hypothyroidism with any related symptoms promotes sensitive case-finding.

Patients should be referred to an endocrinologist if test results are unusual or difficult to interpret, central hypothyroidism is suspected because of a lack of TSH elevation or the response to treatment is inadequate. Education promotes optimal adherence to therapy. GPs should emphasise that thyroxine is a life-long replacement therapy and not a curative treatment.

Conclusion

Mild hypothyroidism is common and usually due to autoimmune thyroid disease. The diagnosis is rarely obvious clinically and confirmatory biochemical testing should be performed for patients with suggestive symptoms. A raised TSH level is indicative of primary thyroid failure.

In general, when the TSH level is more than 10 mIU/L there will be a clinical benefit from treatment. There is almost always a clear clinical benefit from the treatment of patients with overt hypothyroidism. Synthetic thyroxine is the treatment of choice for patients with hypothyroidism, adjusted to optimise TSH levels within the normal range. An increase of thyroxine dose in women during pregnancy is important to optimise fetal outcome. It is important to advise the patient about the need to maintain long-term stable therapy and monitoring is generally only required annually. **ET**

Further reading

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