Modern management of thyroid replacement therapy

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Summary

Hypothyroidism is a common and chronic condition. Finding a high concentration of thyroid stimulating hormone in a symptomatic patient confirms the diagnosis and a cause is usually readily found. Lifelong thyroxine therapy relieves symptoms and restores 'normal' thyroid function. Commencing thyroxine can aggravate cardiac disease but is relatively free of adverse effects. The concentration of thyroid stimulating hormone is used to monitor therapy.

Key words: hypothyroidism, pregnancy, thyroid stimulating hormone, thyroxine.

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Introduction

Hypothyroidism is a common condition with an annual incidence of 3.5/1000 in women and 0.6/1000 in men.[1] The prevalence increases with age. In areas without iodine deficiency the common causes of chronic hypothyroidism are autoimmune thyroid disease, thyroidectomy, radiotherapy (both radioiodine therapy and external beam radiotherapy), congenital disorders and disorders of thyroid hormone metabolism. Secondary hypothyroidism occurs with some pituitary and hypothalamic diseases.

Diagnosis

Patients may not present with the typical clinical features of hypothyroidism. They may have vague symptoms such as tiredness. The diagnosis can be made by finding a persistently elevated serum concentration of thyroid stimulating hormone (TSH). The serum free thyroxine (fT4) concentration will be low. Measuring triiodothyronine (fT3) adds little to the diagnosis or monitoring of hypothyroidism.

In secondary hypothyroidism the pituitary fails to produce TSH appropriately so measurement of TSH is unhelpful. The diagnosis is suggested by a low fT4 and features of pituitary disorder.

In subclinical hypothyroidism the TSH is elevated (usually to 5–10 mIU/L) but the fT4 is normal. The typical symptoms of hypothyroidism are often absent.

The cause of primary hypothyroidism in an adult will usually be determined from a history of thyroidectomy or radiotherapy or finding high titres of antithyroid antibodies (thyroid peroxidase, antimicrosomal or antithyroglobulin antibodies). The use of lithium and iodine-containing preparations (such as amiodarone) can cause a drug-induced hypothyroidism.

Providing patients with a copy of the laboratory results which confirm their need for thyroxine often proves helpful for the patient and future treating doctors.

Treatment

Primary hypothyroidism is treated by giving the patient replacement thyroxine, usually for life. Liothyronine rarely needs to be used unless there is life-threatening hypothyroidism. Alternative sources of thyroid hormones such as thyroid extracts should be avoided.

Thyroxine dose

Thyroxine has a half-life of 7–10 days but a much longer biological effect. Once-daily dosing is appropriate.

The dose is dependent on body weight and age. Children require larger doses of thyroxine per kg body weight than adults who require approximately 1.6 microgram/kg/day.[2] Most adults will maintain euthyroidism with a dose of thyroxine of 100–200 microgram/day. There may be a decline in thyroxine requirements in the elderly.

Both brands of thyroxine currently available in Australia come from the same supplier and are identical. Concerns regarding the bioavailability of different preparations are not relevant in Australia.

Thyroxine tablets should be kept dry and cool and in their original container.[3] Recent advice to refrigerate thyroxine tablets increases the likelihood of moisture causing deterioration in the medication. A month's supply can be kept at room temperature.[4]

Starting thyroxine

The rate of introduction of thyroxine should be determined by the duration of the hypothyroidism and the presence (or risk) of coronary disease or heart failure. Otherwise healthy patients who have recently undergone thyroidectomy or radioiodine treatment for thyrotoxicosis can immediately start at or just below their predicted daily replacement dose of thyroxine 100–200 microgram.

Elderly patients and those with known heart disease should start with a daily dose of thyroxine 25 microgram for 3–4 weeks with a reassessment of their condition before further increments of 25 microgram every 3–4 weeks until the predicted dose is reached. Worsening symptoms of coronary disease or heart failure should be controlled before increasing the dose of thyroxine and a dose reduction may be necessary while cardiac disease is stabilised.

For patients between these two extremes, a starting dose of 50 microgram/day is reasonable. This is increased at intervals of 3–4 weeks until the predicted dose is reached.

Patients should feel some symptomatic improvement within two weeks of starting thyroxine. It may take 3–4 months for the full benefit of the drug to become apparent and for the TSH to normalise.

Monitoring and dose adjustment

In primary hypothyroidism the TSH alone can be used to monitor therapy. The aim should be to maintain the TSH at the lower end of the normal range (0.4–5 mIU/L). Symptoms may be best relieved when the TSH is at the lower end of this range. It takes at least four weeks for the TSH to stabilise after a change in thyroxine dose and so any testing of TSH should be done at least 4–6 weeks after the change. At the start of treatment a patient does not need measurement of their TSH until they have been on their predicted dose of thyroxine for 4–6 weeks (unless symptoms of thyrotoxicosis dictate otherwise). Repeat testing every six weeks is appropriate until the dose is stabilised, however if the patient is approaching euthyroidism and is feeling well this interval can be increased. After the dose is stabilised an annual TSH measurement is usually adequate monitoring unless a problem arises.

> Patients should feel some symptomatic improvement within two weeks of starting thyroxine

When the thyroxine dose is in the range of 100–200 microgram/day, variable daily dosing may be necessary to achieve euthyroidism. Considering the total weekly dose is helpful when changing the dose. For example, 100 microgram/day (700 microgram/week) may be inadequate to control the TSH but 125 microgram/day (875 microgram/week) may be too much. A dose of 800 microgram/week can be taken as 100 microgram/day five days a week and 150 microgram/day two days a week. Variable daily dosing removes the need for patients to cut thyroxine tablets.

Problems

If taken correctly, thyroxine should enable patients to lead a normal life. However, there are some common problems which can affect management.

Persistently elevated TSH

Poor adherence is the most likely explanation of TSH remaining above the normal range. I advise patients to decant a week's supply of thyroxine into a separately labelled bottle and refill the bottle on the same day each week. If the patient discovers they have missed one (or more) doses they can take the missed doses in conjunction with their usual dose over the next few days.

The absorption of thyroxine may be reduced by cholestyramine, colestipol, aluminium hydroxide, ferrous sulfate and possibly fibre. Two hours should elapse between use of thyroxine and these drugs.

Symptoms do not respond to thyroxine

Hypothyroidism is often discovered on biochemical testing after patients present with non-specific complaints. While it is likely that symptoms such as muscle aches and pains, dry skin and dry hair and menstrual irregularity may respond to thyroxine, other symptoms such as lethargy, tiredness and fatigue, weight gain and depressive symptoms may have other causes. It is helpful to consider if the patient's symptoms are likely to be due to hypothyroidism before prescribing thyroxine and to tell them if you suspect that some of their symptoms are unlikely to respond. There is no proven benefit in adding liothyronine to the treatment of patients who have persistent symptoms despite taking thyroxine.

Secondary hypothyroidism

If there is pituitary or hypothalamic disease, TSH is unreliable for diagnosing and monitoring thyroid function and fT4 should be used instead. A low fT4 will be found in secondary hypothyroidism and treatment should aim to maintain fT4 within the reference range.

Most patients with secondary hypothyroidism will be hypogonadal and many will also be cortisol deficient. It is extremely important to consider cortisol deficiency before starting treatment with thyroxine in patients with pituitary and hypothalamic disease as its use will speed the metabolism of cortisol and can induce an adrenal crisis.

When commencing thyroxine in secondary hypothyroidism it is therefore safest to also treat the patient with a corticosteroid (for example prednisone 5 mg daily). Subsequently, cortisol reserve can be assessed with an early morning cortisol measurement. A morning cortisol less than 100 nmol/L always indicates the need for ongoing steroid replacement. Results greater than 500 nmol/L indicate adequate reserve and values in between may require provocation tests.[5]

Drug-induced hypothyroidism

Lithium and iodine are the common causes of drug-induced hypothyroidism. Amiodarone, iodine-containing contrast media and kelp tablets are common sources of large doses of iodine.

All forms of drug-induced hypothyroidism will usually resolve on withdrawal of the drug. Thyroxine can be used to control symptoms if required while recovery occurs. Lithium- and amiodarone-induced hypothyroidism are managed with thyroxine. The ongoing need for the lithium or amiodarone should be considered, but they can be continued if necessary.

Pregnancy and lactation

Thyroxine requirements increase by 25–30% during pregnancy with increased requirements seen as early as the fifth week of pregnancy.[6] Children born to women whose hypothyroidism was inadequately treated in pregnancy are at increased risk of neuropsychological impairment.[7]

I advise women taking thyroxine who are planning to conceive to increase their dose of thyroxine by 30% at the confirmation of the pregnancy. TSH should be monitored every 8–10 weeks during pregnancy with further dose adjustments as necessary. The thyroxine dose returns to the pre-pregnancy dose after delivery whether the mother is breastfeeding or not.

Transient hypothyroidism

Some patients have transient hypothyroidism so it is appropriate to consider withdrawing the drug. For example, women who develop hypothyroidism in the postpartum period (postpartum thyroiditis) may not require long-term thyroxine replacement. In some patients a clear cause of hypothyroidism is not established, but the cause will often have been the hypothyroid phase of subacute (de Quervain's) thyroiditis or possibly iodine-induced hypothyroidism. Other patients may ask if they can stop thyroxine therapy.

If treatment is stopped it usually takes four weeks for the TSH to rise, but it can be tested earlier if symptoms occur. The onset of symptoms and a rising TSH show an ongoing need for thyroxine and patients can immediately recommence their previous dose.

Subclinical hypothyroidism

Some patients have an elevated TSH, but a normal concentration of fT4. The need for treatment is debatable. I consider treating patients who have had an elevated TSH for over six months with persistent symptoms which may be due to hypothyroidism, and also patients who have antibodies suggesting autoimmune thyroid disease. After a 3–6 month trial I continue treatment if there has been a substantial symptomatic improvement, or stop and reassess symptoms and TSH after 4–6 weeks to determine if there is an absolute need for ongoing thyroxine replacement. Patients with a modestly elevated TSH and positive thyroid antibodies have a 5% per year chance of developing overt hypothyroidism.[1] Pregnant women and those considering pregnancy should be treated.

Addison's disease

Addison's disease and autoimmune hypothyroidism occasionally occur together. This is a rare but dangerous association. Increased pigmentation, postural hypotension and possibly weight loss may suggest the additional diagnosis. As in secondary hypothyroidism, give steroid replacement before introducing thyroxine to avoid inducing an adrenal crisis.

Thyroid cancer

Some patients with differentiated thyroid cancer are given thyroxine at a higher dose to suppress TSH (to less than 0.1 mIU/L) with minimum elevation of fT4. This helps prevent recurrence of the cancer.

Conclusion

Treatment of hypothyroidism is usually a lifelong necessity. Determining the cause will detect those patients who need only transient treatment. Except for those patients with or at risk of known cardiac disease, the elderly and those with long-standing symptoms, thyroxine can usually be commenced at or near a full replacement dose. The dose is adjusted to keep the concentration of TSH within the normal range.

> The need for treatment of subclinical hypothyroidism is debatable

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Further reading

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Conflict of interest: none declared