



Management of thyroid disorders in primary care: challenges and controversies

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ABSTRACT

Thyroid diseases are common, and most can be safely and effectively managed in primary care. Two of the most common reasons for thyroid function testing are fatigue and obesity, but the vast majority of affected patients do not have hypothyroidism. There is no plausible basis for the assertion that hypothyroidism commonly occurs despite normal thyroid function tests. In primary hypothyroidism all patients, except the elderly and those with ischaemic heart disease, can safely be started on a full replacement dose of thyroxine; the aim is to restore thyroid stimulating hormone (TSH) to normal.

Triiodothyronine (T3) has no role in the treatment of primary hypothyroidism. Subclinical thyroid disease should not be treated except in certain well defined situations. Its main importance lies in the increased risk of progression to overt thyroid disease. The development of hyperthyroidism is easily overlooked, and it is important to maintain a high index of suspicion, especially in the elderly. The most common causes are Graves' disease and thyroiditis (especially postpartum), and in the elderly toxic nodular goitre and amiodarone. Patients taking amiodarone should have their thyroid function checked every 6 months.

Patients with overt hyperthyroidism should be referred for specialist management; β -blockers and sometimes anti-thyroid drugs may be initiated in primary care. Most thyroid nodules, especially those detected incidentally on ultrasound scanning, are benign. Indications for referral include newly occurring nodules >1cm in diameter, painful nodules, and nodules that are increasing in size.

Thyroid disorders are common; 3% of the population is taking long term thyroid replacement therapy,¹ and every year about 4.1 women and 0.6 men per 1000 of the adult population develop hypothyroidism, and 0.8 women per 1000 develop hyperthyroidism.² Patients with these conditions may present to us with a wide range of different symptoms because of the effects of either over or under production of thyroid hormones on the various organs of the body (table 1). The other reason patients with a thyroid disorder may consult us is in regard to concerns about a swelling in the neck.

This article discusses some of the more challenging and controversial aspects of managing thyroid disorders in primary care. A basic level of knowledge of thyroid disorders is assumed, and can be found in standard textbooks such as Kumar and Clark³ and the *Oxford textbook of primary medical care*.⁴ A useful free online resource with in depth information on all aspects of thyroid disease is the Thyroid Disease Manager (<http://www.thyroid-manager.org/>).

In treating hypo- and hyperthyroidism it is important to remember that these are functional diagnoses. Understanding the underlying cause of the hormonal disturbance is key in management. In hypothyroidism the most important distinction is between primary thyroid failure (most commonly due to autoimmune destruction of the thyroid, thyroidectomy and certain medicines) and pituitary failure. Graves' disease, toxic nodular goitre and amiodarone treatment are the main causes of hyperthyroidism; secondary causes are rare.

AN EPIDEMIC OF THYROID FUNCTION TESTS

Ten million requests for thyroid function test are made every year in the UK, at an estimated annual cost of £30 million (€35 million, US\$50 million).⁵ Thyroid function tests are being ordered with low pre-test probability,⁶ and thorough clinical assessment does not seem to play an important role in the assessment of patients.⁷ Symptoms such as tiredness and lethargy are probably the most common indication given by general practitioners (GPs) for requesting thyroid function tests in patients with no pre-existing thyroid disease. The value of such testing is debatable in the absence of goitre or other clinical features of thyroid dysfunction. There are a wide range of causes of fatigue and psychological factors are frequently important.⁸ Recent evidence has shown that hypothyroidism is uncommonly diagnosed, and supports a strategy of trying to postpone ordering blood tests, in patients with unexplained fatigue.⁹ Spending time talking in some depth with patients who complain of being "tired all the time" is much more likely to provide us with appropriate clues as to the underlying problem rather than ordering blood tests. Thyroid function testing is only recommended as a matter of course when symptoms of fatigue are prolonged and debilitating.¹⁰ A lower threshold for ordering thyroid function tests should also be considered in women aged over 55 years with vague symptoms: subclinical thyroid dysfunction is highly prevalent in this group with its attendant risk of progression to overt thyroid failure.⁵

Another common indication given for thyroid function testing is obesity, and this is often requested by patients who believe that there must be a "glandular cause" for their weight gain. Although a recent review recommended thyroid function testing in the assessment of obesity,¹¹ hypothyroidism is a rare cause and thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) are not affected by obesity.¹² The value of performing thyroid function

Table 1 Common clinical features in hypothyroidism and hyperthyroidism

Organ	Hypothyroidism	Hyperthyroidism
▶ Skin	Cold intolerance, cool dry skin, pallid complexion, puffy face, coarse brittle hair, alopecia, diminished sweating	Heat intolerance, warm moist skin, increased sweating
▶ Nervous system	Paraesthesia, lethargy, deafness, slow speech, depression, slow reflexes	Nervousness, irritability, tremor, eyelid retraction
▶ Musculoskeletal	Weakness, myalgia, muscle cramps, easy fatigability	Weakness, myopathy
▶ Cardiac	Decreased exercise tolerance, slow pulse, cardiomegaly	Shortness of breath, palpitations, arrhythmias, heart failure
▶ Gastrointestinal	Anorexia, constipation, weight gain	Increased appetite, frequent bowel movements, weight loss
▶ Genitourinary	Menorrhagia, reduced fertility	Scanty periods
▶ Others	Raised cholesterol, anaemia	Eye and skin changes of Graves' disease

tests on obese patients in the absence of any other symptoms suggestive of hypothyroidism is therefore doubtful.

There is a dearth of recent work which can provide data for clinicians to guide them on which symptoms and signs mean that the patient has a significantly raised probability of hypo- or hyperthyroidism. The classic studies quoted in textbooks are of limited relevance because they were undertaken when thyroid function tests were much less sensitive than those currently used, and patients generally presented with much more advanced thyroid dysfunction than they do now. One recent study has shown that the most discriminating symptoms and signs of hypothyroidism are dry skin, diminished sweating, weight increase, paraesthesia, delayed ankle reflex, coarse skin, periorbital puffiness and cold skin.¹³ This study suggests that patients with overt hypothyroidism most commonly present with skin manifestations of the condition.

The usual first line test of thyroid function is serum TSH assay⁵; it is important to give adequate clinical information with the request so the laboratory can judge whether T4 concentrations should also be measured even if TSH is normal. Thyroid peroxidase (formerly microsomal) antibodies (TPOAb) should only be tested if TSH concentrations are raised or if the result would have clear clinical relevance. One in 10 women in the general population are positive for TPOAb,² so undue significance can easily be placed on a positive result.

HYPOTHYROIDISM WITH NORMAL THYROID FUNCTION TESTS

There is a vociferous school of thought that hypothyroidism frequently occurs in the absence of abnormalities in standard function tests. One website asserts "Many doctors simplistically think that thyroid disease can be diagnosed, and even worse, can govern treatment, by testing only TSH levels" (<http://www.thyroiduk.org/>).¹⁴ A checklist suggests that a huge range of symptoms may be due to hypothyroidism, and a cut-off of 2 mU/l is proposed for the upper limit of normal for TSH. This is very misleading. In fact TSH assay is extremely sensitive, and in the absence of associated systemic disease a normal TSH concentration (0.3–4 mU/l) has over 99% negative predictive value in ruling out primary hypothyroidism and hyperthyroidism.¹⁵

Hypothyroidism may occur when TSH is normal or even low in pituitary failure, and it is always important to be open to this possibility, although rare. Other features of hypopituitarism will usually be present. The implication that hypothyroidism with normal TSH and T4 commonly occurs due to failure of peripheral conversion of T4 to T3 or tissue unresponsiveness¹⁴ is—in the absence of systemic disease—highly contentious. The conversion of T4 to T3 and TSH secretion are affected in unwell, hospitalised patients, but this is not normally an issue when testing ambulant patients in primary care. True resistance to thyroid hormones has been described but is very rare.¹⁶ Of more practical importance is the effect that certain medicines

may have on thyroid function, notably glucocorticoids and amiodarone.

It is important to respond sympathetically to a patient who believes they have hypothyroidism and is persistent in requesting further tests, despite a normal TSH, and it may be appropriate to specifically request a T4 assay if the patient has typical features of hypothyroidism. However, if TSH and T4 values are both normal, an alternative explanation should be sought for their symptoms. The patient may be reluctant to accept this; in such cases reference to the Royal College of Physicians statement on the diagnosis and management of primary hypothyroidism,¹⁷ and to the available evidence,¹⁸ may be helpful.

OPTIMAL TREATMENT OF HYPOTHYROIDISM: IS THERE A ROLE FOR T3 IN TREATMENT?

All patients with clear-cut hypothyroidism (TSH >10 mU/l, FT4 <10 pmol/l) should be treated: this will almost certainly be lifelong. It is wasteful and unnecessary to titrate up the dose of thyroxine in most cases; rather patients should be started on a full replacement dose of around 1.6 µg/kg daily.¹ For a 60 kg woman this is 100 µg, and 125 µg for a 75 kg man. Those over 60 years and patients with ischaemic heart disease should be started on 25 µg per day and the dose titrated gradually upwards: in severe ischaemic heart disease or older patients with very high initial TSH concentrations, start at 12.5 µg/day.

Thyroid function tests should be checked after at least 8 weeks; testing too soon does not give the pituitary gland sufficient time to adjust. The aim in treatment is to restore the patient's TSH value to normal; fine tuning of the dose may be needed and some patients may only feel better once their TSH is in the lower half of the reference range (0.4–2.5 mU/l).¹ Overtreatment should be avoided, although in younger patients it may be acceptable for TSH concentrations to be below the reference range if a higher dose of levothyroxine is required to fully control symptoms.¹ Maintaining TSH concentrations below 0.1 mU/l is poor practice due to the increased risk of osteoporosis and atrial fibrillation. The exception to this is after thyroidectomy for thyroid cancer, when TSH values may need to be suppressed to and maintained at a concentration <0.1 mU/l.⁵

A source of confusion is that sometimes patients are recommended treatment with a combination of T4 and T3 (as liothyronine), although there is no good evidence to back up the use of this combination. A meta-analysis of randomised, controlled studies of T4–T3 combination therapy found no advantage when compared with standard T4 monotherapy,¹⁹ and the recent College of Physicians statement does not recommend additional T3 in any form, including Armour Thyroid (porcine thyroid extract).¹⁷ Addition of T3 also poses a risk of overtreatment unless doses are carefully controlled, as T3 is five times more active than T4.

SUBCLINICAL THYROID DISEASE: SHOULD IT BE TREATED?

Subclinical thyroid dysfunction occurs when TSH values are outside the normal range (0.3–4 mU/l) while FT4 and FT3 (where relevant) are normal. Subclinical hypothyroidism is very common, especially in older people, with up to 20% of women over 60 years of age affected. Subclinical hyperthyroidism, except when due to overtreatment of hypothyroidism, is much less common. When first identified it is important to exclude known thyroid disease or drugs such as amiodarone which may interfere with thyroid function (see below). Testing should be repeated after 2–3 months and a decision then made on further management. The main importance of subclinical thyroid disease is that affected patients are at increased risk of progression to overt disease. Whether subclinical thyroid disease itself should be treated is controversial; however, there is little robust evidence that treatment is beneficial and it is not recommended except in certain defined situations.²⁰ In subclinical hypothyroidism treatment should be considered in those whose TSH concentrations are >10 mU/l, especially if positive for TPOAb, as they are at higher risk of progressing to overt disease. Treatment should also be offered to women with subclinical hypothyroidism who are pregnant or trying to conceive, and a trial of treatment should be considered in patients who have typical symptoms of hypothyroidism.

In subclinical hyperthyroidism where TSH values are <0.1 mU/l there is an increased risk of atrial fibrillation and osteoporosis.²⁰ However, the evidence that treatment is beneficial even when TSH is at very low concentrations is thin. Treatment might be justified if TSH values remain <0.1 mU/l and there are other features of concern such as typical symptoms or the subject develops atrial fibrillation. In such cases the opinion of an endocrinologist should be sought. If treatment is considered to be warranted, management is broadly along the same lines as overt hyperthyroidism.

In subjects with subclinical hypothyroidism, approximately 2–5% per year will progress to overt hypothyroidism.²⁰ Those with higher TSH values and those positive for TPOAb are more likely to progress. In subclinical hyperthyroidism 1–2% per year of those with TSH values <0.1 mU/l develop overt hyperthyroidism.²⁰ Those with higher TSH values are at much lower risk of progression. Patients considered at a high risk of progression should be offered annual follow up thyroid function tests, and those at lower risk should be tested every 3 years.

MANAGEMENT OF HYPERTHYROIDISM IN PRIMARY CARE

The development of thyrotoxicosis is easily overlooked. Initial symptoms such as fatigue, palpitations and anxiety may easily be attributed to stress. It is important to maintain a high index of suspicion—look carefully for goitre and eye signs, check for tremor, and feel the hands. In primary anxiety they are cold and dry, whereas in thyrotoxicosis they are typically warm and moist. Thyroid function tests will show a suppressed TSH and raised T4 or T3, or both. Hyperthyroidism is a condition and not itself a diagnosis, which depends on the underlying cause. Further investigation will be needed to establish this with certainty, but clinical clues may often give a guide as to what it may be. In younger subjects the most common causes are Graves' disease and thyroiditis (especially postpartum). In the elderly the majority of cases are due to toxic nodular goitre and/or occur in those being treated with amiodarone.

Thyrotoxicosis is particularly easily missed in older subjects. Lethargy or fatigue and tremor are common presenting complaints in this age group. Typical eye signs will often be absent as most cases are not due to Graves' disease.

Comorbidities mean that symptoms may be ascribed to other conditions or drug side effects, and drugs—especially β -blockers—may mask some of the symptoms. Critical clues come from taking into account possible causative factors such as treatment with amiodarone and previous thyroid surgery.

Patients found to have overt hyperthyroidism should be referred to an appropriate specialist for further management unless the GP has relevant training and experience. Those affected may be treated with antithyroid drugs such as carbimazole and propylthiouracil, surgery or radioiodine. Recommendations on treatment in a particular patient are based on a number of factors including underlying cause, the subject's age, severity of the condition, and the presence of comorbidities. Pending referral, a β -blocker may be prescribed to control symptoms if not contraindicated—for example, propranolol 40 mg three times daily. If a long wait is likely before the patient is seen by a specialist it may be appropriate for the GP to initiate treatment with anti-thyroid drugs in consultation with the endocrinologist concerned. In the UK the most commonly used anti-thyroid drug is carbimazole, and the typical starting dose in adults is 20–40 mg daily. This is then reduced to a maintenance dose of 5–15 mg daily after 6–8 weeks according to response. When monitoring thyroid function, T4 values should usually be the marker of choice to guide treatment⁵; TSH concentrations may take several months to return to normal. The main hazard of carbimazole treatment is bone marrow suppression. If the subject develops symptoms or signs of infection, especially a sore throat, a full blood count (FBC) should be checked without delay. If neutropenia is confirmed, carbimazole should be stopped immediately. It is good practice to ensure that an FBC is checked at the same time as each follow up thyroid function test is performed.

Treatment with anti-thyroid drugs alone is a realistic option in uncomplicated Graves' disease on the basis that, after 12–18 months of treatment, 40–60% of patients will enter permanent remission.²¹ Remission is unlikely in severe disease and in those with a large goitre, and it is very unlikely in toxic nodular goitre including toxic adenoma; in such cases it is sensible to opt promptly for definitive treatment, either radioiodine or surgery. The latter is particularly suitable in older subjects with comorbidities. For a more detailed discussion readers are referred to a recent review.²¹

AMIODARONE AND THYROID DISEASE

Amiodarone is widely used for the treatment and prevention of arrhythmias such as atrial fibrillation and ventricular tachycardia; 100 mg of amiodarone contains 37 mg of iodine, and treatment results in severe iodine overload. Thyroid function abnormalities are common in patients taking amiodarone, and both frank hypothyroidism and thyrotoxicosis may occur.²²

Hypothyroidism associated with amiodarone treatment may only be temporary; if sustained it should be treated with thyroxine with the aim of keeping FT4 at the upper end of the normal range. Amiodarone induced thyrotoxicosis is serious, especially because of the potential for life threatening cardiac effects in patients who already have heart disease. Assessment is complicated by the fact that TSH concentrations are often suppressed and T4 (and FT4) values may increase above the normal range in up to 40% of patients taking amiodarone, although they are euthyroid. Diagnosis rests on the presence of typical clinical features and the finding of elevated T3 values. Two types of amiodarone induced thyrotoxicosis are recognised, depending on whether there is a predisposing thyroid abnormality or not.²³ However, it is not always easy to categorise

patients as having one or other type, and in practice the key distinction is whether they respond well to standard antithyroid drugs, possibly with the addition of potassium perchlorate, or whether high doses of steroids are needed. The other important question is whether amiodarone treatment can safely be stopped or not; even if it can, it may take several months for its effects to wane because of its very long half-life (up to 55 days).

The key role of the GP is to ensure that all patients taking amiodarone have their thyroid function measured at least every 6 months,²⁴ and to be especially vigilant if they report new symptoms at any time. Thyrotoxicosis is more likely after treatment has been established for 2–3 years, and may occur quite suddenly.²³ Hypothyroidism can be managed within primary care, but those with thyrotoxicosis should always be referred to an endocrinologist as treatment is challenging. If the patient is obviously unwell the GP should refer urgently; hospitalisation may be necessary in the most severe cases. The GP should also liaise with the cardiologist who initiated amiodarone to discuss whether it can be stopped and, if so, what antiarrhythmic drug should be used instead.

MANAGING THYROID NODULES

Many people have thyroid nodules that are visible and/or palpable, and on high definition ultrasound up to 50–70% of adults are found to have thyroid nodules.²⁵ The vast majority of thyroid nodules are benign, especially those found incidentally. The optimal management of incidentally found non-palpable thyroid nodules is controversial²⁶; a few will be histologically malignant, but the value of detecting all of these at an early stage is debatable and may cause undue anxiety to the patient

and may have other unpleasant consequences such as loading of life insurance. Current guidelines recommend that those patients with a thyroid nodule which has not changed for years, and those who have asymptomatic non-palpable thyroid nodules found incidentally which are <1 cm in diameter with no suspicious features, can be managed in primary care.²⁷ The following groups should be referred non-urgently according to local referral pathways: patients with nodules who have abnormal thyroid function tests; patients with a history of sudden onset of pain in a thyroid lump (who are likely to have bled into a benign thyroid cyst); and patients with a thyroid lump which is newly presenting or increasing in size over months.²⁷ The key investigations are thyroid imaging and fine needle aspiration cytology.

Certain clinical features are particularly suggestive of malignancy: notably large size (>4 cm), rapid growth, pain, hard consistency, fixation to adjacent structures, local lymphadenopathy, stridor (refer same day), and hoarseness.²⁷ All patients with any of these features should be urgently referred to a thyroid surgeon under the 2 week wait rule. A family history of thyroid cancer and a history of irradiation of the neck also put the patient at increased risk and are indications for urgent referral, as are thyroid nodules occurring in children.

IS THE POPULATION OF THE UK AFFECTED BY IODINE DEFICIENCY?

Lack of iodine during pregnancy and early childhood affects the development of the nervous system resulting in neurocognitive defects of varying degree; subtle effects occur even when the deficiency is mild and the visible manifestations of iodine deficiency, especially endemic goitre, are absent. For a long time it has been assumed that the diet in the UK and Ireland is iodine replete, but this does not appear to be the case²⁸—possibly placing the cognitive abilities of future generations at risk. An up-to-date picture of iodine nutrition in the UK is needed, and the British Thyroid Association is embarking on a nationwide survey to assess current iodine status. (For more information on iodine deficiency, see <http://www.iccid.org/>).

Competing interests: The author is a member and former board member of the International Council for Control of Iodine Deficiency Diseases.

Key learning points

- ▶ Most thyroid disorders can be safely and effectively managed in primary care.
- ▶ The vast majority of patients with fatigue and obesity do not have thyroid disease.
- ▶ Skin manifestations are the most commonly presenting feature in overt hypothyroidism.
- ▶ There is no plausible basis for the assertion that hypothyroidism commonly occurs despite normal thyroid function tests.
- ▶ In primary hypothyroidism the aim of treatment is to restore TSH to normal. Most patients can safely be started on a full replacement dose of thyroxine. T3 has no role in the treatment of primary hypothyroidism.
- ▶ Subclinical thyroid disease should not be treated except in certain well defined situations. Its main importance lies in the increased risk of progression to overt thyroid disease.
- ▶ The development of hyperthyroidism is easily overlooked especially in the elderly.
- ▶ Patients taking amiodarone should have their thyroid function checked every 6 months.
- ▶ Patients with overt hyperthyroidism should be referred for specialist management.
- ▶ While the vast majority of thyroid nodules are benign and do not require investigating, patients with newly occurring thyroid nodules >1 cm diameter or ones that are increasing in size should be referred—urgently if any additional suspicious features are present.

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