Endocrinology

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Thyrotoxicosis

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Thyrotoxicosis affects approximately 2% of women and 0.2% of men.[1] The causes are shown in Table 1. Graves' disease and toxic nodular goitre account for most cases. There are three major treatment options, all of which are useful but have different indications depending on the aetiology of thyrotoxicosis and the clinical features:

- thionamide drugs
- radioiodine, and
- surgery.

Clinical presentation and investigation

Classical features include weight loss, palpitation, tremor and hyperactivity. In elderly patients, apathy, depression, weight loss and deterioration of pre-existing heart disease often predominate.

If thyrotoxicosis is suspected, it is essential to confirm the diagnosis biochemically. Serum thyrotrophin (TSH) concentration should be measured. The routine use of sensitive assays for TSH enables normal values in euthyroid subjects to be distinguished from low values in thyrotoxicosis. The finding of a normal serum TSH concentration nearly always excludes thyrotoxicosis, the exception being rare cases of TSH-secreting pituitary tumours or syndromes of thyroid hormone resistance. The converse is not true: serum TSH is often reduced to low levels in patients receiving drugs such as glucocorticoids or dopamine and in 'non-thyroidal' illnesses such as chronic liver and renal disease.

If serum TSH is low, a rise in serum free thyroxine (T4) concentration confirms thyrotoxicosis. If free T4 is normal, serum free triiodothyronine (T3) should also be measured and, if raised, indicates 'T3-toxicosis'. Measurements of free T4 and free T3 have replaced total T4 and total T3 in most centres because total hormone concentrations are affected by changes in thyroid hormone binding proteins, especially T4 binding globulin, for example in pregnancy.

Graves' disease is the commonest cause of thyrotoxicosis. The diagnosis is obvious in the presence of a diffuse goitre and ophthalmopathy. Among other causes, a multinodular goitre and subacute thyroiditis should be evident from the history and examination. Thyroid antibodies (to thyroid peroxidase or thyroglobulin) are often present in cases of Graves' disease and the test is available routinely. Measurement of antibodies to the TSH-receptor (the pathogenic antibodies in this disease and detectable in about 85% of cases) is available in some centres but not indicated routinely. If the cause of thyrotoxicosis is not obvious from history and examination, thyroid isotope scanning (typically with technetium-99m) will distinguish the diffuse thyroid uptake seen in Graves' disease from patchy uptake (with one or more 'hot' nodules) in toxic nodular hyperthyroidism. If thyroiditis is suspected, measurement of iodine uptake into the thyroid is indicated. Low values identify silent or post-partum thyroiditis or iodine-induced thyrotoxicosis.

Treatment of thyrotoxicosis

Beta-adrenergic receptor antagonists can be used for symptomatic relief before results of thyroid function tests are

Table 1. Causes of thyrotoxicosis.

Cause	Mechanism
Common	
Graves' disease	Thyroid-stimulating antibodies
Toxic nodular goitre	Single or multiple autonomous nodules
Thyroiditis:	Inflammation-induced release of T4 and T3
Subacute	
Silent	
Postpartum	
Rare	
Neonatal thyrotoxicosis	Transplacental passage of antibodies
Inappropriate secretion of TSH	Pituitary tumour
	Syndrome of resistance to thyroid hormone
Exogenous iodide/thyroid hormones	
Thyroid cancer	Functioning metastases
Choriocarcinoma	HCG stimulation of thyroid

HCG = human chorionic gonadotrophin; T3 = triiodothyronine; T4 = thyroxine; TSH = thyrotrophin.

Key Points

The diagnosis of thyrotoxicosis must be confirmed biochemically

Antithyroid drugs (eg carbimazole) can be used short-term to prepare patients for definitive therapy or long-term (ca 18 months) to induce remission in Graves' disease

Thionamides induce long-term remission in fewer than 50% of patients with Graves' disease and never in toxic nodular hyperthyroidism

All patients prescribed a thionamide must be warned of the risk of agranulocytosis

Radioiodine is the treatment of choice for most cases of Graves' hyperthyroidism, especially if relapsed after drug therapy, and in toxic nodular hyperthyroidism

Thyroidectomy is useful in selected patients with thyrotoxicosis; total thyroidectomy is increasingly considered the operation of choice

KEY WORDS: Graves' disease, radioiodine, thionamides, thyroidectomy, thyrotoxicosis

known in suspected cases, and are useful short-term (typically 1–3 months) in patients with confirmed thyrotoxicosis until rendered euthyroid. Propranolol is often prescribed, but longer-acting agents such as atenolol, nadolol or long-acting propranolol may result in better compliance and symptom control.

A consensus document outlining good practice recommends that all patients with thyrotoxicosis should be referred to an endocrinologist at presentation.[2]

Antithyroid drugs: thionamides

The thionamide drugs, carbimazole and propylthiouracil, are the mainstays of drug treatment. They act by inhibiting organification of iodide and coupling of iodothyronines, hence blocking synthesis of thyroid hormones. They are equally effective, although carbimazole is preferred because it can be administered once daily, in contrast to propylthiouracil that requires at least twice daily administration.

Thionamides are given short-term (typically 1–3 months) to prepare patients for definitive therapy with radioiodine or surgery, or long-term (12–24 months) in the hope of inducing remission in Graves' disease. In subjects with Graves' disease, however, long-term remission follows a course of thionamides in fewer than 50% of cases. Remission is less likely in those with severe disease (judged biochemically at

presentation), those with significant goitre, in men, and if treatment courses are short. The minimum duration of therapy should be 12–24 months after achieving euthyroidism.[3,4] Since remission rates with carbimazole are low, many centres reserve full courses for young women with a first episode of Graves' thyrotoxicosis, while men, older subjects and those with relapsed disease are treated only in preparation for definitive therapy. Thionamides do not induce remission in toxic nodular hyperthyroidism and are ineffective in thyroiditis.

Reducing dose regimen. Carbimazole is usually given in reducing doses, starting with 10–30 mg once daily, measuring serum free T4 every 4–6 weeks, and titrating the dose gradually according to free T4 until a maintenance dose of 5–10 mg daily is achieved. A rise in serum TSH above normal indicates the need for dose reduction, but suppression of TSH may persist for many months. When a maintenance dose has been achieved, the interval between tests can be extended to several months. Equivalent doses of propylthiouracil are 100–300 mg daily as starting treatment, reducing to 50–100 mg daily.

Block-replace regimen. An alternative to the reducing dose regimen is the 'block-replace' regimen. When euthyroidism has been restored by carbima-

zole alone, high-dose carbimazole (30–40 mg daily) is then given in combination with T4 replacement therapy (100–125 μg daily). This may have the advantage of avoiding iatrogenic hypothyroidism and reducing the frequency of biochemical testing. The use of higher doses of carbimazole is, however, associated with more side effects, and optimism that this regimen would improve remission rates in Graves' disease has not been sustained.

Side effects (Table 2). Agranulocytosis (granulocyte count <500/mm^3) is the most common serious side effect, occurring in approximately three in 1,000 patients. It is idiosyncratic, but is most frequent early during treatment and with high doses. It is mandatory that all subjects prescribed thionamides are instructed to seek an urgent full blood count if they develop fever or sore throat. The prognosis is good if the thionamide is promptly withdrawn and appropriate supportive therapy given. Since bone marrow suppression develops rapidly, routine monitoring of white cell counts is not recommended by most experts. The development of serious side effects with any thionamide represents an absolute contraindication to further therapy with these drugs.

Radioiodine therapy

Iodine-131 is increasingly used as first-line therapy for thyrotoxicosis due to Graves' disease; it is the treatment of

Table 2. Side effects of thioamides.

Serious	
Rare	Agranulocytosis
Very rare	Hepatitis
	Cholestatic jaundice
	Thrombocytopenia
	Aplastic anaemia
	Lupus-like syndromes
Minor	
Common	Pruritus
	Rash
	Arthralgia
	Abnormal taste sensation
Uncommon	Gastrointestinal upset

choice for toxic nodular hyperthyroidism and in most cases of relapsed Graves' disease.[5] Nearly all patients will be cured after administration of one or two doses, a few requiring three. Radioiodine is as effective in toxic nodular goitre as in Graves' disease and similar doses should be given.[6]

Contraindications. Iodine-131 is contra-indicated in pregnancy (since it may ablate the fetal thyroid) and in breast feeding (because it is concentrated in breast milk). It is relatively contraindicated in children because of the theoretical risk of carcinogenesis, and also if ophthalmopathy is present in patients with Graves' hyperthyroidism because of evidence of eye deterioration after radioiodine. In those with stable thyroid eye disease prescribed radioiodine, a course of glucocorticoid therapy is often given to reduce the likelihood of this deterioration.[7]

Administration of radioiodine. It has not proved possible to titrate radioiodine doses precisely (by estimating thyroid size or measuring isotope uptake) to guarantee cure but avoid hypothyroidism. Most centres administer a fixed dose of iodine-131 (400–600 MBq). Approximately one-third of patients so treated will require a further dose (usually administered after an interval of six months) and approximately half will become hypothyroid (and require T4 replacement therapy).[8] Some favour larger doses of iodine-131, which predictably cure thyrotoxicosis at the cost of hypothyroidism.

Thionamides should be withdrawn for at least four days before and after radioiodine. Patients with mild thyrotoxicosis (typically mild toxic nodular hyperthyroidism) may not require pretreatment with carbimazole; others are usually pretreated until rendered euthyroid to reduce the small risk of thyroid storm associated with radiation-induced thyroiditis.

Side effects (other than hypothyroidism) are uncommon after radioiodine; sore throat or thyroid swelling occasionally occur. Thyroid function should be assessed 4–6 weeks after iodine-131 therapy and thereafter at similar intervals until cure is evident. If thionamides have been commenced post-radioiodine, they should be discontinued after four months to determine whether further doses are required. For those not rendered hypothyroid in the short-term it is important that a follow-up system is in place to ensure regular biochemical monitoring. Extensive studies have shown no increase in cancer risk after radioiodine therapy for thyrotoxicosis. A possible, but small increase in thyroid cancer risk is likely to reflect underlying thyroid disease rather than iodine-131.[9]

Radioiodine can be administered only by those who hold a licence and have nuclear medicine facilities. All patients must be warned of restrictions placed upon close physical contact with others for a period of up to three weeks. The need for assistance with physical care, or factors such as dementia or incontinence, sometimes determine that frail or elderly patients are better treated with long-term thionamides.

Surgery

Surgery is usually reserved for those patients:

- who have a large goitre
- who decline radioiodine
- with ophthalmopathy, or
- who require rapid cure before pregnancy.

Patients undergoing surgery must be rendered euthyroid before operation to reduce the risk of 'thyroid storm' (see below). Carbimazole is the standard pre-operative preparation. Lugol's iodine and beta-adrenergic receptor blockers are no longer considered adequate[2] unless there is a contraindication to thionamides. Complications such as recurrent laryngeal nerve palsy, hypoparathyroidism and bleeding into the neck are uncommon (<1%) with experienced thyroid surgeons.

Partial thyroidectomy is associated with medium- and long-term risk of recurrence of thyrotoxicosis (5–20%), and total thyroidectomy is increasingly considered the operation of choice in large centres. Subjects treated by partial thyroidectomy need long-term follow-up to detect recurrent thyrotoxicosis or late hypothyroidism, which occurs in about 50%. A transient rise in serum TSH in the first six months after partial thyroidectomy need not indicate permanent hypothyroidism.

Thyrotoxicosis and the heart

Cardiovascular symptoms and signs are common in thyrotoxicosis. About 15% develop atrial fibrillation (AF) or other dysrhythmias and there is evidence for increased cardiovascular mortality in the early years after treatment.[10] Unless contraindicated, warfarin therapy is recommended for those with thyrotoxic AF because of embolic complications. Rapid cure of thyrotoxicosis (usually with radioiodine) is important in this group of patients who, when rendered permanently euthyroid, should be considered for pharmacological or electrical cardioversion. This is more likely to be successful if the duration of sustained AF is short.

The antiarrhythmic amiodarone is an iodine-containing drug, and itself causes thyrotoxicosis in about 5% of patients treated. Even in euthyroid subjects, amiodarone results in a moderate increase in serum free T4 (reflecting its effect on conversion of T4 to T3). Therefore, thyrotoxicosis should be diagnosed only if there is a rise in serum free T3 and suppression of TSH. Most cases respond to thionamide treatment alone, although adjunctive therapies with glucocorticoids or perchlorate may be required.[11] Radioiodine is ineffective because of the iodine load associated with amiodarone, and amiodarone withdrawal often fails to help because of its long half-life.

Thyrotoxicosis in pregnancy and postpartum

Pregnant women with established thyrotoxicosis should be treated with a thionamide.[12] Propylthiouracil is often considered the drug of choice both because less crosses the placenta and into breast milk than carbimazole and

because of the possible association of carbimazole with the extremely rare congenital abnormality aplasia cutis. The drug chosen should be prescribed at the lowest effective dose that can maintain serum free T4 in the normal range and to reduce the likelihood of fetal goitre and hypothyroidism. Thyrotoxicosis due to Graves' disease is usually easy to manage after the first trimester, and drug doses can be progressively reduced. Graves' hyperthyroidism typically relapses in the postpartum period, necessitating an increase in thionamide doses.

Graves' hyperthyroidism

Graves' hyperthyroidism sometimes presents in early pregnancy, but must be distinguished from a rise in serum thyroid hormones associated with hyperemesis gravidarum since the latter remits spontaneously after a period of days or weeks. Persistent biochemical hyperthyroidism and clinical findings of goitre or ophthalmopathy mean that Graves' disease is more likely and should prompt cautious initiation of antithyroid drugs. Similarly, abnormal tests of thyroid function in the postpartum period may reflect either development of Graves' disease or postpartum thyroiditis. The latter occurs in the first 6–12 months after delivery and is more common in those with thyroid autoantibodies and a past history of Graves' disease.

The distinction between Graves' hyperthyroidism and postpartum thyroiditis is important since the former requires thionamides, whereas rises in serum T4 and T3 in postpartum thyroiditis settle spontaneously and require only symptomatic therapy with a beta-adrenergic receptor blocker. A phase of hypothyroidism commonly occurs.[13]

Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a reduction in serum TSH with normal serum thyroid hormone concentrations. It is a common biochemical finding, being present in up to 5% of subjects aged over 60 years.[14] Reduction in TSH may reflect drug therapy or illness states, but it also serves as a marker of mild thyroid hormone excess, especially in those with multinodular goitre or previous Graves' disease. There is increasing evidence that such mild thyroid hormone excess is a risk factor for development of atrial fibrillation[15] and for cardiovascular mortality in elderly subjects.[16] The finding of low serum TSH should therefore prompt follow-up to identify progression to overt hyperthyroidism and early intervention with antithyroid therapy. Some centres, especially in the USA, consider radioiodine therapy important in those with persistent suppression of TSH and other cardiovascular risk factors.

Thyrotoxic crisis (thyroid storm)

Severe thyrotoxicosis, with tachycardia, fever, agitation and weakness (thyroid storm), is a medical emergency. It is rare, but typically observed in elderly patients with unsuspected thyrotoxicosis undergoing surgery. There are no controlled trials of therapy. Treatment is supportive, particularly with intravenous fluids and glucocorticoids. Propylthiouracil is recommended (100 mg every 6 hours by mouth or nasogastric tube), as well as potassium iodide as aqueous oral iodine solution (Lugol's iodine) 0.1–0.3 ml three times daily, to block thyroid hormone release. High doses of a beta-adrenergic receptor blocker should also be given.

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Adult growth hormone deficiency

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Growth hormone (GH) has an important physiological role in adulthood.[1–3] Before the 1980s anecdotal reports suggested that patients lacking GH experienced symptoms of increased fatigue and low mood, features that improved with GH replacement.[4] Long-term replacement was not considered because of the lack of availability of cadaveric GH. With the development of recombinant GH in the mid-1980s, interest has been increasing in the consequences of GH deficiency (GHD) and the effects of short- and long-term replacement. Adults with hypopituitarism and GHD are both psychologically and physically less healthy than age-matched controls.

This has led to the description of a specific constellation of symptoms and signs, designated the 'adult GHD syndrome'[5] which includes:

- poor self-esteem
- increased levels of anxiety
- lack of social interaction, and
- abnormalities of metabolism, body composition and bone mineralisation.

There has also been considerable interest in the physiological decline in GH secretion with ageing. Integrated GH secretion decreases by approximately 14% per decade in adult life, although peak response to stimulation is still maintained. The effect of GH replacement in older patients has been examined in placebo-controlled trials, but as yet there is little evidence of consistent improvement and this issue will not be considered further here.

Adult-onset growth hormone deficiency

Adult-onset GHD is due to pituitary or peripituitary disease or is a consequence of treatment. The commonest cause (70% of cases) is non-functioning pituitary adenoma. Other causes are shown in Table 1.[6] The prevalence of

Table 1. Causes of growth hormone (GH) deficiency in the first 2,753 adult patients consecutively enrolled into the KIMS* database.[6]

Diagnosis	Patients	
	No.	%
Non-functioning pituitary adenoma	844	30.7
ACTH-secreting pituitary adenoma	200	7.3
GH-secreting pituitary adenoma	55	2.0
Prolactin-secreting pituitary adenoma	305	11.1
Gonadotrophin-secreting pituitary adenoma	11	0.4
TSH-secreting pituitary adenoma	6	0.2
Pituitary tumour – secretory status unknown	40	1.5
Craniopharyngioma	357	13.0
Surgery**	25	0.9
Irradiation**	54	2.0
Idiopathic	353	12.8
Trauma	55	2.0
Other	448	16.3
Total	*2,753*	

* A pharmaco-epidemiological survey of adult GHD and replacement, which has been running since 1994, with approximately 7,500 patients currently registered.
** The terms surgery and irradiation refer to indications other than pituitary adenoma.
ACTH = adrenocorticotropic hormone; TSH = thyrotrophin.