

# Thyrotoxicosis – investigation and management

Author: Jackie Gilbert<sup>A</sup>

## ABSTRACT

Graves' disease (GD) and toxic nodular (TN) goitre account for most cases of thyrotoxicosis associated with hyperthyroidism. Hyperthyroidism is confirmed with measurement of a suppressed serum thyrotropin concentration (TSH) and elevated free thyroid hormones. The three therapeutic options are antithyroid drugs, radioactive iodine and surgery. Thionamides achieve long-term remission in 35% of cases. Many centres administer fixed doses of iodine-131; larger doses result in improved rates of cure at the cost of hypothyroidism. Surgery is usually considered for patients who have a large goitre, compressive symptoms or significant ophthalmopathy.

## Introduction

Thyrotoxicosis describes disorders of excess thyroid hormone with or without the increased synthesis of thyroid hormone (hyperthyroidism).

In the UK, the prevalence of hyperthyroidism is ~2% in women and 0.2% in men.<sup>1</sup> Incidence is highest in Caucasians and in iodine-deficient areas and rises with age.<sup>2</sup>

## Aetiologies

Graves' disease (GD) and toxic nodular (TN) goitre account for most cases of thyrotoxicosis associated with hyperthyroidism. GD accounts for ~80% of cases in iodine-replete areas, whereas TN disease accounts for 50% of cases in iodine-deplete areas<sup>3</sup> (Table 1).

## Presentation

Symptom severity demonstrates moderate correlation with biochemical severity<sup>4</sup> and cardiovascular features often predominate (Table 2). Increasing age, male sex and underlying cardiovascular disease are risk factors for atrial fibrillation (AF),<sup>5</sup> an independent predictor of mortality. Older patients present more frequently with weight loss and cardiovascular decompensation.<sup>6</sup>

## Investigation

Overt hyperthyroidism is confirmed with measurement of serum thyrotropin concentration (TSH), which is usually

undetectable (<0.01 mU/L) because of negative feedback of thyroid hormones on the anterior pituitary. A normal serum TSH nearly always excludes thyrotoxicosis, except in rare cases of TSH-secreting pituitary adenomas or syndromes of thyroid hormone resistance. Free thyroxine (T4) concentrations are usually elevated in overt hyperthyroidism. If the TSH is suppressed and the free T4 is normal, serum free triiodothyronine (T3) concentrations should be measured to assess for T3 toxicosis, which may represent the earliest stage of hyperthyroidism.

Diagnosing GD may be clear from the clinical features, especially if extrathyroidal manifestations are evident. GD may be confirmed by measurement of TSH-receptor antibodies.<sup>7</sup> However, TSH-receptor antibodies may decline and may not be detectable if measured after antithyroid drugs have been commenced.

If the cause of thyrotoxicosis is unclear, thyroid isotope scanning (with technetium-99m) will distinguish focal uptake with one or more 'hot' nodules in TN disease, unless there has been recent exposure to iodine (eg radiocontrast). GD is characterised by diffuse increased uptake in both thyroid lobes. Uptake is very low or absent in thyroiditis, factitious ingestion of thyroid hormone or iodine-induced thyrotoxicosis.

## Key points

Graves' disease and toxic nodular goitre account for most cases of thyrotoxicosis associated with hyperthyroidism

The main therapeutic options are antithyroid drugs, radioactive iodine and surgery

In Graves' disease, carbimazole and propylthiouracil achieve long-term remission in approximately 35% of cases (titration or block and replace regimen)

Patients prescribed carbimazole or propylthiouracil should be advised of the risk of agranulocytosis

Progression of subclinical hyperthyroidism to overt hyperthyroidism is more likely if the TSH<0.01 mU/L

KEYWORDS: Grave's disease, radioiodine, thionamides, thyroidectomy, thyrotoxicosis ■

Author: <sup>A</sup>consultant in endocrinology and general internal medicine, King's College Hospital, Denmark Hill, London

**Table 1. Causes of thyrotoxicosis**

<b>Thyrotoxicosis associated with hyperthyroidism</b>	
<b>Aetiologies (common)</b>	<b>Mechanism</b>
Graves' disease	Thyrotropin receptor antibodies stimulate the thyroid-stimulating hormone (TSH) receptor
Toxic multinodular goitre	Activating mutations in TSH receptor or G proteins
Solitary toxic adenoma	Functional autonomy within a benign lesion
<b>Aetiologies (uncommon)</b>	<b>Mechanism</b>
TSH secreting pituitary adenoma	Pituitary adenoma
Pituitary resistance to thyroid hormone	Mutation of thyroid hormone receptor $\beta$
Neonatal Graves' disease	Thyroid stimulating immunoglobulins
Choriocarcinoma	Human chorionic gonadotropin
Hyperemesis gravidarum	Human chorionic gonadotropin
Congenital hyperthyroidism	Activating mutations in TSH receptor
Struma ovarii	Toxic adenoma within dermoid tumour of the ovary
Metastatic follicular thyroid carcinoma	Foci of functional autonomy
Iodine or iodine containing drugs	Jod-Basedow phenomenon; excess iodine results in unregulated thyroid hormone production
<b>Thyrotoxicosis not associated with hyperthyroidism</b>	
<b>Aetiologies (common)</b>	<b>Mechanism</b>
Thyroiditis Painless including postpartum	Autoimmune, release of stored thyroid hormones
Sub-acute thyroiditis	Viral infection, release of stored thyroid hormones
Exogenous thyroid hormone	Iatrogenic or factitious excess ingestion of thyroid hormone
<b>Aetiologies (uncommon)</b>	<b>Mechanism</b>
Drug induced thyroiditis	Destruction of thyroid follicles
Acute infectious thyroiditis	Bacterial or fungal thyroid infection
Radiation induced thyroiditis	Radioactive iodine induced thyrocyte destruction
Thyroid adenoma infarction	Release of stored hormones

## Treatments

Beta blocking agents are useful for symptom control, especially in older patients, and those with cardiovascular disease. Propranolol is often prescribed but longer acting agents, eg atenolol, may result in improved compliance. Oral calcium channel blockers, eg verapamil and diltiazem, may also be used

**Table 2. Symptoms and signs of thyrotoxicosis**

	<b>Symptoms</b>	<b>Signs</b>
Cardiovascular	Palpitations, shortness of breath	Tachycardia, hypertension, atrial arrhythmia, high output cardiac failure
Gastrointestinal	Increased appetite	Weight loss
Central nervous system	Emotional lability, poor concentration, agitation	Hyperactivity, agitation
Eyes (usually in Graves' disease)	Soreness, grittiness	Periorbital oedema, lid retraction and lid lag, conjunctival injection, ophthalmoplegia
Thyroid	Neck swelling	Goitre
Muscles	Weakness, tremor	Tremor, muscle wasting
Skin	Sweating, heat intolerance	Increased sweating
Hair	Hair thinning	Hair loss
Peripheral nervous system		Hyperreflexia
Reproductive system		Oligomenorrhoea. Reduced fertility (women)

to reduce the pulse rate of patients who cannot tolerate beta blockers.

The main therapeutic options are antithyroid drugs (thionamides), radioactive iodine and surgery.

Treatment should consider goitre size, timing of future pregnancies, the presence of significant comorbidities and patient preference. A randomised study demonstrated similar quality of life for all approaches although radioiodine was most cost-effective.<sup>8</sup>

## Antithyroid drugs (thionamides)

Carbimazole and propylthiouracil (PTU) are the drug treatments of choice for GD. Methimazole is the active metabolite of carbimazole. Their mode of action inhibits organification of iodide and coupling of iodothyronines, blocking thyroid hormone synthesis. PTU also inhibits peripheral monodeiodination of T<sub>4</sub> to T<sub>3</sub>. The serum half-life of methimazole is 6–8 hours whereas the half-life of PTU is 1–2 hours. Carbimazole is administered once daily, whereas PTU is taken two to three times per day. Compliance with the more frequent dosing schedule of PTU has been reported to be lower than with once-daily methimazole. These factors and the side effect profile of PTU have led to carbimazole being the preferred antithyroid drug for most patients.

## Monotherapy titration regimen

Carbimazole is dosed initially at 10–40 mg daily. The fT<sub>4</sub> is measured every 4–6 weeks, titrating the dose until a maintenance of 5–10 mg is achieved. Thereafter, the testing

interval may be extended to several months. Treatment continues for 12–18 months.<sup>9</sup> Equivalent starting doses of PTU are 100–300 mg daily, with a maintenance dose of 50–100 mg daily.

### Block and replace regimen

This is an alternative to titration monotherapy. When carbimazole alone (dose 30–40 mg daily) has restored euthyroidism, thyroxine replacement (100–125 µg daily) commences. This may avoid iatrogenic hypothyroidism and reduce the frequency of biochemical testing. Treatment duration may be 6 months but may be continued for longer, especially in the context of significant thyroid eye disease. Some clinicians also utilise this approach when thyroid function has demonstrated marked fluctuation during treatment.

Either protocol achieves long-term remission in approximately 35% of cases.

### Side effects

#### *Agranulocytosis*

Agranulocytosis (granulocyte count  $<5,000/\text{mm}^3$ ) is the most serious side effect, occurring in approximately 1–3/1,000. It is idiosyncratic, but is most frequently seen early in treatment and with higher doses ( $>40$  mg carbimazole). PTU at any dose appears more likely to cause agranulocytosis compared with low doses of carbimazole.<sup>10</sup> All subjects prescribed thionamides should be advised and provided with written information to stop thionamide therapy and undertake an urgent assessment of white cell count if they develop a fever or sore throat. Routine monitoring of the white cell count is not recommended.

#### *Hepatotoxicity*

Carbimazole hepatotoxicity may be cholestatic or hepatocellular. PTU can cause fulminant hepatic necrosis that may be fatal, necessitating liver transplantation in some cases.<sup>11</sup>

### Radioactive iodine therapy

Iodine-131 may be used as a first-line therapy for thyrotoxicosis due to GD. It is the treatment of choice for TN disease and in many cases of relapsed GD. It is contraindicated in pregnancy (as it may ablate the fetal thyroid) and in breastfeeding (because of concentration in breast milk). In those with stable thyroid eye disease prescribed radioiodine, a course of glucocorticoid therapy is often given to reduce the likelihood of a clinical deterioration.

### Administration of radioactive iodine

It has not proved possible to titrate radioiodine doses precisely (by estimating thyroid size or measuring isotope uptake) to guarantee cure while avoiding hypothyroidism. Many centres administer fixed doses of iodine-131 (370–740 MBq). Others favour larger doses, which result in greater control of thyrotoxicosis at the cost of hypothyroidism. A long-term increase in cardiovascular and cerebrovascular deaths has been reported after radioiodine therapy not resulting in hypothyroidism.<sup>12</sup>

Thionamides should be withdrawn for at least 4 days before and after radioiodine.<sup>13</sup> Patients with mild thyrotoxicosis may not require pre-treatment with carbimazole; others may be rendered euthyroid to reduce the small risk of thyroid storm

associated with radiation-induced thyroiditis. Uncommon side effects include thyroid swelling and sore throat. Thyroid function should be reassessed at 4–6 weeks after iodine-131 therapy and thereafter at similar intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement. Studies have shown no increase in cancer risk after radioiodine therapy for thyrotoxicosis.<sup>14</sup> A possible, but small, increase in thyroid cancer risk is likely to reflect underlying thyroid disease rather than the effect of iodine-131. It appears that patients with TN disease have a higher incidence of thyroid and extrathyroidal malignancy after iodine-131 therapy compared with patients with GD, but this may be due to the confounding influence of smoking and age.

Radioiodine can only be administered by those with a licence and nuclear medicine facilities. Patients are warned of restrictions on close physical contact with others for up to four weeks, especially if higher doses are used. The need for assistance with physical care or comorbidities such as cognitive impairment or incontinence make long-term thionamides (5–10 mg daily) more appropriate for some older, frail patients.

### Surgery

Surgery is usually considered for patients who have a large goitre, compressive symptoms, or significant ophthalmopathy or who require rapid cure before pregnancy.

Patients must be rendered euthyroid pre-surgery to reduce the risk of ‘thyroid storm’. Lugol’s iodine may be given for 10 days prior to surgery for GD, where the operation of choice is a total thyroidectomy.

Complications such as recurrent laryngeal nerve injury, hypoparathyroidism and bleeding necessitating reoperation are uncommon ( $<1\%$ ) when surgery is undertaken by a high-volume thyroid surgeon.<sup>15</sup>

### Thyrotoxicosis in pregnancy and postpartum

Pregnant women with confirmed thyrotoxicosis should be treated with a thionamide using the lowest effective dose that maintains the serum free T4 within the normal range. PTU was preferred because less crosses the placenta and into breast milk. Carbimazole rarely is associated with teratogenicity.<sup>16</sup> Defects include aplasia cutis and choanal atresia. An increased rate of birth defects was also reported after PTU exposure in early pregnancy.<sup>17</sup> However, these tend to be less severe. Concerns about PTU-related hepatotoxicity have led to recommendations that PTU be used for patients in their first trimester of pregnancy. GD typically relapses postpartum, necessitating an increase in thionamide dose.

Thyroidectomy is avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with anaesthetic agents and increased risk of fetal loss (first trimester) and pre-term labour (third trimester). Thyroidectomy may be performed in the second trimester. Abnormal thyroid function tests in the postpartum period may reflect either GD or postpartum thyroiditis. The latter usually occurs in the first 6–12 months after delivery, more commonly in patients with positive thyroid autoantibodies. It settles spontaneously and requires symptomatic therapy alone with beta blockade. A phase of hypothyroidism commonly

occurs, which may be permanent in ~25% of cases, especially in women who presented with higher TSH levels and higher titres of thyroid peroxidase antibodies. The recurrence rate of postpartum thyroiditis is also high, with 70% of women with a prior episode of postpartum thyroiditis developing a recurrence in the subsequent pregnancy.

### Subclinical hyperthyroidism

This is defined as a low serum TSH with normal serum thyroid hormone concentrations. It occurs in up to 5% of subjects aged >60 years and is a risk factor for developing AF. Progression to overt hyperthyroidism appears more likely if the TSH <0.01 mU/L, rather than being low but detectable (0.01–0.4 mU/L).<sup>18</sup>

### Thyroid storm

Severe thyrotoxicosis with tachycardia and hyperpyrexia is a medical emergency. It usually occurs in older patients, in whom mortality rates are 8–25%. Precipitants include cessation of thionamides and acute illness in a patient with unrecognised or untreated thyrotoxicosis. Treatment is supportive with intravenous fluids, corticosteroids and beta blockade. PTU is recommended 100 mg 6 hourly by mouth or nasogastric tube with Lugol's iodine 0.1–0.3 mL three times per day to block thyroid hormone release. ■

### Conflicts of interest

The author has no conflicts of interest to declare.

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**Address for correspondence: Dr Jackie Gilbert, Department of Endocrinology, King's College Hospital, Denmark Hill, London SE5 9RS.**  
**Email: jackiegilbert@nhs.net**