Thyrotoxicosis

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Thyrotoxicosis is a common disorder, especially in women. The most frequent cause is Graves' disease (autoimmune hyperthyroidism). Other important causes include toxic nodular hyperthyroidism, due to the presence of one or more autonomously functioning thyroid nodules, and thyroiditis caused by inflammation, which results in release of stored hormones. Antithyroid drugs are the usual initial treatment (thionamides such as carbimazole or its active metabolite methimazole are the drugs of choice). A prolonged course leads to remission of Graves' hyperthyroidism in about a third of cases. Because of the low remission rate in Graves' disease and the inability to cure toxic nodular hyperthyroidism with antithyroid drugs alone, radioiodine is increasingly used as first line therapy, and is the preferred choice for relapsed Graves' hyperthyroidism. Total thyroidectomy is an option in selected cases. Future efforts are likely to concentrate on novel and safe ways to modulate the underlying disease process rather than stopping excess thyroid hormone production.

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Introduction

Thyrotoxicosis is a disorder of excess thyroid hormone, whereas the term hyperthyroidism specifically describes increased thyroid hormone synthesis and secretion. The tissue effects of high concentrations of thyroid hormones have many clinical manifestations. Two main hormones are synthesised and released by the thyroid: thyroxine (T4) and triiodothyronine (T3). T4 is a prohormone and is present in higher concentrations than T3, whereas T3 is biologically active through interaction with specific nuclear receptors that are present in nearly all tissues. T3 regulates energy production and metabolic rate and has profound effects on cardiac, hepatic, and neuromuscular function, as well as on fetal and postnatal growth and development.

Hyperthyroidism is common; for example, in the USA population prevalence is 1·3% [1] and in the UK it is 2% in women and 0·2% in men.[2] In the USA the incidence among women has been reported as 0·38 per 1000 per year,[1] with figures in Scotland of 0·77 per 1000 women per year and 0·14 per 1000 men per year.[3] Incidence increases with age[3] and is highest in white populations[1] and in iodine-deficient areas. However, in a screening study of almost 6000 participants older than 65 years undiagnosed hyperthyroidism was uncommon at 0·3%, with subclinical (mild) hyperthyroidism identified more frequently at 2·1%.[4]

Causes of thyrotoxicosis and hyperthyroidism

Thyrotoxicosis can be associated with hyperthyroidism or can also occur in the absence of increased thyroid hormone secretion (table 1). The most common cause of thyrotoxicosis is Graves' disease, in which autoantibodies bind to and stimulate the thyrotropin (also called thyroid-stimulating hormone [TSH]) receptors found on the surface of thyroid follicular cells, which results in excess production of T3 and T4. The next most common cause is autonomous overproduction of thyroid hormones by one (solitary toxic adenoma) or more (toxic multinodular goitre) nodules within the thyroid. The frequency of these causes varies with iodine intake. Graves' hyperthyroidism accounts for about 80% of cases in areas of adequate iodine intake, whereas toxic nodular hyperthyroidism is accountable for 50% of cases in areas of low iodine intake,[5] the latter showing the natural history of goitre development, growth of new nodules, and development of thyroid autonomy over time. Iodine fortification in areas of iodine deficiency results in a temporary increase in incidence of thyrotoxicosis of all types,[6] which shows the complex relation between iodine status and thyroid autonomy. Thyroiditis, in which destruction of thyroid cells causes release of thyroid hormones into the circulation, is implicated in about 10% of thyrotoxicosis cases. Other causes include exogenous thyroid hormone excess, drug-induced hyperthyroidism, TSH-secreting pituitary adenomas, and pituitary resistance to thyroid hormones as outlined in table 1.

Graves' hyperthyroidism is one of the most common autoimmune diseases and frequently co-occurs with other autoimmune disorders such as rheumatoid arthritis, which suggests shared pathogenesis.[7] Almost half of people with Graves' hyperthyroidism have a family history of thyroid dysfunction,[8] consistent with a strong genetic influence. Twin concordance studies suggest that up to 80% of susceptibility can be attributed to genetic factors, whereas the other 20% is associated with environmental influences.[9] Three gene regions consistently linked to Graves' hyperthyroidism are the

Search strategy and selection criteria

We searched the Cochrane library (January, 2003–December, 2010), Medline (January, 1995–December, 2010), and Embase (January, 1995–December, 2010) with the terms hyperthyroidism, thyroiditis, Graves' disease, thyrotoxicosis, nodular goitre, radioactive iodine therapy, and antithyroid drugs. We largely selected original contributions and systematic reviews published in the past 5 years, but additionally cited important and frequently referenced older publications. We searched the reference lists of selected articles identified by the search strategy. We also cited key reviews and editorials that provide detailed insight into relevant topics beyond the scope of the Seminar.

human leucocyte antigen region, *CTLA4*, and *PTPN22*, all of which encode proteins that are involved in immune function and linked to the cause of other autoimmune disorders. Genetic studies have shown an association between the TSH receptor (TSHR) gene and altered mRNA isoform expression, dependent on the genotype.[10] Infection with *Yersinia enterocolitica* might be involved in Graves' disease pathogenesis through molecular mimicry of the TSHR.[11] Other environmental factors have yet to be identified, except for cigarette smoking, which is a well established risk factor for Graves' hyperthyroidism.[12,13]

	Pathogenic mechanism
Common causes	
Thyrotoxicosis associated with hyperthyroidism	
Production of abnormal thyroid stimulator	
Graves' disease	TSHR-stimulating antibody
Thyroidal autonomy	
Toxic multinodular goitre	Activating mutations in TSHR or G-proteins
Solitary toxic adenoma	Focus of functional autonomy, benign tumour
Thyrotoxicosis not associated with hyperthyroidism	
Inflammatory disease (thyroiditis)	
Silent (painless) thyroiditis (including post-partum)	Release of stored hormones, autoimmune
Subacute thyroiditis	Probable viral infection
Extrathyroidal source of hormone	
Exogenous thyroid hormone	Excess intake of thyroid hormone (iatrogenic or factitious)
Uncommon causes	
Thyrotoxicosis associated with hyperthyroidism	
Production of thyroid-stimulating hormones	
TSH-secreting pituitary adenoma	Pituitary adenoma
Pituitary resistance to thyroid hormone	Mutated thyroid hormone receptor-β with greater expression in the pituitary than in peripheral tissues
Neonatal Graves' disease	Thyroid-stimulating immunoglobulins
Choriocarcinoma	Human chorionic gonadotropin secretion
Hyperemesis gravidarum	Human chorionic gonadotropin secretion
Thyroidal autonomy	
Congenital hyperthyroidism	Activating mutations in the TSHR
Struma ovarii	Toxic adenoma in dermoid tumour of ovary
Metastatic follicular thyroid carcinoma	Foci of functional autonomy
Drug-induced hyperthyroidism	
Iodine, iodine-containing drugs (eg, amiodarone) and radiographic contrast agents	Jod-Basedow phenomenon; excess iodine results in unregulated thyroid hormone production
Thyrotoxicosis not associated with hyperthyroidism	
Inflammatory disease	
Drug-induced thyroiditis (eg, amiodarone, interferon alfa, lithium)	Destruction of thyroid follicles, direct toxic drug effects
Acute infectious thyroiditis	Thyroid infection (eg, bacterial, fungal)
Radiation thyroiditis	Cell destruction caused by radioactive iodine
Infarction of thyroid adenoma	Release of stored hormones
Extrathyroidal source of hormone	
"Hamburger" thyrotoxicosis	Ingestion of contaminated food

TSHR=thyroid-stimulating hormone receptor. TSH=thyroid-stimulating hormone.

Table 1: **Causes of thyrotoxicosis and hyperthyroidism**

Clinical presentation and long-term consequences

Excess thyroid hormones affect every physiological system (table 2). These effects are caused by T3 uptake by specific membrane transporters such as monocarboxylate transporter 8 and interaction of intracellular T3 with nuclear receptors that regulate transcription of many different genes (figure 1). T3 also has some non-genomic effects and excess T3 results in enhancement of beta-adrenergic receptor activity.

Cardiovascular symptoms and signs often predominate. Increased heart rate and supraventricular ectopic activity are seen in patients with otherwise healthy hearts.[14] Atrial fibrillation, which is an independent predictor of mortality,[15] is one of the most serious consequences and was evident in 6% of a consecutive case-control series of hyperthyroid patients. A population-based study showed that 8·3% of hyperthyroid participants had a new diagnosis of atrial fibrillation within 30 days of diagnosis of hyperthyroidism.[16] These studies showed that increasing age, male sex, and underlying cardiovascular disease are risk factors for development of atrial fibrillation. Additionally, a combination of reduced systemic vascular resistance and increased venous return, blood volume, myocardial contractility, and oxygen consumption leads to reduced functional cardiac reserve and decreased exercise capacity because of an inadequate increase in cardiac output.[17] Hyperthyroidism is associated with increased all-cause and cardiovascular mortality in the UK,[18,19] Finland,[20] and the USA,[21] and is linked to an increased incidence of embolic events and stroke, ischaemic heart disease, and congestive cardiac failure.[22]

Reduced exercise capacity is due to not only cardiovascular abnormalities but also abnormal respiratory muscle function, with reductions in muscle mass and strength.[23] Thyrotoxic periodic paralysis is a serious complication characterised by muscle paralysis and hypokalaemia due to a massive intracellular shift of potassium. An annual incidence of up to 2% has been reported in Asian people with thyrotoxicosis.[24] Ocular involvement might be present in Graves' disease; other diverse complications include anaemia (which has a reported prevalence in thyrotoxicosis of 22%)[25] and ejaculatory disorders.[26] In general, the frequency and severity of symptoms is associated with the biochemical severity of thyrotoxicosis,[27] although older people have fewer classical features and are more likely to present with cardiovascular complications such as atrial fibrillation and heart failure.[28]

Laboratory diagnosis

Measurement of serum TSH has the highest sensitivity for diagnosis and is the most appropriate screening test to exclude thyrotoxicosis (figure 2). In a sensitive assay, serum TSH will be undetectable (commonly reported as <0·01 mIU/L) because of negative feedback of thyroid hormones on the anterior pituitary. Diagnostic accuracy is improved if free T4 serum concentration is measured at the same time. Free T4 concentrations are raised in nearly

all cases of overt hyperthyroidism, although if free T4 is normal and TSH is low, free or total T3 concentration should also be measured to identify potential T3 toxicosis. In some circumstances, such as during pregnancy, physiological increases in thyroxine-binding globulin result in inaccurate free T4 and free T3 measurements, so calculation of the free T4 index could be helpful.[29] Subclinical hyperthyroidism is defined as normal circulating concentrations of T4 and T3 with reduced TSH and is a purely laboratory diagnosis. If TSH concentrations are not reduced then thyrotoxicosis is effectively excluded except for potential rare diagnoses such as pituitary tumours, which secrete TSH, and syndromes of thyroid hormone resistance (table 1 and figure 2). The converse is not true, since low TSH concentrations can be attributed to various causes—eg, non-thyroidal illnesses and drugs such as glucocorticoids and dopamine.

If a patient has raised concentrations of serum free T4 and T3 and undetectable TSH, no further biochemical tests are indicated. The underlying cause of thyrotoxicosis might be obvious from the person's history or clinical features, particularly if extrathyroidal manifestations of Graves' disease are present, or from the character of the goitre, in which case additional tests are not required. If doubt about the cause of thyrotoxicosis remains measurement of iodide uptake into the thyroid might be useful. Uptake is typically low in silent thyroiditis, iodine-induced hyperthyroidism, thyrotoxicosis factitia, struma ovarii, and metastatic thyroid cancer. Isotope imaging, typically with technetium, can be useful to differentiate between focal uptake in one or more autonomous nodules and diffuse uptake in Graves' disease, but is less specific than iodide uptake scans. The usefulness of these investigations for diagnosis or prediction of response to treatment is, however, restricted.[30,31] A diagnosis of Graves' hyperthyroidism can be confirmed by measurement of TSHR antibodies (new technologies can provide sensitive and specific results),[32] but this test is not widely used. Thyroid peroxidase antibodies are present in about 75% of cases of Graves' hyperthyroidism and could help to differentiate autoimmune disease from toxic nodular hyperthyroidism.

Treatment of Graves' hyperthyroidism

After biochemical confirmation of disease, a choice between three main treatment types is required: antithyroid drugs, radioiodine therapy, or surgery (table 3).[33] The choice of treatment seems to vary geographically. Radioiodine therapy is preferred in the USA, whereas antithyroid drugs are favoured in continental Europe and Japan.[34] Data show a rise in the number of thionamide drug prescriptions in the USA, which might suggest a trend towards primary pharmacological treatment rather than use of radioiodine.[35] A prospective randomised study compared outcomes between treatments and showed 90% patient satisfaction, no difference in time to euthyroidism, and similar rates of sick leave for all three.[36] Another randomised study showed long-term quality of life to be similar for all treatment choices, although radioiodine is associated with the lowest cost.[38]

Treatment is best tailored to the individual patient and should take into account the likelihood of remission with antithyroid drugs alone, timing of potential future pregnancies, goitre size, and the presence of comorbidities, as well as patient preference.

	Symptoms	Signs
Central nervous system	Fatigue, nervousness, anxiety, hyperactivity, poor concentration	Hyperactivity
Hair	Thinning, hair loss	
Eyes (usually in Graves' disease)	Soreness, grittiness	Stare, eyelid retraction and lag, periorbital oedema, conjunctival injection, ophthalmoplegia
Thyroid	Neck swelling	Goitre
Muscles	Weakness, tremor	Fine tremor, muscle wasting
Skin	Heat intolerance, increased perspiration	Warm, moist skin, increased perspiration
Cardiovascular system	Palpitation, shortness of breath	Tachycardia, atrial arrhythmia, systolic hypertension, high output failure
Gastrointestinal system	Increased appetite, weight loss	Weight loss
Peripheral nervous system		Hyperreflexia
Reproductive system		Oligomenorrhoea, decreased fertility (women); reduced libido (men)

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

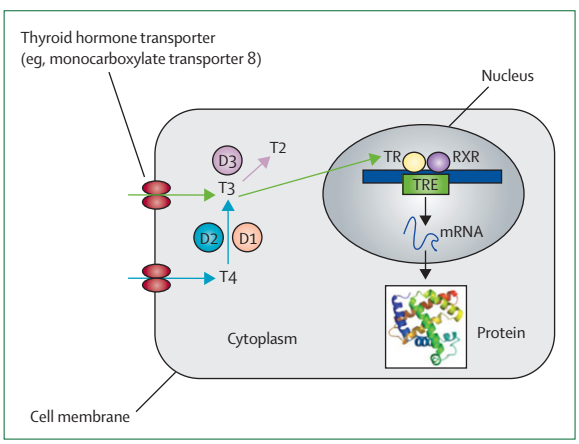

***Figure 1*: Model for thyroid hormone action in the nucleus**
Thyroid hormones (triiodothyronine [T3] and thyroxine [T4]) enter the cell via specific cell membrane transporters including monocarboxylate transporter 8 and 10. T4 is converted to the active T3 through activation of type I (D1) and type II (D2) deiodinase enzymes, and T3 is in turn inactivated through conversion to diiodothyronine (T2) by type III deiodinase enzyme (D3). T3 enters the nucleus where it binds to nuclear thyroid receptors (TR) with high affinity and specificity. TRs are ligand-regulated transcription factors that are closely associated with chromatin and heterodimerise with other members of the nuclear receptor family including the retinoid X receptor (RXR). The TR-RXR complex is bound to target DNA sequences known as thyroid hormone response elements (TRE), which are generally located in the promoter regions of target genes. The formation of a liganded TR-DNA complex and subsequent recruitment of transcriptional coactivators leads to activation of the target gene, which results in gene transcription (mRNA expression) and translation (protein expression).

Antithyroid drugs

Thionamides are the drugs of choice for thyrotoxicosis. Carbimazole (used mainly in the UK), its active metabolite methimazole (used in the USA; 20 mg carbimazole is equivalent to 15 mg methimazole[39]), and propylthiouracil are the main antithyroid drugs. Their main action is to inhibit organification of iodide and coupling of iodothyronines, and hence synthesis of thyroid hormones.

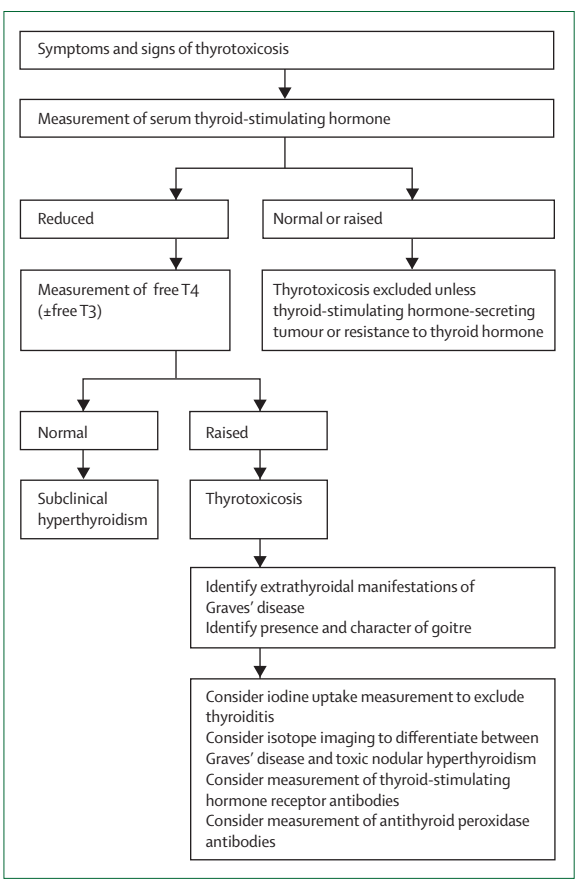

***Figure 2*: Algorithm for diagnosis of thyrotoxicosis**
T4=thyroxine. T3=triiodothyronine.

Propylthiouracil also inhibits peripheral monodeiodination of T4 to T3, but this effect is rarely important. Additionally, these drugs can be immunosuppressive. Compliance is better with carbimazole and methimazole because they are taken once daily, whereas propylthiouracil has to be taken two or three times a day. Propylthiouracil was the preferred drug in the USA until 1996,[35] but evidence emerged about adverse effects, so carbimazole and methimazole are now the starting drugs of choice.[40]

Antithyroid drugs can be used short term to prepare for treatment with radioiodine or surgery or long term with the aim of induction of lasting remission. Methimazole is more effective than propylthiouracil at rapid restoration of euthyroidism.[41] The recommended starting dose of carbimazole or methimazole is 10–20 mg per day. The equivalent dose of propylthiouracil is 50–100 mg twice daily, but severe cases need higher doses. By use of this approach, most patients have a normalised serum concentration of free T4 after 8–12 weeks. The main cause of treatment failure is non-compliance. Thyroid function should be assessed initially every 4–6 weeks, since a hypothyroid state can result if the treatment dose is not reduced as serum free T4 falls. Serum TSH might remain suppressed for weeks or months after free T4 has normalised, but a dose increase is not needed, although a rise in serum TSH above the reference range does necessitate a dose reduction. Once the carbimazole or methimazole dose has been reduced to maintenance levels of 5–10 mg per day, biochemical variables can be monitored less frequently (every 2–3 months). Occasionally, treatment with thionamides can result in low, normal, or reduced free T4, while total or free T3 concentrations remain raised. Measurement of serum T3 might therefore sometimes be useful for adjustment of drug doses.

If the objective of antithyroid drug treatment is to induce remission of Graves' hyperthyroidism (often defined as normal thyroid function tests 1 year after drug withdrawal), then treatment should continue for 12–18 months since shorter courses are associated with higher rates of relapse. Treatment duration longer than 18 months is not

	Indications	Advantages	Disadvantages
Antithyroid drugs	Newly diagnosed Graves' disease, short-term therapy before radioiodine or surgery, children, pregnancy	Non-invasive, outpatient therapy, low initial cost, easily applicable, low risk of permanent hypothyroidism, possible immune-modulatory effects	Low cure rate (average 30–50% in Graves' disease), adverse effects (1–5%), frequent follow-up and compliance required
Radioactive iodine (^{131}I)	Newly diagnosed Graves' disease, relapsed Graves' disease, toxic nodular hyperthyroidism	Effective cure of hyperthyroidism, outpatient therapy, easily applicable, reduction in goitre size	Slow induction of euthyroidism, induction of permanent hypothyroidism in >60% patients, potential worsening of ophthalmopathy, deferral of pregnancy for 6 months, adherence to radiation protection guidance required
Surgery	Presence of large goitre, pregnancy (if clinically significant drug side-effects), serious ophthalmopathy, severe adverse reaction to antithyroid drugs	Rapid control of hyperthyroidism, rapid relief of compressive symptoms, 100% cure	Invasive, expensive, permanent hypothyroidism, inpatient treatment, risk of complications (recurrent laryngeal nerve damage, hypoparathyroidism), pain, scarring

***Table 3*: Indications, advantages, and disadvantages of treatment choices for thyrotoxicosis**

associated with improved rates of remission.[42] Some clinicians prefer to use a block and replace regimen in which high doses of antithyroid drugs are used to block thyroid function in combination with T4 replacement therapy. However, a meta-analysis has shown that this strategy does not improve remission rates compared with dose titration but is associated with increased side-effects, such as skin rash and agranulocytosis.[42] Despite this evidence, some investigators advocate the use of a block and replace approach in thyroid eye disease, if thyroid function tests fluctuate during treatment, or if frequent thyroid function testing is unavailable or undesirable.[43] Continuation of T4 therapy alone after antithyroid drug withdrawal also has no effect on rate of remission or relapse.[42] Measurement of TSHR antibodies before drug withdrawal might indicate the likelihood of relapse,[44] but is of little predictive value before treatment. Preliminary data suggest that adjunctive treatments with iodide supplementation[45] or cholestyramine[46] improve rates of control or remission of hyperthyroidism. Development of novel, safe methods of immune modulation (eg, B-lymphocyte depletion)[47] is likely to have a profound effect on success of medical treatment.

Overall, the rate of remission of Graves' hyperthyroidism after a course of antithyroid drugs is less than 50% in clinical trials[42] and roughly 30% in clinical settings.[48] Factors that predict low likelihood of remission include more severe biochemical disease, male sex, young age (<40 years), high concentrations of TSHR antibodies, presence of large goitre, and smoking.[48–50] These prognostic factors might lead to a preference for treatment with radioiodine or surgery.

Side-effects (table 4) occur in roughly 3% of patients prescribed antithyroid drugs, but many are minor and transient. Agranulocytosis, defined as a granulocyte count of less than $0{\cdot}5\times10^9$ per L, is the most feared severe side-effect, occurs in 0·2–0·5% of patients (usually within the first 2–3 months of treatment), and can occur irrespective of dose, length of treatment, and previous exposure to the antithyroid drug. Although agranulocytosis is an idiosyncratic reaction, it is more common with a starting dose of methimazole of 30 mg per day than with 15 mg per day.[51] Minor side-effects such as rashes and arthralgia are also more common with higher doses of drug than with lower doses. All patients given antithyroid drugs must be warned (preferably in writing) of the risk of agranulocytosis and instructed to seek an urgent full blood count if they develop a sore throat or fever (the most common presenting features). Routine monitoring of full blood counts, suggested by some workers, has little support because of concerns about cost-effectiveness and the rapidity with which the disorder develops. The usefulness of full blood count before the start of drug therapy must be studied further since a low white cell count can be a feature of thyrotoxicosis itself and of black ethnic origin, which could cause diagnostic confusion.

	Carbimazole or methimazole	Propylthiouracil
Major side-effects (rare)	Agranulocytosis (0·2–0·5%), cholestatic hepatitis, teratogenic effects: choanal atresia and aplasia cutis, aplastic anaemia, thrombocytopenia, and hypoglycaemia (anti-insulin antibodies)	Agranulocytosis (0·2–0·5%), toxic hepatitis and fulminant liver failure, ANCA-positive vascultis, aplastic anaemia, thrombocytopenia, and hypoprothrombinaemia
Common minor side-effects (1–5%)	Urticaria or other rash, arthralgia, fever, and transient granulocytopenia	Urticaria or other rash, arthralgia, fever, and transient granulocytopenia
Uncommon minor side-effects (<1%)	Nausea and vomiting, abnormalities of taste or smell, and arthritis	Nausea and vomiting, abnormalities of taste or smell, and arthritis

ANCA=antineutrophil cytoplasmic antibody.

Table 4: **Side-effects of antithyroid drugs**

Propylthiouracil can cause antineutrophil cytoplasmic antibody-positive vasculitis and lupus-like syndromes, the risks of which increase with duration of therapy.[52] Antineutrophil cytoplasmic antibody positivity is much more common than clinically apparent disease[53] and seems specific to propylthiouracil. Carbimazole and methimazole can cause hepatotoxic effects, which are typically cholestatic and reversible. Propylthiouracil can result in fulminant hepatic failure, which can necessitate liver transplantation or cause death. Propylthiouracil-related acute liver failure occurs in an estimated one in 10 000 adults (more frequently in children[54]), which has led the US Food and Drug Administration to issue a warning on its use. Experts now recommend that propylthiouracil should no longer be used as first line treatment in adults or children, unless the patient is in the first trimester of pregnancy (although hepatic failure can occur in pregnancy), if he or she reports side-effects from carbimazole or methimazole, if radioiodine or surgery is not an option, or possibly in life-threatening thyrotoxicosis (thyroid storm).[40]

If thyrotoxicosis is strongly suspected or confirmed, treatment with β blockers improves symptoms such as tremor, palpitation, and anxiety and should be considered in symptomatic cases. Propranolol, metoprolol, nadolol, and atenolol are all effective. Response between drugs varies little. Treatment with a long-acting drug is preferable and can be continued until euthyroidism has been restored by antithyroid drugs. β blockers might be the only treatment required in mild cases before the use of radioiodine as first line therapy. These drugs should be used cautiously, if at all, in patients with a history of asthma or Raynaud's phenomenon.

Radioiodine treatment

Radioiodine can be used as first-line treatment of Graves' hyperthyroidism and is the treatment of choice in relapsed cases. Contraindications are pregnancy or lactation, desire for pregnancy within the next 6 months, suspicion or diagnosis of coexisting thyroid cancer, and inability to comply with radiation protection regulations.

Radioiodine is safe and effective, albeit followed frequently by hypothyroidism, and has been used for more than 60 years.

The goal of therapy with radioiodine is to return the patient to a euthyroid state (with or without T4 treatment). Many investigators have attempted to find a method to calculate the radioiodine dose needed to cure hyperthyroidism (and avoid hypothyroidism) on the basis of factors such as thyroid size or isotope uptake or turnover. Prospective studies have shown that the use of a calculated dose has no advantages over a fixed dose in terms of outcome,[55] and is more costly and inconvenient because of the need for extra investigations and visits. Many researchers now advocate the administration of a fixed dose sufficient to render the patient hypothyroid in the short term.[56,57] A single, fixed dose of 400–600 MBq is generally recommended because lower doses are associated with a higher rate of failure and a need for further therapies.[58] Administration of 600 MBq is associated with higher rates of cure (85% at 1 year in the UK) and hypothyroidism (60% at 1 year[59]) than lower fixed doses. Several factors predict need for a second dose (typically given 6–12 months after the first), such as male sex, high free T4 at diagnosis, and palpable goitre.[59] High initial doses should be used in patients in these groups. Because of the risk of hypothyroidism, thyroid function should be checked every 4–6 weeks. Once euthyroidism has been achieved, life-long annual thyroid function tests are required.

In the UK, antithyroid drugs are usually given for a few weeks before radioiodine[56] to provide more rapid symptomatic relief (since radioiodine works slowly over several weeks to months) and to avoid exacerbations (such as thyroid storm) associated with short-term destructive thyroiditis resulting from radioiodine. In the USA, radioiodine is typically given as first line therapy without previous use of antithyroid drugs, because these risks are deemed low. Expert opinion in the USA varies,[57] but pretreatment with methimazole is recommended for patients with pronounced symptoms, biochemically severe disease, and cardiovascular complications. Pretreatment with propylthiouracil induces more radioresistance and a lower rate of hypothyroidism than treatment with radioiodine alone.[60] If antithyroid drugs are given, they should be withdrawn 5–7 days before treatment with radioiodine because continuous use reduces thyroid iodide uptake and retention, which in turn reduces cure rates.[61] Carbimazole or methimazole is typically recommenced 5–7 days after radioiodine and is withdrawn as radioiodine becomes effective. Methimazole recommencement does not reduce the cure rate.[62] Several studies have shown that pretreatment with lithium improves radioiodine efficacy, which allows lower doses to be given and prevents thyroid storm,[63] but this approach is not widely used because lithium can have toxic effects, determination of a safe dosage regimen is difficult, and cost-effectiveness has yet to be established.

Graves' ophthalmopathy is a relative contraindication to radioiodine treatment. Roughly half of patients with Graves' disease have ophthalmopathy and 5% have severe eye disease. Risk factors for development of eye complications include severe biochemical hyperthyroidism and cigarette smoking.[8,64] Radioiodine has been associated with development or worsening of Graves' ophthalmopathy,[65] and development of eye disease is associated with poor quality of life scores.[66] Steroid prophylaxis is effective in prevention of progression of pre-existing ophthalmopathy.[65] Development of hypothyroidism is another risk factor for development or worsening of thyroid eye disease and should be avoided through prompt T4 replacement therapy. Radioiodine treatment is not recommended for patients with active eye disease, whereas steroid prophylaxis is recommended for patients with clinically apparent but stable or quiescent eye disease.[56,57] Typical steroid regimens involve a high dose of oral glucocorticoids for 2 months,[67] but lower doses given for 6 weeks could be equally effective.[68] Prophylactic steroid treatment is not recommended for patients without evidence of ophthalmopathy because of the low absolute risk of developing severe eye disease after radioiodine. Patients who smoke are at a higher risk of worsening of Graves' ophthalmopathy than non-smokers, regardless of the type of treatment given.[69] A consensus statement recommends routine steroid prophylaxis in smokers given radioiodine treatment, even if signs of ophthalmopathy are absent.[70]

A long-term increase in all-cause and vascular mortality after treatment of hyperthyroidism with radioiodine has been described,[18] but is probably due to an underlying diagnosis of thyrotoxicosis rather than radioiodine itself. Induction of hypothyroidism after radioiodine treatment reduces this risk,[19,20] perhaps because hypothyroidism is the best marker of reversal of adverse tissue effects. Fears about development of cancer after radioiodine have not been realised,[71–73] although Graves' hyperthyroidism itself might be associated with a slight increase in the absolute risk of thyroid cancer.[71]

Surgery

Surgery is used infrequently in the treatment of hyperthyroidism.[34] Patients should be returned to the euthyroid state with antithyroid drugs before surgery to avoid thyroid storm. Some recommend potassium iodide for at least 7 days to reduce thyroidal blood flow and intraoperative blood loss,[74] but this practice is not common.

Relative indications for surgery include large goitre (suspicion or diagnosis of coexisting thyroid cancer are absolute indications), pregnancy (if drug side-effects are serious) or desire for pregnancy, and pronounced ophthalmopathy. Relapse after a course of antithyroid drugs is also a relative indication. Even though radioiodine is the preferred option in relapsed disease, a study in the USA reported total thyroidectomy to be more cost effective

than radioiodine or life-long antithyroid drugs in treatment of Graves' disease relapse.[75] Patient preference is another frequent driver for surgery.[76]

Total thyroidectomy is the preferred surgical approach in view of the relapse rate after partial thyroidectomy (30% in one study)[77] and because the rate of complications is similar between both procedures in experienced hands. Improved outcomes in rates of complication and length of hospital stay are independently associated with the number of thyroidectomy operations performed by the surgeon.[78] In experienced hands, the rates of permanent hypoparathyroidism and recurrent laryngeal nerve damage are less than 2% and 1%, respectively.[79]

Thyrotoxicosis in pregnancy and in the post-partum period

Graves' hyperthyroidism is common in women of reproductive age and complicates one in 500 pregnancies.[80] Healthy pregnancy is associated with changes in thyroid function tests, especially suppression of TSH in the first trimester due to a rise in serum human chorionic gonadotropin, with consequent stimulation of thyroid function. Serum concentrations of total T4 and total T3 rise in parallel with a rise in thyroxine-binding globulin, and measurements of free T4 and free T3 show assay-dependent and trimester-dependent changes. Biochemical confirmation of hyperthyroidism in pregnancy therefore requires suppression of serum TSH and raised free T4 and free T3 defined with trimester-specific reference ranges.

Hyperemesis gravidarum is a common complication of early pregnancy and is often associated with biochemical hyperthyroidism, which resolves as hyperemesis improves. The differential diagnosis of Graves' hyperthyroidism and transient self-limiting hyperthyroidism in early pregnancy is a challenge, especially since accurate measurement of serum thyroid hormones can be problematic.[29] Clinical features such as goitre and ophthalmopathy, as well as persistence or worsening of abnormal biochemical values, lend support to the diagnosis of Graves' disease and suggest need for antithyroid drugs. Radioiodine is contraindicated because of the risk that fetal hypothyroidism could be induced. Surgery is rarely indicated and should be reserved for patients with serious side-effects from antithyroid drugs. Thyroidectomy is best done in the second trimester,[57] although could still result in fetal loss.[81] Despite side-effects, propylthiouracil remains the drug of choice during the first trimester because carbimazole and methimazole have been linked to teratogenic effects such as omphalocele and choanal atresia.[82] Historically, propylthiouracil has been used throughout pregnancy, but in view of the risk of liver damage a shift towards switching to carbimazole or methimazole from the second trimester has occurred.[40]

Untreated, or incompletely treated, Graves' hyperthyroidism is associated with poor pregnancy outcomes[83] and might be complicated by maternal heart failure.[84] The aim is to use the lowest dose of drug to control maternal thyrotoxicosis, because antithyroid drugs cross the placenta and can induce fetal hypothyroidism (after the fetal thyroid starts to function at around 15 weeks) even if the mother is euthyroid.[85] Because maternal T4 crosses the placenta less well than antithyroid drugs, the block–replace regimen is contraindicated.[86] Maternal thyroid function should be assessed every 4–6 weeks and drug dose should be adjusted to keep free T4 concentrations at, or slightly above, the trimester-specific range.[57,87] Graves' hyperthyroidism tends to enter remission as pregnancy proceeds, so doses can be reduced or withdrawn in the third trimester. Maternal TSHR antibodies can cross the placenta and cause fetal and neonatal thyrotoxicosis. Ability to reduce antithyroid drug dose and maintain normal maternal thyroid function suggests a reduction in maternal TSHR antibodies and normal fetal thyroid function. If the mother has had previous thyroid ablation (radioiodine or thyroidectomy) and is euthyroid, fetal and neonatal thyrotoxicosis can still occur because of persistent maternal TSHR antibodies. Many investigators advocate measurement of TSHR antibodies in Graves' hyperthyroidism in pregnancy, both at diagnosis and at 22–26 weeks' gestation, as well as after thyroid ablation for Graves' disease, to identify patients with high antibody concentrations for whom fetal and neonatal monitoring of thyroid size and function is appropriate.[57,87]

Relapse of Graves' hyperthyroidism is common in the post-partum period,[88] even if the patient was in remission before pregnancy.[89] Pregnancy has been suggested as a risk factor for Graves' hyperthyroidism (because of the higher incidence in older parous women than control nulliparous women),[90] a risk that extends for many years and is not specific to the post-partum period.[91]

The complex interaction between pregnancy and thyroid autoimmunity is further evidenced by the fact that post-partum thyroid dysfunction occurs after about 10% of pregnancies, and is more common in women with underlying thyroid autoimmunity and thyroid peroxidase antibodies than in those without these features.[92] Post-partum thyroiditis has a typical pattern of transient hyperthyroidism followed by hypothyroidism before a return to euthyroidism over 6–12 months. In a third of cases only hyperthyroidism is detected,[93] whereas a diagnosis of hypothyroidism is more common. The differential diagnosis of post-partum thyroiditis from Graves' hyperthyroidism can be difficult. Graves' disease is suggested by the presence of goitre or ophthalmopathy. Measurement of TSHR antibodies or thyroid uptake of iodine-123 or technetium might be helpful (uptake is low in post-partum thyroiditis and high in Graves' hyperthyroidism). Thyrotoxicosis due to post-partum thyroiditis needs only symptomatic treatment with β blockers whereas Graves' hyperthyroidism needs antithyroid treatment with carbimazole or methimazole that is safe in the context of breastfeeding. Post-partum thyroiditis frequently recurs in subsequent pregnancies (up to 80%) and up to 50% of women eventually develop permanent hypothyroidism.[94]

Thyrotoxicosis in children

Thyrotoxicosis is less common in children than in adults, with an incidence in the UK and Ireland of 0·9 per 100 000 per year, of which 96% of cases are autoimmune.[95] Antithyroid drugs are the first line therapy, and carbimazole or methimazole should be used in preference to propylthiouracil because of hepatotoxic effects.[96] Most cases of thyrotoxicosis recur after drug withdrawal, with a relapse rate of 68% after a 2 year course in one study, especially in non-white patients and in more severe disease.[97] For relapse, medium-term to long-term carbimazole or methimazole (eg, until the child has completed education) is an option if biochemical control without side-effects can be achieved. Otherwise, definitive treatment with surgery or radioiodine must be considered. The use of radioiodine in children is controversial, mainly because of fears about cancer risk,[98] especially if the patient is younger than 5 years of age.[99] Radioiodine is highly effective in children and adolescents[100,101] and is not associated with adverse long-term outcomes in small series.[102] Some consider it the optimum treatment, at least after age 5.[57,103] Total thyroidectomy is also effective, but has greater risks in children than in adults,[104] and should be done only by experienced surgeons.[105]

Other forms of hyperthyroidism

Subclinical hyperthyroidism

Low serum TSH with normal free T4 and free T3 concentrations is a common finding, especially in the elderly, in whom the prevalence is about 2%. The prevalence is higher in women than men and rises with increasing age.[4] To establish if the abnormality is persistent is important since it often resolves on repeat testing, especially if TSH is low but detectable (ie, not fully suppressed).[106–108] Cases that resolve include those where low TSH is caused by non-thyroidal illness or treatment with drugs such as glucocorticoids. Progression to overt hyperthyroidism is uncommon with low but detectable TSH (1% per year).[109] If subclinical hyperthyroidism persists, especially if TSH is undetectable, then evidence for underlying thyroid disease should be sought. The most common cause of true subclinical hyperthyroidism is toxic nodular goitre, especially in the elderly. This diagnosis might be obvious from physical examination but if not thyroid isotope imaging might show a hot nodule.

Evidence that subclinical hyperthyroidism is associated with adverse clinical outcomes is increasing,[110] particularly atrial fibrillation,[111,112] coronary heart disease,[113] and mortality in people with underlying cardiac disease.[114] Several, but not all, studies suggest a general association with all-cause mortality.[115,116] Meta-analyses have had conflicting results,[113,117] perhaps because association with mortality is age-related. Even variation in serum free T4 within the reference range with normal TSH concentrations might be associated with atrial fibrillation,[118] which suggests pronounced cardiac sensitivity for this arrhythmia. High free T4 is also associated with reduced bone mineral density and risk of non-vertebral fractures in euthyroid people, which suggests that bone is another sensitive target.[119] That subclinical hyperthyroidism is associated with increased fracture risk, especially in postmenopausal women,[120] lends support to this possibility. Results conflict with regard to possible associations with reduced cognitive function and dementia.[121,122]

The need for treatment of subclinical hyperthyroidism is controversial since no controlled studies that show beneficial clinical outcomes have been done, although small studies have shown improvements in echocardiographic variables and bone mineral density.[123,124] Because of associations with adverse outcomes, expert panels have recommended treatment of subclinical hyperthyroidism, proven to be associated with true thyroid disease, specifically in patients with persistently undetectable TSH, the elderly, and those with cardiac risks, heart disease, or osteoporosis.[57,125] One suggestion is that treatment should be considered for low but detectable TSH in the elderly or in people with heart disease, on the basis of a study showing high atrial fibrillation risk in such groups.[111] If the decision is made to treat, radioiodine is generally the therapy of choice, especially in toxic nodular goitre. Long-term carbimazole or methimazole at low dose is another option. Because of the absence of evidence for benefit from treatment,[126] population screening for minor abnormalities of thyroid function is not recommended.

Thyrotoxicosis due to toxic nodular goitre or solitary toxic nodules

The principles of treatment of thyrotoxicosis due to one or more autonomously functioning thyroid nodules are the same as those for Graves' hyperthyroidism, except that underlying disease does not remit, so antithyroid drugs should only be used in preparation for radioiodine or surgery. Long-term low-dose carbimazole or methimazole is an option in patients with short life expectancy or who are unfit for radioiodine or surgery. Total thyroidectomy is the treatment of choice for patients with large goitre and is highly effective.[127] More restricted surgery (eg, lobectomy) can be done for solitary toxic nodule, and T4 replacement might not be needed. Compressive symptoms from goitre are relieved by thyroidectomy but such improvement is less common after radioiodine,[128] probably because radioiodine is ineffective in shrinking large goitres.[129] Advanced age, substantial comorbidity, and small goitre size (as well as patient preference) can each identify preference for radioiodine. Radioiodine cures roughly 80% of patients by 6 months; the remainder need re-treatment.[127,130] In selected cases of toxic nodular hyperthyroidism, fixed-dose radioiodine leads to high rates of cure similar to those in Graves' hyperthyroidism, although rates of subsequent hypothyroidism are lower than in Graves' disease[59] because isotope uptake is confined to autonomous nodules. Although radioiodine is effective, by contrast with surgery it does not clarify thyroid pathological features and, if concerns about thyroid

malignancy exist (especially in young patients), surgery remains the treatment of choice.

Thyroiditis

Thyroiditis is inflammation of the thyroid. Subacute (de Quervain's) thyroiditis is a painful disorder with pronounced thyroid tenderness, fever, and malaise associated with biochemical and clinical thyrotoxicosis. Inflammatory markers are raised and thyroid isotope uptake is low, which suggests thyroid cell damage. Treatment is symptomatic with β blockers, aspirin, or other non-steroidal anti-inflammatory drugs. In severe cases, glucocorticoids are used and rapidly resolve symptoms.[131] Restoration of euthyroidism usually occurs spontaneously after 4–6 weeks, although transient hypothyroidism can occur.

Silent or painless thyroiditis is associated with lymphocytic infiltration of the thyroid and often positive thyroid antibodies. Because thyrotoxicosis is a destructive process, antithyroid drugs are ineffective and contraindicated. Hypothyroidism usually follows hyperthyroidism and resolves spontaneously, although many patients eventually develop permanent hypothyroidism. Post-partum thyroiditis is a variant of silent thyroiditis.

Amiodarone-associated thyrotoxicosis

Amiodarone is an iodine-containing drug (37% by molecular weight), whose use frequently results in abnormal tests of thyroid function in euthyroid patients, specifically a slight rise in free T4, a slight fall in free T3, and a transient increase in TSH, largely because of effects on peripheral deiodination of T4 to T3.[132] Although these changes are common they do not show thyroid dysfunction. However, amiodarone-associated thyrotoxicosis occurs in 6–10% of people given the drug and is more common in iodine-deficient areas.[133] This complication is serious and is associated with more than doubling of adverse cardiac events[134] and worse outcomes than in Graves' or toxic nodular hyperthyroidism, especially in patients with left ventricular dysfunction.[135]

For a diagnosis of amiodarone-associated thyrotoxicosis free T4 and free T3 must be increased and TSH must be suppressed. Two types are described: type 1 is iodine-induced thyrotoxicosis and occurs in people predisposed to thyroid autoimmunity or with pre-existing thyroid nodules; type 2 is destructive thyroiditis due to toxic effects of amiodarone on thyroid cells. Various ways to distinguish the types have been suggested, although distinction is often not possible because patients have features of both. The most specific test is colour flow doppler ultrasonography which detects increased vascularity in type 1, a finding absent in type 2.[136]

Type 1 amiodarone-associated thyrotoxicosis is best treated with carbimazole or methimazole. Doses of at least 40 mg daily are often required. Addition of potassium perchlorate can be helpful,[137] but this drug is not widely available. Type 2 is best treated with prednisolone (40 mg per day), which typically leads to rapid resolution,[136,137] although use of prednisolone can worsen outcomes from cardiovascular events.[138] When a clear distinction between types 1 and 2 is not possible, a combination of thionamides and glucocorticoids should be given until biochemical improvement occurs, at which point drugs can be gradually withdrawn. Discontinuation of amiodarone might be contraindicated because of serious underlying heart disease and requires joint decisions between the endocrinologist and cardiologist. Because of the very long drug half-life (100 days), discontinuation of amiodarone is largely ineffective.[133] Furthermore, control or resolution of thyrotoxicosis is achievable while amiodarone is being given.[139] Iodine uptake is low in both types of thyrotoxicosis because of the iodine load in the drug, so radioiodine treatment is unfeasible for at least for 6–12 months after amiodarone withdrawal. Thyroidectomy has been used in patients resistant to other therapies, but is associated with risk of morbidity and mortality.[140] Thyroidectomy under local anaesthesia has also been used.[141]

Future developments

The mainstays of treatment of thyrotoxicosis—namely, antithyroid drugs, radioiodine, and surgery—have not changed for more than 60 years, although the evidence base directing treatment choices and modes of administration is improving. That thyrotoxicosis, even if mild, is not benign but associated with serious consequences, especially cardiovascular effects, is increasingly recognised. Efforts to better understand the genetic basis of autoimmune and other types of thyrotoxicosis should ultimately provide novel approaches to treat the underlying disease process rather than inhibition or destruction of the thyroid.

Contributors

JAF wrote the first draft and both authors critically reviewed and revised the manuscript and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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