HHS Public Access

Author manuscript

Lancet. Author manuscript; available in PMC 2016 September 27.

Published in final edited form as:

Lancet. 2016 August 27; 388(10047): 906–918. doi:10.1016/S0140-6736(16)00278-6.

Hyperthyroidism

Simone De Leo[#], **Sun Y Lee**[#], and **Lewis E Braverman**[#]

Endocrine Unit, Fondazione IRCCS Cà Granda, Milan, Italy (S De Leo MD); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (S De Leo); and Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston, MA, USA (S De Leo, S Y Lee MD, Prof L E Braverman MD)

[#] These authors contributed equally to this work.

Abstract

Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source. The most common cause of hyperthyroidism is Graves' disease, followed by toxic nodular goitre. Other important causes of thyrotoxicosis include thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and factitious ingestion of excess thyroid hormones. Treatment options for Graves' disease include antithyroid drugs, radioactive iodine therapy, and surgery, whereas antithyroid drugs are not generally used long term in toxic nodular goitre, because of the high relapse rate of thyrotoxicosis after discontinuation. β blockers are used in symptomatic thyrotoxicosis, and might be the only treatment needed for thyrotoxicosis not caused by excessive production and release of the thyroid hormones. Thyroid storm and hyperthyroidism in pregnancy and during the post-partum period are special circumstances that need careful assessment and treatment.

Introduction

Hyperthyroidism is a pathological disorder in which excess thyroid hormone is synthesised and secreted by the thyroid gland. It is characterised by normal or high thyroid radioactive iodine uptake (thyrotoxicosis with hyperthyroidism or true hyperthyroidism). Thyrotoxicosis without hyperthyroidism is caused by extrathyroidal sources of thyroid hormone or by a release of preformed thyroid hormones into the circulation with a low thyroid radioactive iodine uptake (table 1).[1] Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is characterised by low serum thyroid-stimulating hormone (TSH) concentrations and raised serum concentrations of thyroid hormones: thyroxine (T_4), tri-iodothyronine (T_3), or both. Subclinical hyperthyroidism is characterised by low serum TSH, but normal serum T_4 and T_3 concentrations. We do not discuss subclinical hyperthyroidism here, but it was recently reviewed in another *Lancet* Seminar.[2]

Correspondence to: Prof Lewis E Braverman, Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, 88 East Newton St, Evans 201, Boston, MA 02118, USA, **lewis.braverman@bmc.org**.

Declaration of interests

We declare no competing interests.

Epidemiology

Prevalence of hyperthyroidism is 0·8% in Europe,[3] and 1·3% in the USA.[4] Hyperthyroidism increases with age and is more frequent in women. The prevalence of overt hyperthyroidism is 0·5–0·8% in Europe,[3] and 0·5% in the USA.[4] Data for ethnic differences are scarce, but hyperthyroidism seems to be slightly more frequent in white people than in other races.[3] The incidence of mild hyperthyroidism is also reported to be higher in iodine-deficient areas than in iodine-sufficient areas, and to decrease after introduction of universal salt iodisation programmes.[5]

Aetiology

Thyrotoxicosis with hyperthyroidism

The most common cause of hyperthyroidism in iodine-sufficient areas is Graves' disease. In Sweden, the annual incidence of Graves' disease is increasing, with 15–30 new cases per 100 000 inhabitants in the 2000s.[6,7] The cause of Graves' disease is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the TSH receptor. Several studies have provided some evidence for a genetic predisposition to Graves' disease;[8] however, the concordance rate in monozygotic twins is only 17–35%, suggesting low penetrance. The genes involved in Graves' disease are immune-regulatory genes (HLA region, *CD40*, *CTLA4*, *PTPN22*, and *FCRL3*) and thyroid autoantigens such as the thyroglobulin and TSH-receptor genes.[8] Non-genetic risk factors for development of Graves' disease include psychological stress,[9] smoking,[10] and female sex.[11,12] Given the higher prevalence of Graves' disease in women, sex hormones and chromosomal factors, such as the skewed inactivation of the X chromosome, are suspected to be triggers.[13] Other factors such as infection (especially with *Yersinia enterocolitica*, due to a mechanism of molecular mimicry with the TSH receptor), vitamin D and selenium deficiency, thyroid damage, and immunomodulating drugs are also suspected.[8] Further studies to ascertain the more precise role of these factors in the cause of Graves' disease are needed.

Other common causes of hyperthyroidism are toxic multinodular goitre and solitary toxic adenoma. Although in iodine-sufficient areas about 80% of patients with hyperthyroidism have Graves' disease, toxic multinodular goitre and toxic adenoma account for 50% of all cases of hyperthyroidism in iodine-deficient areas,[14] and are more predominant in elderly people. Thyroid nodules become autonomous and produce thyroid hormones independent of signals from either TSH or TSH-receptor antibodies (figure 1).[15,16] Less common causes of hyperthyroidism include thyrotropin-induced thyrotoxicosis[17] and trophoblastic tumours,[18] in which TSH receptors are stimulated by excess TSH and human chorionic gonadotropin, respectively.

Thyrotoxicosis without hyperthyroidism

These causes of thyrotoxicosis are less common and generally transient. In patients with silent thyroiditis, post-partum thyroiditis, or subacute painful thyroiditis, the destruction of thyrocytes leads to release of preformed hormones into the circulation.[19,20] Drug-induced

thyrotoxicosis has the same pathogenic mechanism as thyroiditis. Lithium, interferon α, and amiodarone are commonly involved in drug-induced thyroid dysfunction.

Exogenous thyrotoxicosis is factitious or iatrogenic, develops after ingestion of excessive amounts of thyroid hormone, and is associated with low serum thyroglobulin concentrations. Ectopic hyperthyroidism is extremely rare, including functional thyroid cancer metastases and struma ovarii, an ovarian tumour that contains functioning thyroid tissue.

Clinical presentation and complications

Signs and symptoms due to excess thyroid hormones

Excess thyroid hormone affects many different organ systems (table 2). Commonly reported symptoms are palpitations, fatigue, tremor, anxiety, disturbed sleep, weight loss, heat intolerance, sweating, and polydipsia. Frequent physical findings are tachycardia, tremor of the extremities, and weight loss.[21–23]

Signs and symptoms specific to the underlying causes of hyperthyroidism

Signs and symptoms include ophthalmopathy, thyroid dermopathy, and thyroid acropachy in Graves' disease; globus sensation, dysphagia, or orthopnoea due to oesophageal or tracheal compression in nodular goitre; and anterior neck pain in painful subacute thyroiditis.

Ophthalmopathy, also known as Graves' orbitopathy, occurs in 25% of patients with Graves' disease.[24] The main signs are proptosis, periorbital oedema, and diplopia. Clinicians who do not have expertise in managing active or moderate-to-severe Graves' orbitopathy should refer patients to a combined thyroid–eye clinic for assessment and management.[25–27]

Thyroid dermopathy is a rare extrathyroidal manifestation of Graves' disease, occurring in 1–4% of patients with thyroid ophthalmopathy. Almost all patients have coexisting ophthalmopathy.[28] The lesions are characterised by slightly pigmented thickened skin, primarily involving the pretibial area.[29]

Acropachy is the rarest extrathyroidal manifestation of Graves' disease and presents with clubbing of the fingers and toes.[30]

Complications seen in hyperthyroidism

Clinical manifestation varies depending on several factors, such as the patient's age and sex, comorbidities, duration of the disease, and cause. Older patients present with fewer and less pronounced symptoms than do younger patients,[21–23] but are more likely to develop cardiovascular complications. When compared with people older than 60 years with a healthy thyroid, those who are hyperthyroid have three times the risk of atrial fibrillation.[31] Embolic stroke related to atrial fibrillation secondary to hyperthyroidism is significantly more prevalent than embolic stroke related to atrial fibrillation from non-thyroidal causes.[32,33] However, anticoagulant therapy in patients with atrial fibrillation secondary to hyperthyroidism is still debated.[34] Atrial fibrillation is also thought to be an independent predictor of the development of congestive heart failure in patients with hyperthyroidism.[35]

An increased risk of all-cause mortality was reported in patients with hyperthyroidism, with heart failure being the main cause of cardiovascular events.[36]

Another serious complication associated with hyperthyroidism is thyrotoxic periodic paralysis. It is more prevalent in Asian patients: incidence ranges from 0·2% in North America to 2% in Japan.[37] It is characterised by the triad of muscle paralysis, acute hypokalaemia, and thyrotoxicosis, and caused by a shift of potassium into the muscle cells. Mutations in potassium channels, which are transcriptionally regulated by thyroid hormones, might be responsible for the disease.[38] If suspected, treatment with low doses of potassium and non-selective β blockers should be initiated as soon as possible to prevent arrhythmias and restore muscle function.

Other complications of long-standing thyrotoxicosis include osteoporosis[39] and abnormalities in the reproductive system, such as gynaecomastia in men[40] and decreased fertility and menstrual irregularities in women.[41]

Diagnosis

Serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid disorders.[42] If low, serum free T_4 or free T_4 index, and free or total T_3 concentrations should be measured to distinguish between subclinical hyperthyroidism (with normal circulating hormones) and overt hyperthyroidism (with increased thyroid hormones). It also identifies disorders with increased thyroid hormone concentrations and normal or only slightly raised TSH concentrations, as in patients with TSH-secreting pituitary adenomas or peripheral resistance to thyroid hormone.[43] The modalities preferred for assessing the cause of thyrotoxicosis vary widely. Different population characteristics, cultural backgrounds, and socioeconomic reasons partly explain these differences. American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines for hyperthyroidism and thyrotoxicosis recommend a thyroid radioactive iodine uptake test, unless the diagnosis of Graves' disease is established clinically.[44] The use of thyroid ultrasound and assessment of TSH-receptor antibodies (TRAb; ie, thyroid-stimulating immunoglobulins, or thyroid-stimulating antibodies) are preferred in Europe,[45,46] Japan,[47] and Korea.[48] The US guidelines consider measurement of TRAb as an alternative way to diagnose Graves' disease, especially when the radioactive iodine uptake test is unavailable or contraindicated. This recommendation is shared by the Brazilian Thyroid Consensus that consider TRAb testing useful only in selected cases and prefer radioactive iodine uptake for initial assessment of thyrotoxicosis.[49] In our clinical practice, we follow the approach of our European and Asian colleagues, using ultrasound and TRAb measurements.

A thyroid radioactive iodine uptake test in patients with Graves' disease would show diffusely increased uptake. However, radioactive iodine uptake would be normal or high with an asymmetrical and irregular pattern in toxic multinodular goitre, and a localised and focal pattern in toxic adenoma, with suppressed uptake in the remaining thyroid tissue. Radioactive iodine uptake in patients with thyrotoxicosis from extrathyroidal sources of

thyroid hormone or from release of preformed thyroid hormones, as in silent or painful thyroiditis, will be very low (figure 2).

Thyroid ultrasound and thyroid radioactive iodine uptake have similar sensitivity for the diagnosis of Graves' disease (95·2% and 97·4%, respectively).[50] Advantages of ultrasound are absence of exposure to ionising radiation, and higher accuracy in the detection of thyroid nodules and lower cost than with radioactive iodine uptake.[45] Moreover, colour-flow Doppler ultrasound differentiates between Graves' disease (increased blood flow, diffusely enlarged hypoechogenic) and destruction-induced thyrotoxicosis (decreased blood flow).[51] The differences in approach between European and American endocrinologists might be a result of the different epidemiology of hyperthyroidism, because nodular goitre is the predominant cause of hyperthyroidism in many European areas.

TRAb assays have become more reliable and inexpensive in recent years.[52] Furthermore, TRAb measurements are useful to predict patients at risk for relapse after discontinuation of antithyroid drugs, and to detect fetal or neonatal thyrotoxicosis in women with Graves' disease, since these antibodies readily cross the placenta.[53]

Treatment

The three options for treating patients with hyperthyroidism are antithyroid drugs (ATDs), radioactive iodine ablation, and surgery. All three therapeutic options would be effective in the treatment of patients with Graves' disease, whereas patients with toxic adenoma or toxic multinodular goitre should have either radioactive iodine therapy or surgery, since these patients rarely go into remission.[54] In patients with toxic nodular goitre, ATDs are generally used to restore euthyroidism before definitive treatment with surgery or radioactive iodine, and infrequently used as long-term treatment when the other two therapies are contraindicated or the patient has a short life expectancy.

The choice of treatment for Graves' disease differs depending upon geographical regions. Radioactive iodine therapy is frequently used as the first therapy in North America.[46] Outside of the USA, ATDs are preferred as primary treatment, whereas definitive therapy is reserved only for patients with persistent or recurrent hyperthyroidism.[46,55] Additionally, patients can take β blockers for relief of the symptoms of thyrotoxicosis.

Antithyroid drugs

Overview—The antithyroid thionamide drugs are propylthiouracil, thiamazole, and carbimazole. All are actively transported into the thyroid where they inhibit iodide oxidation and organification by inhibiting thyroid peroxidase and the coupling of the iodotyrosines to synthesise T_4 and T_3.[56] Carbimazole is available in some European and Asian countries and is converted to the active form, thiamazole, with similar properties to thiamazole. Propylthiouracil in large doses, but not thiamazole, decreases the conversion of T_4 to T_3 in peripheral tissues by inhibiting the outer ring deiodinase of T_4.[57] These drugs might also have anti-inflammatory and immunosuppressive effects.[56,58]

ATA/AACE guidelines recommend thiamazole as the preferred drug in Graves' disease.[44] The exceptions are therapy during the first trimester of pregnancy and in patients with adverse reactions to thiamazole. Thiamazole has several advantages over propylthiouracil, such as better efficacy;[59] longer half-life and duration of action,[60] allowing once-daily dosing compared with two to three times daily dosing of propylthiouracil; and less severe side-effects. Reports of liver damage in patients who had received propylthiouracil[61,62] prompted the ATA and the US Food and Drug Administration to reassess the role of propylthiouracil in the management of Graves' disease, recommending against propylthiouracil as the first-line therapy.[63] Although combined early treatment with ATD and potassium iodide has been suggested, this approach is not generally recommended.[64,65]

Protocols for ATD therapy and follow-up—There are two approaches to the treatment of Graves' disease: titration and block and replace. With titration, the dose of ATD is titrated over time to the lowest dose needed for maintaining a euthyroid state.[66] In the block and replace regimen, a higher dose of ATD is used with concurrent replacement with levothyroxine. The two regimens are equally effective but the block and replace regimen seems to be associated with a higher incidence of side-effects than does the titration method.[67] Therefore, the titration regimen should be the first-line approach,[44] even if some authors regard both approaches as equally safe.[68]

The starting dose of thiamazole depends on the severity of the hyperthyroidism and the size of the thyroid gland: mild hyperthyroidism and small glands need 10–15 mg of thiamazole daily, and severe hyperthyroidism and large thyroids need 20–40 mg daily. The equivalent dose of carbimazole is 140% of that of thiamazole. The starting dose of propylthiouracil is usually 50–150 mg administered three times daily. Thyroid function should be checked 4–6 weeks after initiation of therapy and then every 2–3 months once the patient is euthyroid,[44] although we usually see the patient every 4 months when they are euthyroid. TSH might remain suppressed for several months, which is why serum T_4 and T_3 should be monitored to assess efficacy of therapy. Once euthyroidism is achieved, a maintenance dose of thiamazole of 5–10 mg daily, or 50 mg propylthiouracil two or three times daily, or lower, should be continued for 12–18 months,[69] and some suggest an even longer duration of therapy.[70]

A drawback of ATD therapy is the high rate of relapse of hyperthyroidism after the drug has been discontinued. Relapse is more frequent in the first year than subsequent years, particularly in the first 6 months after stopping the drug, but uncommon after 4–5 years.[71] The risk of recurrence varies greatly among patients,[72] but is estimated to be 50–55% according to a Cochrane review of 26 randomised clinical trials.[67] Patients at higher risk of recurrence are those with severe hyperthyroidism, large goitre, high T_3:T_4 ratios,[56,73] persistently suppressed TSH,[74] and high baseline concentrations of TRAb.[75] Assessment of TRAb concentrations at the end of treatment might be useful to identify patients in whom hyperthyroidism will recur after discontinuation of therapy.[76] A prospective study suggested that a second course of thionamide drugs after recurrence of hyperthyroidism can result in long-term remission.[77] Nevertheless, further studies are needed to confirm these data, and to compare the efficacy and side-effects of the second course of ATD therapy with those of radioactive iodine ablation or surgery.

Side-effects—Minor side-effects of ATDs occur in about 5% of patients.[56] These side-effects include pruritus, arthralgia, and gastrointestinal distress. In patients with minor skin reactions, an antihistamine can be added or one ATD can be substituted for the other.[78]

Major side-effects of ATDs are rare. Agranulocytosis, in which the absolute granulocyte count is less than 500 cells/mm³, is the most frequent major side-effect and can be life-threatening. Patients usually present with fever or sore throat, or both, and sometimes with other less common symptoms such as chills, diarrhoea, and myalgia.[79] The annual incidence of agranulocytosis has been estimated to be 0·1–0·3%,[80,81] and generally occurs within 90 days after initiation of therapy. When patients receiving ATDs present with these symptoms, a white blood cell count with differential should be obtained and the ATD should be immediately discontinued if the granulocyte count is less than 1000 cells/mm³.[56] Treatment of agranulocytosis and its associated infections might be also necessary, such as administration of broad-spectrum antibiotics and granulocyte colony-stimulating factor, which has been shown to reduce the recovery time.[80] Trial of another ATD is contraindicated in this circumstance because of the documented cross-reactivity between thiamazole and propylthiouracil. The ATA/AACE guidelines suggest that all patients have a baseline complete blood count before initiation of therapy,[44] but recommend against routine monitoring during therapy. This practice is also accepted outside of the USA, except in Japan where periodic monitoring of white blood cells is recommended every 2 weeks during the first 2 months of therapy.[80] Patients should be instructed to recognise symptoms of agranulocytosis, and to discontinue the drug and contact their physicians as soon as possible, once fever or sore throat occur. A survey showed a lack of knowledge of this potentially serious side-effect in patients taking ATDs.[79] Other very rare haematological side-effects of ATDs include aplastic anaemia, thrombocytopenia, and hypoprothrombinaemia.[56]

Another major side-effect is hepatotoxicity, which occurs in 0·1–0·2% of patients.[56] It usually develops within 3 months of therapy and the incidence peaks in the first 30 days of treatment.[82] The most common manifestation of hepatotoxicity in patients taking either thiamazole or propylthiouracil is hepatitis. Hepatotoxicity can rarely present as acute liver failure, which is associated with propylthiouracil more frequently than with thiamazole, and might require liver transplant.[82] The ATA/AACE guidelines recommend obtaining a serum liver profile at baseline, but recommend against periodic monitoring unless the patient complains of symptoms of hepatic dysfunction, such as pruritic rash, jaundice, light-coloured stool, or dark urine.[44] In patients taking thiamazole, cholestasis can occur; this side-effect is rare with propylthiouracil, for which liver problems are mainly related to hepatocellular necrosis.[83]

Vasculitis is a very rare complication that has been reported during therapy with ATDs.[84] Vasculitis is often associated with antineutrophil cytoplasmic antibody and is more frequent in patients taking propylthiouracil than in those taking thiamazole.[84] Patients might present with fever, arthralgia, and skin involvement, or might have organ failure—mainly of the kidneys and lungs.

Radioactive iodine therapy

Overview—Radioactive iodine therapy is safe and cost-effective and can be the first-line treatment for Graves' disease, toxic adenoma, and toxic multinodular goitre. Absolute contraindications include pregnancy, breastfeeding, planning pregnancy, and inability to comply with radiation safety recommendations. In patients with thyroid nodules whose biopsy samples are suspicious for or diagnostic of thyroid cancer, radioactive iodine is contraindicated and surgery is recommended.[44] Radioactive iodine therapy has been shown to be responsible for de-novo development or worsening of Graves' orbitopathy,[85] although others disagree.[86,87] A meta-analysis reported an increased risk of worsening Graves' orbitopathy in patients who received radioactive iodine treatment compared with those who received ATD (relative risk [RR] 4·23, 95% CI 2·04–8·77), and a slightly increased risk compared with surgery (RR 1·59; 0·89–2·81).[88] Therefore, radioactive iodine therapy is contraindicated in patients with active moderate-to-severe or sight-threatening Graves' orbitopathy.[44] In patients with mild active Graves' orbitopathy, radioactive iodine treatment should be followed by prophylactic steroid treatment (0·3–0·5 mg/kg of prednisone daily, starting 1–3 days after radioactive iodine and tapered over 3 months).[25] Patients with inactive Graves' orbitopathy, but no risk factors, can be given radioactive iodine therapy without corticosteroids.[25,44] Risk factors for development and worsening of Graves' orbitopathy after radioactive iodine therapy include smoking,[89] high pretreatment T_3 concentrations (≥5 nmol/L),[90] high TRAb titres,[87,91] and untreated hypothyroidism after radioactive iodine therapy.[88,92] The need for glucocorticoid prophylaxis in patients with risk factors but with inactive or without pre-existing Graves' orbitopathy is debated.[93]

Management of patients receiving radioactive iodine therapy—Some patients, especially elderly patients and those with comorbidities (in particular cardiovascular complications) or severe thyrotoxicosis, might need pretreatment with ATDs. The need for pretreatment and the effect of ATDs on radioactive iodine therapy is debatable. Some argue that thiamazole pretreatment has no effect on the efficacy of radioactive iodine therapy,[94] but is protective because it lowers baseline thyroid hormone concentrations before radioactive iodine therapy.[95] Others suggest that it is not protective against exacerbation of thyrotoxicosis.[95] A meta-analysis showed that pretreatment with ATDs increased the risk of treatment failure (RR 1·28, 95% CI 1·07–1·52) and reduced the risk of hypothyroidism after radioactive iodine (RR 0·68, 0·53–0·87).[96] When an ATD is used before radioactive iodine therapy, thiamazole is the preferred drug, because propylthiouracil has been related to higher rates of treatment failure.[97] ATD should be stopped 3–5 days before radioactive iodine therapy,[98] then restarted 3–7 days later, and withdrawn as soon as thyroid function normalises.

The optimum radioactive iodine dose is debated between a fixed dose versus a dose calculated on the basis of thyroidal radioactive iodine uptake. Several studies found no significant differences in treatment outcomes[99] and in rates of permanent hypothyroidism between the two regimens.[100] 10–15 mCi is the suggested dose for treating Graves' disease and 10–20 mCi is suggested for toxic nodular goitre when using fixed doses.[44,101]

Follow-up of patients who receive radioactive iodine therapy—Thyroid function should be monitored 1–2 months after radioactive iodine therapy. Some suggest measuring free T_4 no more than 6 weeks after radioactive iodine therapy, to detect hypothyroidism, especially in patients at risk for developing or worsening Graves' orbitopathy.[92] If the patient is still thyrotoxic 1–2 months after radioactive iodine therapy, thyroid function should be monitored every 4–6 weeks until the patient is euthyroid or hypothyroid. Levothyroxine replacement should be started as soon as hypothyroidism occurs. Subsequent monitoring is important because some patients given radioactive iodine might have transient hypothyroidism, followed by relapse of hyperthyroidism.[102] These patients are usually younger, have larger goitres, and have received pretreatment with propylthiouracil. Patients with relapse or persistent hyperthyroidism after 6 months can be given radioactive iodine again.

Side-effects—Except for ophthalmopathy, adverse effects of radioactive iodine are rare and not well established. One side-effect is acute thyroiditis. It occurs in 1% of patients, lasts for a few weeks, and is easily treated with non-steroidal anti-inflammatory drugs (NSAIDs) and β blockers for the associated exacerbation of hyperthyroidism. Some patients with severe cases might need glucocorticoids.[103] Other adverse effects of radioactive iodine therapy have been postulated, but no clear consensus has been reached.[104] Increased risks of cardiovascular diseases and cerebrovascular events are considered,[105] but whether the events are caused by hyperthyroidism itself or radioactive iodine therapy is unclear. Cancer incidence is slightly higher in patients who are hyperthyroid than in those who are euthyroid, but is not associated with type of thyroid treatment.[106] Finally, impairment of gonadal function has been shown with higher doses of radioactive iodine usually used in the treatment of thyroid cancer,[107] but not with the lower doses used for hyperthyroidism. No adverse effects were reported on the health of offspring of patients given radioactive iodine for hyperthyroidism before pregnancy.[104]

Thyroidectomy

Overview—Thyroidectomy is the most successful treatment for Graves' hyperthyroidism.[108] Total thyroidectomy is recommended, since the frequency of successful outcomes are significantly higher than with subtotal thyroidectomy (odds ratio 40·37, 95% CI 15·03–108·44),[108] with no differences in the rate of complications.[109,110] Thyroidectomy is particularly recommended in patients with the following characteristics: large goitres or low uptake of radioactive iodine (or both); suspected or documented thyroid cancer; moderate-to-severe ophthalmopathy, for which radioactive iodine therapy is contraindicated; and finally, a preference for surgery.[44] Conversely, thyroidectomy should be avoided in patients who are not good surgical candidates. Pregnancy is only thought to be a relative contraindication.

Preoperative management and follow-up of patients who receive thyroidectomy—Before surgery, patients should be euthyroid. Pretreatment with ATD reduces the risk of thyroid storm precipitated by surgery, and β blockers control hyperthyroid symptoms. Pretreatment with inorganic iodide, such as potassium iodide (50 mg iodide, three times daily, for 7–10 days before surgery) can also be considered in patients

with Graves' disease.[111] Inorganic iodide reduces thyroid hormone release and thyroid vascularity,[112] which in turn decreases intraoperative blood loss. After surgery, levothyroxine replacement should be started and TSH concentration monitored 6–8 weeks after surgery. Oral calcium and calcitriol supplementation can be used before surgery and according to postoperative serum calcium concentrations.[44]

Side-effects—Surgical complications are rare, occurring in 1–3% of patients.[113,114] The most frequent complication is hypocalcaemia due to permanent hypoparathyroidism, followed by permanent recurrent laryngeal nerve injury. The risk of these complications is lower when thyroidectomy is done by a high-volume thyroid surgeon.[115,116]

Special circumstances

Thyroid storm

Thyroid storm is a rare disorder with an incidence of 0·2 per 100 000 person-years in Japan and occurring in 1–5% of patients admitted to hospital for thyrotoxicosis.[117–119] It is an emergency with a high mortality rate of 8–25%.[119,120] The presentation does not depend on serum thyroid hormones concentrations, which are similar to compensated thyrotoxicosis. An apparent trigger can be identified in up to 70% of cases: usually unreliable use or discontinuation of ATD, followed by infection.[117] Other risk factors include acute illness, thyroid or non-thyroid surgery (now less common, as a result of appropriate preoperative preparation), trauma, stress, and pregnancy. The pathogenesis of thyroid storm is still poorly understood. Diagnosis is clinical and based on the presence of hyperthyroidism in a patient with severe and life-threatening manifestations. To make the diagnosis, Burch and Wartofsky proposed a scoring system (table3),[121] modified by Akamizu and colleagues.[117] A multidisciplinary treatment approach should be used. Goals of treatment are lowering of thyroid hormone synthesis and secretion, reduction of circulating thyroid hormones, control of the peripheral effects of thyroid hormone, resolution of systemic manifestation, and treatment of precipitating illness. The treatment options are listed in table 4.[44,118,122–126] After improvement of thyroid function, which generally occurs in 24 h, iodine can be gradually discontinued and glucocorticoids tapered and discontinued. ATD and β blockers should be titrated according to thyroid function. Definitive therapy with thyroidectomy or radioactive iodine is suggested after the patient becomes euthyroid.

Hyperthyroidism in pregnancy and post partum

The most common cause of hyperthyroidism during pregnancy is Graves' disease. The incidence of hyperthyroidism in the USA is 5·9 per 1000 pregnant women per year.[127] Results of a population-based cohort study in Denmark showed a large variation in the risk of hyperthyroidism during pregnancy: high during the first trimester (RR 1·5, 95% CI 1·09–20·6) and very low in the third trimester (RR 0·26, 0·15–0·44). The highest risk occurred 7–9 months post partum (RR 3·8, 2·88–5·02).[128] The ATA guidelines for the diagnosis and management of thyroid disease during pregnancy and post partum recommend obtaining serum free T_4 concentrations in all women with serum TSH concentrations of less than 0·1 mIU/L.[129] This recommendation is in agreement with the Endocrine Society guidelines,[130] which suggest measuring total T_3 and TRAb concentrations as well. TRAb assessment is

useful to detect the risk for fetal or neonatal hyperthyroidism because thyroid antibodies cross the placenta, and TRAb concentrations should be assessed at 20–24 weeks' gestation.[129,130] Assessment of serum thyroid hormone concentrations is important for distinguishing overt from subclinical hyperthyroidism, because subclinical hyperthyroidism usually does not need to be treated during pregnancy. When overt hyperthyroidism is confirmed, the syndrome of gestational thyrotoxicosis should be excluded. Gestational thyrotoxicosis is a benign and transient disorder, typically occurring in the first trimester, probably due to high concentrations of human chorionic gonadotropin or a variant human chorionic gonadotropin. Clinical characteristics of Graves' disease and TRAb are absent. Gestational thyrotoxicosis only needs symptomatic treatment. By contrast, Graves' disease or toxic nodular goitre should be treated with ATDs.[129,130] Propylthiouracil is generally used during the first trimester of pregnancy and then switched to thiamazole in the second trimester, because of the associated risk of first trimester thiamazole-induced embryopathy. Although some authors argue that this association could be explained by hyperthyroidism, rather than by ATD administration,[131] birth defects including aplasia cutis, choanal atresia, oesophageal atresia, and omphalocele have been described with thiamazole administration and not in patients with hyperthyroidism per se.[132–134] Although less common, propylthiouracil has also been shown to be associated with birth defects in the face and neck, and urinary systems.[132] After the first trimester, thiamazole is the preferred ATD because propylthiouracil has a greater risk of hepatotoxicity.[130] The starting dose is 5–15 mg daily for thiamazole and 50–300 mg daily for propylthiouracil. When one ATD is switched to the other, the equivalent dose of propylthiouracil to thiamazole is thought to be 10–15:1. Thyroid function should be assessed 2 weeks after the change of ATD.[130] TSH, T_4 (normally 150% higher during pregnancy), and free T_4 (or free T_4 index) should be monitored every 2–6 weeks in pregnant women who are taking ATDs.[129] T_4 and free T_4 (or free T_4 index) should be in the upper limit[130] or slightly above[129] the normal reference range, although some free T_4 assays are not reliable during pregnancy because of the presence of high serum T_4-binding globulin concentrations. When ATDs are contraindicated or hyperthyroidism cannot be adequately controlled by ATDs, thyroidectomy is an alternative. Thyroidectomy should be done during the second trimester of pregnancy[129,130] to minimise the potential teratogenic effects of anaesthetic agents. Radioactive iodine therapy is contraindicated in pregnancy because it crosses the placenta and can cause severe hypothyroidism in the fetus.

In the post-partum period, hyperthyroidism due to Graves' disease should be distinguished from post-partum lymphocytic thyroiditis.[137] If Graves' disease is diagnosed post partum, lactating mothers can safely take moderate doses of ATD—ie, thiamazole up to 20 mg daily or propylthiouracil to 300 mg daily.[129] Lactating mothers are recommended to take ATDs immediately after breastfeeding.

Subacute painful and painless thyroiditis

Patients with painful subacute or painless (most commonly occurring during the early post-partum period) thyroiditis have a self-limited course of thyrotoxicosis followed by hypothyroidism and usually restoration of thyroid function.[138] Painless or post-partum lymphocytic thyroiditis frequently recurs during subsequent pregnancies and can result in

permanent hypothyroidism. Positive thyroid peroxidase antibodies are almost always present in painless or post-partum lymphocytic thyroiditis. Thus, these patients need periodic monitoring for the development of hypothyroidism over their lifetime. ATDs and radioactive iodine therapy are contraindicated in both disorders, because thyroid hormone synthesis is not increased and thyroid radioactive iodine uptake is low. Patients are usually given β blockers during the thyrotoxic phase. In patients with painful subacute thyroiditis, NSAIDs or salicylates might be helpful in relieving the thyroid pain and systemic symptoms. Glucocorticoids, such as prednisone 15–40 mg daily, with a slow taper over 4–6 weeks, are preferred in more severe cases.[139] By contrast with patients with painless post-partum lymphocytic thyroiditis, those with painful subacute thyroiditis rarely develop permanent hypothyroidism.[19,20,140]

Amiodarone and iodine-induced thyrotoxicosis

When a patient develops amiodarone-induced thyrotoxicosis, it is extremely important to distinguish between the two forms of amiodarone-induced thyrotoxicosis, because treatment differs. Type I amiodarone-induced thyrotoxicosis usually occurs when patients with an underlying euthyroid nodular goitre or latent Graves' disease are exposed to the high iodine content of amiodarone. This exposure leads to excess thyroid hormone synthesis and release, similar to iodine-induced hyperthyroidism in patients receiving excess iodine from other sources. Type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis caused by a direct toxic effect of amiodarone on thyrocytes. This form is usually self-limiting and, when necessary, amiodarone can be continued.[141] Type I amiodarone-induced thyrotoxicosis is treated with ATDs and, in some cases, by adding potassium perchlorate, an inhibitor of the sodium/iodide symporter (NIS), to inhibit thyroidal iodine uptake. In type II amiodarone-induced thyrotoxicosis, glucocorticoids are used to treat the inflammation and to inhibit conversion of T_4 to the more active T_3 in peripheral tissues and are usually tapered over 6–8 weeks.[141] Thyroidectomy might be a last resort in an occasional patient resistant to the other forms of therapy.

Future research

Treatment of hyperthyroidism has not changed greatly in the past several decades. Choices are between long-term therapy, with risk of relapse, or destruction of the thyroid gland with subsequent hypothyroidism. ATDs are a conservative option, but have about a 50% relapse rate; however, thyroidectomy and radioactive iodine treatment are definitive therapies, but with subsequent hypothyroidism needing lifelong therapy with thyroid hormone replacement. Future research should be directed towards a better understanding of the pathogenesis of Graves' hyperthyroidism to direct therapy at the underlying cause of the hyperthyroidism and to obtain a cure that is safe, conservative, and definitive.

Since the assessment and management strategy of Graves' hyperthyroidism differ between geographical regions, guidelines by non-US thyroid societies would be useful, because they might better represent the different cultural and population characteristics and be more suitable for the practice of their members.

Acknowledgments

This Seminar was supported in part by the National Institutes of Health (NIH T32DK007201–37 to SYL) and the National Italian American Foundation and Fondazione Bracco (to SDL).

References

1. Hedberg CW, Fishbein DB, Janssen RS, et al. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. N Engl J Med. 1987; 316:993–98. [PubMed: 3561455]
2. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012; 379:1142–54. [PubMed: 22273398]
3. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014; 99:923–31. [PubMed: 24423323]
4. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99. [PubMed: 11836274]
5. Vejbjerg P, Knudsen N, Perrild H, et al. Lower prevalence of mild hyperthyroidism related to a higher iodine intake in the population: prospective study of a mandatory iodization programme. Clin Endocrinol (Oxf). 2009; 71:440–45. [PubMed: 19067717]
6. Nyström HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. Clin Endocrinol (Oxf). 2013; 78:768–76. [PubMed: 23421407]
7. Abraham-Nordling M, Byström K, Törring O, et al. Incidence of hyperthyroidism in Sweden. Eur J Endocrinol. 2011; 165:899–905. [PubMed: 21908653]
8. Marinò M, Latrofa F, Menconi F, Chiovato L, Vitti P. Role of genetic and non-genetic factors in the etiology of Graves' disease. J Endocrinol Invest. 2015; 38:283–94. [PubMed: 25421156]
9. Winsa B, Adami HO, Bergström R, et al. Stressful life events and Graves' disease. Lancet. 1991; 338:1475–79. [PubMed: 1683917]
10. Wiersinga WM. Smoking and thyroid. Clin Endocrinol (Oxf). 2013; 79:145–51. [PubMed: 23581474]
11. Menconi F, Marcocci C, Marinò M. Diagnosis and classification of Graves' disease. Autoimmun Rev. 2014; 13:398–402. [PubMed: 24424182]
12. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine. 2012; 42:252–65. [PubMed: 22644837]
13. Brix TH, Hegedüs L. Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. Clin Endocrinol (Oxf). 2012; 76:457–64. [PubMed: 22168537]
14. Laurberg P, Cerqueira C, Ovesen L, et al. Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metab. 2010; 24:13–27. [PubMed: 20172467]
15. Krohn K, Paschke R. Clinical review 133: progress in understanding the etiology of thyroid autonomy. J Clin Endocrinol Metab. 2001; 86:3336–45. [PubMed: 11443209]
16. Paschke R, Ludgate M. The thyrotropin receptor in thyroid diseases. N Engl J Med. 1997; 337:1675–81. [PubMed: 9385128]
17. Beck-Peccoz, P.; Persani, L. Thyrotropin-induced thyrotoxicosis. In: Braverman, LE.; Cooper, DS., editors. Werner & Ingbar's the thyroid: a fundamental and clinical text. 10th. Lippincott Williams & Wilkins; Philadelphia: 2013. p. 393-99.
18. Hershman, JM. Trophoblastic tumors. In: Braverman, LE.; Cooper, DS., editors. Werner & Ingbar's the thyroid: a fundamental and clinical text. 10th. Lippincott Williams & Wilkins; Philadelphia: 2013. p. 409-14.
19. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab. 2003; 88:2100–05. [PubMed: 12727961]

20. Schwartz F, Bergmann N, Zerahn B, Faber J. Incidence rate of symptomatic painless thyroiditis presenting with thyrotoxicosis in Denmark as evaluated by consecutive thyroid scintigraphies. Scand J Clin Lab Invest. 2013; 73:240–44. [PubMed: 23438331]
21. Goichot B, Caron P, Landron F, Bouée S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin Endocrinol (Oxf). 2015 published online May 9. DOI:10.1111/cen.12816.
22. Devereaux D, Tewelde SZ. Hyperthyroidism and thyrotoxicosis. Emerg Med Clin North Am. 2014; 32:277–92. [PubMed: 24766932]
23. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab. 2010; 95:2715–26. [PubMed: 20392869]
24. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Graves' disease: a 2014 update. J Endocrinol Invest. 2014; 37:691–700. [PubMed: 24913238]
25. Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid. 2008; 18:333–46. [PubMed: 18341379]
26. Bahn R. The EUGOGO consensus statement on the management of Graves' orbitopathy: equally applicable to North American clinicians and patients. Thyroid. 2008; 18:281–82. [PubMed: 18341375]
27. Wiersinga WM, Perros P, Kahaly GJ, et al. European Group on Graves' Orbitopathy (EUGOGO). Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol. 2006; 155:387–89. [PubMed: 16914591]
28. Fatourechi V. Thyroid dermopathy and acropachy. Best Pract Res Clin Endocrinol Metab. 2012; 26:553–65. [PubMed: 22863396]
29. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. J Clin Endocrinol Metab. 2002; 87:438–46. [PubMed: 11836263]
30. Fatourechi V, Ahmed DD, Schwartz KM. Thyroid acropachy: report of 40 patients treated at a single institution in a 26-year period. J Clin Endocrinol Metab. 2002; 87:5435–41. [PubMed: 12466333]
31. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994; 331:1249–52. [PubMed: 7935681]
32. Chen Q, Yan Y, Zhang L, Cheng K, Liu Y, Zhu W. Effect of hyperthyroidism on the hypercoagulable state and thromboembolic events in patients with atrial fibrillation. Cardiology. 2014; 127:176–82. [PubMed: 24434544]
33. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nat Rev Endocrinol. 2010; 6:431–43. [PubMed: 20585347]
34. Traube E, Coplan NL. Embolic risk in atrial fibrillation that arises from hyperthyroidism: review of the medical literature. Tex Heart Inst J. 2011; 38:225–28. [PubMed: 21720457]
35. Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart. 2007; 93:483–87. [PubMed: 17005710]
36. Selmer C, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab. 2014; 99:2372–82. [PubMed: 24654753]
37. Vijayakumar A, Ashwath G, Thimmappa D. Thyrotoxic periodic paralysis: clinical challenges. J Thyroid Res. 2014; 2014:649502. [PubMed: 24695373]
38. Ryan DP, da Silva MR, Soong TW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. Cell. 2010; 140:88–98. [PubMed: 20074522]
39. Abe E, Marians RC, Yu W, et al. TSH is a negative regulator of skeletal remodeling. Cell. 2003; 115:151–62. [PubMed: 14567913]
40. Meikle AW. The interrelationships between thyroid dysfunction and hypogonadism in men and boys. Thyroid. 2004; 14(suppl 1):S17–25. [PubMed: 15142373]

41. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010; 31:702–55. [PubMed: 20573783]
42. de los Santos ET, Starich GH, Mazzaferri EL. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. Arch Intern Med. 1989; 149:526–32. [PubMed: 2493228]
43. Vaidya B, Pearce SH. Diagnosis and management of thyrotoxicosis. BMJ. 2014; 349:g5128. [PubMed: 25146390]
44. Bahn Chair RS, Burch HB, Cooper DS, et al. American Thyroid Association and American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011; 21:593–646. [PubMed: 21510801]
45. Kahaly GJ, Bartalena L, Hegedüs L. The American Thyroid Association/American Association of Clinical Endocrinologists guidelines for hyperthyroidism and other causes of thyrotoxicosis: a European perspective. Thyroid. 2011; 21:585–91. [PubMed: 21663420]
46. Burch HB, Burman KD, Cooper DSA. A 2011 survey of clinical practice patterns in the management of Graves' disease. J Clin Endocrinol Metab. 2012; 97:4549–58. [PubMed: 23043191]
47. Yamashita S, Amino N, Shong YK. The American Thyroid Association and American Association of Clinical Endocrinologists hyperthyroidism and other causes of thyrotoxicosis guidelines: viewpoints from Japan and Korea. Thyroid. 2011; 21:577–80. [PubMed: 21663418]
48. Moon JH, Yi KH. The diagnosis and management of hyperthyroidism in Korea: consensus report of the Korean Thyroid Association. Endocrinol Metab (Seoul). 2013; 28:275–79. [PubMed: 24396691]
49. Maia AL, Scheffel RS, Meyer EL, et al. Brazilian Society of Endocrinology and Metabolism. The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism. Arq Bras Endocrinol Metabol. 2013; 57:205–32. [PubMed: 23681266]
50. Cappelli C, Pirola I, De Martino E, et al. The role of imaging in Graves' disease: a cost-effectiveness analysis. Eur J Radiol. 2008; 65:99–103. [PubMed: 17459638]
51. Ota H, Amino N, Morita S, et al. Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. Clin Endocrinol (Oxf). 2007; 67:41–45. [PubMed: 17437515]
52. Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N. TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. Autoimmun Rev. 2012; 12:107–13. [PubMed: 22776786]
53. Barbesino G, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab. 2013; 98:2247–55. [PubMed: 23539719]
54. van Soestbergen MJ, van der Vijver JC, Graafland AD. Recurrence of hyperthyroidism in multinodular goiter after long-term drug therapy: a comparison with Graves' disease. J Endocrinol Invest. 1992; 15:797–800. [PubMed: 1283983]
55. Bartalena L. Diagnosis and management of Graves disease: a global overview. Nat Rev Endocrinol. 2013; 9:724–34. [PubMed: 24126481]
56. Cooper DS. Antithyroid drugs. N Engl J Med. 2005; 352:905–17. [PubMed: 15745981]
57. Koenig RJ. Regulation of type 1 iodothyronine deiodinase in health and disease. Thyroid. 2005; 15:835–40. [PubMed: 16131326]
58. Antonelli A, Ferrari SM, Corrado A, Ferrannini E, Fallahi P. Increase of interferon-γ inducible CXCL9 and CXCL11 serum levels in patients with active Graves' disease and modulation by methimazole therapy. Thyroid. 2013; 23:1461–69. [PubMed: 23721189]
59. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2007; 92:2157–62. [PubMed: 17389704]

60. Okamura K, Ikenoue H, Shiroozu A, Sato K, Yoshinari M, Fujishima M. Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab. 1987; 65:719–23. [PubMed: 3654917]

61. Kim HJ, Kim BH, Han YS, et al. The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. Am J Gastroenterol. 2001; 96:165–69. [PubMed: 11197248]

62. Rivkees SA, Mattison DR. Propylthiouracil (PTU) hepatoxicity in children and recommendations for discontinuation of use. Int J Pediatr Endocrinol. 2009; 2009:132041. [PubMed: 19946400]

63. Bahn RS, Burch HS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid. 2009; 19:673–74. [PubMed: 19583480]

64. Takata K, Amino N, Kubota S, et al. Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease. Clin Endocrinol (Oxf). 2010; 72:845–50. [PubMed: 19912243]

65. Sato S, Noh JY, Sato S, et al. Comparison of efficacy and adverse effects between methimazole 15 mg+inorganic iodine 38 mg/day and methimazole 30 mg/day as initial therapy for Graves' disease patients with moderate to severe hyperthyroidism. Thyroid. 2015; 25:43–50. [PubMed: 25178068]

66. Benker G, Reinwein D, Kahaly G, et al. European Multicentre Trial Group of the Treatment of Hyperthyroidism with Antithyroid Drugs. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. Clin Endocrinol (Oxf). 1998; 49:451–57. [PubMed: 9876342]

67. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2010; 1:CD003420. [PubMed: 20091544]

68. Razvi S, Vaidya B, Perros P, Pearce SH. What is the evidence behind the evidence-base? The premature death of block-replace antithyroid drug regimens for Graves' disease. Eur J Endocrinol. 2006; 154:783–86. [PubMed: 16728536]

69. Allannic H, Fauchet R, Orgiazzi J, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab. 1990; 70:675–79. [PubMed: 1689737]

70. Anagnostis P, Adamidou F, Polyzos SA, et al. Predictors of long-term remission in patients with Graves' disease: a single center experience. Endocrine. 2013; 44:448–53. [PubMed: 23397523]

71. Mohlin E, Filipsson Nyström H, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000–2010. Eur J Endocrinol. 2014; 170:419–27. [PubMed: 24366943]

72. Laurberg P, Krejbjerg A, Andersen SL. Relapse following antithyroid drug therapy for Graves' hyperthyroidism. Curr Opin Endocrinol Diabetes Obes. 2014; 21:415–21. [PubMed: 25111942]

73. Azizi F. The safety and efficacy of antithyroid drugs. Expert Opin Drug Saf. 2006; 5:107–16. [PubMed: 16370960]

74. Quadbeck B, Hoermann R, Roggenbuck U, Hahn S, Mann K, Janssen OE, Basedow Study Group. Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves' disease. Thyroid. 2005; 15:1047–54. [PubMed: 16187913]

75. Schott M, Morgenthaler NG, Fritzen R, et al. Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease. Horm Metab Res. 2004; 36:92–96. [PubMed: 15002058]

76. Carella C, Mazziotti G, Sorvillo F, et al. Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period. Thyroid. 2006; 16:295–302. [PubMed: 16571093]

77. Liu X, Qiang W, Liu X, et al. A second course of antithyroid drug therapy for recurrent Graves' disease: an experience in endocrine practice. Eur J Endocrinol. 2015; 172:321–26. [PubMed: 25468954]

78. Otsuka F, Noh JY, Chino T, et al. Hepatotoxicity and cutaneous reactions after antithyroid drug administration. Clin Endocrinol (Oxf). 2012; 77:310–15. [PubMed: 22332800]

79. Robinson J, Richardson M, Hickey J, et al. Patient knowledge of antithyroid drug-induced agranulocytosis. Eur Thyroid J. 2014; 3:245–51. [PubMed: 25759801]
80. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab. 2013; 98:4776–83. [PubMed: 24057289]
81. Watanabe N, Narimatsu H, Noh JY, et al. Antithyroid drug-induced hematopoietic damage: a retrospective cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Graves' disease. J Clin Endocrinol Metab. 2012; 97:E49–53. [PubMed: 22049174]
82. Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. Br J Clin Pharmacol. 2014; 78:619–29. [PubMed: 25279406]
83. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab. 2010; 95:3260–67. [PubMed: 20427502]
84. Noh JY, Yasuda S, Sato S, et al. Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. J Clin Endocrinol Metab. 2009; 94:2806–11. [PubMed: 19491223]
85. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998; 338:73–78. [PubMed: 9420337]
86. Chen DY, Schneider PF, Zhang XS, Luo XY, He ZM, Chen TH. Changes in Graves' ophthalmopathy after radioiodine and anti-thyroid drug treatment of Graves' disease from 2 prospective, randomized, open-label, blinded end point studies. Exp Clin Endocrinol Diabetes. 2014; 122:1–6. [PubMed: 24203649]
87. Watanabe N, Noh JY, Kozaki A, et al. Radioiodine-associated exacerbation of Graves' orbitopathy in the Japanese population: randomized prospective study. J Clin Endocrinol Metab. 2015; 100:2700–08. [PubMed: 25965082]
88. Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf). 2008; 69:943–50. [PubMed: 18429949]
89. Träisk F, Tallstedt L, Abraham-Nordling M, et al. Thyroid Study Group of TT 96. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. J Clin Endocrinol Metab. 2009; 94:3700–07. [PubMed: 19723755]
90. Tallstedt L, Lundell G, Tørring O, et al. The Thyroid Study Group. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. N Engl J Med. 1992; 326:1733–38. [PubMed: 1489388]
91. Eckstein AK, Plicht M, Lax H, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab. 2006; 91:3464–70. [PubMed: 16835285]
92. Stan MN, Durski JM, Brito JP, Bhagra S, Thapa P, Bahn RS. Cohort study on radioactive iodine-induced hypothyroidism: implications for Graves' ophthalmopathy and optimal timing for thyroid hormone assessment. Thyroid. 2013; 23:620–25. [PubMed: 23205939]
93. Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. Thyroid. 2014; 24:1515–23. [PubMed: 25068172]
94. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab. 2001; 86:3488–93. [PubMed: 11502768]
95. Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after (131)I ablation for Graves' disease. J Clin Endocrinol Metab. 2001; 86:3016–21. [PubMed: 11443161]
96. Walter MA, Briel M, Christ-Crain M, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ. 2007; 334:514. [PubMed: 17309884]

97. Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves' disease. Thyroid. 2004; 14:525–30. [PubMed: 15307942]

98. Walter MA, Christ-Crain M, Schindler C, Müller-Brand J, Müller B. Outcome of radioiodine therapy without, on or 3 days off carbimazole: a prospective interventional three-group comparison. Eur J Nucl Med Mol Imaging. 2006; 33:730–37. [PubMed: 16607544]

99. de Rooij A, Vandenbroucke JP, Smit JW, Stokkel MP, Dekkers OM. Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. Eur J Endocrinol. 2009; 161:771–77. [PubMed: 19671708]

100. Rokni H, Sadeghi R, Moossavi Z, Treglia G, Zakavi SR. Efficacy of different protocols of radioiodine therapy for treatment of toxic nodular goiter: systematic review and meta-analysis of the literature. Int J Endocrinol Metab. 2014; 12:e14424. [PubMed: 24803943]

101. Boelaert K, Syed AA, Manji N, et al. Prediction of cure and risk of hypothyroidism in patients receiving 131I for hyperthyroidism. Clin Endocrinol (Oxf). 2009; 70:129–38. [PubMed: 18462261]

102. Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2002; 87:1073–77. [PubMed: 11889166]

103. Ross DS. Radioiodine therapy for hyperthyroidism. N Engl J Med. 2011; 364:542–50. [PubMed: 21306240]

104. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev. 2012; 33:920–80. [PubMed: 22961916]

105. la Cour JL, Jensen LT, Vej-Hansen A, Nygaard B. Radioiodine therapy increases the risk of cerebrovascular events in hyperthyroid and euthyroid patients. Eur J Endocrinol. 2015; 172:771–78. [PubMed: 25920711]

106. Ryödi E, Metso S, Jaatinen P, et al. Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism. J Clin Endocrinol Metab. 2015; 100:3710–17. [PubMed: 26262435]

107. Ceccarelli C, Canale D, Battisti P, et al. Testicular function after 131I therapy for hyperthyroidism. Clin Endocrinol (Oxf). 2006; 65:446–52. [PubMed: 16984236]

108. Genovese BM, Noureldine SI, Gleeson EM, Tufano RP, Kandil E. What is the best definitive treatment for Graves' disease? A systematic review of the existing literature. Ann Surg Oncol. 2013; 20:660–67. [PubMed: 22956065]

109. Bojic T, Paunovic I, Diklic A, et al. Total thyroidectomy as a method of choice in the treatment of Graves' disease—analysis of 1432 patients. BMC Surg. 2015; 15:39. [PubMed: 25888210]

110. Palit TK, Miller CC 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res. 2000; 90:161–65. [PubMed: 10792958]

111. Shinall MC Jr, Broome JT, Baker A, Solorzano CC. Is potassium iodide solution necessary before total thyroidectomy for Graves disease? Ann Surg Oncol. 2013; 20:2964–67. [PubMed: 23846785]

112. Erbil Y, Ozluk Y, Giriş M, et al. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. J Clin Endocrinol Metab. 2007; 92:2182–89. [PubMed: 17389702]

113. Werga-Kjellman P, Zedenius J, Tallstedt L, Träisk F, Lundell G, Wallin G. Surgical treatment of hyperthyroidism: a ten-year experience. Thyroid. 2001; 11:187–92. [PubMed: 11288990]

114. Pradeep PV, Agarwal A, Baxi M, Agarwal G, Gupta SK, Mishra SK. Safety and efficacy of surgical management of hyperthyroidism: 15-year experience from a tertiary care center in a developing country. World J Surg. 2007; 31:306–12. discussion 313. [PubMed: 17219271]

115. Kandil E, Noureldine SI, Abbas A, Tufano RP. The impact of surgical volume on patient outcomes following thyroid surgery. Surgery. 2013; 154:1346–52. discussion 1352–53. [PubMed: 24238052]

116. Hauch A, Al-Qurayshi Z, Randolph G, Kandil E. Total thyroidectomy is associated with increased risk of complications for low- and high-volume surgeons. Ann Surg Oncol. 2014; 21:3844–52. [PubMed: 24943236]

117. Akamizu T, Satoh T, Isozaki O, et al. Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012; 22:661–79. [PubMed: 22690898]
118. Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Med Clin North Am. 2012; 96:385–403. [PubMed: 22443982]
119. Swee DS, Chng CL, Lim A. Clinical characteristics and outcome of thyroid storm: a case series and review of neuropsychiatric derangements in thyrotoxicosis. Endocr Pract. 2015; 21:182–89. [PubMed: 25370315]
120. Angell TE, Lechner MG, Nguyen CT, Salvato VL, Nicoloff JT, LoPresti JS. Clinical features and hospital outcomes in thyroid storm: a retrospective cohort study. J Clin Endocrinol Metab. 2015; 100:451–59. [PubMed: 25343237]
121. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993; 22:263–77. [PubMed: 8325286]
122. Pearce EN, Hennessey JV, McDermott MT. New American Thyroid Association and American Association of Clinical Endocrinologists guidelines for thyrotoxicosis and other forms of hyperthyroidism: significant progress for the clinician and a guide to future research. Thyroid. 2011; 21:573–76. [PubMed: 21663417]
123. Kaykhaei MA, Shams M, Sadegholvad A, Dabbaghmanesh MH, Omrani GR. Low doses of cholestyramine in the treatment of hyperthyroidism. Endocrine. 2008; 34:52–55. [PubMed: 18946743]
124. Tsatsoulis A, Johnson EO, Kalogera CH, Seferiadis K, Tsolas O. The effect of thyrotoxicosis on adrenocortical reserve. Eur J Endocrinol. 2000; 142:231–35. [PubMed: 10700716]
125. Milner MR, Gelman KM, Phillips RA, Fuster V, Davies TF, Goldman ME. Double-blind crossover trial of diltiazem versus propranolol in the management of thyrotoxic symptoms. Pharmacotherapy. 1990; 10:100–06. [PubMed: 2349134]
126. Isozaki O, Satoh T, Wakino S, et al. Treatment and management of thyroid storm: analysis of the nationwide surveys: The taskforce committee of the Japan Thyroid Association and Japan Endocrine Society for the establishment of diagnostic criteria and nationwide surveys for thyroid storm. Clin Endocrinol (Oxf). 2015 published online Sep 21. DOI:10.1111/cen.12949.
127. Korelitz JJ, McNally DL, Masters MN, Li SX, Xu Y, Rivkees SA. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. Thyroid. 2013; 23:758–65. [PubMed: 23194469]
128. Andersen SL, Olsen J, Carlé A, Laurberg P. Hyperthyroidism incidence fluctuates widely in and around pregnancy and is at variance with some other autoimmune diseases: a Danish population-based study. J Clin Endocrinol Metab. 2015; 100:1164–71. [PubMed: 25485728]
129. Stagnaro-Green A, Abalovich M, Alexander E, et al. American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011; 21:1081–125. [PubMed: 21787128]
130. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97:2543–65. [PubMed: 22869843]
131. Gianetti E, Russo L, Orlandi F, et al. Pregnancy outcome in women treated with methimazole or propylthiouracil during pregnancy. J Endocrinol Invest. 2015; 38:977–85. [PubMed: 25840794]
132. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab. 2013; 98:4373–81. [PubMed: 24151287]
133. Yoshihara A, Noh J, Yamaguchi T, et al. Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. J Clin Endocrinol Metab. 2012; 97:2396–403. [PubMed: 22547422]
134. Bowman P, Vaidya B. Suspected spontaneous reports of birth defects in the UK associated with the use of carbimazole and propylthiouracil in pregnancy. J Thyroid Res. 2011; 2011:235130. [PubMed: 21922050]

135. Pearce EN. Thyroid disorders during pregnancy and postpartum. Best Pract Res Clin Obstet Gynaecol. 2015; 29:700–06. [PubMed: 26028555]

136. Lee RH, Spencer CA, Mestman JH, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol. 2009; 200:e1–6.

137. Ide A, Amino N, Kang S, et al. Differentiation of postpartum Graves' thyrotoxicosis from postpartum destructive thyrotoxicosis using antithyrotropin receptor antibodies and thyroid blood flow. Thyroid. 2014; 24:1027–31. [PubMed: 24400892]

138. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003; 348:2646–55. [PubMed: 12826640]

139. Kubota S, Nishihara E, Kudo T, Ito M, Amino N, Miyauchi A. Initial treatment with 15 mg of prednisolone daily is sufficient for most patients with subacute thyroiditis in Japan. Thyroid. 2013; 23:269–72. [PubMed: 23227861]

140. Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. J Clin Endocrinol Metab. 2012; 97:334–42. [PubMed: 22312089]

141. Eskes SA, Endert E, Fliers E, et al. Treatment of amiodarone-induced thyrotoxicosis type 2: a randomized clinical trial. J Clin Endocrinol Metab. 2012; 97:499–506. [PubMed: 22130792]

Search strategy and selection criteria

We searched MEDLINE (January, 2000, to October, 2015) and the Cochrane Library (January, 2000, to October, 2015), using the terms “hyperthyroidism” or “thyrotoxicosis” combined with the terms “Graves’ disease”, “toxic adenoma”, “toxic multinodular goiter”, “thyroiditis”, “radioactive iodine therapy”, “antithyroid drugs”, “thyroidectomy”. We also used the reference lists of the selected publications identified by the search strategy and textbooks. Most of the references were selected from publications from the past 5 years, but we included relevant older articles. Only publications written in English were included.

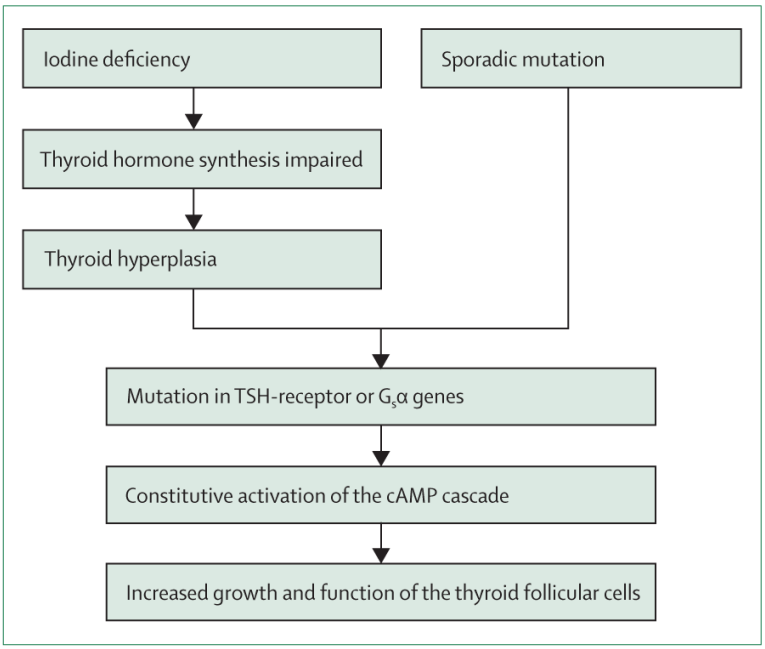

Figure 1. Pathogenesis of thyroid autonomy

cAMP=cyclic adenosine monophosphate. $G_s\alpha$=G protein alpha subunit. TSH=thyroid-stimulating hormone.

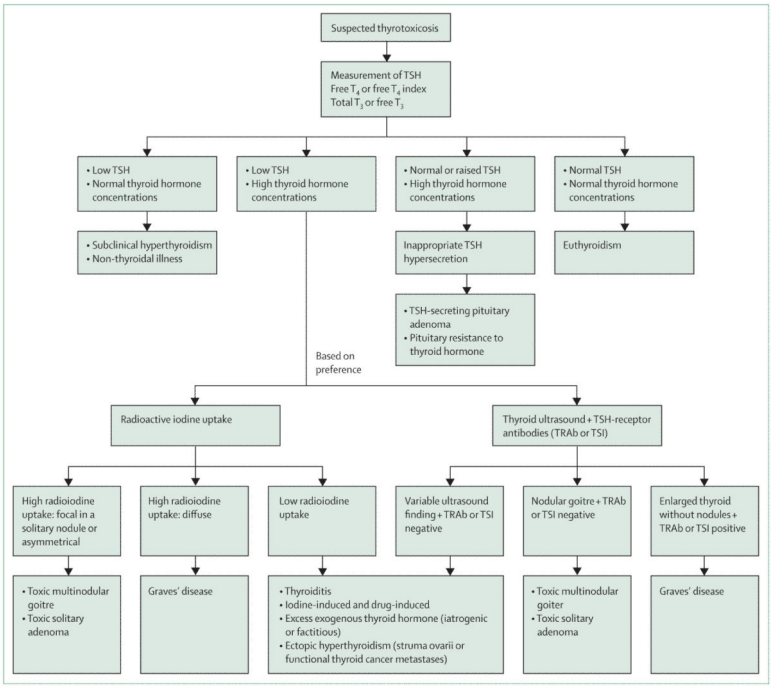

Figure 2. Algorithm for the assessment of thyrotoxicosis

T_3=tri-iodothyronine. T_4=thyroxine. TRAb=TSH-receptor antibodies. TSH=thyroid-stimulating hormone. TRAb=TSH-receptor antibodies. TSI=thyroid-stimulating immunoglobulins.

Table 1

Pathogenic mechanisms and causes of thyrotoxicosis

	Cause
Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
Effect of increased thyroid stimulators	
TSH-receptor antibody	Graves' disease
Inappropriate TSH secretion	TSH-secreting pituitary adenoma; pituitary resistance to thyroid hormone
Excess hCG secretion	Trophoblastic tumours (choriocarcinoma or hydatidiform mole); hyperemesis gravidarum
Autonomous thyroid function	
Activating mutations in TSH receptor or $G_s\alpha$ protein	Solitary hyperfunctioning adenoma; multinodular goitre; familial non-autoimmune hyperthyroidism
Thyrotoxicosis without hyperthyroidism (low radioactive iodine uptake)	
Inflammation and release of stored hormone	
Autoimmune destruction of thyroid gland	Silent (painless) thyroiditis; post-partum thyroiditis
Viral infection *	Subacute (painful) thyroiditis (De Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon α)
Bacterial or fungal infection	Acute suppurative thyroiditis
Radiation	Radiation thyroiditis
Extrathyroidal source of hormone	
Excess intake of thyroid hormone	Excess exogenous thyroid hormone (iatrogenic or factitious)
Ectopic hyperthyroidism (thyroid hormone produced outside the thyroid gland)	Struma ovarii; functional thyroid cancer metastases
Ingestion of contaminated food	Hamburger thyrotoxicosis[1]
Exposure to excessive iodine	
Jod-Basedow effect	Iodine-induced hyperthyroidism (iodine, iodine-containing drugs, radiographic contrast agents)

TSH=thyroid-stimulating hormone. hCG=human chorionic gonadotropin. $G_S\alpha$=G protein alpha subunit.

*Aetiology is not definitive.

Table 2

Clinical manifestation of thyrotoxicosis

	Symptoms	**Signs**
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating, and polydipsia)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyper-reflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension; irregular heartbeat (atrial fibrillation)
Pulmonary	Dyspnoea, shortness of breath	Tachypnoea
Gastrointestinal	Hyperdefecation; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive	..	Menstrual disturbances
Ocular (Graves' disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital oedema; conjunctival injection and chemosis; ophthalmoplegia

Table 3

Diagnostic criteria for thyroid storm

	Points
Temperature °F (°C)	
99–99·9 (37·2-37·7)	5
100-100·9 (37·8-38·2)	10
101-101·9 (38·3-38·8)	15
102-102·9 (38·9-39·4)	20
103-103·9 (39·4-39·9)	25
≥104·0 (>40·0)	30
Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Gastrointestinal–hepatic dysfunction	
Absent	0
Moderate (diarrhoea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular dysfunction	
Tachycardia	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal oedema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary oedema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitating history	
Absent	0
Present	10

A score ≥45 is highly suggestive of thyroid storm; a score of 25–44 is suggestive of impending thyroid storm; a score of <25 is unlikely to represent thyroid storm. Data are from Burch and Wartofsky.[121]

Table 4

Treatment of thyrotoxic storm

	Doses and formulations	Notes
Lowering of thyroid hormone synthesis and/or secretion		
Antithyroid drugs	Propylthiouracil 250 mg every 4 h, after a loading dose of 500–1000 mg, or thiamazole 20 mg every 6 h	Antithyroid drugs in high doses block thyroid hormone synthesis; propylthiouracil is preferred over thiamazole because of the additional effect of blocking T_4 to T_3 conversion, although there is some disagreement in avoiding thiamazole in this setting[122] since no data show the superior efficacy of propylthiouracil in thyroid storm
Inorganic iodine	Saturated solution of potassium iodide, 5 drops (0·25 mL or 250 mg) every 6 h, given orally (or 1 g intravenously over 12 h)	Inorganic iodine decreases release of preformed T_4 and T_3 and should be given 1 h after antithyroid drugs because iodine can increase hormone production by acting as a substrate for the thyroid synthesis of T_4 and T_3 if synthesis has not already been blocked with antithyroid drugs
Reduction of circulating thyroid hormones*		
Bile acid sequestrants	Doses of colestyramine up to 4 g every 6 h are recommended	After conjugation in the liver, free thyroid hormones are excreted in the intestine and then reabsorbed into the circulation; colestyramine has been shown to decrease serum thyroid hormone concentrations more rapidly and thoroughly than treatment with thionamide alone by enhancing thyroid hormone faecal excretion via sequestration of free hormones in the intestine[123]
Control of the peripheral effects of thyroid hormone†		
β blockers	Propranolol 60–80 mg every 4 h, orally (it can also be given intravenously); other β-blocking drugs are also useful	β blockers can control the peripheral effects of excess thyroid hormones, in addition to slightly decreasing T_4 to T_3 conversion; in patients with heart failure or contraindication to β blockers, such as asthma or bronchospasm, strict monitoring and extreme caution is recommended
Resolution of systemic manifestations		
Glucocorticoids	Hydrocortisone, at a dose of 100 mg every 8 h after an intravenous loading dose of 300 mg, or dexamethasone, at a dose of 2 mg twice a day, intravenously or orally	Glucocorticoids reduce T_4 to T_3 conversion and treat the potential risk of adrenal insufficiency due to severe thyrotoxicosis[124]
Paracetamol (acetaminophen), external cooling	650 mg every 6–8 h as needed	Fever should be treated with paracetamol; salicylates should be avoided, because they increase free T_3 and free T_4 concentrations by inhibiting T_3 and T_4 binding to serum proteins
Treatment of precipitating illness		
Dependent on underlying illness	Not applicable	The underlying illness that triggered the thyroid storm should be diagnosed and treated appropriately

T_4=thyroxine. T_3=tri-iodothyronine.

*In severe cases or in those refractory to conventional treatments, plasmapheresis has been used to reduce T_3 and T_4 concentrations from plasma in 36 h,[118] and also removes pro-inflammatory cytokines and antibodies.

†In patients for whom β blockers are contraindicated, calcium-channel blockers, such as diltiazem, can be used.[125]