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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 (T₄), tri-iodothyronine (T₃), or both. Subclinical hyperthyroidism is characterised by low serum TSH, but normal serum T₄ and T₃ concentrations. We do not discuss subclinical hyperthyroidism here, but it was recently reviewed in another *Lancet* Seminar.²

what about normal TSH but high T4 and/or T3??

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 thyrotoxicosis¹⁷ 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 osteoporosis³⁹ and abnormalities in the reproductive system, such as gynaecomastia in men⁴⁰ 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 T₄ or free T₄ index, and free or total T₃ 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 hypoechoic) 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 T₄ and T₃ 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 T₃:T₄ 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 T₃ 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 outcomes⁹⁹ 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 T₄ 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 (table 3),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 T₄ 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 T₃ 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, T₄ (normally 150% higher during pregnancy), and free T₄ (or free T₄ index) should be monitored every 2–6 weeks in pregnant women who are taking ATDs.¹²⁹ T₄ and free T₄ (or free T₄ index) should be in the upper limit¹³⁰ or slightly above¹²⁹ the normal reference range, although some free T₄ assays are not reliable during pregnancy because of the presence of high serum T₄-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.

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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.

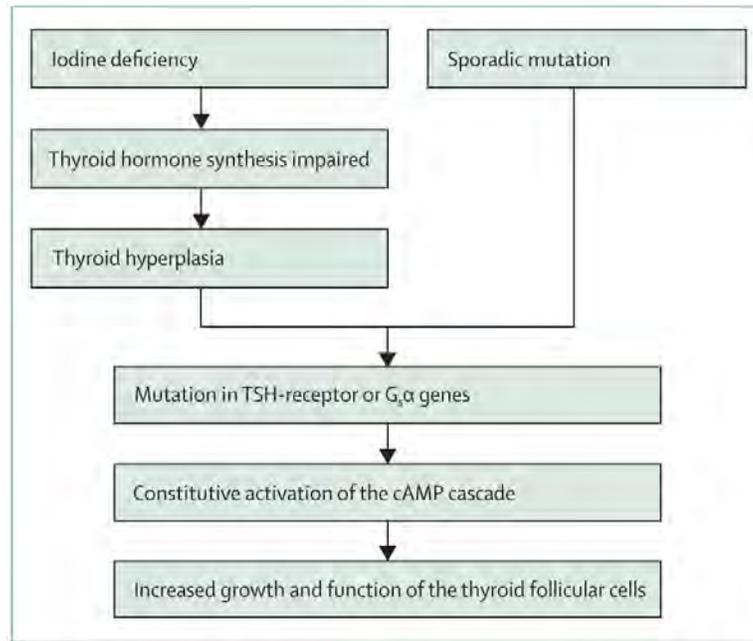


Figure 1. Pathogenesis of thyroid autonomy

cAMP=cyclic adenosine monophosphate. G α =G protein alpha subunit. TSH=thyroid-stimulating hormone.

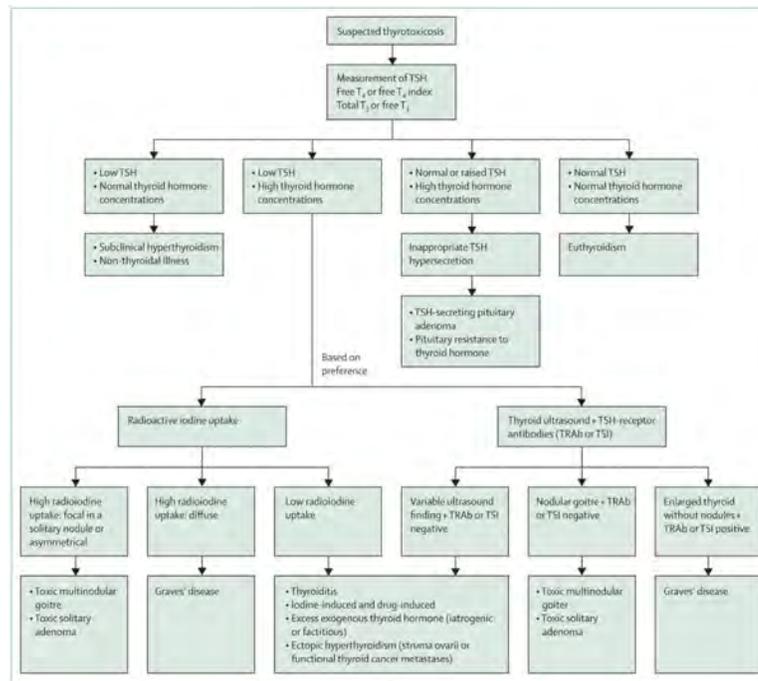


Figure 2. Algorithm for the assessment of thyrotoxicosis

T₃=tri-iodothyronine. T₄=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 α 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_sα=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

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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

T₄=thyroxine. T₃=tri-iodothyronine.

* In severe cases or in those refractory to conventional treatments, plasmapheresis has been used to reduce T₃ and T₄ 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

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