Hyperthyroidism: aetiology, pathogenesis, diagnosis, management, complications, and prognosis

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Hyperthyroidism is a common condition with a global prevalence of 0·2–1·3%. When clinical suspicion of hyperthyroidism arises, it should be confirmed by biochemical tests (eg, low TSH, high free thyroxine [FT_4], or high free tri-iodothyonine [FT_3]). If hyperthyroidism is confirmed by biochemical tests, a nosological diagnosis should be done to find out which disease is causing the hyperthyroidism. Helpful tools are TSH-receptor antibodies, thyroid peroxidase antibodies, thyroid ultrasonography, and scintigraphy. Hyperthyroidism is mostly caused by Graves' hyperthyroidism (70%) or toxic nodular goitre (16%). Hyperthyroidism can also be caused by subacute granulomatous thyroiditis (3%) and drugs (9%) such as amiodarone, tyrosine kinase inhibitors, and immune checkpoint inhibitors. Disease-specific recommendations are given. Currently, Graves' hyperthyroidism is preferably treated with antithyroid drugs. However, recurrence of hyperthyroidism after a 12–18 month course of antithyroid drugs occurs in approximately 50% of patients. Being younger than 40 years, having FT_4 concentrations that are 40 pmol/L or higher, having TSH-binding inhibitory immunoglobulins that are higher than 6 U/L, and having a goitre size that is equivalent to or larger than WHO grade 2 before the start of treatment with antithyroid drugs increase risk of recurrence. Long-term treatment with antithyroid drugs (ie, 5–10 years of treatment) is feasible and associated with fewer recurrences (15%) than short-term treatment (ie, 12–18 months of treatment). Toxic nodular goitre is mostly treated with radioiodine (^{131}I) or thyroidectomy and is rarely treated with radiofrequency ablation. Destructive thyrotoxicosis is usually mild and transient, requiring steroids only in severe cases. Specific attention is given to patients with hyperthyroidism who are pregnant, have COVID-19, or have other complications (eg, atrial fibrillation, thyrotoxic periodic paralysis, and thyroid storm). Hyperthyroidism is associated with increased mortality. Prognosis might be improved by rapid and sustained control of hyperthyroidism. Innovative new treatments are expected for Graves' disease, by targeting B cells or TSH receptors.

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Introduction

Thyrotoxicosis refers to a syndrome caused by excessive thyroid hormones. Hyperthyroidism refers to excessive thyroid hormone production in the thyroid gland (ie, thyrotoxicosis with hyperthyroidism), whereas excessive thyroid hormones derived from extrathyroidal sources or destructive thyrotoxicosis is known as thyrotoxicosis without hyperthyroidism. However, the terms hyperthyroidism and thyrotoxicosis are often used almost interchangeably, as we do in in this Review. Thyroxine (T_4) is produced by the thyroid gland and and considered as the prohormone of tri-iodothyronine (T_3). 80% of the daily T_3 production is generated extrathyroidally from T_4 by deiodinases in extrathyroidal tissues such as the liver, kidney, and brain. Thyroid hormone predominantly works by binding to nuclear T_3 receptors that are present in almost all tissues. However, thyroid hormones can also have non-genomic effects on plasma membranes (eg, ion channels). Thyrotoxicosis is a common condition: the estimated global prevalence of overt hyperthyroidism (ie, elevated T_4 or T_3, or both) in iodine-sufficient populations is 0·2–1·3%. In Europe, the prevalence of overt hyperthyroidism is 0·75%, and the annual incidence is 51 cases per 100 000 people per year.[1] The prevalence and incidence of hyperthyroidism are higher in historically iodine-deficient areas than in iodine-sufficient area.

Clinical presentation

The typical patient with hyperthyroidism is a woman of reproductive age with symptoms such as nervousness, heat intolerance, palpitations, and weight loss despite increased appetite. Physical examination might reveal brisk tendon reflexes, fine finger tremor, moist skin, tachycardia, and goitre. The prevalence of these symptoms and signs in overt hyperthyroidism is greater than 50%.[2] Less frequent systemic manifestations could happen in all tissues because thyroid hormone stimulates metabolism in general (table 1).

The clinical presentation of hyperthyroidism is modulated by sex, age, and aetiology of hyperthyroidism. Hyperthyroidism is four to seven times more frequent in women than in men, irrespective of cause.[3] It is most

	Symptoms	Signs
Metabolic	Increased appetite	Weight loss
Mood and cognition	Nervousness; anxiety; depression; disturbed sleep; poor concentration	Hyperactivity; irratibility; emotional lability
Neuromuscular	Fatigue; weakness; tremor; periodic paralysis	Brisk tendon reflexes; finger or tongue tremor, or both; muscle wasting
Cardiovascular	Palpitations; ankle oedema	Tachycardia; irregular heartbeat; atrial fibrillation; systolic hypertension; heart failure
Gastrointestinal	Loose stools; nausea; diarrhoea	Frequent bowel movements
Eyes	Stare	Upper lid retraction
Skeletal	Fragility fractures	Osteoporosis
Respiratory	Shortness of breath	Dyspnoea; tachypnoea
Reproductive	Irregular menses in women; impaired libido in men	Subfertility in women; gynaecomastia in men
Skin	Sweating; heat intolerance	Warm and moist skin; onycholysis

Table 1: **Symptoms and signs of systemic manifestations of hyperthyroidism**

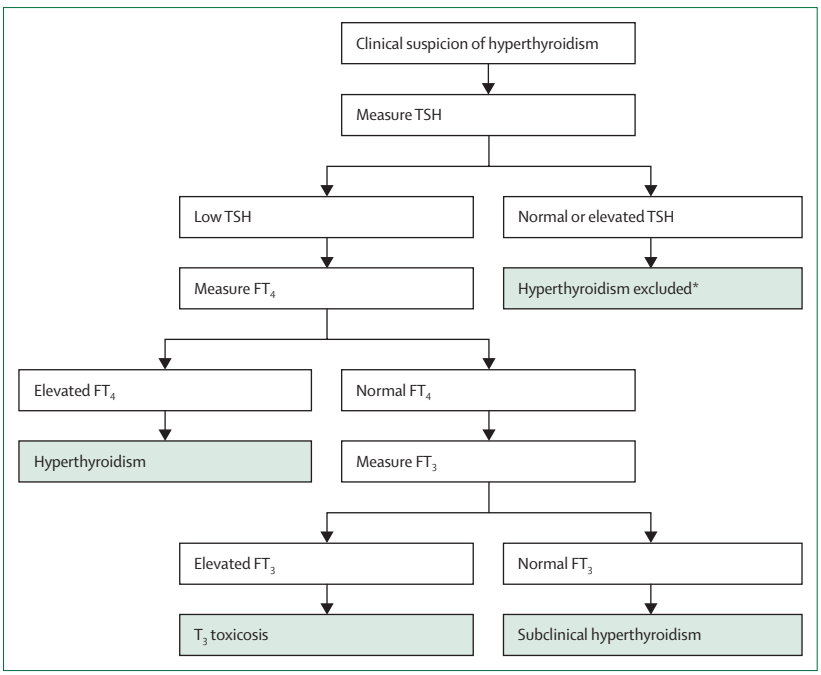

Figure 1: **Algorithm for the diagnosis of hyperthyroidism**
Low TSH is below the TSH reference range of 0·4–4·0 mU/L; normal TSH is within the TSH reference range of 0·4–4·0 mU/L; and elevated TSH is is above the TSH reference range of 0·4–4·0 mU/L (reference range may differ slightly between laboratories). FT_3=free tri-iodothyronine. FT_4=free thyroxine. T_3=tri-iodothyronine. *Except the rare TSH-secreting pituitary adenoma and resistance to thyroid hormone.

common in women aged between 20 and 50 years. Hyperthyroidism in older adults (older than 65 years) is usually oligosymptomatic and less severe than hyperthyroidism in adults younger than 65 years, but older adults with hyperthyroidism have a higher prevalence of atrial fibrillation than younger adults with hyperthyroidism.[4–6] Hyperthyroidism can present with lethargy (as opposed to the usual hyperkinesis and mental alertness), which is known as apathetic thyrotoxicosis. Severity is more pronounced in Graves' hyperthyroidism than in toxic adenoma or toxic multinodular goitre. Toxic adenoma is more frequent between the ages of 30 and 60 years, whereas toxic multinodular goitre tends to occur after the age of 50. Toxic multinodular goitre occurs more often in iodine-deficient areas than in iodine-sufficient areas.[6] The clinical picture of thyrotoxicosis has become less severe over the past four decades, which could be caused by factors such as earlier diagnosis of hyperthyroidism (facilitated by the advent of sensitive TSH assays), wider iodoprophylaxis, and a trend towards declining rates of smoking.[2,7]

Diagnosis

If clinical suspicion of hyperthyroidism arises, thyroid hormone excess must be confirmed or excluded by biochemical tests (figure 1). TSH values within the reference range (ie, 0·4–4·0 mU/L) accurately exclude hyperthyroidism, the sole exceptions being the rare TSH-producing pituitary adenoma and thyroid hormone resistance associated with a normal or slightly increased TSH. Confirmation of low TSH concentration (ie, <0·4 mU/L) should be followed by a free T_4 (FT_4) assay. Increased FT_4 values confirm thyrotoxicosis, but an FT_4 value that is within the normal range could indicate either T_3 toxicosis or subclinical hyperthyroidism, which is defined as TSH concentration lower than 0·4 mU/L and FT_4 and free T_3 (FT_3) within their reference ranges. Progression of subclinical hyperthyroidism (not discussed in this Review, but see ETA guidelines[8]) to T_3 toxicosis occurs in about 10% of all patients with hyperthyroidism, especially in those with nodular goitre (figure 1).[6] The thyroid function tests are susceptible to analytical interference by macro-TSH, antibodies, and the use of biotin.[9] Fortunately, analytical interference rarely occurs, and the advice is to consult the biochemical lab in case of discrepancies between TSH and FT_4 or results that do not make sense.

If hyperthyroidism is confirmed, a nosological diagnosis should be made to assess the cause of thyrotoxicosis. Graves' disease (ie, diffuse goitre) is the most common cause, followed by toxic multinodular goitre and solitary toxic adenoma.[6] Sometimes the correct diagnosis is self-evident. For example, a diffuse goitre with bruit or the presence of thyroid eye disease (ie, Graves' orbitopathy) strongly suggests Graves' hyperthyroidism. Nevertheless, it is recommended to measure TSH-receptor antibodies whenever Graves' disease is suspected.[10,11] TSH-receptor antibodies can be assessed by immunoassays that detect binding of antibodies to the TSH receptors (ie, TSH-binding inhibitory immunoglobulins [TBII]) or cell-based bioassays that also provide information on whether the functional activity of these antibodies is stimulating or blocking.[12] Sensitivity and specificity of current TBII assays for Graves' disease are above 95%, and that of the bioassays approach 100%.[11] Clinicians should know which assay type is performed.

Next to TSH-receptor antibodies, thyroid imaging by either thyroid scintigraphy or ultrasound is the most effective diagnostic test (table 2, figure 2). Thyroidal uptake of radioiodine or other tracers (eg, technetium) will be enhanced in all conditions characterised by TSH-receptor activation by either TSH-receptor antibodies, human chorionic gonadotropin (hCG), or gain-of-function mutations of TSH receptor and G-protein α-subunit ($G_s\alpha$; table 2). In contrast, the inflammation of destructive thyroiditis results in disruption of follicular architecture, release of iodine-rich and hormone-rich follicular contents into the blood, and thyrotoxicosis. Radioiodine uptake will be low or absent, which is the case with extrathyroidal sources of excessive thyroid hormone (table 2). Thyroid ultrasonography (especially using colour flow Doppler methodology) can also distinguish thyroid hyperactivity (increased vascularity in Graves' hyperthyroidism, toxic adenoma, and toxic multinodular goitre) from destructive thyroiditis and extrathyroidal thyrotoxicosis

	Prevalence*	Diagnostic clue	Preferred management†
Excessive TSH-receptor stimulation			
..		Thyroid RAIU increased, ultrasonography vascularity increased	..
Graves' hyperthyroidism	70%	TSH-receptor antibodies; Graves' orbitopathy	Antithyroid drugs
hCG-related thyrotoxicosis	..	Pregnancy; high serum hCG	..
Gestational transient thyrotoxicosis	2–3%‡	Hyperemesis gravidarum	Wait-and-see
Familial gestational hyperthyroidism	<0·1%	Mutant TSH receptors, sensitive for hCG	Antithyroid drugs
Hydatiform mole, choriocarcinoma	<0·1%	Trophoblast tumour	Mole evacuation
TSH-producing pituitary adenoma	<0·1%	Serum TSH normal or increased; pituitary tumour	Trans-sphenoidal resection; somatostatin analogues
Autonomous thyroid hormone secretion			
..	..	Thyroid RAIU increased, ultrasonography vascularity increased	..
Toxic multinodular goitre	10%	Somatic activating TSH receptors or mutations in $G_s\alpha$	^{131}I therapy or thyroidectomy
Solitary toxic adenoma	6%	Somatic activating TSH receptors or mutations in $G_s\alpha$	^{131}I therapy or thyroidectomy
Familial or sporadic non-autoimmune hyperthyroidism	<0·1%	Germline activating TSH receptor mutations	Thyroidectomy and ^{131}I therapy
Destructive thyroiditis			
..		Thyroid RAIU decreased, ultrasonography vascularity decreased	..
Subacute de Quervain thyroiditis	3%	Viral infection; pain in the neck; C-reactive protein increased	Wait-and-see; non-steroidal anti-inflammatory drugs; prednisone
Silent or painless thyroiditis; post-partum thyroiditis	..	Autoimmune thyroiditis; serum TPO antibodies; up to 1 year post partum	Wait-and-see
Acute suppurative thyroiditis	<0·1%	Bacterial, fungal, or parasitic infections	Antibiotics, antifungals, or surgical drainage
Drug-induced thyroiditis	9%	Drug history	..
Iodide-induced thyrotoxicosis	..	Iodine excess	Wait-and-see
Amiodarone	..	Amiodarone	Antithyroid drugs with or without perchlorate for type 1 amiodarone-induced thyrotoxicosis; prednisone for type 2 amiodarone-induced thyrotoxicosis
Cytokines	..	Interferon alfa; IL-2	Wait-and-see
Tyrosine-kinase inhibitors	..	Sorafenib, vandetanib, axitinib	Wait-and-see
Immune checkpoint inhibitors	..	Anti-CTLA4: ipilimumab, tremelimumab; anti-PD1: nivolumab, pembrolizumab; anti-PDL1: atezolizumab, oravelumab, durvalumab	Wait-and-see
Extrathyroidal source of thyroid hormone			
..		Thyroid RAIU decreased, ultrasonography vascularity decreased	..
Thyrotoxicosis factitia	..	Excess thyroid hormone drug; serum thyroglobulin decreased	Reduce dose of thyroid hormone drug
Hamburger thyrotoxicosis	..	Beef neck meat contains thyroid tissue	Stop eating contaminated beef
Struma ovarii	..	Ovary tumour with focal radioiodine uptake	Ovarian surgery
Metastases of differentiated thyroid cancer	..	Functional metastases with radioiodine uptake	^{131}I therapy

$G_s\alpha$=G-protein α-subunit. hCG=Human chorionic gonadotropin. RAIU=radioidoine uptake. *Prevalence among 1144 overt hyperthyroid patients, calculated from Goichot and colleagues.[6] †β-blockers can be considered in every suitable patient. ‡2–3% of all pregnancies.

Table 2: **Causes of hyperthyroidism, disease-specific diagnostic clues and preferred treatment**

(low or absent flow).[10,11] Currently, ultrasound has become the preferred imaging procedure because it is very convenient and avoids the use of radioactivity.[3,13] Thyroid scintigraphy could be useful before ^{131}I therapy, especially for solitary toxic adenoma or toxic multinodular goitre.[10,11]

Aetiology and pathogenesis

Excessive TSH-receptor stimulation

Graves' hyperthyroidism

Graves' disease is a multisystem autoimmune disorder characterised by stimulating TSH-receptor antibodies that bind to and activate the TSH receptors in thyroid follicular

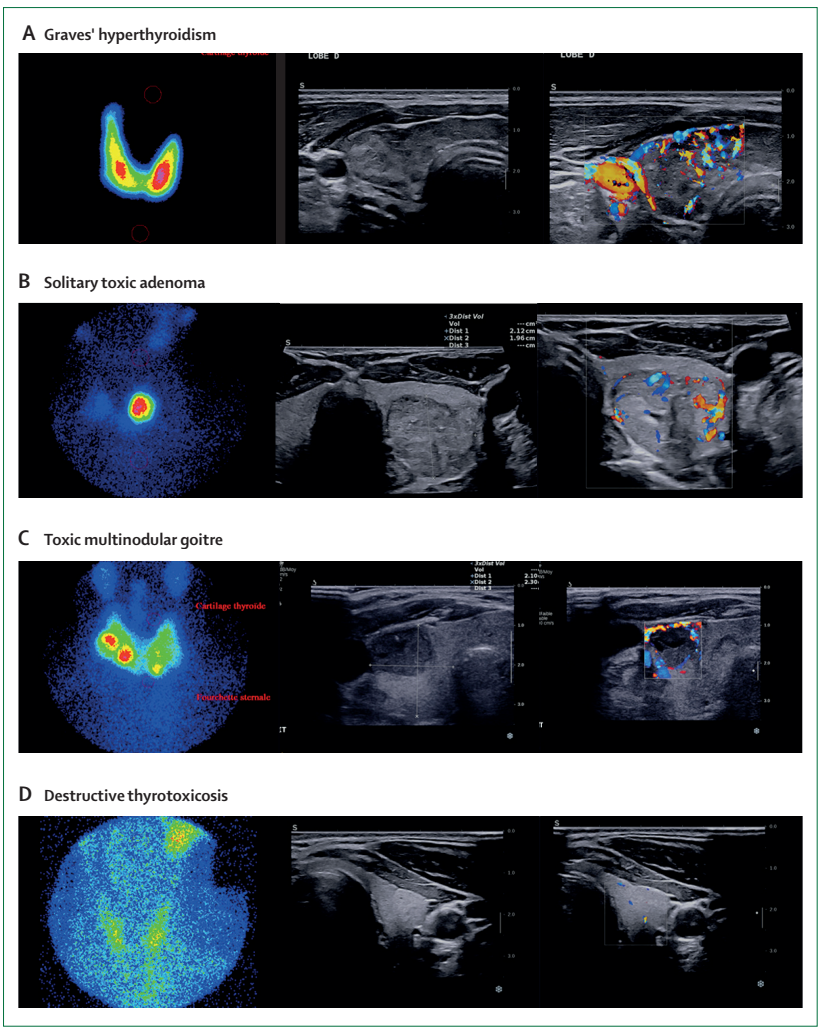

Figure 2: **Thyroid imaging as a tool for the nosological diagnosis of hyperthyroidism.**
(A) Graves' hyperthyroidism. Scintigraphy shows increased diffuse and homogeneous uptake of the radioisotope (left panel). Ultrasonography shows very heterogeneous parenchyma without nodules; volume of right thyroid lobe is 14·2 mL and volume of left thyroid lobe 11·8 mL (middle panel). Ultrasound with colour Doppler shows clear hyperaemia (right panel). (B) Solitary toxic adenoma: scintigraphy shows increased circumscribed uptake of radioisotope in the left thyroid lobe nodule with no uptake in the remainder of the thyroid gland (left panel). Ultrasonography shows a macronodule measuring 21 mm deep × 20 mm wide × 23 mm long in the left lobe; volume of right thyroid lobe is 9·2 mL and volume of left thyroid lobe 15·2 mL (middle panel). Ultrasound with colour Doppler shows hypervascularity in the macronodule left (right panel). (C) Toxic multinodular goitre. Scintigraphy shows two nodules with high uptake (hot) in the right lobe and two nodules with low uptake in the left thyroid lobe (left panel). Ultrasonography shows a hypoechoic macronodule measuring 20 mm deep × 13 mm wide × 28 mm long in the upper right lobe and an isoechoic nodule of 7 mm deep × 9 mm wide × 9 mm long in the lower part of the right lobe; volume of right thyroid lobe is 19·4 mL and volume of left thyroid lobe 16·0 mL (middle panel). Ultrasound with colour Doppler shows hypervascularity in both nodules (right panel). (D) Destructive thyrotoxicosis. Scintigraphy shows faint uptake of the radioisotope in both thyroid lobes (left panel). Ultrasonography shows a normal echostructure without nodules; volume of right thyroid lobe is 4·4 mL and volume of left thyroid lobe 3·8 mL (middle panel). Ultrasound with colour Doppler is normal in both thyroid lobes without increased velocities of the thyroid arteries (right panel). Images provided by Dr Ringo Manta, Department of Nuclear Medicine, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium.

cells, orbital fibroblasts, and dermal fibroblasts, which via cAMP and PI3 post-receptor signalling pathways result in increased synthesis and release of thyroid hormones (Graves' hyperthyroidism), swelling of extraocular muscles and orbital fat (Graves' orbitopathy), and pretibial myxo-oedema (Graves' dermopathy). Genomic immunisation with the α-subunit of the TSH receptor induces hyperthyroidism but also extrathyroidal manifestations such as Graves' orbitopathy in experimental animals.[14,15] Graves' orbitopathy is not discussed in this Review because guidelines have been published in 2021.[16] The annual incidence of Graves' hyperthyroidism is 20–50 cases per 100 000 people per year, with a peak between 30 and 50 years of age.[17] The lifetime risk is 3·0% for women and 0·5% for men. The female preponderance in Graves' disease is incompletely understood. Parity might be a risk factor for Graves' hyperthyroidism,[18,19] and fetal microchimerism (ie, persistence of fetal cells in maternal tissues) and inactivation of the X chromosome in early embryonic life are possibly involved.[20,21] Both genetic and environmental factors play a role in this multifactorial disease. Twin studies suggest genetic factors contribute 79% to the risk of developing Graves' disease.[22] Polymorphisms in thyroid-specific genes (ie, *TSH-R* and *Tg*) and immune-regulatory genes (ie *HLA, FOXP3, CD25, CD40, CTLA4,* and *PTPN22*) are involved, with *HLA-DR3* carrying the highest risk.[23] A positive family history of autoimmune thyroid disease is present in about 50% of people with Graves' disease, with some evidence for genetic anticipation (ie, younger age of onset in patients with a positive family history).[24,25] Environmental factors are iodine, smoking, alcohol, stress, and infections. Iodine fortification in iodine-deficient areas leads to a small transient increase in the incidence of thyrotoxicosis, in older adults (older than 60 years) due to toxic nodular goitre and in younger people (aged 20–39 years) possibly due to Graves' hyperthyroidism.[26] Iodine excess can sometimes lead to the Jod-Basedow phenomenon, which occurs upon failure of normal protective mechanisms against iodine excess. Smoking is a clear risk factor for Graves' hyperthyroidism: the odds ratio is 3·3 (95% CI 2·1–5·2) in current smokers compared with people who have never smoked.[27] The risk diminishes with time and disappears 10–15 years after cessation of smoking.

Moderate alcohol consumption seems to reduce the risk of Graves' hyperthyroidism.[28] Strong circumstantial evidence supports a causal relationship between severe emotional stress and the onset of Graves' hyperthyroidism.[29] Infections have been implicated as a risk factor, without conclusive evidence. *Yersinia enterocolitica* infection, despite cross-reactivity (ie, molecular mimicry) between *Yersinia enterocolitica* outer membrane proteins and epitopes of TSH-receptor antibodies, has not been linked to autoimmune hyperthyroidism.[30,31] The possible role of altered gut microbiota composition in the development of autoimmune thyroid diseases is far from resolved.[32] Graves' hyperthyroidism can develop as part of the immune reconstitution syndrome when lymphocytes recover after induced severe lymphopoenia.[33] Immune reconstitution syndrome could happen after bone marrow or haematopoietic stem-cell transplantation, during highly active antiretroviral therapy for HIV infection, and during

alemtuzumab treatment for multiple sclerosis. Up to 30% of patients treated with alemtuzumab develop Graves' hyperthyroidism, mainly within 3 years after the last dose.[34] Both stimulating and blocking TSH-receptor antibodies are observed in these patients. The high incidence of Graves' hyperthyroidism in patients treated with alemtuzumab contrasts with the rare occurrence of Graves' hyperthyroidism in patients treated with other drugs (table 2), which more commonly cause transient destructive thyrotoxicosis frequently followed by a hypothyroid phase. Other autoimmune diseases occur in 9·7% of patients with Graves' hyperthyroidism, especially rheumatoid arthritis, pernicious anaemia, systemic lupus erythematosus, coeliac disease, Addison's disease, and vitiligo.[35]

Human chorionic gonadotropin-related thyrotoxicosis

Human chorionic gonadotropin (hCG) has some thyroid-stimulating activity: 1 U of purified hCG is equivalent to 0·0013 µU of human TSH as evident in vitro from de novo synthesised thyroid hormone release in human thyroid follicles.[36] hCG acts by binding to the TSH receptor and activating adenylyl cyclase. In normal pregnancy, serum hCG peaks at 9–12 weeks of gestation, coinciding with a decrease of serum TSH. TSH concentrations lower than 0·2 mU/L are reported in about 18% of pregnant women at a mean hCG of 52 400 IU/L.[37] Higher hCG concentrations increase the risk of overt hyperthyroidism. At serum hCG concentrations higher than 200 000 IU/L, serum TSH concentrations lower than or equal to 0·2 mU/L are observed in 67% of patients; at serum hCG concentrations higher than 400 000 IU/L, serum TSH concentrations lower than or equal to 0·2 mU/L are observed in 100% of patients. At serum hCG concentrations higher than 200 000 IU/L, elevated serum FT_4 is observed in 32% of patients; at hCG higher than 400 000 IU/L, elevated serum FT_4 is observed in 80% of patients.[38] High hCG concentrations occur in hyperemesis gravidarum, and a hCG concentration higher than 180 000 IU/L is associated with clinically obvious gestational transient thyrotoxicosis (prevalence 2–3%).[37,39] Gestational transient thyrotoxicosis usually resolves spontaneously by 16 weeks of gestation when hCG concentration falls.[39] Long-lasting and severe gestational thyrotoxicosis due to enhanced hCG sensitivity of a mutant TSH receptor has been described occasionally.[40] hCG produced by some trophoblast tumours, particularly asialo-hCG, has potent TSH activity and could cause overt hyperthyroidism when produced excessively.[36,41]

TSH-secreting pituitary adenoma

TSH-secreting pituitary adenoma is a rare disease usually presenting as a macroadenoma, which causes visual field defects and headache, and mild hyperthyroidism around the fifth or sixth decade of life.[42] Concomitant hypersecretion of growth hormone or prolactin occurs in 25% of patients with TSH-secreting pituitary adenoma. Diagnosis is often delayed, especially in patients with a normal serum TSH value. Similar thyroid function tests are found in resistance to thyroid hormone. A proper diagnosis of TSH-secreting pituitary adenoma can be established by pituitary imaging, elevated serum concentrations of glycoprotein α subunits, a blunted TSH response to TRH (TSH releasing hormone), and insufficient TSH suppression after exposure to exogenous T_3.[42]

Autonomous thyroid hormone secretion

Toxic multinodular goitre and toxic adenoma

In toxic multinodular goitre and toxic adenoma there is autonomous production and release of thyroid hormones by thyrocytes, independent from TSH or TSH-receptor antibodies, due to constitutive activation of the TSH receptor or—less commonly—to somatic mutations in $G_s\alpha$.[43] The production and release of thyroid hormones by the autonomous nodules results in suppressed TSH, circumscribed uptake of radioisotopes in autonomous nodules, but decreased uptake of radioisotopes in non-autonomous thyroid tissue, and ultimately thyrotoxicosis (figure 2). Thyroid autonomy develops slowly; the transition from euthyroidism to subclinical hyperthyroidism, T_3-toxicosis, and finally overt hyperthyroidism could take decades.[44] The pathogenesis can start with iodine deficiency, which induces hyperplasia and increases mutagenesis, leading to cell clones containing somatic mutations featuring nodular transformation.[43] Iodine fortification in iodine-deficient areas initially increases thyrotoxicosis incidence, but after approximately 10 years decreases the prevalence of goitre, thyroid autonomy, and hyperthyroidism.[26,45] Activating germline TSH-receptor mutations can be inherited in an autosomal dominant manner (ie, familial non-autoimmune hyperthyroidism), or might occur sporadically as a de novo condition (ie, persistent sporadic congenital non-autoimmune hyperthyroidism).[46] Patients have no signs of thyroid autoimmunity (ie, no thyroid antibodies and no hypoechogenicity on ultrasonography), and their goitre is initially diffuse but can become nodular over time.

Destructive thyrotoxicosis

The typical triphasic course of destructive thyroiditis is first a thyrotoxic episode of about 1–3 months, followed by a more long-lasting hypothyroid period of up to 6 months, which is then followed by a spontaneous return to euthyroidism.[47] The presentation of destructive thyrotoxicosis varies greatly. Some patients have only mild thyrotoxicosis or hypothyroidism, and for many patients the disease passes unnoticed.

Subacute granulomatous thyroiditis of De Quervain is rather common (present in 3% of all patients who have thyrotoxicosis). Subacute granulomatous thyroiditis of De Quervain is often preceded by an upper respiratory

tract infection and is probably caused by a viral infection of the thyroid gland. Subacute granulomatous thyroiditis of De Quervain is characterised by pain in the neck, a tender thyroid on palpation, fever, malaise, high erythrocyte sedimentation rate, and high C-reactive protein serum concentrations. Thyroglobulin (Tg) and TPO antibodies can be positive in low titre. In contrast, the silent painless thyroiditis and post-partum thyroiditis (occurring following 8–11% of all pregnancies) have an autoimmune aetiology; erythrocyte sedimentation rate is within normal range and thyroid antibodies are often persistent in high titre, associated with a high rate of permanent hypothyroidism.[47] Thyrotoxicosis is usually asymptomatic. Acute suppurative thyroiditis is a rare condition caused by bacterial, fungal, or parasitic infections.[48] Pyriform sinus fistula (located in 90% of patients on the left side) is the most common route of infection and thyrotoxicosis seldom occurs.

Iodine-induced thyrotoxicosis is caused by high doses of iodine from sources such as potassium iodide, seaweed (eg, kelp tablets), and iodinated contrast media. Currently, iodinated contrast media are the most frequent cause of iodine-induced thyrotoxicosis. Administration of 60–150 mL of contrast containing 300 mg of iodine per mL delivers 18–45 g of iodine.[49] The prevalence of overt hyperthyroidism after iodinated contrast media is 0·1%, and develops 3–10 weeks after exposure.[50] Risk factors for iodine-induced thyrotoxicosis are iodine deficiency and previous thyroid autonomy (eg, latent Graves' disease or nodular goitre). Radioiodine uptake is usually low or suppressed in patients with iodine-induced thyrotoxicosis, but is sometimes preserved in patients with underlying diffuse or nodular goitre (ie, Jod-Basedow phenomenon).[51,52] Amiodarone-induced thyrotoxicosis develops in about 8% of patients taking this potent anti-arrhyhmic drug, which generates huge iodine excess. FT_4 might be slightly increased by amiodarone itself, and therefore the biochemical diagnosis of amiodarone-induced thyrotoxicosis usually also requires measurement of FT_3,which could be low due to inhibition of type 1 deiodinase activity in the liver and non-thyroidal illness.[53] If the biochemical picture is compatible with T_4 toxicosis, a wait-and-see strategy might be considered depending on the clinical condition of the patient. Amiodarone-induced thyrotoxicosis is classified into two subtypes. Type 1 amiodarone-induced thyrotoxicosis is relatively rare, making up 11% of all cases, which is much lower than the 60% prevalence of this subtype 25 years ago.[52] Type 1 amiodarone-induced thyrotoxicosis is superimposed on latent Graves' disease or nodular goitre, and is characterised by low to normal radioiodine uptake, increased thyroid vascularity, and thyroid antibodies.[53] Type 1 amiodarone-induced thyrotoxicosis develops rather soon (ie, 3 months) after starting amiodarone, whereas the more common type 2 amiodarone-induced thyrotoxicosis type (89% of all patients with amiodarone-induced thyrotoxicosis)[52] develops later (median 30 months after starting amiodarone). Type 2 amiodarone-induced thyrotoxicosis is characterised by sudden onset, suppressed radioiodine uptake, absent hypervascularity, spontaneous remissions, and high likelihood of late hypothyroidism. The rare presence of thyroid antibodies does not exclude the possibility of type 2 amiodarone-induced thyrotoxicosis.[54] Amiodarone-induced thyrotoxicosis might be preceded by subclinical hyperthyroidism, which can remit spontaneously and does not always progress to overt amiodarone-induced thyrotoxicosis.[55] Therefore, regular thyroid function testing during amiodarone use has little value. Tyrosine-kinase inhibitors (TKIs) target multiple receptor tyrosine kinases, thereby inhibiting growth and spread of several cancers. TKIs targeting VEGF and PDGF receptors cause transient destructive thyrotoxicosis after approximately 6 weeks in 16% of patients, due to vascular damage. Hypothyroidism could occur after 5 months of treatment with TKIs.[56] In patients who have had thyroidectomies, TKIs increase serum TSH, which necessitates an increase of the daily levothyroxine dose due to increased type 3 deiodinase activity.[56,57] Immune checkpoint inhibitors counteract CTLA-4, PD-1, or PDL-1 (ie, the ligand of PD-1), which all play key roles in the maintenance of immunological tolerance to self-antigens. Therefore, whereas immune checkpoint inhibitors can unleash cytotoxic T cells to fight cancer, they can also trigger autoimmune manifestations.[58] Immune checkpoint inhibitors induce destructive thyrotoxicosis, which occurs 4–6 weeks after initiation independent of immune checkpoint inhibitor dosage, cancer subtype, or age. The reported incidence of thyrotoxicosis is 0·2–5·2% after anti-CTLA-4, 0·6–3·7% after anti-PD-1 or anti-PDL-1, and 8·0–11·1% after a combination of both.[57–60] Hypothyroidism induced by immune checkpoint inhibitors could occur later, after 1–2 months, and has a higher incidence than hyperthyroidism. As in all other conditions that predominantly result in destructive thyrotoxicosis, Tg antibodies, TPO antibodies, and even TSH-receptor antibodies might develop. However, actual cases of Graves' hyperthyroidism with increased radioiodine uptake and increased thyroid vascularity are rarely observed.[61] The emergence of immune-related adverse events of immune checkpoint inhibitors are associated with longer progression-free survival and overall survival compared with patients with cancer who do not develop these immune-related adverse events.[62,63] Thyroid function tests (ie, TSH, FT_4) are recommended before treatment and every 3–6 weeks in the early phase of treatment. The frequency of these tests can be decreased at later stages depending on thyroid hormones concentrations and their trend. [60]

Thyrotoxicosis due to extrathyroidal source of thyroid hormone

Thyrotoxicosis factitia refers to surreptitious ingestion of excess thyroid hormone.[64] The hallmark is low to suppressed serum thyroglobulin. Outbreaks of so-called Hamburger thyrotoxicosis have been observed by the

consumption of ground beef prepared from neck trimmings containing thyroid tissue.[65] Struma ovarii is a teratoma containing ectopic thyroid tissue, which can become autonomous and cause hyperthyroidism.[66] Characteristics are low thyroidal radioiodine uptake but intensely focal radioiodine uptake in a pelvic mass. Thyrotoxicosis due to functioning metastases of differentiated thyroid cancer is rare.[67]

Management

Treatment modalities

Non-selective β-adrenergic antagonists alleviate thyrotoxic symptoms and signs. The clinical response to β-blockers is independent of their effect on serum T_3. Propranolol (10–40 mg, 3–4 times per day) can be used, or long-acting β-blockers or cardioselective β-blockers such as atenolol and metoprolol might be preferred. [10] Antithyroid drugs reduce thyroid hormone synthesis by inhibition of thyroid peroxidase. The preferred antithyroid drug is methimazole. Carbimazole is a prodrug of methimazole and propylthiouracil is more toxic than methimazole.[10,11] The starting dose of methimazole depends on the severity of hyperthyroidism: 5–10 mg per day is recommended for FT_4 concentrations 1·0–1·5 times the upper limit of normal, 10–20 mg per day for FT_4 concentrations 1·5–2·0 times the upper limit of normal, and 30–40 mg per day for FT_4 concentrations 2·0–3·0 times the upper limit of normal. After about 4 weeks, the methimazole dose is titrated according to FT_4 and FT_3 concentrations. The usual methimazole dose to maintain euthyroidism is 2·5–10·0 mg per day. Alternatively, the high initial dose (ie, 20–40 mg methimazole per day) can be maintained and levothyroxine can be added (the so-called block-and-replace regimen). The superiority of the block-and-replace approach over the titration approach has not been shown.[68] Most side-effects of antithyroid drugs occur in the first 3 months. Skin rash and arthralgia are common (1·0–5·0%); abnormalities in taste or smell and agranulocytosis are rare (0·2–1·0%); and hepatotoxicity, cholestatic jaundice, and lupus-like vasculitis are very rare (<0·1%).[11] In 2019, acute pancreatitis was recognised as another side-effect of methimazole (but not of propylthiouracil).[69,70] In view of the very few reported patients who developed pancreatitis due to this treatment (six in total), methimazole remains the preferred antithyroid drug outside the settings of thyroid storm and early pregnancy. Patients should be informed to stop antithyroid drugs pending a complete blood count in the case of sore throat with fever. The efficacy of granulocyte colony-stimulating factor in the treatment of agranulocytosis has not been proven.[71] Monitoring liver function and white-cell count before starting treatment with antithyroid drugs or during treatment is generally not recommended.[10,11]

^{131}I causes thyroid cell damage and death. ^{131}I dose is either fixed (eg, 10 mCi or 370 MBq) or calculated on the basis of goitre size and radioiodine uptake. ^{131}I should not be used in active Graves' orbitopathy, during pregnancy, and during breastfeeding. Hypothyroidism develops eventually in most patients.[10] A meta-analysis of cancer risk after ^{131}I therapy for hyperthyroidism describes the overall pooled cancer risk after exposure to ^{131}I therapy versus non-exposure as not statistically significant, although a linear dose-response association between ^{131}I therapy and solid cancer mortality is observed.[72] These findings suggest that radiation-induced cancer risks following ^{131}I therapy for hyperthyroidism are small, and might only be detectable at higher concentrations of the administered dose. To advise patients, one could say the risk of cancer from ^{131}I therapy is seemingly small enough to be indistinguishable from the risk of cancer that patients treated with antithyroid drugs or surgery have.[73] Thyroidectomy ensures rapid restoration of euthyroidism at the expense of a low rate (1–2%) of adverse events (eg, postoperative bleeding, wound infection, hypoparathyroidism, and recurrent laryngeal nerve damage with voice problems). Complication rate is lower in in patients operated by surgeons who are skill and experienced.[10,11]

Disease-specific management

Management of Graves' hyperthyroidism

Antithyroid drugs, ^{131}I, and thyroidectomy are the three treatment options for Graves' hyperthyroidism. Antithyroid drugs (specifically methimazole) are currently the treatment of choice.[10,11,74] However, ^{131}I or surgery, might be preferred in particular conditions like liver disease, congestive heart failure, large thyroid nodule, suspicion of thyroid cancer, old age with comorbidities, or periodic paralysis.[10,11] For both patients and clinicians, remission rate is an important determinant of treatment choice but antithyroid drugs remain the most preferred treatment option.[75] Although clinicians prefer ^{131}I over surgery, patients express a negative attitude towards ^{131}I. American but not European guidelines state that, if ^{131}I is chosen, the goal of treatment is to render the patient hypothyroid.[10,11] Relapse rates after antithyroid drugs are 52–53%, 8–15% after ^{131}I, and 0–10% after thyroidectomy.[76,77] Total thyroidectomy is preferred over subtotal thyroidectomy due to its association with a lower rate of recurrent hyperthyroidism.[78] A long-term follow-up study published in 2009 of patients randomly assigned to receive antithyroid drugs, ^{131}I, or surgery found no differences in quality of life.[79] In contrast, a 2019 study found that patients treated with ^{131}I had a worse quality of life than those treated with antithyroid drugs or surgery.[80] The major difference between the studies is the larger sample size and the use of the validated ThyPRO questionnaire in the 2019 study.[80,81] Weight gain during treatment is a frequent outcome that is unwanted by many patients.[82] Over a mean follow-up of 2 years, patients treated with antithyroid drugs gained 5·2 kg, patients treated with ^{131}I gained 4·8 kg, and patients who had thyroidectomies gained 10·3 kg.[83] Thyroidectomy is

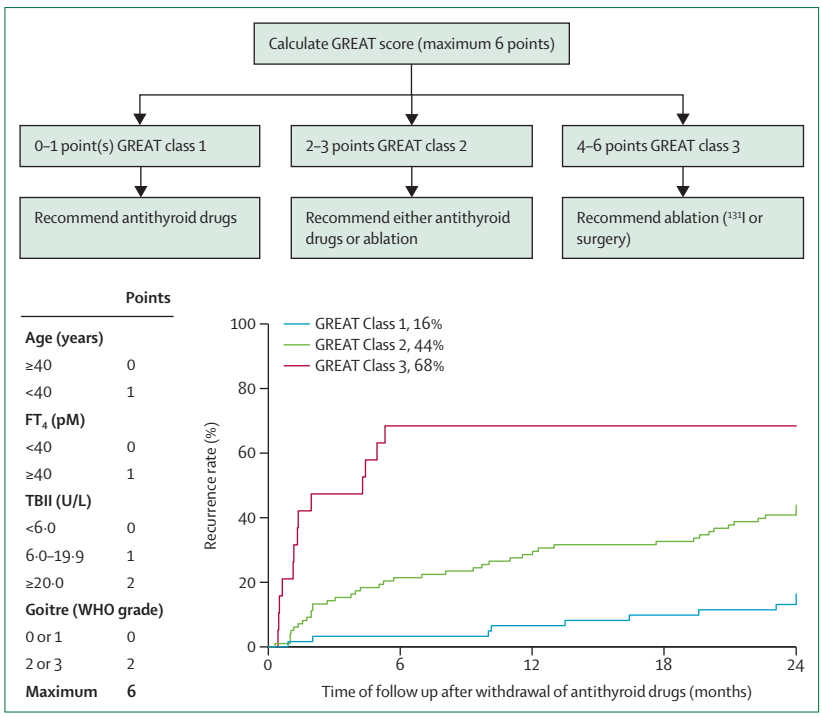

Figure 3: **The GREAT score for predicting recurrence of Graves' hyperthyroidism after antithyroid drug therapy**
Figure adapted with permission from Vos XG and colleagues.[85] FT_4=free thyroxine. GREAT=Graves' Recurrent Events After Therapy. TBII=TSH-binding inhibitory immunoglobulins.

associated with a lower all-cause mortality than antithyroid drugs or ^{131}I.[84] Thyroidectomy or antithyroid drugs are associated with a decline in TSH-receptor antibodies, but a sustained increase in these antibodies is observed after ^{131}I, putting the patient at risk of developing—or worsening of—Graves' orbitopathy and (in pregnancy) of fetal hyperthyroidism.[16] Guidelines therefore recommend that management choices should be considered by patients and physicians together in a shared decision-making process.[10,11]

The common duration of antithyroid drug therapy is 12–18 months; thereafter the drug is tapered to see if the patient with Graves' disease has gone into remission. Recurrent hyperthyroidism develops in about 50% of patients, but is difficult to predict. Patients who are younger than 40 years have FT_4 concentrations higher than or equal to 40 pmol/L, have TBII concentrations higher than or equal to 6 U/L, and have a goitre size corresponding to WHO grade 2 or grade 3 (measured before the start of treatment with antithyroid drugs) are good predictors for recurrences, as summarised in the Graves Recurrent Events After Therapy (GREAT) score (figure 3).[85] When TSH-receptor antibody assays other than TBII are applied, TSH-receptor antibody concentrations higher than three times the upper limit of normal could be given the same score as TBII concentrations higher than or equal to 6 U/L. The predictive value of the GREAT score can be enhanced by adding *HLA* and *PTPN22* genotypes. The GREAT score has been externally validated in several studies.[86–88] During treatment with antithyroid drugs, TBII concentrations could become lower or even undetectable, which increases the chance of remission. Guidelines recommend to measure TBII before stopping treatment with antithyroid drugs, and consider continuing antithyroid drugs if TBII concentrations remain high.[10,11] According to a Cochrane systematic review, maximum remission rates of 50–55% are achieved at 12–18 months of treatment.[89] Consequently it is not advised to discontinue antithyroid drugs before 1 year of treatment even if TSH-receptor antibodies have already become negative.

When recurrent hyperthyroidism develops, guidelines traditionally recommend ^{131}I or surgery because the chance of remission after an extended course of antithyroid drugs does not increase.[10,11] However, this finding might not be entirely true, and interest in long-term treatment with antithyroid drugs has grown over the past decade because they could have unexpected long-term efficacy.[90] Compared with a 53% rate of recurrence after short-term treatment with antithyroid drugs (1–2 years), long-term treatment with antithyroid drugs (5–10 years) has a much lower recurrence rate of 15%.[91] The maintenance dose for long-term treatment with antithyroid drugs is 2·5–7·5 mg of methimazole per day, almost without major side-effects. Major side-effects occurred in 15 out of 1660 patients exposed to methimazole (mean duration 5·8 years) for about 10 000 patient years. 14 patients developed major side-effects within the first year of treatment and only one patient developed side-effects after the first year.[92–94] Long-term antithyroid drug treatment seems a viable alternative to ablative therapies.[90,95]

Management of thyrotoxicosis with hyperthyroidism

Specific guidelines are available for the treatment of hyperthyroidism due to Graves' disease (antithyroid drugs), immune reconstitution (antithyroid drugs), TSH-secreting pituitary adenoma (neurosurgical resection or somatostatin analogues) and familial or sporadic non-autoimmune hyperthyroidism (total thyroidectomy followed by ^{131}I; table 2).[11,42,96,97] Gestational transient thyrotoxicosis usually requires no treatment with antithyroid drugs but in more severe cases propranolol can be considered.[39] Toxic multinodular goitre is treated with near-total or total thyroidectomy or ^{131}I, because recurrent hyperthyroidism after a course of antithyroid drugs is the rule rather than the exception.[10,98] ^{131}I therapy is often preferred, but ^{131}I-induced Graves' hyperthyroidism develops in 5% of patients after 3–6 months especially if TPO antibodies were positive before treatment.[10,99] 10 years after a fixed dose of 15 mCi (555 MBq), hyperthyroidism is cured in 94% of patients, with 60% developing euthyroidism and 34% developing hypothyroidism.[100] Frequently, more than one dose of ^{131}I

is required, resulting in a higher rate of post-radioiodine hypothyroidism. Solitary toxic adenoma is treated with lobectomy or ^{131}I.[10] The rate of hypothyroidism after treatment with ^{131}I is rather low because radioiodine uptake in extranodular thyroid tissue is suppressed (figure 2B). Radiofrequency ablation is a safe and effective alternative. Radiofrequency ablation normalises thyroid function in about 50% of medium-sized nodules (>12 mL) and in more than 80% of small-sized nodules (<12 mL).[10,101,102]

Management of thyrotoxicosis without hyperthyroidism

Destructive thyrotoxicosis is transient in nature, and usually requires only supportive care (table 2).[10] Neck pain in subacute granulomatous thyroiditis can be quite substantial, necessitating non-steroidal, anti-inflammatory drugs; if the pain persists after 2–3 days, prednisone (40 mg per day) offers fast pain relief.[10,47] In mild iodine-induced thyrotoxicosis, close monitoring will suffice. In more severe cases of thyrotoxicosis, antithyroid drugs, eventually combined with perchlorate (not available in the USA), might be helpful.[49] A similar management is recommended in type 1 amiodarone-induced thyrotoxicosis: 40–60 mg of methimazole per day with or without 500 mg perchlorate twice per day, and discontinuation of amiodarone.[53] In contrast, prednisone suffices for most patients with type 2 amiodarone-induced thyrotoxicosis, and amiodarone could even be continued. However, patients with mixed types of amiodarone-induced thyrotoxicosis or very severe amiodarone-induced thyrotoxicosis would probably benefit most from treatment with thyroidectomy.[53,103] Thyrotoxicosis due to cytokines, lithium, TKIs or immune checkpoint inhibitors are mostly mild and can be monitored and treated with β-blockers if patients are symptomatic.[10,60] The best treatment options for thyrotoxicosis of extrathyroidal origin are self-explanatory: reduce dose of thyroid hormone pills, stop eating contaminated beef, ovarian surgery for struma ovarii, and ^{131}I therapy for functional metastases.

Specific conditions

Pregnancy

For women with hyperthyroidism who want to get pregnant, it is recommended to postpone pregnancy until euthyroidism is reached and maintained for more than 2 months after total thyroidectomy or treatment with antithyroid drugs and for at least 6 months after ^{131}I.[104] The incidence of neonatal hyperthyroidism among newborns of mothers with Graves' disease who conceived within 2 years after ^{131}I therapy has been reported to be 5·5%.[105] No congenital malformations were observed if conception was postponed at least 6 months after ^{131}I therapy (>925 MBq) for thyroid cancer.[106]

In pregnant women, the prevalence of pre-existing Graves' hyperthyroidism is 0·5–1·3%, the prevalence of new onset Graves' hyperthyroidism is 0·05%, and the prevalence of autonomous thyroid hormone secretion is 0·1%.[107] Serum TSH-receptor antibodies should be measured at first presentation in pregnancy whenever a history of Graves' disease is present, and again—if elevated—at 18–22 weeks gestation.[11,104]

Overt hyperthyroidism during pregnancy is associated with hypertensive disorders, preterm delivery, small for gestational age neonates, and intrauterine fetal death according to the current largest population-based study.[11,104,108] However, statistically significant evidence on the beneficial effect of medical treatment has only been shown for outcomes such as abruptio placentae, fetal growth retardation, gestational diabetes, postpartum hemorrhage, and stillbirth.[109]

Women should be informed about the slightly increased risk of birth defects associated with antithyroid drugs. Literature on congenital malformations is complex. Facial dysmorphia, aplasia cutis, and choanal or oesophageal atresia have been described after exposure to carbimazole or methimazole. Face and neck cysts and urinary tract abnormalities (males only) have been described after exposure to propylthiouracil.[110] A meta-analysis published in 2022 found an anomaly rate of 61·5 per 1000 live births in the unexposed disease-free population. The excess number of anomalies was 17·2 for exposure to carbimazole or methimazole, 9·8 for exposure to propylthiouracil, and 31·4 for exposure to both carbimazole or methimazole and propylthiouracil.[110] The high figure of 31·4 is a new finding, and does not support current guidelines recommending a switch from carbimazole or methimazole to propylthiouracil in the first trimester.[11,104,110] The teratogenic risk appears to correlate with carbimazole or methimazole dose in the first trimester; hyperthyroidism by itself is not associated with these anomalies.[110,111]

To avoid or minimise exposure to antithyroid drugs, several strategies can be adopted.[112] The first strategy is to replace carbimazole or methimazole with propylthiouracil before pregnancy, the second strategy is to stop treatment with antithyroid drugs as soon as pregnancy is confirmed. The second strategy should be followed by monitoring of thyroid function every 2 weeks during the first trimester, and every 4 weeks during the second and third trimesters. Conditions for stopping treatment with antithyroid drugs include a stable, low dose of methimazole(5–10 mg) or propylthiouracil (100–200 mg); a long treatment period (>6 months); normal concentrations of TSH, absent TSH-receptor antibodies, and no goitre.[113] Discontinuation of treatment with antithyroid drugs is often feasible at the end of the second trimester or in the third trimester due to the disappearance of maternal TSH-receptor antibodies.[111] A third strategy could be switching from methimazole to potassium iodide (10–30 mg) in the first trimester. However, almost half of women do not show antithyroid effects with iodide excess, and more studies are needed in areas outside Japan with a lower iodine intake.[114]

If treatment is necessary during the first trimester, propylthiouracil should be initiated (or carbimazole or methimazole if propylthiouracil is not available). The aim is to keep FT_4 in the range of the upper limit of normal with the lowest possible dose of antithyroid drug. The block-and-replace regimen is contraindicated in pregnancy in view of the risk on fetal hypothyroidism. Propylthiouracil could be replaced by carbimazole or methimazole after the first trimester to reduce the risk of propylthiouracil-associated fulminant hepatic failure. However, firm evidence to support this recommendation is scarce, and one might prefer to continue with a low dose of propylthiouracil. If thyroidectomy is indicated, it should be performed in the second trimester of pregnancy.[11,104] As symptomatic treatment, 10–40 mg propranolol 3–4 times per day could be used, but long-term treatment and treatment after the fifth month of pregnancy should be avoided in view of the risk of fetal bradycardia, intrauterine growth restriction, and neonatal hypoglycaemia.[115] In the post-partum phase, small amounts of antithyroid drug enter breastmilk, but daily doses of up to 250 mg of propylthiouracil or of 20 mg of methimazole are considered safe. Antithyroid drugs should be taken after having breastfed the child.[11,104]

COVID-19

SARS-CoV-2 binds to ACE2, which functions as a receptor for the virus to enter the cell.[116] ACE2 is highly expressed in the thyroid gland, and patients with COVID-19 consequently might manifest changes in thyroid function such as thyrotoxicosis, hypothyroidism, and non-thyroidal illness syndrome.[117,118]

COVID-19-related thyrotoxicosis can occur after infection, in relation with the thyrotoxic phase of subacute thyroiditis.[117] An atypical inflammatory form of thyroiditis without neck pain, characterised by low serum TSH, normal or low FT_3, and normal or elevated FT_4 (ie, T_4 thyrotoxicosis) has been described in hospitalised patients with COVID-19, correlated with elevation of IL-6 and C-reactive protein.[117,119,120] If the biochemical picture is compatible with T_4 toxicosis, a wait-and-see strategy might be considered depending on the clinical condition of the patient. New onset, relapse, or exacerbation of well controlled Graves' hyperthyroidism has been described in relation with COVID-19.[116] COVID-19 might also be a precipitating factor for thyroid storm.[121] To maintain control of Graves' hyperthyroidism during the COVID-19 pandemic, the block-and-replace regimen of antithyroid drugs might be chosen in view of scarce availability of biochemical testing during lockdowns, and one should also be specifically attentive to the development of antithyroid drug-induced neutropaenia.[122]

Vaccination against SARS-CoV-2 is rarely followed by subacute thyroiditis (mean time to symptoms is 9 days) or Graves' hyperthyroidism (mean time to symptoms is 15 days).[123,124] The underlying pathogenetic mechanisms could be molecular mimicry or the autoimmune or inflammatory syndrome induced by adjuvants. Patients with Graves' hyperthyroidism that occurred within 4 weeks after COVID-19 vaccination, are older (51 years old), more likely to be male (40%), and need lower doses of methimazole than patients with Graves' hyperthyroidism who did not receive a COVID-19 vaccination 4 weeks before the occurrence of Graves' hyperthyroidism (35 years old; male sex 14%).[125] There is no evidence that patients with hyperthyroidism are at greater risk of developing COVID-19 or have worse prognosis due to COVID-19 than the general population.[122]

Atrial fibrillation

TSH measurement is recommended in all patients with atrial fibrillation, but only 3% of patients with new-onset atrial fibrillation develop hyperthyroidism.[126–128] Atrial fibrillation will develop in 8% of patients within 30 days after the diagnosis of hyperthyroidism. The risk of atrial fibrillation in patients with hyperthyroidism increases for people older than 60 years, and for those with ischaemic heart disease, congestive heart failure, or cardiac valvular disease.[129]

Hyperthyroidism is a correctable cause of atrial fibrillation. At least 75% of patients with thyrotoxic atrial fibrillation and no underlying cardiac or valvular disease will reverse spontaneously to sinus rhythm within 3–6 months of antithyroid drug therapy.[130,131] In addition to antithyroid drugs, non-selective β-blockers such as propranolol can be used for rate control of atrial fibrillation.[131] Current data do not reveal a higher risk of stroke in patients with hyperthyroidism-related atrial fibrillation than in patients with non-hyperthyroidism-related atrial fibrillation.[131,132] Nevertheless, data concerning the use of anticoagulants to prevent thromboembolism in patients with hyperthyroidism-related atrial fibrillation is controversial and based on little evidence. To date, stroke prevention in hyperthyroidism-related atrial fibrillation should follow the same principles as in other patients with atrial fibrillation. The CHA_2DS_2-VASc score can help to establish the risk of a thromboembolic event in a patient with non-valvular atrial fibrillation who has not used an anticoagulant. The score gives one point each to the presence of congestive heart failure, hypertension, age between 65 and 74 years, diabetes, and vascular disease, and two points each to being older than 75 years and previous stroke. If the CHA_2DS_2-VASc score is 1 or higher, early anticoagulation is recommended for patients with hyperthyroidism-related atrial fibrillation.[126,131,132] Warfarin dosage should be adjusted cautiously because hyperthyroidism enhances sensitivity to anticoagulant effects, which can result in supratherapeutic international normalised ratio values and bleeding. Few data indicate that novel direct oral anticoagulants are not superior to warfarin in terms of stroke or thromboembolism prevention, but might have a lower risk of major bleeding than warfarin.[133,134]

Hyperthyroidism-related atrial fibrilliation usually has a lower recurrence rate than non-thyrotoxic atrial fibrillation. Determinants of persistent arrhythmia are older age (older than 55 years), longer pre-treatment duration of atrial fibrillation, and uncontrolled hyperthyroidism.[130,131] Pharmacological or electrical cardioversion is recommended in patients with persistent atrial fibrillation for at least 4 months after TSH normalisation.[130,131] Anti-arrhythmic drugs should be used after successful cardioversion to reduce the risk of recurrent atrial fibrillation.[130,131] Ablation of the thyroid gland should be considered in case of recurrent atrial fibrillation when the patient had developed euthyroidism.[131] Consultation with a cardiologist might be required.

Thyrotoxic periodic paralysis

Thyrotoxic periodic paralysis is an uncommon, dangerous, but reversible complication of hyperthyroidism, with a much higher frequency in men than in women (ratio 30:1) and a higher frequency in people of Asian origin than in people not of Asian origin (2·0% *vs* 0·1%).[135] Patients with thyrotoxic periodic paralysis present with acute attacks varying from mild weakness to total paralysis, starting at night or in the early morning, a few hours after a heavy or carbohydrate-rich meal, alcohol abuse, or strenuous exercise with complete recovery within 72 h.[136] The lower limbs are affected first followed by the girdle muscles and then the upper limbs.[135] The respiratory muscles are rarely involved. Most patients have not been diagnosed with hyperthyroidism before the thyrotoxic periodic paralysis attack, although these attacks develop only when the patient is thyrotoxic.[136] The hallmark is hypokalaemia caused by thyroid hormone-induced Na^+K^+-ATPase pump activity with increased transport of K^+ from the extracellular to the intracellular space, together with reduced K^+ output.[137] Loss-of-function mutations of the skeletal muscle-specific, inward-rectifying K^+ (Kir2.6) channel have been associated with thyrotoxic periodic paralysis. These mutations could explain how reduced outward K^+ efflux in skeletal muscle, from either channel mutations or inhibition by hormones (eg, adrenaline or insulin), can lead to hypokalaemia and paradoxical depolarisation, which in turn inactivates Na^+ channels and causes muscle inexcitability and paralysis.[137] Thyrotoxic periodic paralysis thus arises from the combination of thyrotoxicosis, environmental factors, and genetic susceptibility.[136] The degree of hypokalaemia varies, and normokalaemia does not exclude thyrotoxic periodic paralysis. In the acute phase, thyrotoxic periodic paralysis must be treated with K^+ to prevent the development of life-threatening arrhythmias and respiratory complications and to shorten the episode of paralysis. Nonselective β-blockers can ameliorate and prevent recurrences of paralytic attacks.[135] Euthyroidism should be promptly restored and stably maintained. It has been proposed that all patients with thyrotoxic periodic paralysis should receive ablative treatment of the thyroid gland. Prophylactic potassium supplementation is not indicated when patients have euthyroidism.

Thyroid storm

Thyroid storm is a rare, acute, and life-threatening form of thyrotoxicosis. Thyroid storm is associated with a mortality rate that is 12 times higher than the mortality rate of thyrotoxicosis without storm among patients admitted to hospital.[138] Although the mortality rate associated with thyroid storm has been reduced over the past four decades, it remains high (up to 3·6% in the USA, 10% in Japan, and 17% in France).[138–140] National surveys revealed the incidence of thyroid storm is 0·2 per 100 000 patients admitted to hospital per year in Japan and 4·8–5·6 per 100 000 patients admitted to hospital per year in the USA.[138,140] Thyroid storm develops in patients with hyperthyroidism who have not received treatment or those who are non-compliant to treatment. Thyroid storm is usually precipitated by an acute event (eg, surgery, trauma, infection, or iodine excess).

A diagnosis of thyroid storm is made on the basis of clinical presentation that is compatible with hyperthyroid symptoms and signs, because thyroid-function tests in thyroid storm are similar to those in uncomplicated hyperthyroidism.[140] Patients with thyroid storm present with an exaggeration of the usual features of hyperthyroidism. The Burch-Wartofsky score has been developed to establish the likelihood of thyroid storm (table 3).[141,142] A scoring system that is slightly different from the Burch-Wartofsky score is used in Japan.[140] It must be noted that a diagnosis of thyroid storm should be made on the basis of clinical judgement and the scores should be ancillary.

Treatment for thyroid storm should be aggressive and includes specific treatment (targeting the thyroid hormone excess) and supportive treatment (directed against the precipitating event and systemic decompensation). Specific treatment includes thionamides (500–1000 mg load of propylthiouracil, followed by 250 mg every 4 h; or 60–80 mg of methimazole per day), β-blockers (propranolol, 60–80 mg every 4 h), iodine (5 drops, equalling to 0·25 mL or 250 mg, of saturated solution of potassium iodide orally every 6 h), and glucocorticoids (300 mg load of hydrocortisone intravenously, followed by 100 mg every 8 h).[10] Propylthiouracil is preferred over methimazole due to its additional inhibitory effect on T_4 to T_3 conversion. However, antithyroid drugs should be administrated 1 h before potassium iodide.[10] Supportive therapy includes cooling blankets, volume resuscitation, antibiotics, nutritional support, respiratory care, and monitoring in intensive care units.[10,11] In case of poor response,

	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 or vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular dysfunction	
Tachycardia	
90–109 BPM	5
110–119 BPM	10
120–129 BPM	15
130–139 BPM	20
≥140 BPM	25
Atrial fibrillation	10
Heart failure	
Absent	0
Mild (pedal oedema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary oedema)	15
Precipitating history	
Negative	0
Positive	10

A score ≥45 is highly suggestive of thyroid storm; scores between 25 and 44 points support the diagnosis of thyroid storm; and scores of less than 25 points suggest that thyroid storm is unlikely. Data are from Burch and Wartofsky.[141] BPM=beats per minute.

***Table 3*: Scoring system for the diagnosis of thyroid storm**

plasmapheresis or plasma exchange and emergency thyroidectomy could be considered.[10]

Prognosis

Long-term prognosis of hyperthyroidism has become more understood in the past decade. In a large hospital-based study with a mean follow-up of 11 years, Graves' disease (hazard ratio [HR] 1·42, 95% CI 1·25–1·60) and toxic nodular goitre (1·22, 1·07–1·40) were both associated with increased all-cause mortality.[143] Graves' disease was associated with increased mortality due to cardiovascular disease (1·49, 1·25–1·77) and lung disease (1·91, 1·37–2·65), whereas toxic nodular goitre was associated with increased cancer mortality (1·36, 1·06–1·75). Another very large prospective study was done in women who were certified as radiological technologists between 1926 and 1982. Cause-specific mortality risks were compared according to self-reported thyroid status, with adjustments for regular confounders and, in case of breast cancer, for family history, duration of the use of hormone replacement therapy and oral contraceptives, and organ doses from radiation exposures.[144] Women with hyperthyroidism older than 60 years had an elevated risk of breast cancer mortality (2·04, 1·16–3·60), compared with women without thyroid disease. Other causes of cancer death were not associated with hyperthyroidism. Breast cancer and hyperthyroidism might be associated via various mechanisms.[145]

In a study including 85 856 patients with hyperthyroidism and 847 057 people in a matched population-based control group, with a mean follow-up of 9·2 years, the HR for all-cause mortality was highest in the first 3 months after diagnosis of hyperthyroidism (HR 4·62, 95% CI 4·40–4·85) and remained elevated during long-term follow-up (>3 years).[146] Sensitivity analysis for gender and Graves' disease as cause of hyperthyroidism did not change the study results.

A Danish register-based cohort study included 235 547 individuals who had at least one TSH measurement between 1995 and 2011 (7·3 years median follow-up).[147] The authors defined hyperthyroidism when patients had at least two TSH values lower than 0·3 mU/L within 6 months, with at least 14 days between measurements. Mortality rates were recorded for treated and untreated patients with hyperthyroidism compared with people in the control group with euthyroidism. Cox regression analyses were controlled for age, sex, and comorbidities by using the Charlson comorbidity index. An excess all-cause mortality rate was noted in patients with untreated overt hyperthyroidism (HR 1·24, 95% CI 1·12 to 1·37) but not in patients receiving treatment for hyperthyroidism (1·01, 0·92 to 1·10). The mortality was increased in patients with untreated overt hyperthyroidism who were 65 years or older, but not those younger than 65 years. Taking into account cumulative periods of serum TSH lower than 0·3 mU/L, mortality per every 6 months of decreased TSH was also increased in patients with treated hyperthyroidism (1·13, 1·11 to 1·15) compared with patients with untreated overt hyperthyroidism.[147] The cumulated dose-dependent (adjusted) mortality analysis showed an 11% increase in mortality per 6 months of decreased TSH in patients with untreated hyperthyroidism and a 13% increase in mortality per 6 months of decreased TSH in patients with treated hyperthyroidism.[147] In patients with hyperthyroidism treated with levothyroxine, the HR for (all-cause) mortality increased by a factor of 1·18 (1·15–1·21) every 6 months of exposure to TSH lower than 0·3 mU/L.[148]

It must be concluded that hyperthyroidism is associated with increased mortality. The precise mechanisms behind this association require further investigation. The

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 2000, to Oct 1, 2022, using the search terms "clinical presentation", "symptoms", "signs", "diagnosis", "pathogenesis", "nodular goitre", "thyroiditis", "treatment", "atrial fibrillation", "management", "prognosis", "pregnancy", "covid-19". In addition, the terms "Graves' disease", "thyrotoxic periodic paralysis", "thyroid storm", "gestational transient thyrotoxicosis", "radioactive iodine therapy", and "antithyroid drugs" in combination with the terms "hyperthyroidism", and "thyrotoxicosis". Articles resulting from these searches and relevant references cited in those articles were reviewed and selected. We mainly included original studies and systematic reviews that were published in English.

excess mortality might not be driven by absence of therapy or by the method of treatment, but rather by an inability to ensure patients develop and maintain euthyroidism.[147,149]

Future perspectives

Promising innovative treatments are expected for Graves' hyperthyroidism, focusing on B cells and the TSH receptors.[150] These include iscalimab, an anti-CD40 monoclonal antibody, that blocks CD40-receptor interaction with its ligand and attenuates B-cell activation; efgarigimod α and rozanolixizumab, which block the neonatal immunoglobulin Fc receptor, thereby accelerating the removal of IgG autoantibodies; belimumab, which inhibits B-cell proliferation and differentiation via blockade of the B-cell activating factor; low molecular weight TSH-receptor antagonists (eg, ANTAG-3, VA-K-14 and S37a) and TSH-receptor blocking monoclonal antibodies (eg, K1-70), which target directly the TSH receptors; and finally, TSH receptor-specific immunotherapy using a soluble antigen (ie, TSH-receptor peptide ATX-GD-59) that aims to lead to tolerogenic immune responses.[150,151]

Contributors

All authors have been involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Declaration of interests

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