Thyroid gland

Diseases of the thyroid predominantly affect females and are common, occurring in about 5% of the population. The thyroid axis is involved in the regulation of cellular differentiation and metabolism in virtually all nucleated cells, so that disorders of thyroid function have diverse manifestations. Structural diseases of the thyroid gland, such as goitre, commonly occur in patients with normal thyroid function.

18.4 Classification of thyroid disease

	Primary	Secondary
Hormone excess	Graves' disease Multinodular goitre Adenoma Subacute thyroiditis	TSHoma
Hormone deficiency	Hashimoto's thyroiditis Atrophic hypothyroidism	Hypopituitarism
Hormone hypersensitivity	–	
Hormone resistance	Thyroid hormone resistance syndrome 5′-monodeiodinase deficiency	
Non-functioning tumours	Differentiated carcinoma Medullary carcinoma Lymphoma	

Functional anatomy, physiology and investigations

The parafollicular C cells secrete calcitonin, which is of no apparent physiological significance in humans. The follicular epithelial cells synthesise thyroid hormones by incorporating iodine into the amino acid tyrosine on the surface of thyroglobulin (Tg), a protein secreted into the colloid of the follicle. Iodide is a key substrate for thyroid hormone synthesis; a dietary intake in excess of 100 µg/day is required to maintain thyroid function in adults. The thyroid secretes predominantly thyroxine (T4) and only a small amount of triiodothyronine (T3); approximately 85% of T3 in blood is produced from T4 by a family of monodeiodinase enzymes which are active in many tissues, including liver, muscle, heart and kidney.

T4 can be regarded as a pro-hormone, since it has a longer half-life in blood than T3 (approximately 1 week compared with approximately 18 hours), and binds and activates thyroid hormone receptors less effectively than T3. T4 can also be converted to the inactive metabolite, reverse T3. T3 and T4 circulate in plasma almost entirely (> 99%) bound to transport proteins, mainly thyroxine-binding globulin (TBG). It is the unbound or free hormones which diffuse into tissues and exert diverse metabolic actions.

Production of T3 and T4 in the thyroid is stimulated by thyrotrophin (thyroid-stimulating hormone, TSH), a glycoprotein released from the thyrotroph cells of the anterior pituitary in response to the hypothalamic tripeptide, thyrotrophin-releasing hormone (TRH).

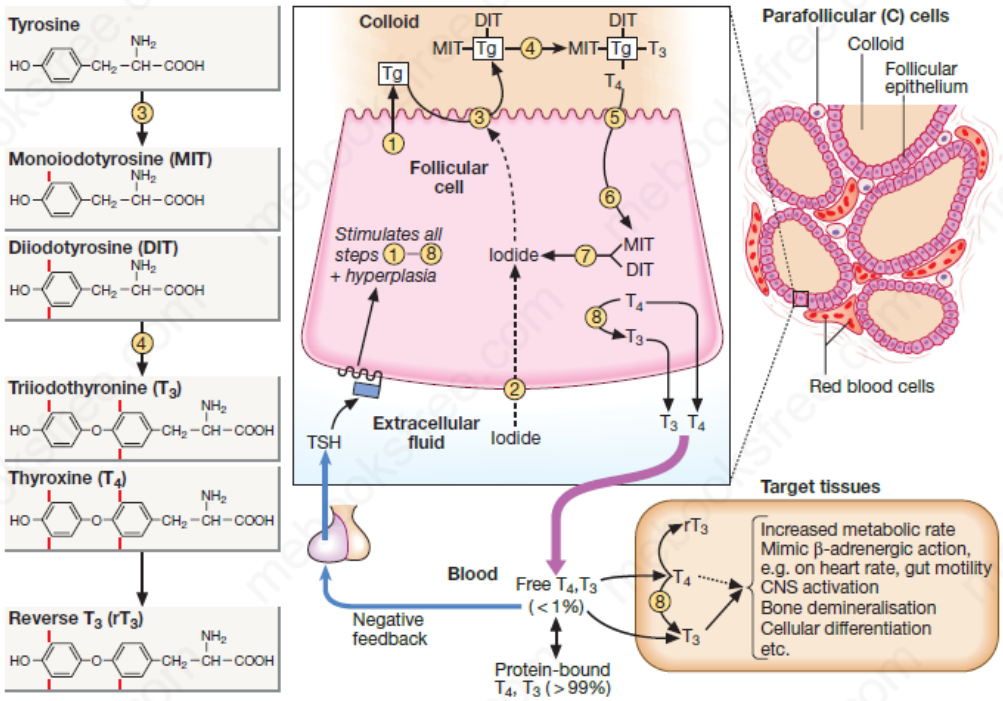

Fig. 18.3 Structure and function of the thyroid gland. (1) Thyroglobulin (Tg) is synthesised and secreted into the colloid of the follicle. (2) Inorganic iodide (I^-) is actively transported into the follicular cell ('trapping'). (3) Iodide is transported on to the colloidal surface by a transporter (pendrin, defective in Pendred's syndrome, p. 650) and 'organified' by the thyroid peroxidase enzyme, which incorporates it into the amino acid tyrosine on the surface of Tg to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). (4) Iodinated tyrosines couple to form T_3 and T_4. (5) Tg is endocytosed. (6) Tg is cleaved by proteolysis to free the iodinated tyrosine and thyroid hormones. (7) Iodinated tyrosine is dehalogenated to recycle the iodide. (8) T_4 is converted to T_3 by 5′-monodeiodinase.

There is a negative feedback of thyroid hormones on the hypothalamus and pituitary such that in thyrotoxicosis, when plasma concentrations of T3 and T4 are raised, TSH secretion is suppressed. Conversely, in hypothyroidism due to disease of the thyroid gland, low T3 and T4 are associated with high circulating TSH levels.

TSH is usually regarded as the most useful investigation of thyroid function. However, interpretation of TSH values without considering thyroid hormone levels may be misleading in patients with pituitary disease; for example, TSH is inappropriately low or 'normal' in secondary hypothyroidism.

Other modalities commonly employed in the investigation of thyroid disease include measurement of antibodies against the TSH receptor or other thyroid antigens, radioisotope imaging, fine needle aspiration biopsy and ultrasound.

18.5 How to interpret thyroid function test results

TSH	T_4	T_3	Most likely interpretation(s)
U.D.	Raised	Raised	Primary thyrotoxicosis
U.D. or low	Raised	Normal	Over-treatment of hypothyroidism with levothyroxine Factitious thyrotoxicosis
U.D.	Normal[1]	Raised	Primary T_3 toxicosis
U.D.	Normal[1]	Normal[1]	Subclinical thyrotoxicosis
U.D. or low	Raised	Low or normal	Non-thyroidal illness Amiodarone therapy
U.D. or low	Low	Raised	Over-treatment of hypothyroidism with liothyronine (T_3)
U.D.	Low	Low	Secondary hypothyroidism[4] Transient thyroiditis in evolution
Normal	Low	Low[2]	Secondary hypothyroidism[4]
Mildly elevated 5–20 mIU/L	Low	Low[2]	Primary hypothyroidism Secondary hypothyroidism[4]
Elevated > 20 mIU/L	Low	Low[2]	Primary hypothyroidism
Mildly elevated 5–20 mIU/L	Normal[3]	Normal[2]	Subclinical hypothyroidism
Elevated 20–500 mIU/L	Normal	Normal	Artefact Heterophilic antibodies (host antibodies with affinity to the animal antibodies used in TSH assays)
Elevated	Raised	Raised	Non-adherence to levothyroxine replacement – recent 'loading' dose Secondary thyrotoxicosis[4] Thyroid hormone resistance

[1]Usually upper part of reference range. [2]T_3 is not a sensitive indicator of hypothyroidism and should not be requested. [3]Usually lower part of reference range. [4]i.e. Secondary to pituitary or hypothalamic disease. Note that TSH assays may report detectable TSH.
(TSH = thyroid-stimulating hormone; U.D. = undetectable)

18.8 Prevalence of thyroid autoantibodies (%)

	Antibodies to:		
	Thyroid peroxidase[1]	Thyroglobulin	TSH receptor[2]
Normal population	8–27	5–20	0
Graves' disease	50–80	50–70	80–95
Autoimmune hypothyroidism	90–100	80–90	10–20
Multinodular goitre	~30–40	~30–40	0
Transient thyroiditis	~30–40	~30–40	0

[1]Thyroid peroxidase (TPO) antibodies are the principal component of what was previously measured as thyroid 'microsomal' antibodies. [2]Thyroid-stimulating hormone receptor antibodies (TRAb) can be agonists (stimulatory, causing Graves' thyrotoxicosis) or antagonists ('blocking', causing hypothyroidism).

Presenting problems in thyroid disease

The most common presentations are hyperthyroidism(thyrotoxicosis), hypothyroidism and enlargement of the thyroid(goitre or thyroid nodule). Widespread availability of thyroid function tests has led to the increasingly frequent identification of patients with abnormal results who either are asymptomatic or have non-specific complaints such as tiredness and weight gain.

Thyrotoxicosis

Thyrotoxicosis describes a constellation of clinical features arising from elevated circulating levels of thyroid hormone. The most common causes are Graves' disease, multinodular goitre and autonomously functioning thyroid nodules (toxic adenoma) . Thyroiditis is more common in parts of the world where relevant viral infections occur, such as North America.

18.6 Causes of thyrotoxicosis and their relative frequencies

Cause	Frequency[1] (%)
Graves' disease	76
Multinodular goitre	14
Solitary thyroid adenoma	5
Thyroiditis	
Subacute (de Quervain's)[2]	3
Post-partum[2]	0.5
Iodide-induced	
Drugs (amiodarone)[2]	1
Radiographic contrast media[2]	–
Iodine supplementation programme[2]	–
Extrathyroidal source of thyroid hormone	
Factitious thyrotoxicosis[2]	0.2
Struma ovarii[2,3]	–
TSH-induced	
TSH-secreting pituitary adenoma	0.2
Choriocarcinoma and hydatidiform mole[4]	–
Follicular carcinoma ± metastases	0.1

[1]In a series of 2087 patients presenting to the Royal Infirmary of Edinburgh over a 10-year period. [2]Characterised by negligible radioisotope uptake. [3]i.e. Ovarian teratoma containing thyroid tissue. [4]Human chorionic gonadotrophin has thyroid-stimulating activity.
(TSH = thyroid-stimulating hormone)

Clinical assessment

18.7 Clinical features of thyroid dysfunction

Thyrotoxicosis	
Symptoms	**Signs**
Common	
Weight loss despite normal or increased appetite	Weight loss
Heat intolerance, sweating	Tremor
Palpitations, tremor	Palmar erythema
Dyspnoea, fatigue	Sinus tachycardia
Irritability, emotional lability	Lid retraction, lid lag
Less common	
Osteoporosis (fracture, loss of height)	Goitre with bruit[1]
Diarrhoea, steatorrhoea	Atrial fibrillation[2]
Angina	Systolic hypertension/increased pulse pressure
Ankle swelling	Cardiac failure[2]
Anxiety, psychosis	Hyper-reflexia
Muscle weakness	Ill-sustained clonus
Periodic paralysis (predominantly in Chinese and other Asian groups)	Proximal myopathy
	Bulbar myopathy[2]
Pruritus, alopecia	
Amenorrhoea/oligomenorrhoea	
Infertility, spontaneous abortion	
Loss of libido, impotence	
Excessive lacrimation	
Rare	
Vomiting	Gynaecomastia
Apathy	Spider naevi
Anorexia	Onycholysis
Exacerbation of asthma	Pigmentation

[1]In Graves' disease only. [2]Features found particularly in elderly patients.

The most common symptoms are **weight loss** with a **normal or increased appetite, heat intolerance, palpitations, tremor and irritability**. **Tachycardia, palmar erythema and lid lag are common signs**. Not all patients have a palpable goitre, but experienced clinicians can discriminate the diffuse soft goitre of Graves' disease from the irregular enlargement of a

multinodular goitre. All causes of thyrotoxicosis can cause lid retraction and lid lag, due to potentiation of sympathetic innervation of the levator palpebrae muscles, but only Graves' disease causes other features of ophthalmopathy, including periorbital oedema, conjunctival irritation, exophthalmos and diplopia. Pretibial myxedema and the rare thyroid acropachy (a periosteal hypertrophy, indistinguishable from finger clubbing) are also specific to Graves'disease.

Investigations

The first-line investigations are serum T3, T4 and TSH. If abnormal values are found, the tests should be repeated and the abnormality confirmed in view of the likely need for prolonged medical treatment or destructive therapy. In most patients, serum T3 and T4 are both elevated, but T4 is in the upper part of the reference range and T3 is raised (T3 toxicosis) in about 5%. Serum TSH is undetectable in primary thyrotoxicosis, but values can be raised in the very rare syndrome of secondary thyrotoxicosis caused by a TSH-producing pituitary adenoma. When biochemical thyrotoxicosis has been confirmed, further investigations should be undertaken to determine the underlying cause, including measurement of TSH receptor antibodies (TRAb, elevated in Graves' disease) and radioisotope scanning.

i 18.9 Non-specific laboratory abnormalities in thyroid dysfunction*

Thyrotoxicosis

- Serum enzymes: raised alanine aminotransferase, γ-glutamyl transferase (GGT), and alkaline phosphatase from liver and bone
- Raised bilirubin
- Mild hypercalcaemia
- Glycosuria: associated diabetes mellitus, 'lag storage' glycosuria

Other investigation like an electrocardiogram (ECG) may demonstrate sinus tachycardia or atrial fibrillation.

Radio-iodine uptake tests measure the proportion of isotope that is trapped in the whole gland but have been largely superseded by 99mtechnetium scintigraphy scans, which also indicate trapping, are quicker to perform with a lower dose of radioactivity, and provide a higher-resolution image. In low-uptake thyrotoxicosis, the cause is usually a transient thyroiditis. Occasionally, patients induce 'factitious thyrotoxicosis' by consuming excessive amounts of a thyroid hormone preparation, most often levothyroxine. The exogenous levothyroxine suppresses pituitary TSH secretion and hence iodine uptake, serum thyroglobulin and release of

endogenous thyroid hormones. The T4:T3 ratio (typically 30 : 1 in conventional thyrotoxicosis) is increased to above 70 : 1 because circulating T3 in factitious thyrotoxicosis is derived exclusively

from the peripheral monodeiodination of T4 and not from thyroid secretion. The combination of negligible iodine uptake, high T4:T3 ratio and a low or undetectable thyroglobulin is diagnostic.

Management

Definitive treatment of thyrotoxicosis depends on the underlying cause and may include **antithyroid drugs, radioactive iodine or surgery**. A non-selective β-adrenoceptor antagonist (β-blocker), such as propranolol (160 mg daily) or nadolol (40–80 mg daily), will alleviate but not abolish symptoms in most patients within 24–48 hours. Beta-blockers should not be used for long-term treatment of thyrotoxicosis but are extremely useful in the short term, while patients are awaiting hospital consultation or following 131I therapy. Verapamil may be used as an alternative to β-blockers, e.g. in patients with asthma, but usually is only effective in improving tachycardia and has little effect on the other systemic manifestations of thyrotoxicosis.

Atrial fibrillation in thyrotoxicosis

Atrial fibrillation occurs in about 10% of patients with thyrotoxicosis. The incidence increases with age, so that almost half of all males with thyrotoxicosis over the age of 60 are affected. Moreover, subclinical thyrotoxicosis is a risk factor for atrial fibrillation.

Characteristically, the ventricular rate is little influenced by digoxin but responds to the addition of a β-blocker. Thromboembolic vascular complications are particularly common in thyrotoxic

atrial fibrillation so that anticoagulation is required, unless contraindicated. Once thyroid hormone and TSH concentrations have been returned to normal, atrial fibrillation will spontaneously revert to sinus rhythm in about 50% of patients but cardioversion may be required in the remainder.

Thyrotoxic crisis (‘thyroid storm’)

This is a rare but life-threatening complication of thyrotoxicosis. The most prominent signs are fever, agitation, delirium, tachycardia or atrial fibrillation and, in the older patient, cardiac failure. The thyrotoxic crisis is a medical emergency and has a mortality of 10% despite early recognition and treatment. It is most commonly precipitated by infection in a patient with previously unrecognised or inadequately treated thyrotoxicosis. It may also develop in known thyrotoxicosis shortly after thyroidectomy in an ill-prepared patient or within a few days of 131I therapy, when acute radiation damage may lead to a transient rise in serum thyroid hormone levels.

Patients should be rehydrated and given propranolol, either orally (80 mg 4 times daily) or intravenously (1–5 mg 4 times daily). Sodium ipodate (500 mg per day orally) will restore serum T3 levels to normal in 48–72 hours. This is a radiographic contrast medium that not only inhibits the release of thyroid hormones but also reduces the conversion of T4 to T3, and is therefore more effective than potassium iodide or Lugol’s solution. Dexamethasone (2 mg 4 times daily) and amiodarone have similar effects. Oral carbimazole 40–60 mg daily should be given to inhibit the synthesis of new thyroid hormone.If the patient is unconscious or uncooperative,

carbimazole can be administered rectally with good effect but no preparation is available for parenteral use. After 10–14 days the patient can usually be maintained on carbimazole alone.

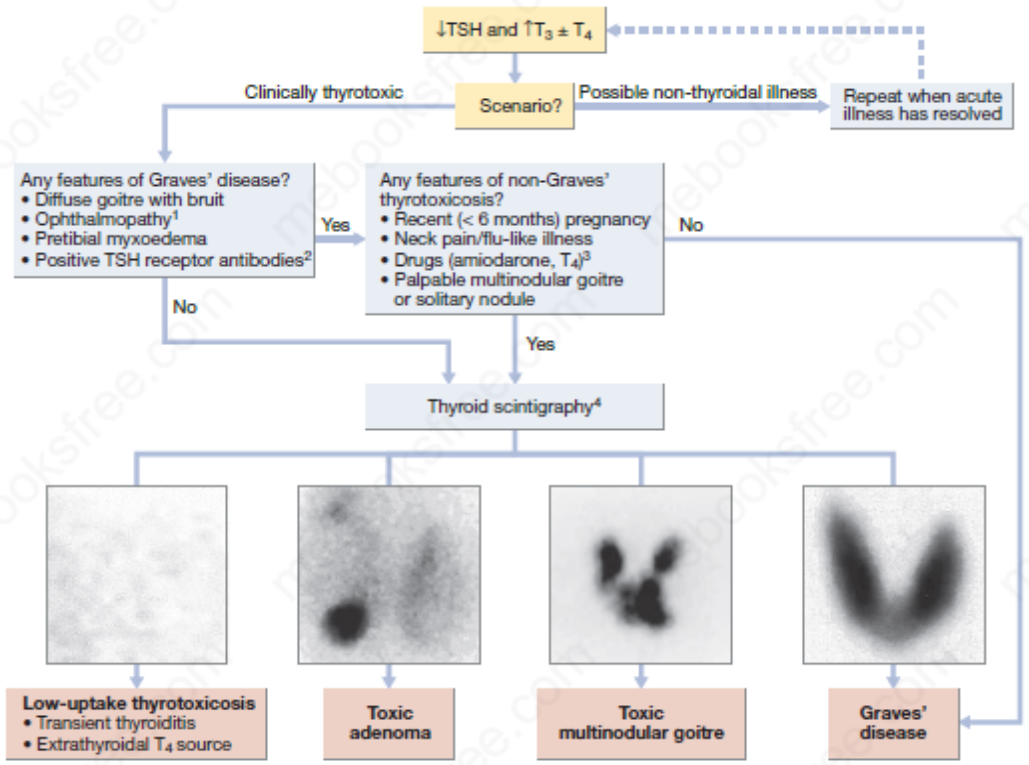

Fig. 18.5 Establishing the differential diagnosis in thyrotoxicosis. [1]Graves' ophthalmopathy refers to clinical features of exophthalmos and periorbital and conjunctival oedema, not simply the lid lag and lid retraction that can occur in all forms of thyrotoxicosis. [2]Thyroid-stimulating hormone (TSH) receptor antibodies are very rare in patients without autoimmune thyroid disease but occur in only 80–95% of patients with Graves' disease; a positive test is therefore confirmatory but a negative test does not exclude Graves' disease. Other thyroid antibodies (e.g. anti-peroxidase and anti-thyroglobulin antibodies) are unhelpful in the differential diagnosis since they occur frequently in the population and are found with several of the disorders that cause thyrotoxicosis. [3]Scintigraphy is not necessary in most cases of drug-induced thyrotoxicosis. [4] ^{99m}Technetium pertechnetate scans of patients with thyrotoxicosis. In low-uptake thyrotoxicosis, most commonly due to a viral, post-partum or iodine-induced thyroiditis, there is negligible isotope detected in the region of the thyroid, although uptake is apparent in nearby salivary glands (not shown here). In a toxic adenoma there is lack of uptake of isotope by the rest of the thyroid gland due to suppression of serum TSH. In multinodular goitre there is relatively low, patchy uptake within the nodules; such an appearance is not always associated with a palpable thyroid. In Graves' disease there is diffuse uptake of isotope.