LECTURE NOTES

Endocrinology and Diabetes

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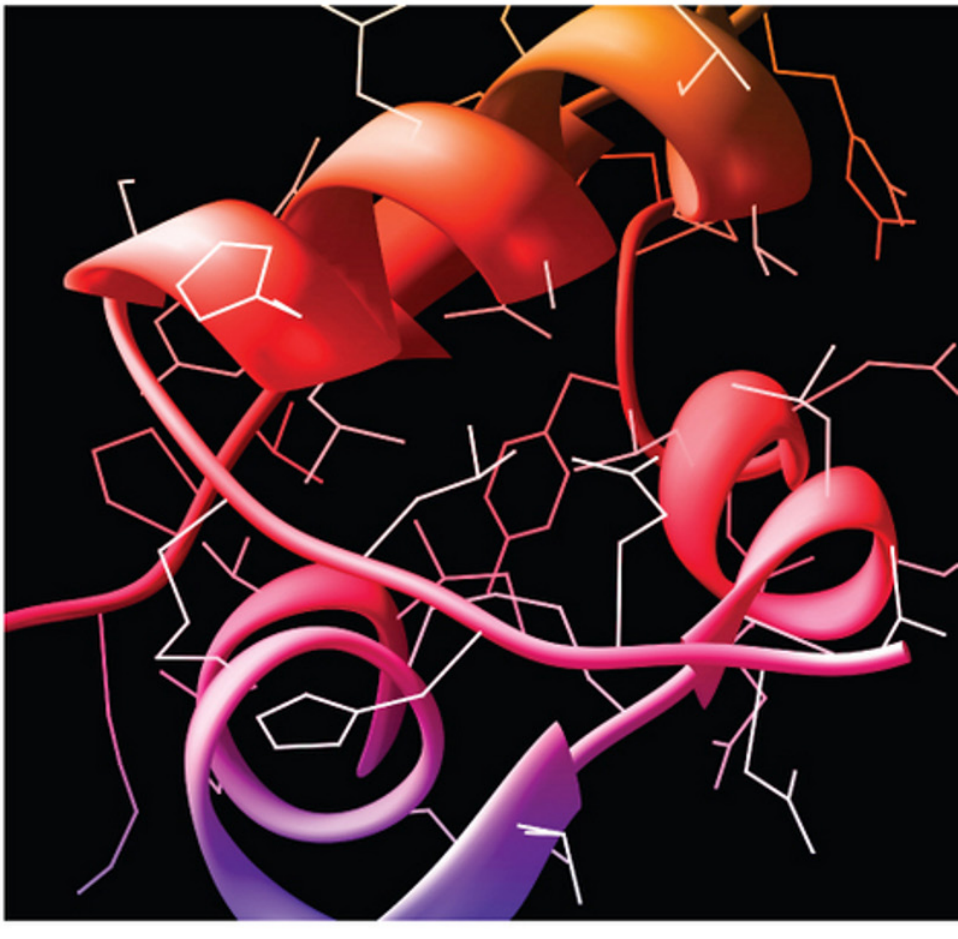

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Lecture Notes

Endocrinology and Diabetes

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Preface

In the conception of this book, we used our teaching experience to cover the main topics in endocrinology and diabetes in a simple and easy-to-understand style.

We have tried to discuss the basic anatomy and physiology of the endocrine system, which is fundamental to the understanding of pathophysiology and presentation of the endocrine diseases. *Lecture Notes: Endocrinology and Diabetes* also contains detailed sections on the practical management of diabetes and endocrine disorders. Therefore we believe that this book is suitable for medical students and doctors training in endocrinology, and can be used for exam revision as well as rapid consultation in the clinic.

Amir Sam
Karim Meeran

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Abbreviations

5-HIAA 5-hydroxyindoleacetic acid
ABPI ankle–brachial pressure index
ACCORD Action to Control Cardiovascular Risk in Diabetes trial
ACE angiotensin-converting enzyme
ACR albumin-to-creatinine ratio
ACTH adrenocorticotrophic hormone
ADH antidiuretic hormone
ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AGB adjustable gastric banding
AGE advanced glycosylation end-product
AHO Albright's hereditary osteodystrophy
AIDS acquired immune deficiency syndrome
ALT alanine transaminase
AMPK adenosine monophosphate-activated protein kinase
APS autoimmune polyglandular syndrome
ARB angiotensin receptor blocker
AVP arginine vasopressin
BFGF basic fibroblast growth factor
BMD bone mineral density
BMI body mass index
BMP-7 bone morphogenic protein-7
CAH congenital adrenal hyperplasia
CARDS Collaborative AtoRvastatin Diabetes Study
CARE Cholesterol and Recurrent Events trial
CDGP constitutional delay of growth and puberty
CEA carcinoembryonic antigen
CNS central nervous system
CPT I carnitine palmitoyltransferase-I
CRH corticotrophin-releasing hormone
CSW cerebral salt wasting
CT computed tomography
CTLA-4 cytotoxic T-lymphocyte antigen 4
CVD cardiovascular disease
DAFNE Dose Adjustment for Normal Eating
DCCT Diabetes Control and Complications Trial
DEXA dual-energy X-ray absorptiometry
DHEA dehydroepiandrosterone
DHEA-S dehydroepiandrosterone sulphate
DIEP Diabetes in Early Pregnancy study
DKA diabetic ketoacidosis
DMSA dimercaptosuccinic acid
DPP-IV dipeptidyl peptidase-IV
ECG electrocardiogram
EDIC Epidemiology of Diabetes Interventions and Complications study
eGFR estimated glomerular filtration rate
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
FIELD Fenofibrate Intervention and Event Lowering in Diabetes study
FNA fine needle aspiration
FSH follicle-stimulating hormone
GAD glutamic acid decarboxylase
GEMINI Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives
GFR glomerular filtration rate
GH growth hormone
GHRH growth hormone-releasing hormone
GLP-1 glucagon-like peptide-1
GSH glucocorticoid-suppressible hyperaldosteronism
HbA_{1c} glycated haemoglobin
hCG human chorionic gonadotrophin
HDL high-density lipoprotein
HHS hyperosmolar hyperglycaemic state
HIF hypoxia-inducible factor
HIV human immunodeficiency virus
HPA hypothalamic–pituitary–adrenal
HRT hormone replacement therapy
ICSI intracytoplasmic sperm injection
IGF-I insulin-like growth factor-I
IGFBP-3 insulin-like growth factor-binding protein-3

Abbreviations

IRMA intraretinal microvascular abnormality
IRS insulin receptor substrate
ITT insulin tolerance test
IVF in vitro fertilization
JNK c-Jun amino-terminal kinase
LADA latent autoimmune diabetes in adults
LDL low-density lipoprotein
LH luteinizing hormone
MAPK mitogen-activated protein kinase
MC4R melanocortin-4 receptor
MDRD Modification of Diet in Renal Disease study
MEN multiple endocrine neoplasia
MI myocardial infarction
MODY maturity-onset diabetes of the young
MRI magnetic resonance imaging
MSH melanocyte-stimulating hormone
MTC medullary thyroid carcinoma
NET neuroendocrine tumour
NF neurofibromatosis
NPH neutral protamine Hagedorn
NSAID non-steroidal anti-inflammatory drug
NSC National Screening Committee
NVD new vessels on disc
NVE new vessels elsewhere
OGTT oral glucose tolerance test
PAC plasma aldosterone concentration
PCOS polycystic ovary syndrome
POMC proopiomelanocortin
POPADAD Prevention of Progression of Arterial Disease and Diabetes study
PPAR peroxisome proliferator-activated receptor
PPNAD primary pigmented nodular adrenocortical disease
PRA plasma renin activity
PSA prostate-specific antigen
PTH parathyroid hormone
PTTG pituitary tumour transforming gene
PTU propylthiouracil
PYY peptide YY
RANK receptor activator of nuclear factor kappa B
RANKL RANK ligand
RYGB roux-en-Y gastric bypass
SD standard deviation
SDHB succinate dehydrogenase subunit B
SG specific gravity
SHBG sex hormone-binding globulin
SIADH syndrome of inappropriate antidiuretic hormone
SOS Swedish Obese Subjects study
SRS somatostatin receptor scintigraphy
StAR steroidogenic acute regulatory protein
STAT signal transduction and activators of transcription
T_3 triiodothyronine
T_4 thyroxine
TGF transforming growth factor
TNF tumour necrosis factor
TRAb thyroid-stimulating hormone receptor antibody
TRH thyrotrophin-releasing hormone
TSH thyroid-stimulating hormone
UKPDS United Kingdom Prospective Diabetes Study
VEGF vascular endothelial growth factor
WHI Women's Health Initiative trials
WHO World Health Organization

Chapter 1

Thyroid anatomy and physiology

Anatomy

The thyroid gland consists of left and right *lobes* connected by a midline isthmus (Fig. 1.1). The isthmus lies below the cricoid cartilage, and the lobes extend upward over the lower half of the thyroid cartilage. The thyroid is covered by the strap muscles of the neck and overlapped by the sternocleidomastoids. The pretracheal fascia encloses the thyroid gland and attaches it to the larynx and the trachea. This accounts for the upward movement of the thyroid gland on swallowing.

The thyroid gland develops from the floor of the pharynx in the position of the foramen caecum of the adult tongue as a downgrowth that descends into the neck. During this descent, the thyroid gland remains connected to the tongue by the thyroglossal duct, which later disappears. However, aberrant thyroid tissue or thyroglossal cysts (cystic remnants of the thyroglossal duct) may occur anywhere along the course of the duct (Fig. 1.2). Such thyroid remnants move upward when the tongue is protruded.

The thyroid gland is composed of epithelial spheres called *follicles* (Fig 1.3), whose lumens are filled with a proteinaceous colloid containing *thyroglobulin*. Two basic cell types are present in the follicles. The follicular cells secrete thyroxine (T_4) and triiodothyronine (T_3) and originate from a downward growth of the endoderm of the floor of the pharynx (see above). The parafollicular or C cells secrete calcitonin and arise from neural crest cells that migrate into the developing thyroid gland. The follicles are surrounded by an extensive capillary network.

Physiology

Thyroid hormones act on many tissues. They regulate:

- organogenesis, growth and development (central nervous system, bone)
- energy expenditure
- protein, carbohydrate and fat metabolism
- gut motility
- bone turnover
- heart rate and contractility, and peripheral vascular resistance
- beta-adrenergic receptor expression
- muscle contraction and relaxation
- the menstrual cycle
- erythropoiesis.

Iodine is essential for normal thyroid function. It is obtained by the ingestion of foods such as seafood, seaweed, kelp, dairy products, some vegetables and iodized salt. The recommended iodine intake for adults is 150 µg per day (250 µg per day for pregnant and lactating women). Dietary iodine

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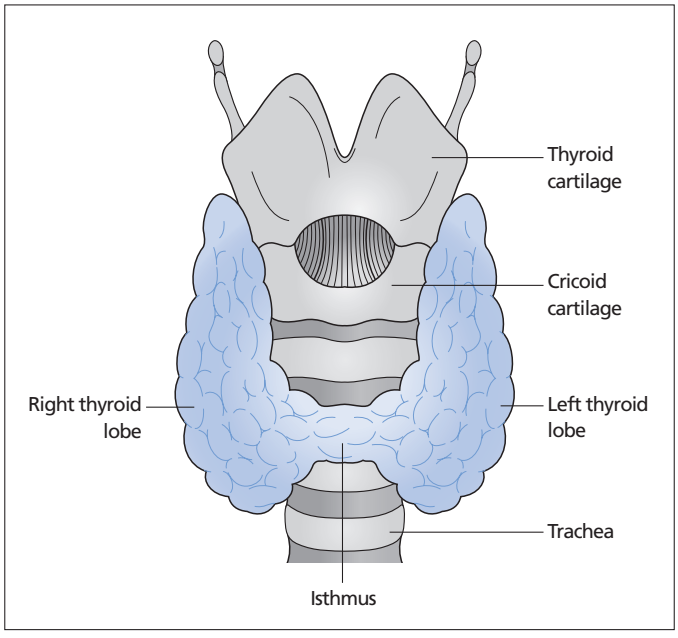


Figure 1.1 Thyroid gland.

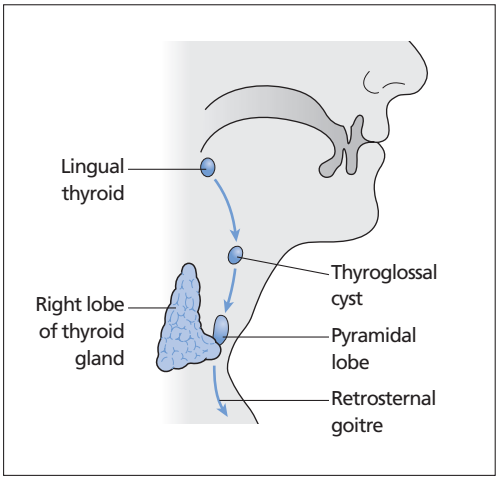


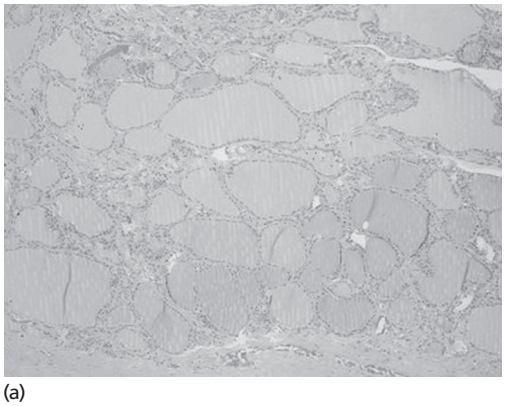
Figure 1.2 Possible sites of remnants of the thyroglossal duct.

is absorbed as iodide. Iodide is excreted in the urine.

Thyroid hormone synthesis

Figure 1.4 illustrates different steps in thyroid hormone synthesis:

- *Thyroglobulin* is synthesized in the rough endoplasmic reticulum and is transported into the follicular lumen by exocytosis.
- Iodide is transported into the thyroid follicular cells via a sodium–iodide symporter on the basolateral membrane of the follicular cells. Iodide transport requires oxidative metabolism.
- Inside the follicular cells, iodide diffuses to the apical surface and is transported by pendrin (a membrane iodide–chloride transporter) into the follicular lumen.
- *Thyroid peroxidase* (TPO) enzyme catalyzes the process of oxidation of the iodide to iodine and its binding (organification) to the tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- DIT and MIT molecules are linked by TPO to form *thyroxine* (T_4) and *triiodothyronine* (T_3) in a process known as coupling.
- Thyroglobulin containing T_4 and T_3 is resorbed into the follicular cells by endocytosis and is cleaved by lysosomal enzymes (proteases and peptidases) to release T_4 and T_3. T_4 and T_3 are then secreted into the circulation.
- Uncoupled MIT and DIT are deiodinated, and the free tyrosine and iodide are recycled.



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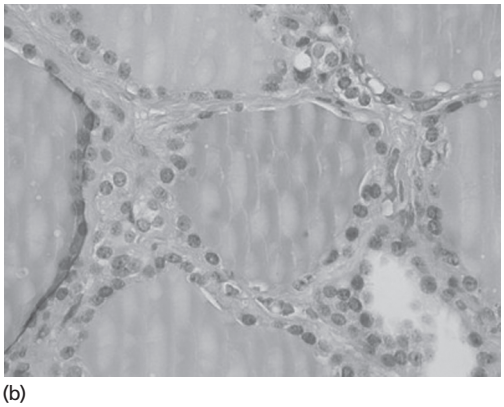

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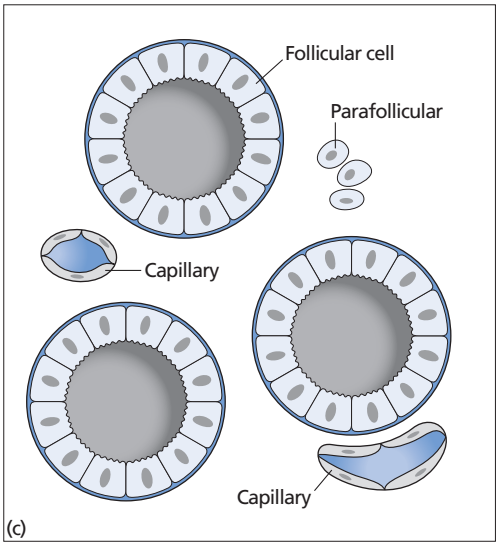

Figure 1.3 (a) A low-power histological image of thyroid tissue showing numerous follicles filled with colloid and lined by cuboidal epithelium. (b) A high-power view of follicles lined by cuboidal epithelium. (c) Thyroid follicles (lined by follicular cells), surrounding capillaries and parafollicular cells.

The thyroid gland stores T_4 and T_3 incorporated in thyroglobulin, and can therefore secrete T_4 and T_3 more quickly than if they had to be synthesized.

Extra-thyroidal T_3 production

T_4 is produced entirely by the thyroid gland. The production rate of T_4 is about 100 µg per day. However, only 20% of T_3 is produced directly by the thyroid gland (by coupling of MIT and DIT). Around 80% of T_3 is produced by the deiodination of T_4 in peripheral extra-thyroidal tissues (mainly liver and kidney). The total daily production rate of T_3 is about 35 µg.

T_4 is converted to T_3 (the biologically active metabolite) by *5′-deiodination* (outer-ring deiodination). 5′-Deiodination is mediated by deiodinases type 1 (D1) and type 2 (D2). D1 is the predominant deiodinating enzyme in the liver, kidney and thyroid. D2 is the predominant deiodinating enzyme in muscle, brain, pituitary, skin and placenta. Type 3 deiodinase (D3) catalyzes the conversion of T_3 to reverse T_3 (the inactive metabolite) by 5-deiodination (inner ring deiodination), as shown in Fig. 1.5.

Changes in T_3 concentration may indicate a change in the rate of peripheral conversion and may not be an accurate measure of the change in thyroid hormone production. For example, the rate of T_3 production (by 5′-deiodination of T_4) is reduced in acute illness and starvation.

Total and free T_4 and T_3

Approximately 99.97% of circulating T_4 and 99.7% of circulating T_3 are bound to plasma proteins: *thyroid-binding globulin* (TBG), *transthyretin* (also

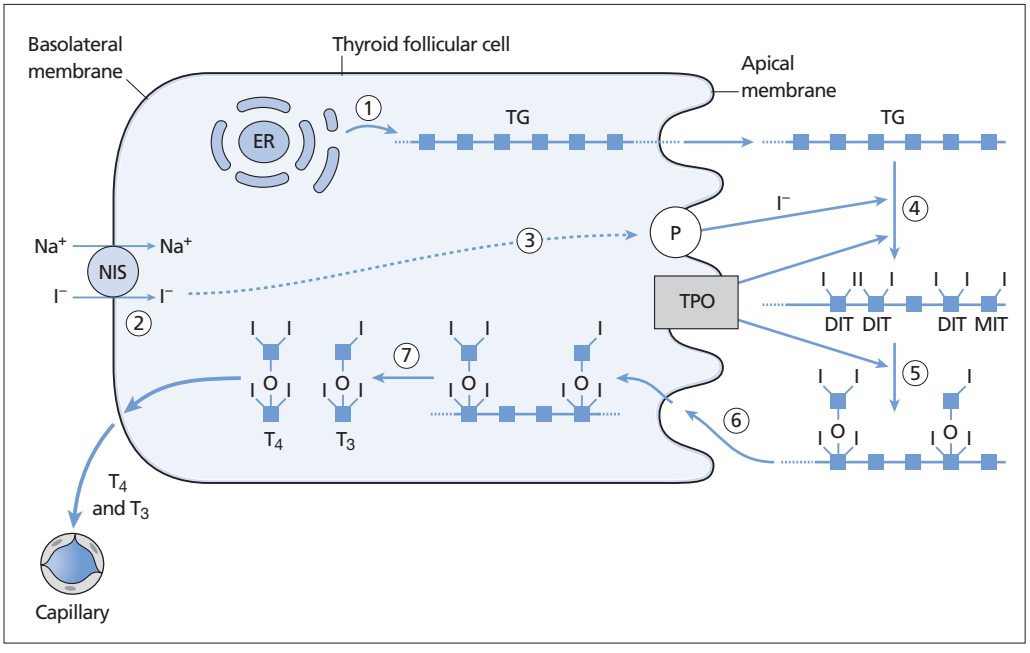

Figure 1.4 Steps in thyroid hormone synthesis. (1) Thyroglobulin (TG) is synthesized in the endoplasmic reticulum (ER) in the thyroid follicular cells and is transported into the follicular lumen. The small blue squares represent the amino acid residues comprising TG. (2) Iodide is transported into the follicular cell by the sodium–iodide (Na^+/I^-) symporter (NIS). (3) Iodide diffuses to the apical surface and is transported into the follicular lumen by pendrin (P). (4) Iodide is oxidized and linked to tyrosine residues in TG to form diiodotyrosine (DIT) and monoiodotyrosine (MIT) molecules. (5) Within the TG, T_4 is formed from two DIT molecules, and T_3 is formed from one DIT and one MIT molecule. (6) TG containing T_4 and T_3 is resorbed into the follicular cell by endocytosis. (7) TG is degraded by lysosomal enzymes to release T_4 and T_3 molecules, which move across the basolateral membrane of the follicular cell into the adjacent capillaries. TPO, thyroid peroxidase.

known as thyroid-binding pre-albumin), albumin and lipoproteins.

Only the unbound thyroid hormone is available to the tissues. T_3 is less strongly bound and therefore has a more rapid onset and offset of action. The binding proteins have both storage and buffer functions. They help to maintain the serum free T_4 and T_3 levels within narrow limits, and also ensure continuous and rapid availability of the hormones to the tissues.

Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels. This is because the level of bound hormone alters with changes in the levels of thyroid-binding proteins, even though free T_4 (and T_3) concentrations do not change and the patient remains euthyroid (Fig. 1.6). Box 1.1 summarizes factors that may alter TBG levels.

Box 1.1 Factors that may alter thyroid-binding globulin (TBG) levels

↑ TBG

Hereditary TBG excess (X-linked dominant)
Pregnancy
Drugs, e.g. oestrogen, tamoxifen, opiates, phenothiazines, 5-fluorouracil, clofibrate
Hepatitis
Acute intermittent porphyria

↓ TBG

Genetically determined
Malnutrition
Chronic liver disease
Nephrotic syndrome
Drugs, e.g. androgens, corticosteroids, phenytoin
Cushing's syndrome
Acromegaly

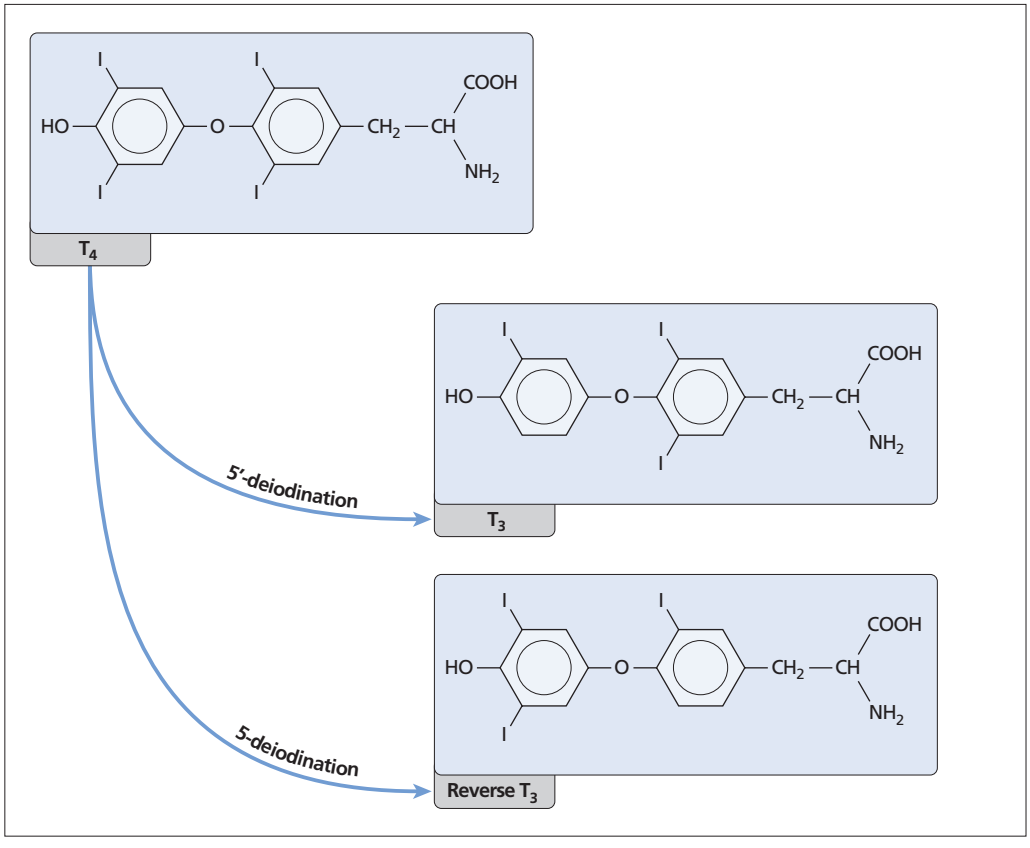

Figure 1.5 The conversion of T_4 to T_3 by 5′-deiodination and to reverse T_3 by 5-deiodination.

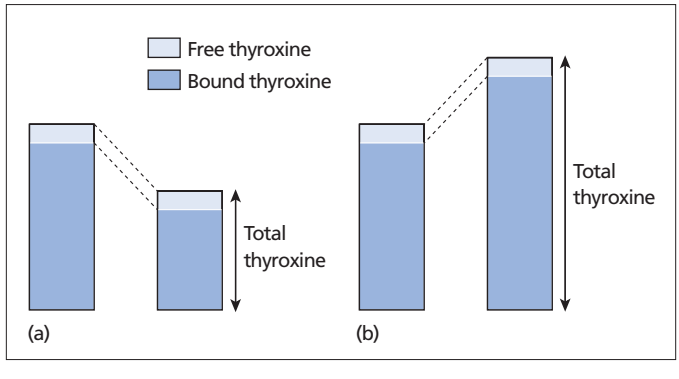

Figure 1.6 (a) If serum thyroid-binding globulin (TBG) levels are decreased, the level of thyroid hormone bound to TBG also decreases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free thyroid hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be lower. (b) If TBG levels are increased, the level of thyroid hormone bound to TBG also increases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be higher.

Other causes of increased serum total T_4 and T_3 levels include familial dysalbuminaemic hyperthyroxinaemia (due to the presence of an abnormal albumin with a higher affinity for T_4) and the presence of anti-T_4 antibodies. Patients with these conditions are euthyroid, have normal serum thyroid-stimulating hormone (TSH) levels, and usually have normal serum free T_4 and T_3 levels when measured by appropriate methods.

Thyroid hormone metabolism

T_4 is degraded at a rate of 10% per day. Around 40% of the T_4 is deiodinated to T_3 and 40% to reverse T_3. The remaining T_4 is conjugated with glucuronide and sulphate, deaminated and decarboxylated, or cleaved between the two rings.

T_3 is degraded (mostly by deiodination) at a rate of 75% per day. Reverse T_3 is degraded even more rapidly than T_3, mostly by deiodination.

Regulation of thyroid hormone production and release

T_3 and T_4 synthesis and secretion is stimulated by the *thyroid-stimulating hormone* (TSH) released from the anterior pituitary gland (Fig. 1.7). TSH production and release is increased by hypothalamic *thyrotrophin-releasing hormone* (TRH).

Thyrotrophin-releasing hormone

TRH is a tripeptide synthesized and released by the hypothalamus. TRH content is highest in the median eminence and paraventricular nuclei of the hypothalamus. TRH stimulates TSH secretion by activating a G-protein-coupled receptor and the phospholipase C-phosphoinositide pathway, resulting in mobilization of calcium from intracellular storage sites.

Chronic TRH stimulation also increases the synthesis and glycosylation of TSH, which increases its biological activity.

Thyroid-stimulating hormone

TSH is a glycoprotein secreted by the thyrotroph cells of the anterior pituitary. TSH is composed of alpha and beta subunits that are non-covalently bound. The alpha subunit is the same as that of luteinizing hormone, follicle-stimulating hormone and human chorionic gonadotrophin. However, the beta subunit is unique to TSH. TSH binds to specific plasma membrane receptors and activates adenylyl cyclase. TSH also stimulates phospholipase C activity.

TSH stimulates every step in thyroid hormone synthesis and secretion. It also stimulates the expression of many genes in thyroid tissue and causes thyroid hyperplasia and hypertrophy.

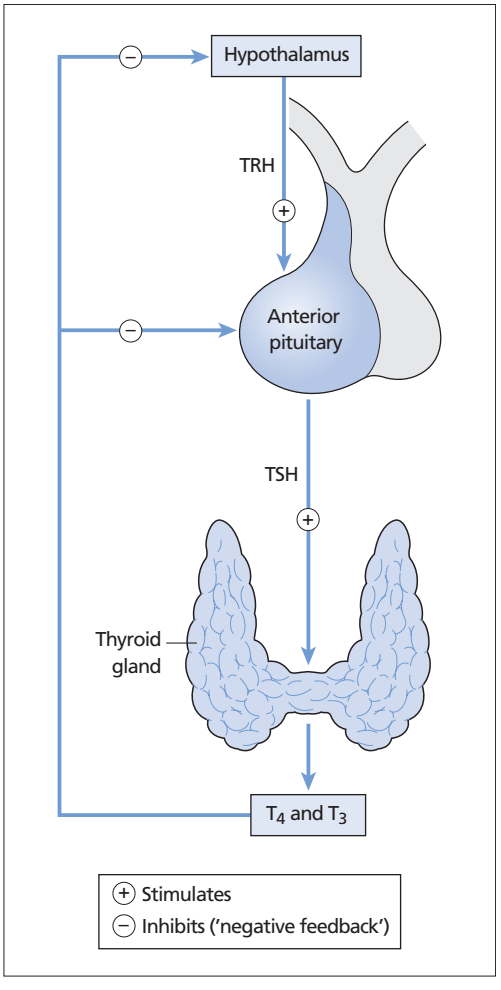

Figure 1.7 Hypothalamic–pituitary–thyroid axis. TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone.

Box 1.2 Causes of increased and decreased thyroid-stimulating hormone (TSH) concentration

Increased TSH secretion

Primary/subclinical hypothyroidism
Secondary hyperthyroidism
Recovery from non-thyroidal illness
Thyroid hormone resistance
Primary adrenal insufficiency
Drugs: dopamine antagonists (metoclopramide, domperidone), amiodarone
Patients with antibodies to the murine immunoglobulins used in the assay

Decreased TSH secretion

Primary/subclinical hyperthyroidism
Secondary hypothyroidism
Non-thyroidal illness
Drugs: dopamine agonists, octreotide, phenytoin, steroids
Increased human chorionic gonadotrophin, e.g. early pregnancy, molar pregnancy, choriocarcinoma

T_4 and T_3 inhibit TSH synthesis and release both directly (by inhibiting transcription of the TSH subunit genes) and indirectly (by inhibiting TRH release). T_4 and T_3 also decrease the glycosylation and hence bioactivity of TSH.

TSH secretion is regulated by very small changes in serum T_4 and T_3 concentrations. However, an important exception is that the reduced T_3 levels in patients with non-thyroidal illness have little effect on TSH secretion. This may be due to a greater contribution of serum T_4 to the nuclear T_3 content of the pituitary than other tissues.

Box 1.2 shows a list of the causes of increased and decreased TSH concentration.

Mechanism of action of thyroid hormones

Thyroid hormones enter cells via active membrane transporter proteins (e.g. MCT8). Inside the cells, T_3 formed from the deiodination of T_4 and T_3 that enters the cells from the serum is transferred to the nucleus. The thyroid hormone receptors (TRs) heterodimerize with the retinoid X receptor and act as nuclear transcription factors. TRs bind thyroid hormone response elements in the promoter region of thyroid hormone-responsive genes. In the absence of T_3, TRs bind co-repressor proteins that repress transcription. On T_3 binding, co-repressors are displaced and co-activator proteins bind the TRs, resulting in histone acetylation, generation of a permissive chromatin structure and induction of gene transcription.

There are two T_3 nuclear receptors—alpha and beta—encoded by separate genes located on chromosomes 17 and 3. Two forms of each TR are generated by alternative splicing. Only the beta-1, beta-2 and alpha-1 receptors bind T_3. Liver predominantly expresses beta receptors, whereas heart and bone express alpha receptors. The hypothalamus and pituitary express beta-2 receptors which mediate the negative feedback regulation.

Key points:

- Thyroid hormone synthesis involves the transport of iodide into follicular cells, iodide oxidation into iodine, binding of iodine to thyroglobulin tyrosine residues (organification) to form MIT and DIT, and coupling of DIT and MIT to form T_4 and T_3. The processes of iodide oxidation, organification and coupling are catalyzed by the thyroid peroxidase enzyme.
- Thyroid hormone synthesis and secretion is stimulated by the TSH released from the anterior pituitary gland. TSH production and release is increased by hypothalamic TRH.
- 80% of T_3 is produced by the 5′-deiodination of T_4 in peripheral extra-thyroidal tissues (mainly liver and kidney).
- Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels as the level of bound hormone alters with changes in the levels of thyroid-binding proteins.
- T_4 is largely a prohormone, and almost the entire nuclear-bound hormone is T_3.

Chapter 2

Hypothyroidism

Hypothyroidism results from insufficient secretion of thyroid hormones.

- *Primary* hypothyroidism is characterized by low serum free thyroxine (T_4) and high serum thyroid-stimulating hormone (TSH) levels (due to a reduced negative feedback effect of T_4 on TSH synthesis/secretion).
- *Subclinical* hypothyroidism is defined as normal serum free T_4 and T_3 levels and a high serum TSH. This reflects the sensitivity of TSH secretion to very small decreases in thyroid hormone secretion.
- *Central* hypothyroidism is much less common and results from reduced TSH secretion from the anterior pituitary (secondary hypothyroidism) or reduced thyrotrophin-releasing hormone (TRH) secretion from the hypothalamus (tertiary hypothyroidism).

Epidemiology

The prevalence of congenital hypothyroidism in the UK is about 1 in 4000 of the population. The frequency of hypothyroidism varies from 0.1% to 2% of adults. Hypothyroidism is 5–8 times more common in females. Primary hypothyroidism accounts for more than 95% of cases of hypothyroidism. Around 5% of adults and 15% of women over the age of 60 have subclinical hypothyroidism.

Aetiology

Box 2.1 summarizes the causes of hypothyroidism.

Subclinical hypothyroidism (see above) may result from the same causes as primary hypothyroidism or from inadequate T_4 replacement in a patient with overt hypothyroidism.

Congenital hypothyroidism may be secondary to thyroid agenesis, dysgenesis or inherited defects in thyroid hormone biosynthesis.

Box 2.1 Causes of hypothyroidism

Congenital

Thyroid agenesis, dysgenesis or inherited defects in thyroid hormone biosynthesis

Acquired

Primary

Chronic autoimmune (Hashimoto's) thyroiditis

Iatrogenic (drugs, thyroidectomy, radioiodine, neck radiotherapy)

Iodine deficiency/excess

Thyroiditis

Central

Pituitary/hypothalamic damage (e.g. due to tumours, trauma, radiotherapy, hypophysitis, infarction, infiltration)

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Acquired hypothyroidism may be primary or central as mentioned above. Primary hypothyroidism may be due to chronic autoimmune (Hashimoto's) thyroiditis, iatrogenic causes (e.g. drugs, thyroidectomy, radioiodine), iodine deficiency/excess or thyroiditis.

Chronic autoimmune (Hashimoto's) thyroiditis is caused by cellular and antibody-mediated injury to the thyroid tissue. There are two forms, goitrous and atrophic, which have similar pathophysiology but are different in the extent of thyroid follicular cell hyperplasia, lymphocytic infiltration and fibrosis. Chronic autoimmune thyroiditis is usually but not always permanent. These patients are more likely to have a personal or family history of other autoimmune conditions, such as Addison's disease and type 1 diabetes mellitus, vitiligo (Fig. 2.1), pernicious anaemia and premature ovarian failure. An increased incidence of Hashimoto's thyroiditis is also found in those with Down's or Turner's syndrome.

Drugs such as the antithyroid drugs carbimazole and propylthiouracil (used to treat hyperthyroidism) may cause hypothyroidism. Amiodarone is an iodine-containing drug and may cause both hypothyroidism (see below) and thyrotoxicosis (see Chapter 3). Other drugs that may cause hypothyroidism include lithium, alpha-interferon and interleukin-2. Patients on these drugs should have their serum TSH checked every 6–12 months.

T_4 has a half-life of 7 days, and hypothyroidism occurs about 2–4 weeks following total *thyroidectomy*. After subtotal thyroidectomy for the treatment of Graves' disease, hypothyroidism occurs within the first year in the majority of patients. The annual risk of hypothyroidism in those who are euthyroid at 1 year is 0.5–1%. Some patients become transiently hypothyroid after 4–8 weeks but recover several weeks or months later.

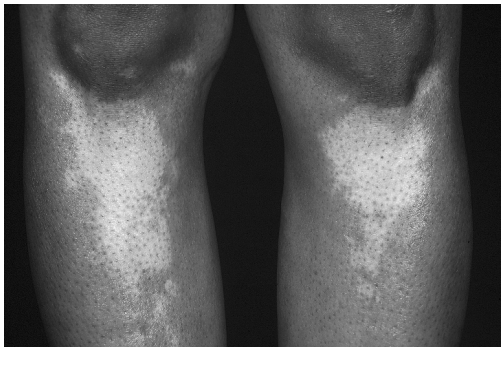


Figure 2.1 Vitiligo in a patient with Hashimoto's thyroiditis.

Following *radioiodine therapy* for the treatment of Graves' disease, the majority of patients become hypothyroid within the first year. The rest have a 0.5–2% annual risk of hypothyroidism. Some patients with toxic multinodular goitre or thyroid adenomas who receive radioiodine therapy also become hypothyroid.

External irradiation of the neck may result in hypothyroidism with a gradual onset. Many patients develop overt hypothyroidism after several years of subclinical hypothyroidism.

Iodine deficiency and excess can both cause hypothyroidism. Iodine deficiency is the most common worldwide cause of hypothyroidism and is more prevalent in mountainous areas. Iodine excess can also result in hypothyroidism by inhibiting iodine organification and T_4 and T_3 synthesis (Wolff–Chaikoff effect).

In *postpartum* and *subacute thyroiditis*, transient hypothyroidism (lasting weeks to a few months) may follow transient thyrotoxicosis.

Rarer causes include infiltrative diseases, for example fibrous (Reidel's) thyroiditis, haemochromatosis, sarcoidosis, amyloidosis, leukaemia, and consumptive hypothyroidism due to an ectopic production of the type 3 deiodinase in vascular and fibrotic tumours, which metabolizes T_4 to reverse T_3.

Clinical presentations

Hypothyroidism often has an insidious and non-specific onset. Patients may present with fatigue, lethargy and cold intolerance. Clinical presentations of thyroid hormone deficiency result from a generalized slowing of metabolic processes and an accumulation of hydrophilic glycosaminoglycans in the interstitial spaces of the tissues (*myxoedema*). Box 2.2 summarizes the clinical presentations of hypothyroidism in adults and possible explanations for these manifestations.

Box 2.2 Clinical presentations of hypothyroidism

General
Tiredness, cold intolerance, depression, goitre

Skin and hair
Skin: dry and coarse (decreased acinar gland secretion), pale (reduced blood flow), yellowish tinge (carotenaemia), oedematous (accumulation of glycosaminoglycans in the dermis with associated water retention)
Coarse hair, hair loss and brittle nails

Cardiovascular
Bradycardia, exertional breathlessness and reduced exercise tolerance (reduced heart rate and contractility as thyroid hormone regulates genes involved in myocardial contractility and relaxation), exacerbation of heart failure or angina, diastolic hypertension (increased systemic vascular resistance), pericardial effusion, hypercholesterolaemia and hypertriglyceridaemia (decreased lipid metabolism)

Respiratory
Exertional breathlessness, hypoventilation (respiratory muscle weakness and reduced ventilatory responses to hypoxia and hypercapnia), obstructive sleep apnoea (macroglossia), pleural effusion

Gastrointestinal
Constipation (decreased gut motility), weight gain (reduced metabolic rate and accumulation of glycosaminoglycan-rich fluid), ascites (rare)

Reproductive
Hyperprolactinaemia (high thyrotrophin-releasing hormone in primary hypothyroidism stimulates prolactin production)
Women: oligomenorrhoea/amenorrhea or menorrhagia, early abortion
Men: reduced libido, erectile dysfunction, delayed ejaculation, reduced serum total testosterone due to low sex hormone-binding globulin levels

Neurological
Slowing of intellectual activities, movement and speech, impaired memory, delayed relaxation of deep tendon reflexes, carpal tunnel syndrome, peripheral neuropathy, cerebellar ataxia, encephalopathy, muscle abnormalities (asymptomatic rise in serum creatine kinase, muscle cramps, proximal muscle weakness, rarely rhabdomyolysis)

Myxoedema coma
May present with coma, hypothermia, hypercapnia and hyponatraemia. Precipitating factors include infection, cold exposure, trauma and drugs (hypnotics or opiates) in patients with severe hypothyroidism

Anaemia
Normocytic anaemia, macrocytic anaemia (in those with pernicious anaemia associated with autoimmune thyroiditis), microcytic anaemia (in female patients with menorrhagia)

Metabolic
Hyperlipidaemia, hyponatraemia (reduced cardiac output sensed by the carotid sinus baroreceptors can result in increased antidiuretic hormone release; also decreased glomerular filtration results in reduced free water excretion), hyperhomocysteinaemia

In secondary hypothyroidism due to hypothalamic/pituitary disease, the symptoms are usually milder than in primary hypothyroidism and may be masked by symptoms of other hormone deficiencies (see Chapter 12). For example, hot flushes secondary to hypogonadism may make the cold intolerance caused by hypothyroidism less obvious.

Investigations

The diagnosis of hypothyroidism is made by measuring serum TSH and free T_4. In many developed countries, congenital hypothyroidism is diagnosed during the routine screening of all infants by measuring TSH or T_4 in blood obtained from a heel prick in the first week of life.

Table 2.1 shows the results of thyroid function tests in primary, subclinical and secondary hypothyroidism. In general, younger patients presenting with primary hypothyroidism have much higher TSH levels than older patients.

Other laboratory test abnormalities in hypothyroid patients include *hyperlipidaemia* and *hyponatraemia*.

Patients with central hypothyroidism should have pituitary function tests and a magnetic resonance imaging scan of the hypothalamus and pituitary. A TRH test may occasionally be done to differentiate between pituitary and hypothalamic causes of TSH deficiency. A dose of 200 µg of TRH is given intravenously over 2 minutes. Blood samples are taken at 30 and 60 minutes. The 60-minute value exceeds the 30-minute value in hypothalamic hypothyroidism.

Pituitary enlargement may occasionally be seen in severe primary hypothyroidism owing to hypertrophy and hyperplasia of the thyrotroph cells. It is important to distinguish this entity, which is reversible with T_4 replacement, from a pituitary adenoma.

Treatment

Hypothyroidism usually requires lifelong treatment with synthetic levothyroxine. Exceptions include cases of transient hypothyroidism following subacute or postpartum thyroiditis, or reversible hypothyroidism due to a drug that can be stopped.

Treatment objectives are the resolution of symptoms, a normalization of TSH and a reduction in the size of the goitre in patients with Hashimoto's thyroiditis.

There is no proven benefit in using a combined T_3/T_4 replacement.

Dose and administration of levothyroxine

Younger patients (under 50 years) can be started on levothyroxine 50 µg daily. Thyroid function tests are repeated after 6 weeks and the dose is increased by 25 µg until the TSH is in the normal range and ideally as close to 1.0 mU/L as possible.

Older patients should be started on a lower dose (25 µg daily) as they may have ischaemic heart disease, and levothyroxine increases myocardial oxygen demand. The dose may be gradually increased; however, a suboptimal replacement may have to be accepted if an optimal dose causes cardiac symptoms.

The average dose of levothyroxine in hypothyroid adults is about 100 µg per day, but the range varies from 50 to 200 µg daily. It is important to advise patients on the potential adverse effects of levothyroxine over-replacement, such as arrhythmias and osteoporosis.

Table 2.1 Thyroid function tests in various forms of hypothyroidism

	Thyroid-stimulating hormone	Free thyroxine	Free triiodothyronine
Primary hypothyroidism	↑	↓	↓ or N
Subclinical hypothyroidism	↑	N	N
Central hypothyroidism	↓ or inappropriately N	↓	↓ or N

N, normal.

Levothyroxine should be taken on an empty stomach, and medications that interfere with its absorption (e.g. ferrous salts, cholestyramine) should be taken several hours after the levothyroxine dose. Some drugs (e.g. phenytoin, carbamazepine) may increase levothyroxine metabolism.

Patients with poor compliance with levothyroxine replacement may occasionally receive their total weekly dose of levothyroxine once per week. This should probably be avoided in coronary heart disease.

Follow-up and monitoring

Levothyroxine has a half-life of 1 week and it takes about 6 weeks (six half-lives) to reach a steady-state concentration. Serum T_4 increases first, and then TSH secretion starts to fall. Follow-up appointments for clinical assessment, measurements of thyroid function and adjustment of the dose should be arranged every 6 weeks. After stabilization of TSH levels and establishment of the proper maintenance dose, clinical assessment and serum TSH measurements should be carried out annually.

When levothyroxine is commenced, TSH occasionally rises further initially before it starts to fall. This may be because the pituitary itself has begun to suffer from the profound hypothyroidism and has failed to make TSH. On commencement of the levothyroxine, the pituitary starts to recover.

It is worth noting that hair loss may initially be made worse by commencing levothyroxine. This is because new hair follicles start growing and push up the old hair follicles. It may take about 9 months before this stabilizes.

Special circumstances

Myxoedema coma

Myxoedema coma should be treated aggressively as it has a high mortality of up to 80%. Patients should be monitored closely in an intensive care unit. Mechanical ventilation should be instituted for respiratory failure. Blood should be taken for culture, free T_4, T_3, TSH and cortisol before starting treatment. Treatment must be started before diagnosis is established.

- No consensus has yet been reached about the optimal replacement regimen of *thyroid hormone* replacement. An accepted regimen includes the administration of intravenous levothyroxine 300–500 µg (depending on the patient's age, weight and risk of myocardial ischaemia or arrhythmia) followed by daily intravenous doses of 50–100 µg until the patient can take oral levothyroxine. If there is no improvement within 24–48 hours, intravenous T_3 (10 µg, 8-hourly) is added.
- Intravenous *hydrocortisone* (100 mg 6–8-hourly) must be given until coexisting adrenal insufficiency can be excluded.
- Treat possible *precipitating factors* such as infection with broad-spectrum antibiotics.
- Replace intravenous *fluids* (and glucose) appropriately.
- Correct *hypothermia* using a heating blanket. Aim for an hourly rise of 0.5 °C in core temperature. Rapid external warming can cause inappropriate vasodilatation and cardiovascular collapse.

Suspected adrenal insufficiency

Levothyroxine replacement in patients with untreated adrenal insufficiency can precipitate an Addisonian crisis (see Chapter 6). A short Synacthen test should always be done prior to levothyroxine replacement if adrenal insufficiency or secondary hypothyroidism is suspected. Hydrocortisone must be given with the levothyroxine if adrenal insufficiency is confirmed.

Subclinical hypothyroidism

Indications for levothyroxine replacement in subclinical hypothyroidism include pregnancy, a serum TSH above 10 mU/L, goitre, symptoms of hypothyroidism such as fatigue, constipation or depression, or high serum antithyroid peroxidase (microsomal) antibody. Patients who are not treated should have periodic thyroid function tests to detect progression to overt hypothyroidism.

Oestrogen therapy

Oestrogens may increase the need for levothyroxine. In women receiving levothyroxine replacement, serum TSH should be measured about 12 weeks after starting oestrogen therapy to determine whether an increase in levothyroxine dose is needed.

Surgery

Patients on thyroxine replacement who are unable to eat or drink following surgery should receive intravenous levothyroxine (80% of oral dose) *only* if they have not resumed oral intake after 5–7 days.

Transient hypothyroidism

Transient hypothyroidism, for example following thyroiditis, can last from a few weeks to as long as 6 months. Patients with minimal symptoms may not require therapy. Symptomatic patients should receive levothyroxine for several months. A normal serum TSH level 6 weeks after stopping levothyroxine indicates a recovery of thyroid function.

Pregnancy

See Chapter 31.

Key points:

- Primary hypothyroidism (low serum free T_4 and high serum TSH) may be due to chronic autoimmune (Hashimoto's) thyroiditis, iatrogenic causes (antithyroid drugs, thyroidectomy, radioiodine), iodine deficiency/excess or thyroiditis.
- Clinical presentations of thyroid hormone deficiency result from a generalized slowing of metabolic processes and an accumulation of hydrophilic glycosaminoglycans in the interstitial spaces of the tissues (myxoedema).
- Hypothyroidism usually requires lifelong treatment with synthetic thyroxine. Hypothyroid patients with a history of ischaemic heart disease should be started on a lower dose of levothyroxine.
- Levothyroxine replacement in patients with untreated adrenal insufficiency can precipitate an Addisonian crisis.

Chapter 3

Thyrotoxicosis

Thyrotoxicosis is the syndrome resulting from an excess of circulating free thyroxine (T_4) and/or free triiodothyronine (T_3). Thyrotoxicosis may be due to either increased thyroid hormone synthesis (*hyperthyroidism*) or increased release of stored thyroid hormone from an inflamed thyroid gland (e.g. in subacute thyroiditis).

- *Primary* hyperthyroidism is characterized by raised free T_4 and/or T_3 and low thyroid-stimulating hormone (TSH). TSH is suppressed due to the negative feedback effect of thyroid hormones on TSH synthesis/secretion.
- *Secondary* hyperthyroidism is characterized by raised T_4 and T_3 due to increased TSH secretion from a pituitary tumour ('thyrotroph adenoma').

T_3 toxicosis (high free T_3, normal free T_4, low TSH) tends to occur early in the course of hyperthyroidism, when patients have relatively few symptoms. T_4 toxicosis (high free T_4, normal free T_3, low TSH) may be seen in hyperthyroid patients in whom a concurrent non-thyroidal illness reduces the conversion of T_4 to T_3.

Subclinical hyperthyroidism is defined as suppressed TSH in the presence of normal free T_4 and T_3. These patients may have few or no symptoms or signs of hyperthyroidism.

Lecture Notes: Endocrinology and Diabetes. By A. Sam and K. Meeran. Published 2009 by Blackwell Publishing. ISBN 978-1-4051-5345-4.

Epidemiology

Thyrotoxicosis affects 1% of females and 0.1% of males. Graves' disease accounts for 70–80% of all cases of hyperthyroidism. Toxic multinodular goitre is the most common cause of hyperthyroidism in the elderly. Secondary hyperthyroidism is very rare.

Aetiology

Box 3.1 summarizes the causes of thyrotoxicosis.

Box 3.1 Causes of thyrotoxicosis

Graves' disease
Toxic multinodular goitre
Toxic adenoma
Thyroiditis (de Quervain's and postpartum)
Secondary hyperthyroidism (due to a TSH-secreting pituitary adenoma)
Drugs: excessive exogenous thyroxine, amiodarone

Rarer causes
Metastatic thyroid cancer
McCune–Albright syndrome
Ectopic thyroid tissue (e.g. struma ovarii)
Gestational thyrotoxicosis
Human chorionic gonadotrophin-secreting trophoblastic tumours

Graves' disease

Graves' disease is caused by autoantibodies that stimulate the TSH receptor and hence thyroid hormone synthesis and secretion, and thyroid growth (causing a diffuse goitre). Possible precipitating and predisposing factors include genetic susceptibility (suggested by an association with certain alleles of CTLA-4 and HLA) and environmental factors such as infection.

The mechanisms that may be involved in the pathogenesis of Graves' hyperthyroidism include molecular mimicry (similarity between some infectious/exogenous antigens and human proteins) and thyroid cell expression of HLA class II molecules (which may act as antigen-presenting cells to initiate an autoimmune response).

Patients with Graves' disease may have a personal or family history of other autoimmune disorders such as vitiligo, alopecia areata, pernicious anaemia, type 1 diabetes mellitus, myasthenia gravis or coeliac disease.

Toxic multinodular goitre and toxic adenoma

These are the result of focal and/or diffuse hyperplasia of thyroid follicular cells whose function is independent of regulation by TSH. Between 20% and 80% of toxic adenomas and some nodules of toxic multinodular goitres have somatic mutations of the TSH receptor gene that confer autonomous hyperactivity.

Thyroiditis

Thyroiditis (e.g. subacute viral, postpartum) can result in thyrotoxicosis by the release of preformed thyroid hormones from a damaged thyroid gland into the circulation.

Subacute (de Quervain's) viral thyroiditis presents initially with thyrotoxicosis followed by hypothyroidism several weeks later. Recovery of normal thyroid function occurs 3–6 months later, but 10% of patients may have late relapses. A similar but painless thyroiditis may occur 3–6 months after delivery (postpartum thyroiditis) possibly due to the exacerbation of a previously subclinical autoimmune thyroiditis. The thyrotoxic phase lasts for about 1–4 weeks.

Secondary hyperthyroidism

Secondary hyperthyroidism due to a TSH-secreting pituitary tumour is very rare. A similar biochemical picture (high free T_4/T_3 and normal or high TSH) may be seen in the uncommon 'thyroid hormone resistance syndrome' (see below).

Amiodarone

Amiodarone (an iodine-containing antiarrhythmic drug) may affect thyroid function in several ways. Amiodarone inhibits the conversion of T_4 to T_3 and results in a high or high-normal free T_4, low-normal free T_3 and initially high TSH that normalizes within 2–3 months. In addition, amiodarone may cause both hypothyroidism (see Chapter 2) and thyrotoxicosis.

In amiodarone-induced thyrotoxicosis, clinical manifestations are often masked by the drug's beta-blocking activity. Patients may present with atrial arrhythmias, exacerbation of ischaemic heart disease or heart failure, unexplained weight loss, restlessness or low-grade fever. There are two types of amiodarone-induced thyrotoxicosis. However, some patients may have a mixture of both types:

- *Type 1* thyrotoxicosis is caused by amiodarone's high iodine content, which provides the substrate for excessive thyroid hormone synthesis in patients with a previously silent multinodular goitre.
- *Type 2* thyrotoxicosis is due to a direct toxic effect of the drug on the thyroid gland, resulting in a destructive thyroiditis and the release of preformed T_4 and T_3.

Subclinical hyperthyroidism

This condition may be endogenous (due to the same conditions that cause overt hyperthyroidism) or due to excess exogenous T_4.

Clinical presentations

Clinical presentations of thyrotoxicosis are summarized in Box 3.2.

Box 3.2 Clinical presentations of thyrotoxicosis

General
Heat intolerance, anxiety, irritability, hyperactivity, fatigue, insomnia

Skin, nails and hair
Increased sweating, warm moist skin (increased blood flow), palmar erythema, pruritus
Onycholysis (loosening of the nails from the nail bed)
Hair loss
Graves' disease: pretibial myxoedema, acropachy
Alopecia areata and vitiligo (associated with autoimmune disorders)

Ocular
Lid retraction and lid lag
Graves' ophthalmopathy: periorbital oedema, grittiness, increased tear production, chemosis, proptosis (unilateral in 5–10%), ophthalmoplegia, optic nerve compression

Cardiovascular
Palpitations (sinus tachycardia, atrial fibrillation)
Widened pulse pressure (a combination of systolic hypertension and reduced peripheral vascular resistance), congestive heart failure, mitral valve prolapse/regurgitation

Respiratory
Exertional breathlessness (due to increased oxygen consumption and carbon dioxide production, and respiratory muscle weakness), tracheal obstruction secondary to large goitre

Gastrointestinal
Diarrhoea, increased appetite, weight loss, weight gain (10% of younger patients), dysphagia (due to a large goitre)

Neurological
Tremor, proximal muscle weakness, brisk tendon reflexes, inability to concentrate, chorea
Hypokalaemic (thyrotoxic) periodic paralysis: seen particularly in Asian men, characterized by intermittent weakness, usually after exercise or a high-carbohydrate meal

Psychiatric
Depression, apathetic thyrotoxicosis in the elderly, psychosis (rare)

Genitourinary
Females: oligomenorrhoea/amenorrhoea
Males: gynaecomastia, reduced libido, erectile dysfunction, abnormal or decreased spermatogenesis, polyuria (possibly due to primary polydipsia or hypercalciuria)

Musculoskeletal
Osteoporosis (thyroid hormone stimulates bone resorption), raised serum alkaline phosphatase (increased bone turnover), hypercalcaemia

Examination of the neck may reveal a diffusely enlarged goitre (90% of patients with Graves' disease), a multinodular goitre or a solitary nodule. A diffuse goitre may also be seen in painless thyroiditis and TSH-secreting pituitary tumours. Subacute (de Quervain's) thyroiditis presents with a small tender goitre, and patients may have had a preceding flu-like illness.

Clinical signs specific to Graves' disease include *ophthalmopathy*, *pretibial myxoedema* and *thyroid*

acropachy. These are mediated by different autoantibodies that may co-exist in Graves' disease.

Graves' ophthalmopathy

Graves' ophthalmopathy (Fig. 3.1) may be clinically obvious in 20–25% of patients with Graves' hyperthyroidism at the time of diagnosis of the hyperthyroidism. It is more common in females. Many more (>90%) may have evidence of ophthalmopathy on computed tomography/magnetic resonance imaging (CT/MRI) of the orbits. Around 10% of patients with Graves' ophthalmopathy do not have Graves' disease; they may have autoimmune hypothyroidism or thyroid autoantibodies.

Graves' ophthalmopathy may present with periorbital oedema, conjunctival oedema (chemosis) and injection, grittiness, corneal ulceration, proptosis (60%), ophthalmoplegia and diplopia (40%), retrobulbar pain or pain on eye movement, and optic nerve compression (6%), which may result in impaired visual acuity or visual field defects. Graves' ophthalmopathy may be unilateral in 15% of patients.

Pathogenesis involves activated T cell cytokines and TSH receptor antibodies that activate TSH receptors on fibroblasts and adipocytes. This sets off an inflammatory process and causes the secretion of hydrophilic glycosaminoglycans, resulting in an increased retro-orbital volume.

Patients with thyrotoxicosis due to any cause may have *lid retraction* and *lid lag* (sclera visible above the iris as the patient looks downward) caused by sympathetic overactivity, possibly mediated by increased beta-adrenergic receptors.

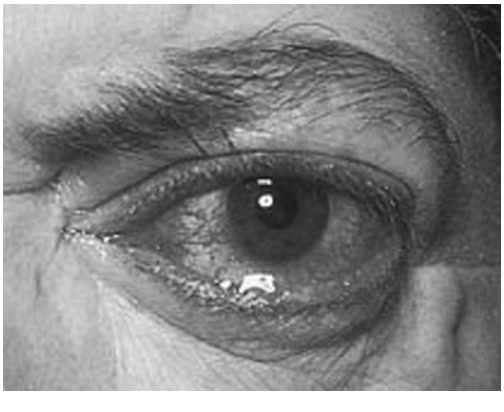


Figure 3.1 Graves' ophthalmopathy.

Pretibial myxoedema

Pretibial myxoedema (Fig. 3.2) is specific to Graves' disease. It is seen in up to 2% of patients and results from an accumulation of hydrophilic glycosaminoglycans secreted by fibroblasts in the dermis. Pretibial myxoedema is characterized by raised, pigmented, orange-peel textured nodules or plaques on the anterior aspect of the leg or the dorsum of the foot. They are usually asymptomatic, but may be pruritic or painful.

Thyroid acropachy

Thyroid acropachy (Fig. 3.3) is seen in fewer than 1% of the patients with Graves' disease and resembles clubbing. It is due to periosteal new bone formation in the phalanges.

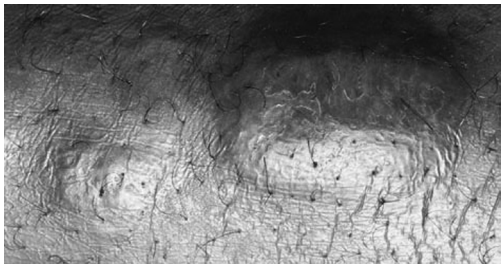


Figure 3.2 Pretibial myxoedema.

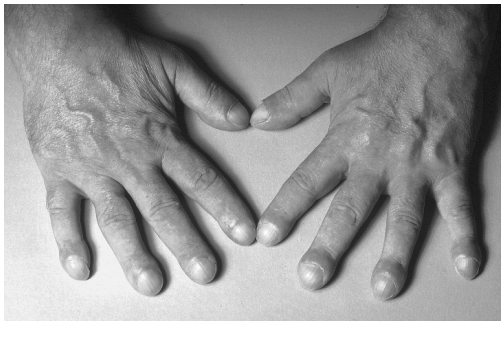


Figure 3.3 Thyroid acropachy.

Thyroid storm

A thyroid storm ('thyrotoxic crisis') may present with:

- fever, sweating
- cardiovascular symptoms: tachyarrhythmias, cardiac failure
- neurological symptoms: agitation, delirium, seizure, coma
- gastrointestinal symptoms: diarrhoea, vomiting, jaundice.

It has an untreated mortality of 50%. It may be precipitated by thyroid surgery, radio-iodine, iodinated contrast agents, withdrawal of thionamides (antithyroid drugs) and acute illnesses such as infection, stroke, diabetic ketoacidosis or trauma.

Investigations

Thyroid function tests

- In *primary hyperthyroidism*, thyroid function tests show suppressed serum TSH and high free T_4 and or free T_3.
- In *secondary hyperthyroidism*, TSH is either high or inappropriately normal in the presence of a raised free T_4/T_3. The differential diagnosis of this state includes thyroid hormone resistance (see below).
- In *subclinical hyperthyroidism*, TSH is low, but free T_4 and free T_3 levels are normal. Therefore free T_3 levels should always be measured when TSH is low in the presence of a normal T_4 to differentiate between subclinical hyperthyroidism and T_3 thyrotoxicosis.

Patients on amiodarone therapy should have their thyroid function checked before starting therapy, every 3–4 months during treatment and for at least 1 year after the drug has been stopped.

Radioisotope uptake scan

A radioisotope (intravenous [i.v.] ^{99}technetium pertechnetate or oral ^{123}iodine) uptake scan is helpful in differentiating between different causes of thyrotoxicosis (Fig. 3.4):

- Graves' disease is characterized by a diffuse increased uptake of the radioisotope. (Normal uptake is up to 3% of the administered dose.)
- Toxic multinodular goitre is characterized by multiple areas of increased radioisotope uptake ('hot' nodules) with suppression of uptake in the rest of the gland.
- A solitary toxic adenoma is seen as a single area of increased radioisotope uptake ('hot nodule') with suppression of uptake in the rest of the gland.
- A low or absent radioisotope uptake indicates either thyroiditis (inflammation and destruction of thyroid tissue) or an extra-thyroidal (e.g. exogenous) source of excess thyroid hormone.

The scanning time is earlier with ^{99}technetium pertechnetate (maximum thyroid uptake occurring within 30 minutes of i.v. injection), and there is no need to stop antithyroid drugs before the scan (technetium is transported into the thyroid follicular cells, but it is not organified).

Patients must not have any iodine-containing medications, supplements or radiocontrast dyes before the radioisotope scan as they block radioisotope uptake. It is essential to make sure that the patient is not pregnant prior to the radioisotope scan.

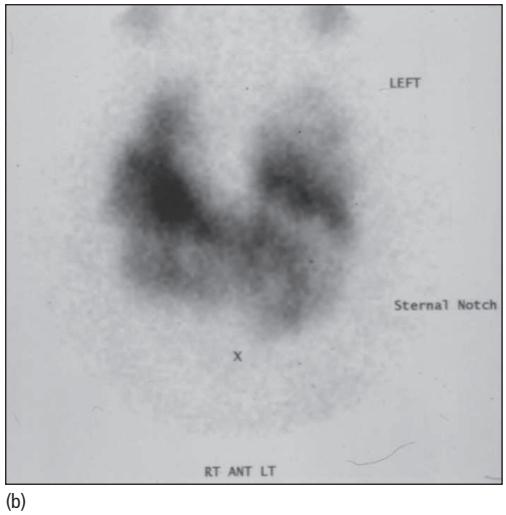
TSH receptor-stimulating antibodies

TSH receptor-stimulating antibodies are positive in Graves' disease. However, this test is expensive, and the aetiology of thyrotoxicosis can often be determined with a combination of thyroid function tests and a radioisotope uptake scan.

Some laboratories measure 'TBII' (TSH-binding inhibitor immunoglobulin). This test shows that there is an antibody that competes with TSH for the TSH receptor, but it does not differentiate between stimulating and blocking antibodies (some patients with Graves' disease have a mixture of stimulating and blocking TSH receptor antibodies).

Antithyroglobulin and antithyroid peroxidase (microsomal) antibodies are present in up to 87% of patients with Graves' disease. However, these have low specificity and are present in 15% of healthy females and 5% of males.

(a)



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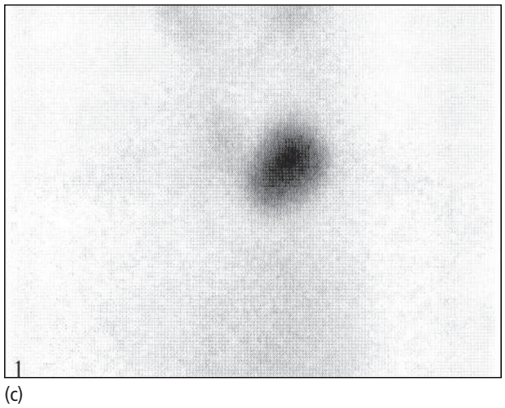

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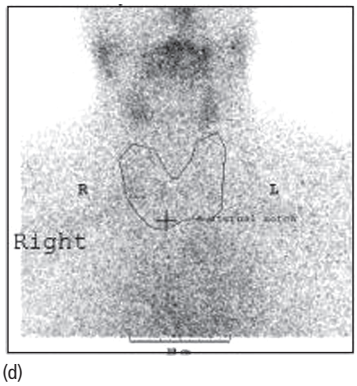

(d)

Figure 3.4 ^{99}Technetium pertechnetate uptake scan: (a) Graves' disease, (b) toxic multinodular goitre, (c) solitary toxic adenoma, and (d) thyroiditis.