11 Thyroid function

Lec. 6

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It is important to understand thyroid biochemistry, as it helps to interpret thyroid function tests, which are among the most common endocrine requests in clinical practice. Thyroid disease is relatively common, and therefore is likely to be encountered clinically.

Briefly, thyroxine (T_4), tri-iodothyronine (T_3) and calcitonin are secreted by the thyroid gland. Both T_4 and T_3 are products of the follicular cells and influence the rate of all metabolic processes. Calcitonin is produced by the specialized C cells and influences calcium metabolism (see Chapter 6).

PHYSIOLOGY

Thyroid hormones are synthesized in the thyroid gland by the iodination and coupling of two molecules of the amino acid tyrosine, a process that is dependent on an adequate supply of iodide. Iodide in the diet is absorbed rapidly from the small intestine. In areas where the iodide content of the soil is very low, there used to be a high incidence of enlargement of the thyroid gland (goitre), but the general use of artificially iodized salt has made this a less common occurrence. Seafoods generally have a high iodide content. Therefore fish and iodized salt are the main dietary sources of the element. Normally about a third of dietary iodide is taken up by the thyroid gland and the rest is renally excreted.

Synthesis of thyroid hormones

Iodide is actively taken up by the thyroid gland under the control of thyroid-stimulating hormone (TSH) via a sodium/iodide symporter. Uptake is blocked by thiocyanate and perchlorate. The concentration of iodide in the gland is at least 20 times that in plasma and may exceed it by 100 times or more.

Iodide is rapidly converted to iodine within the thyroid gland, catalysed by thyroid peroxidase (TPO). Iodination of tyrosine residues in a large 660-kDa glycoprotein, thyroglobulin, takes place to form mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) mediated by the enzyme TPO. This step is inhibited by carbimazole and propylthiouracil.

Iodotyrosines are coupled to form T_4 (DIT and DIT) and T_3 (DIT and MIT) (Fig. 11.1), which are stored in the lumen of the thyroid follicular cells. Normally much more T_4 than T_3 is synthesized, but, if there is an inadequate supply of iodide, the ratio of T_3 to T_4 in the gland increases. The thyroid hormones, still incorporated in thyroglobulin, are stored in the colloid of the thyroid follicle.

Prior to the secretion of thyroid hormones, thyroglobulin is taken up by the follicular cells, by a process involving endocytosis and then phagocytosis, and T_4 and T_3 are released by proteolytic enzymes into the bloodstream. This process is stimulated by TSH and inhibited by iodide. The thyroid hormones are immediately bound to plasma proteins. Mono-iodotyrosine and DIT, released at the same time, are de-iodinated and the iodine is reused.

Each step is controlled by specific enzymes, and congenital deficiency of any of these enzymes can lead to goitre and, if severe, hypothyroidism. The uptake of iodide, as well as the synthesis and secretion of thyroid hormones, is regulated by TSH, secreted from the anterior pituitary gland. About 10 times more T_4 than T_3 is formed, with most of the latter being formed by de-iodination in the liver, kidneys and muscle.

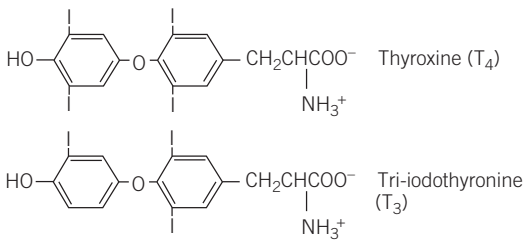

Figure 11.1 Chemical structure of the thyroid hormones.

Protein binding of thyroid hormones in plasma

Most of the plasma T_4 and T_3 is protein bound, mainly (70 per cent) to an α-globulin, thyroxine-binding globulin (TBG), and, to a lesser extent (15 per cent), transthyretin (previously called pre-albumin), with about 10–15 per cent bound to albumin. In keeping with many other hormones, the free unbound fraction is the physiologically active form, which also regulates TSH secretion from the anterior pituitary. Modern laboratory assays tend to measure the free hormones. Changes in the plasma concentrations of the binding proteins, particularly TBG, alter plasma total T_4 and T_3 concentrations, but not the concentrations of free hormones.

Peripheral conversion of thyroid hormone

Some of the circulating T_4 is de-iodinated by enzymes in peripheral tissues, especially in the liver and kidneys. About 80 per cent of the plasma T_3 is produced by the removal of an iodine atom from the outer (β) ring; the remaining 20 per cent is secreted by the thyroid gland. De-iodination of the inner (α) ring produces reverse T_3, which is probably inactive. The T_3 binds more avidly to thyroid receptors than T_4 and is the main active form. The conversion of T_4 to T_3 may be:

- *reduced* by many factors, of which the most important are:
  - systemic illness,
  - prolonged fasting,
  - drugs such as β-blockers, for example propranolol or amiodarone (200 mg of this anti-arrhythmic drug contains about 75 mg of iodine);
- *increased* by drugs that induce hepatic enzyme activity, such as phenytoin.

The plasma T_3 concentration is therefore a poor indicator of thyroid hormone secretion because it is influenced by many non-thyroidal factors and its measurement is rarely indicated, except if thyrotoxicosis is suspected.

Action of thyroid hormones

Thyroid hormones affect many metabolic processes, increasing oxygen consumption. They bind to specific receptors in cell nuclei and change the expression of certain genes. Thyroid hormones are essential for normal growth, mental development and sexual maturation and also increase the sensitivity of the cardiovascular and central nervous systems to catecholamines, thereby influencing cardiac output and heart rate.

Control of thyroid-stimulating hormone secretion

Thyroid-stimulating hormone stimulates the synthesis and release of thyroid hormones from the thyroid gland. Its secretion from the anterior pituitary gland is controlled by thyrotrophin-releasing hormone (TRH) and circulating concentrations of thyroid hormones.

Effect of thyrotrophin-releasing hormone

Pituitary TSH synthesis and release are stimulated by TRH, a tripeptide produced in the hypothalamus and released into the portal capillary plexus. The action of TRH can be over-ridden by high circulating free T_4 (fT_4) concentrations, and therefore exogenous TRH has little effect on TSH secretion in hyperthyroidism (see later for TRH test). Once TRH reaches the pituitary, it binds to TRH receptors, members of the seven-transmembrane-spanning receptor family, which are coupled to G proteins.

Effects of thyroid hormones in the control of thyroid-stimulating hormone secretion

Thyroid hormones reduce TSH secretion by negative feedback. Tri-iodothyronine binds to anterior pituitary nuclear receptors. In the anterior pituitary gland, most of the intracellular T_3 is derived from circulating fT_4. Therefore this gland is more sensitive to changes in plasma T_4 than to T_3 concentrations.

The secretion and control of thyroid hormones is summarized in Figure 11.2.

THYROID FUNCTION TESTS

Assessment of thyroid hormone secretion can be made by measuring plasma TSH as well as either fT_4 or total T_4 [sometimes also free T_3 (fT_3) or total T_3]. Each test has its advantages and disadvantages, although probably most laboratories now offer fT_4 and fT_3 assays rather than total hormone concentrations. Thus, regarding assays this chapter will mainly discuss free hormones.

Plasma thyroid-stimulating hormone

Concentrations of TSH are high in primary hypothyroidism and low in secondary or pituitary hypothyroidism. In hyperthyroidism, high plasma T_4 and T_3 concentrations suppress TSH release from the pituitary, resulting in very low or undetectable plasma TSH concentrations. Plasma TSH assays are used as first-line assays for thyroid function assessment. New-generation assays have high sensitivity and have a detection limit for plasma TSH of less than 0.1 mU/L.

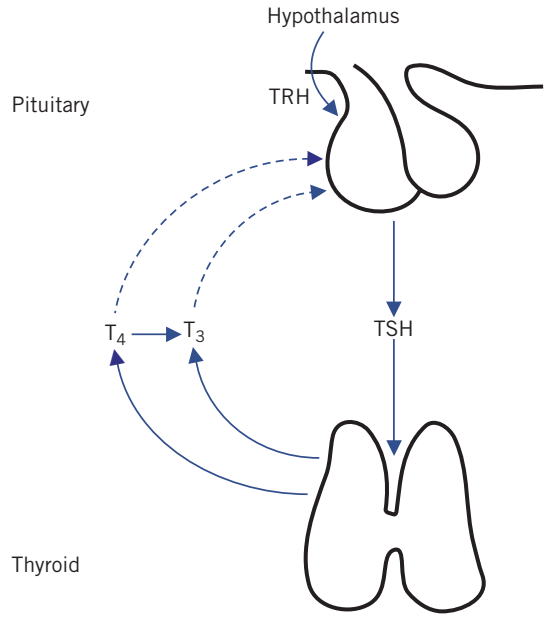

Figure 11.2 Secretion and control of thyroid hormones. Solid lines indicate secretion and interconversion of hormones; dotted lines indicate negative feedback. T_4, thyroxine; T_3, tri-iodothyronine; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone.

In normal individuals there is a log-linear relationship between plasma fT_4 and TSH concentrations; that is to say, exponential increases in TSH concentration occur with small incremental changes in fT_4 concentration.

Plasma total thyroxine or free thyroxine assays

Plasma T_4 is more than 99 per cent protein bound; therefore, plasma total T_4 assays reflect the protein-bound rather than the free hormone fraction. Total T_4 reflects fT_4 concentrations, unless there are abnormalities of binding proteins.

- In the *euthyroid* state, about a third of the binding sites on TBG are occupied by T_4 and the remainder are unoccupied, irrespective of the concentration of the binding protein.
- In *hyperthyroidism*, both plasma total and fT_4 concentrations are increased and the number of unoccupied binding sites on TBG is decreased.
- In *hypothyroidism*, the opposite of the above occurs.

An increase in plasma TBG concentration causes an increase in both bound T_4 and unoccupied binding sites but no change in plasma fT_4 concentrations. Such an increase may occur because of:

- a high oestrogen concentration during pregnancy or in the newborn infant,
- oestrogen therapy, for example certain oral contraceptives or hormone replacement therapy,
- inherited TBG excess (rare).

A decrease in plasma TBG concentration decreases both bound T_4 concentrations and unoccupied binding sites, but does not alter the plasma fT_4 concentration. Such changes may occur because of:

- severe illness, but this is usually temporary,
- loss of low-molecular-weight proteins, usually in the urine, for example nephrotic syndrome,
- androgens or danazol treatment,
- inherited TBG deficiency (rare).

These changes might be misinterpreted as being diagnostic of hyperthyroidism or hypothyroidism respectively if only plasma total T_4 was assayed and it is for this reason that fT_4 concentrations are now generally preferred.

Some drugs, such as salicylates and danazol, bind to TBG and displace T_4. The change in unoccupied binding sites is variable and TBG concentrations are unaffected. Measurement of plasma TBG concentrations may occasionally be indicated to confirm either congenital TBG excess or deficiency.

Plasma total or free tri-iodothyronine

Total T_3 or fT_3 concentrations may help in the diagnosis of hyperthyroidism but are not usually used routinely to diagnose hypothyroidism because normal plasma concentrations are very low. In hyperthyroidism, the increase in plasma T_3 or fT_3 concentrations is greater, and usually occurs earlier than that of T_4 or fT_4.

Occasionally in hyperthyroidism the plasma T_3 or fT_3 concentrations are elevated but not those of T_4 or fT_4 (T_3 toxicosis). Like T_4, T_3 is bound to protein. It is usually preferable to measure the plasma concentration of fT_3 rather than total T_3, as the latter may be altered by changes in the plasma concentrations of TBG.

Thyrotrophin-releasing hormone test

The TRH test is used to confirm the diagnosis of secondary hypothyroidism, or occasionally to diagnose early primary hypothyroidism. Since the development of sensitive TSH assays, it is rarely used to diagnose hyperthyroidism, although it may have a place in the differential diagnosis of thyroid resistance syndrome or TSH-secreting pituitary tumours (TSHomas).

It is sometimes used as part of the combined pituitary stimulation test (see Chapter 7).

Allergic reactions may occur, and therefore resuscitation facilities should be available and the test should be carried out by experienced staff.

Procedure

- A basal blood sample is taken.
- 200 µg of TRH is injected intravenously over about a minute.
- Further blood samples are taken 20 and 60 min after the TRH injection, and TSH is measured in all samples.

Note that certain drugs, such as dopamine agonists and glucocorticoids, reduce the response, and oestrogens, metoclopramide and theophylline enhance it.

Interpretation

In normal subjects, plasma TSH concentration increases at 20 min by at least 2 mU/L and exceeds the upper limit of the reference range, with a small decline at 6 min.

- An exaggerated response at 20 min and a slight fall at 60 min are suggestive of primary hypothyroidism.
- A normal or exaggerated increment but delayed response, with plasma TSH concentrations higher at 60 min than at 2 min, suggests secondary hypothyroidism. If clinically indicated, pituitary and hypothalamic function should be investigated.
- A flat response of TSH of less than 5 mU/L is compatible with primary hyperthyroidism, although this may also occur in some euthyroid patients with multinodular goitre.

Drug effects on thyroid function tests

Drugs may alter plasma T_4 and T_3 concentrations. The more common effects are summarized in Table 11.1. If the primary change is in binding protein concentrations, plasma free hormone concentrations are usually normal.

Interference of assays by immunoglobulins

Anti-T_4 or anti-T_3 immunoglobulins or heterophilic antibodies (induced by external antigens, e.g. derived from other species that cross-react with self-antigens) can cause a spurious elevation of T_4 or T_3 (or free hormones), respectively, when assayed by immunoassay. This needs to be remembered when interpreting thyroid function test results.

DISORDERS OF THE THYROID GLAND

The most common presenting clinical features of thyroid disease are the result of:

- *hypothyroidism*, due to deficient thyroid hormone secretion,
- *hyperthyroidism*, due to excessive thyroid hormone secretion,
- *goitre*, either diffuse or due to one or more nodules within the gland – there may or may not be abnormal thyroid hormone secretion and thus the patient may be euthyroid.

Hypothyroidism

Hypothyroidism is caused by suboptimal circulating concentrations of thyroid hormones. It becomes more

Table 11.1 Drug effects on thyroid function tests

Drug	T_4	fT_4	T_3	fT_3	Remarks
Amiodarone	↑	Normal or ↑	Normal	Normal	Blocking T_4 to T_3 conversion
Androgens	↓	Normal	↓	Normal	Reduced TBG
Carbamazepine	↓	↓	Normal	Normal	Increased T_4 to T_3 conversion
Carbimazole	↓	↓	↓	↓	Therapeutic if thyrotoxic
Lithium	↓	↓	↓	↓	Lithium may inhibit iodination
Estrogens	↑	Normal	↑	Normal	Increased TBG
Phenytoin	↓	↓	Normal	Normal	Increased T_4 to T_3 conversion
Propranolol	Normal	Normal	↓	↓	Blocking T_4 to T_3 conversion
Propylthiouracil	↓	↓	↓	↓	Therapeutic if thyrotoxic
Salicylate	↓	Normal	↓	Normal	Reduced TBG binding
Some radiocontrast media	↑	Normal	↓	Normal or ↓	Blocking T_4 to T_3 conversion (transient effect)

T_4, thyroxine; T_3, tri-iodothyronine; fT_4, free thyroxine; fT_3, free tri-iodothyronine; TBG, thyroxine-binding globulin.

CASE 1

A 57-year-old woman consulted her general practitioner because of weight gain, constipation and weakness. The following thyroid function test results were returned:

Plasma thyroid-stimulating hormone (TSH) 54.6 mU/L (0.20–5.0)
Free thyroxine (fT_4) 5.7 pmol/L (12–25)

DISCUSSION

The results show primary hypothyroidism with high plasma TSH and low fT_4 concentrations. The symptoms are typical of hypothyroidism. The patient was also shown to have positive thyroid antibodies (anti-thyroid peroxidase). The thyroid function tests normalized on treatment with 100 µg a day of thyroxine.

prevalent with age, affecting about 6 per cent of people over 60 years, and is more common in women.

The condition may develop insidiously and in its early stages may cause only vague symptoms. There is a generalized slowing down of metabolism, with lethargy, bradycardia, depression and weakness.

If the hormone deficiency is caused by a primary disorder of the thyroid gland, the patient may present with weight gain, myopathy, menstrual disturbances, such as menorrhagia, and constipation. The skin may be dry, the hair may fall out and the voice may be hoarse. Subcutaneous tissues are thickened; this pseudo-oedema, with a histological myxoid appearance, accounts for the term myxoedema, which is sometimes used to describe advanced hypothyroidism. In severe cases, coma with profound hypothermia may develop.

The following laboratory changes may be associated with hypothyroidism, particularly if severe:

- Plasma cholesterol concentration. In hypothyroidism the clearance of plasma low-density lipoprotein (LDL) cholesterol is impaired and plasma cholesterol concentrations may be moderately high.
- Plasma creatine kinase activity is often raised in hypothyroidism, due to possible myopathy.
- Hyponatraemia may very rarely present in patients with profound hypothyroidism or myxoedema coma. It is caused by increased antidiuretic hormone release with excessive water retention, occasionally worsened by a constrictive pericardial effusion that some patients develop.
- Hypothyroidism may be associated with hyperprolactinaemia.
- Plasma sex-hormone-binding globulin (SHBG) concentration is reduced in hypothyroidism.
- A macrocytic anaemia may be observed, with raised mean corpuscular volume (MCV).
- In severe hypothyroidism a reduced estimated glomerular filtration rate may occur probably due to impaired renal perfusion.

The most common cause of hypothyroidism worldwide is iodine deficiency. In areas of adequate iodine intake, acquired hypothyroidism is mainly due to autoimmune thyroiditis or Hashimoto's thyroiditis, which is more frequently seen in women and the elderly. About 90 per cent of patients have positive thyroid antibodies, for example anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg) or TSH receptor-blocking antibodies. There may also be a goitre. Hypothyroidism may also be associated with other autoimmune diseases such as type 1 diabetes mellitus, adrenal insufficiency and pernicious anaemia.

Rare causes of primary hypothyroidism are exogenous goitrogens (substances that interfere with thyroid iodine uptake and thus can result in a goitre) and dyshormonogenesis, a term that includes inherited deficiencies of any of the enzymes involved in thyroid hormone synthesis, which may present in childhood. Although the biochemical and clinical features differ, the end result is hypothyroidism. In most cases, prolonged TSH stimulation, due to reduced negative feedback, causes goitre. The most common form is due to failure to incorporate iodine into tyrosine. The perchlorate discharge test may be useful to diagnose iodination and trapping defects, although it is rarely used.

Secondary hypothyroidism is due to low concentrations of TSH from the anterior pituitary or to hypothalamic TRH deficiency; this is much less common than primary hypothyroidism. In long-standing secondary hypothyroidism, the thyroid gland may atrophy irreversibly. The essential biochemical difference between primary and secondary hypothyroidism is in the plasma TSH concentration, which is high in the former and inappropriately low in the latter

Very rarely a 'consumption' hypothyroidism is seen in individuals with extensive haemangioma which contains iodothyronine deiodinase. This

selenoenzyme catalyses the conversion of T_4 to reverse tri-iodothyronine and the conversion of T_3 to 3,3′-di-iodothyronine, both of which are biologically inactive.

Pathophysiology

As primary hypothyroidism develops, TSH secretion from the anterior pituitary gland increases as the negative feedback (associated with the falling plasma T_4 or fT_4 concentration) decreases. Plasma T_3 or fT_3 concentrations may be normal and thus not usually useful in making the diagnosis.

Generally in primary hypothyroidism the plasma TSH concentration is high, but it is low in secondary hypothyroidism due to pituitary or hypothalamic disease. Initially, the plasma T_4 or fT_4 concentration may be within the population reference range, although abnormally low for the individual. For this reason the plasma TSH concentration is the most sensitive index of early hypothyroidism. If the patient is very ill, investigations should be deferred (see 'Sick euthyroid' below).

Pregnancy and neonatal hypothyroidism

In about 0.3 per cent of pregnancies the mother has Hashimoto's disease. Thyroid hormones are essential for fetal development, hence the importance of treating the mother with thyroxine.

Routine screening for congenital hypothyroidism (Fig. 11.3) is discussed in Chapters 26 and 27.

Treatment of hypothyroidism

This is usually with T_4, which can be titrated until the plasma TSH is within the reference range. However, this has recently been challenged, as plasma TSH concentrations may not adequately reflect tissue hypothyroidism, and it may be better to be guided by plasma fT_4 concentrations and clinical features. On rare occasions, such as in hypothyroid comas, T_3 is given instead, as its action is more immediate. The response to T_4 therapy can be checked every 2–3 months until the patient is stable, after which 6- to 12-month blood checks may be useful.

Thyroxine should be used with caution in patients with ischaemic heart disease for fear of worsening angina pectoris, and low doses initially plus β-blockers may be indicated. Thyroid-stimulating hormone assays are of little value in monitoring secondary hypothyroidism; fT_4 is better. Thyroxine therapy may precipitate an Addisonian crisis in patients with concomitant adrenal insufficiency. Overtreatment with T_4 can evoke atrial fibrillation and osteoporosis; in such cases, plasma TSH concentrations are often low or suppressed.

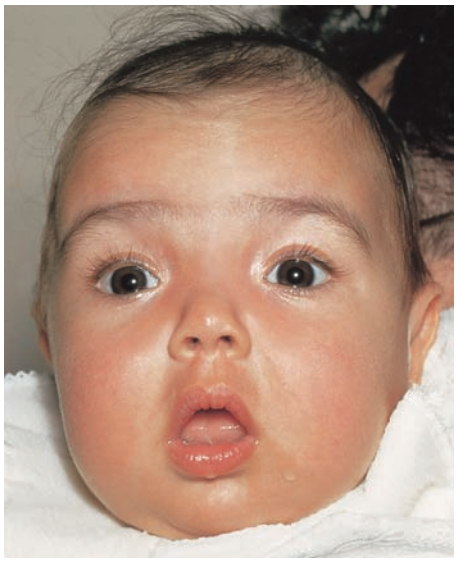

Figure 11.3 Congenital hypothyroidism. The head is broad, the eyes wide apart, the tongue protrudes from the mouth and all movements and responses are slow and sluggish. Reproduced with kind permission from Browse NL, Black J, Burnand KG and Thomas WEG (eds). *Browse's Introduction to the Symptoms and Signs of Surgical Disease, 4th edition*. London: Hodder Arnold, 2005.

If a patient is non-compliant with treatment and only takes T_4 near to the time of thyroid function testing, a high plasma TSH may be observed with high plasma fT_4 concentrations. This is because there is insufficient T_4 to normalize plasma TSH, and yet the high plasma fT_4 reflects the recent taking of T_4.

Subclinical hypothyroidism

Subclinical (compensated hypothyroidism) is the state in which plasma TSH concentration is raised but the total or fT_4 concentration still falls within the reference range. In individuals over the age of 60 years, the prevalence may be as high as 10 per cent. Some of these patients have positive thyroid antibodies, for example anti-TPO or anti-Tg, and each year about 2–5 per cent of thyroid antibody-positive patients go on to develop hypothyroidism.

Some patients may be asymptomatic, whereas others have symptoms suggestive of hypothyroidism. Thyroxine therapy may be indicated particularly in pregnancy, when the patient is symptomatic, or with positive thyroid antibodies and plasma TSH more than 10 mU/L. It can be associated with increased risk of cardiovascular disease.

Thyroid hormone resistance

In generalized thyroid hormone resistance, the plasma total T_4 and fT_4 concentrations are elevated, with normal or slightly raised TSH concentration. Some patients appear euthyroid, but others may present with hypothyroid symptoms, and the defect may be inherited as an autosomal dominant trait in some patients. The defect is thought to be due to a defect in T_4 and/or T_3 receptors and may be associated with other end-organ resistance states.

Laboratory investigation of suspected hypothyroidism

A careful history (including drugs) should be taken and an examination performed, checking for a goitre.

- The plasma TSH and total T_4 or fT_4 concentrations should be measured.
- Slightly elevated plasma TSH and normal fT_4 concentrations suggest compensated hypothyroidism. Measuring circulating thyroid antibodies may be useful, that is, anti-TPO. Tests should be repeated after 3–6 months as some patients may develop full-blown hypothyroidism.
- Raised plasma TSH and low fT_4 concentrations suggest primary hypothyroidism. The thyroid antibodies should be measured and, if positive, other autoimmune diseases excluded.
- Low plasma TSH and low fT_4 concentrations may indicate that the hypothyroidism is caused by a hypothalamic or pituitary disorder. A TRH test should be done, if indicated, and the pituitary gland assessed (see Chapter 7).
- Raised plasma TSH and raised/normal plasma fT_4 concentrations in the presence of hypothyroid symptoms may indicate thyroid hormone resistance.

Some causes of hypothyroidism are shown in Box 11.1.

CASE 2

A 49-year-old woman was investigated in the medical out-patient department for tiredness. The following test results were returned:

Plasma thyroid-stimulating hormone (TSH) 10.6 mU/L (0.20–5.0)
Free thyroxine (fT_4) 13.9 pmol/L (12–25)

DISCUSSION

These results are suggestive of compensated hypothyroidism, in which the plasma TSH concentration is raised and the fT_4 concentration still remains within the reference range. The patient also had positive thyroid antibodies (anti-thyroid peroxidase). A trial of thyroxine of 50 µg a day brought her plasma TSH concentration to within the reference range and improved her symptoms.

Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism causes sustained high plasma concentrations of T_4 and T_3. There is often generalized increase in the metabolic rate, evidenced clinically by, for example, heat intolerance, a fine tremor, tachycardia including atrial fibrillation, weight loss, tiredness, anxiety, sweating and diarrhoea.

The following biochemical features may be associated with hyperthyroidism:

- Hypercalcaemia is occasionally found in patients with severe thyrotoxicosis. There is an increased turnover of bone cells, probably due to a direct action of thyroid hormone.

Box 11.1 Some causes of hypothyroidism

Primary hypothyroidism
Iodine deficiency
Autoimmune thyroid disease
- Hashimoto's disease
- Subacute thyroiditis
- Transient subacute thyroiditis (de Quervain's)

Following treatment of hyperthyroidism
- Post thyroidectomy
- Post radioiodine treatment

External irradiation to neck region
Surgery or trauma to neck
Defects of thyroid hormone synthesis
Congenital absence of thyroid gland
Infiltrative disease of the thyroid, e.g. sarcoid, haemochromatosis, fibrosis (Riedel's struma)
Drugs
- Carbimazole
- Propylthiouracil
- Amiodarone
- Lithium
- Interferon-α
- Tyrosine kinase inhibitors

Secondary hypothyroidism
Pituitary or hypothalamic disease
Drugs: bexarotene

Thyroid hormone resistance
Generalized thyroid resistance

- Hypocholesterolaemia can occur, due to increased LDL clearance.
- Hypokalaemia may also occur, associated with hyperthyrotoxic periodic paralysis.
- Plasma SHBG is increased.
- Plasma creatine kinase may be increased with thyrotoxic myopathy.

Some causes of hyperthyroidism are shown in Box 11.2.

Graves' disease

This is the most common form of thyrotoxicosis and occurs more often in females than in males. It may be caused by relatively autonomous secretion from a diffuse goitre and is characterized by:

- exophthalmos, due to lymphocytic infiltration and swelling of retro-orbital tissues of the eyes (Fig. 11.4),
- sometimes localized thickening of the subcutaneous tissue over the shin (pretibial myxoedema).

Graves' disease is an autoimmune thyroid disease characterized by a variety of circulating antibodies, including anti-TPO, as well as being associated with other autoimmune diseases such as type 1 diabetes mellitus, adrenal insufficiency and pernicious anaemia. Thyroid antibodies are detectable in some cases, such as thyroid-stimulating immunoglobulin (TSI), which is directed towards epitopes of the TSH receptor and thus acts as a TSH receptor agonist. Nuclear medicine tests may show a high radioactive uptake of iodine by the thyroid gland.

Subacute thyroiditis

This is a destructive thyroiditis resulting in the release of preformed thyroid hormones. There are three subtypes: granulomatous or painful, lymphocytic or silent and painless, and post-partum. This condition is associated with extremely elevated thyroid hormones and no radioactive iodine uptake by the thyroid gland. The clinical course progresses through 6–8 weeks of thyrotoxicosis, 2–4 months of hypothyroidism and a return to euthyroidism in about 90 per cent of patients.

The painful or granulomatous variety is thought to be a viral disease and is associated with human leucocyte antigen (HLA)-Bw35. The lymphocytic variety is autoimmune, as is post-partum thyroiditis. The post-partum form occurs in about 5–8 per cent of pregnant women in Europe and the USA, but in 20 per cent in Japan. Treatment is supportive, as in many cases the condition is self-limiting.

Box 11.2 Some causes of hyperthyroidism

Autonomous secretion
Graves' disease
Toxic multinodular goitre (Plummer's disease) or a single functioning nodule (occasionally an adenoma)
Subacute thyroiditis
Some metastatic thyroid carcinomas

Excessive ingestion of thyroid hormones or iodine
Amiodarone
Thyrotoxicosis factitia (self-administration of thyroid hormones)
Administration of iodine to a subject with iodine-deficiency goitre
Jod–Basedow syndrome

Rare causes
Thyroid-stimulating hormone secretion by tumours, including pituitary tumours or those of trophoblastic origin
Struma ovarii (thyroid tissue in an ovarian teratoma)
Excess human chorionic gonadotrophin, e.g. molar pregnancy or choriocarcinoma
Pituitary resistance to thyroid hormone

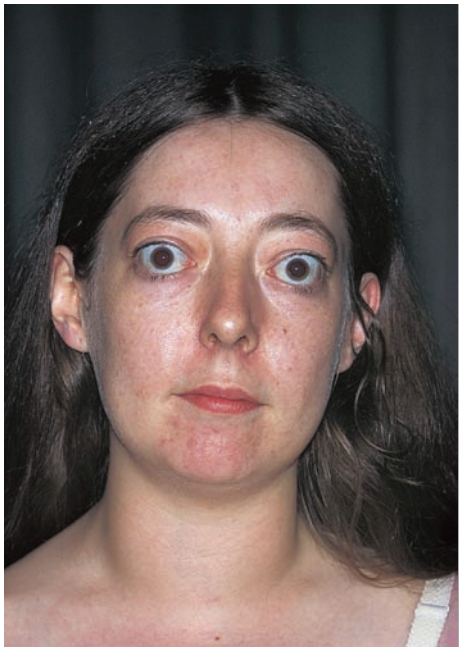

Figure 11.4 A patient with primary hyperthyroidism. Note exophthalmos and diffuse thyroid swelling. Reproduced with kind permission from Kinirons M and Ellis H. *French's Index of Differential Diagnosis*, 15th edition. London: Hodder Arnold, 2011.

CASE 3

A 29-year-old woman was seen in the thyroid clinic because of exophthalmos and a goitre. She had the following thyroid function test results:

Plasma thyroid-stimulating hormone (TSH) < 0.05 mU/L (0.20–5.0)
Free thyroxine (fT_4) 68.8 pmol/L (12–25)
Free tri-iodothyronine (fT_3) 18.7 pmol/L (3–7)

DISCUSSION

The patient had biochemical results typical of hyperthyroidism. In fact she had Graves' disease and was shown to have positive thyroid-stimulating immunoglobulins and increased diffuse radiolabelled iodine uptake by the thyroid gland.

Compare these results with those of another patient (a 54-year-old woman) in the same clinic:

Plasma TSH < 0.05 mU/L (0.20–5.0)
Free T_4 18.1 pmol/L (12–25)
Free T_3 14.4 pmol/L (3–7)

Here, the plasma fT_4 concentration is within the reference range, but the plasma fT_3 concentration is raised, with suppressed plasma TSH concentration, suggesting T_3 thyrotoxicosis.

Toxic nodules

Toxic nodules, either single or multiple, in a nodular goitre may secrete thyroid hormones autonomously. The secretion of TSH is suppressed by negative feedback, as in Graves' disease. The nodules may be detected by their uptake of radioactive iodine or technetium, with suppression of uptake in the rest of the thyroid tissue ('hot nodules'). Toxic nodules are found most commonly in older patients, who may present with only one of the features of hyperactivity, usually cardiovascular symptoms such as atrial fibrillation. Toxic multinodular goitre is also called Plummer's disease.

Rare hyperthyroid states

Jod–Basedow syndrome is hyperthyroidism in patients with excess iodide intake, for example from the diet or from iodine-containing contrast medium. High iodine intake may be assessed by urinary iodide assay. Metastatic thyroid carcinoma can produce thyroid hormones. In struma ovarii, ectopic thyroid tissue is found in dermoid tumours or ovarian teratomas. Patients with choriocarcinoma or molar hydatidiform pregnancy have extremely high concentrations of β-human chorionic gonadotrophin that can activate the TSH receptor. Rarely, the pituitary tumour releases TSH, resulting in thyrotoxicosis.

Pathophysiology of hyperthyroidism

Plasma T_4 or fT_4 and T_3 and fT_3 concentrations are usually increased in hyperthyroidism. Much of the T_3 is secreted directly by the thyroid gland, and the increase in plasma T_3 concentrations is greater, and usually evident earlier, than that of T_4. Rarely, only plasma T_3 and fT_3 concentrations are elevated (T_3 toxicosis). In both situations, TSH secretion is suppressed by negative feedback, and plasma TSH concentrations are either very low or undetectable.

Treatment

The aetiology of hyperthyroidism must be fully investigated and treatment started. Various forms of treatment are available, the selection of which depends on the cause, the clinical presentation and the age of the patient. β-blocker drugs such as propranolol, which inhibit the peripheral conversion of T_4 to T_3, may be used initially. Additional treatment includes the use of such drugs as carbimazole or propylthiouracil. Carbimazole inhibits the synthesis of T_3 and T_4; propylthiouracil additionally inhibits T_4 to T_3 conversion. Some clinicians use block-and-replace regimens: carbimazole is used to 'block' thyroid secretion, and simultaneous exogenous T_4 maintains and replaces T_4 concentrations. It is important to remember that carbimazole can have the potentially lethal side effect of bone marrow suppression, and patients should be warned about infections such as sore throats and about the need to have their full blood count monitored.

Radioactive iodine can be used in resistant or relapsing cases; surgery is rarely indicated, but may have a place if there is a large toxic goitre that is exerting pressure or if drug therapy fails but radioactive iodine is contraindicated. Thyroid function must be checked regularly, as some patients may become hypothyroid or may relapse after radioiodine or surgery.

The progress of a patient being treated for hyperthyroidism is usually monitored by estimating plasma TSH, fT_4 and fT_3 concentrations, and trying to restore these to normal (although TSH concentration may be slow to normalize). Overtreatment may induce hypothyroidism, with a rise in plasma TSH

concentrations and low plasma T_4/fT_4 and T_3/fT_3 concentrations. In some patients with severe prolonged hyperthyroidism, such a rise in plasma TSH may be delayed because of the effects of prolonged feedback suppression of T_4 on the pituitary.

Subclinical hyperthyroidism

Subclinical hyperthyroidism may occur with a low or suppressed TSH concentration but normal (usually high-normal) plasma fT_4 and fT_3 concentrations. The condition may progress to full-blown hyperthyroidism with suppressed plasma TSH and raised plasma fT_4 and fT_3 concentrations. Subclinical hyperthyroidism may be associated with atrial fibrillation, decreased bone mineral density and other features of hyperthyroidism. Plasma TSI may be raised.

Laboratory investigation of suspected hyperthyroidism

A careful history (including drugs) should be taken and examination performed, checking for a goitre. The plasma TSH, fT_3 and fT_4 concentrations should be measured.

- The plasma fT_4 and fT_3 concentrations are clearly high and the TSH concentration is suppressed in clinically thyrotoxic patients.
- In the face of suppressed plasma TSH, a clearly elevated plasma fT_3 concentration confirms the diagnosis of hyperthyroidism. Remember that in T_3 thyrotoxicosis the plasma fT_4 may be normal.
- If the plasma fT_4 concentration is raised and the TSH concentration is normal, this is suggestive of biochemical euthyroid hyperthyroxaemia (see below for causes).
- Measurement of thyroid antibodies is useful, particularly if the concentration of TSIs is raised, which supports a diagnosis of Graves' disease.
- The rare TSH-secreting pituitary tumours need pituitary assessment (see Chapter 7). α-subunit concentrations may be useful, as they are usually raised in such circumstances.
- In difficult cases, determination of plasma SHBG concentration can help decide whether the patient is hyperthyroid, as it is lowered in hypothyroidism and raised in hyperthyroidism.
- Radioiodine uptake studies of the thyroid can be useful to distinguish some of the causes of hyperthyroidism (see Box 11.2).
- The TRH test is sometimes useful in the diagnosis of unclear cases.

Euthyroid goitre

If plasma T_4 concentrations fall, enlargement of the thyroid gland (goitre) may be caused by TSH stimulation resulting in cellular hyperplasia. Thyroxine synthesis may be impaired by iodide deficiency, caused by drugs such as para-aminosalicylic acid, or possibly by partial deficiency of the enzymes involved in T_4 synthesis. Under the influence of prolonged stimulation by TSH, the number of thyroid cells increases and plasma thyroid hormone concentrations are maintained at the expense of the development of a goitre.

Inflammation of the thyroid gland (thyroiditis), whether acute or subacute, may produce marked but temporary aberrations of thyroid function tests (see above). Ultrasound scanning can be useful in the diagnosis of goitre, as can radiolabelled uptake studies to see if there are hot (T_4-producing) or cold (non-producing) nodule(s).

'Sick euthyroid'

Any severe illness may be associated with low plasma total or fT_4 concentrations and may make the interpretation of thyroid function tests extremely difficult. Plasma TSH concentrations may be normal or slightly high or low. The TSH response to TRH may also be impaired. There may be impaired conversion of T_4 to T_3 with low plasma T_3 concentrations. Consequently, the assessment of thyroid function is best deferred until the patient has recovered from the illness.

Euthyroid hyperthyroxinaemia

This is defined as a condition in which either the plasma total or fT_4 concentration is abnormally raised without clinical evidence of thyroid disease. These changes may be transient or persistent, with high, normal or low total or fT_3 concentrations. Heterophilic antibodies to fT_4 and/or fT_3 should be excluded [these can sometimes be removed by the laboratory by treating the sample with polyethylene glycol (PEG), which can precipitate these antibodies], as they can interfere with some assays.

Causes

- Physiological conditions resulting in raised plasma TBG concentration, for example pregnancy. Concentrations of total T_4 and T_3 are both elevated, but there are usually normal fT_4 and fT_3 concentrations.
- TBG concentration is raised in newborn babies.
- Hereditary causes:
  - hereditary TBG excess is X-linked,
  - hereditary transthyretin excess,

  - familial dysalbuminaemic hyperthyroxinaemia (FDH) due to an abnormal form of albumin.
- Drugs causing hyperthyroxinaemia:
  - oestrogens raise TBG concentration, as do 5-fluorouracil, heroin and methadone,
  - amiodarone blocks conversion of T_4 to T_3, resulting in an elevation of T_4 and reverse T_3 concentrations,
  - heparin, due to fatty acid release, inhibits fT_4 binding to TBG,
  - propranolol inhibits extrathyroidal conversion of T_4 to T_3.
- Some patients with certain illnesses, for example hyperemesis gravidarum, have low total and fT_3 concentrations due to reduced peripheral conversion of T_4 to T_3 because 5-deiodinase is inhibited. This results in elevated total T_4 and fT_4 concentrations. Some hepatic disorders, including acute hepatitis, result in raised concentrations of TBG and T_4 and fT_4. In up to 10 per cent of cases of acute psychosis, total and fT_4 concentrations are raised. The exact mechanism is unknown, but it may be due to central activation of the hypothalamic–pituitary axis.

Amiodarone and thyroid function

Amiodarone is sometimes used to treat certain cardiac arrhythmias. This drug can evoke hypothyroidism, partly because it interrupts the conversion of T_4 to T_3. However, it contains iodine and can also evoke thyrotoxicosis by the Jod–Basedow or type 1 phenomenon. Conversely, it may elicit disruptive thyroiditis and thyrotoxicosis with raised interleukin-6 concentration (type 2 phenomenon). The drug has a long half-life (40–100 days) and thus takes a long time to clear from the body (see Chapter 25).

STRATEGY FOR THYROID FUNCTION TESTING AND INTERPRETATION

- A first-line test for thyroid function (as stated above) is plasma TSH, although this can be difficult to interpret in the absence of fT_4. (Sometimes fT_3 is also required, particularly if hyperthyroidism is suspected – Table 11.2.)
- If the plasma TSH concentration is *normal* and the patient is clinically euthyroid, look at plasma fT_4:
  - If fT_4 concentration is low, consider sick euthyroid/non-thyroidal illness, certain drugs, such as carbamazepine or phenytoin (see Table 11.1).
  - If fT_4 concentration is also normal, thyroid function is likely to be normal.
  - If fT_4 concentration is high, consider euthyroid hyperthyroxinaemia, interfering assay autoantibodies.
- If the plasma TSH concentration is *low*, look at plasma fT_4:
  - If fT_4 concentration is low, consider sick euthyroid/non-thyroid illness, pituitary or hypothalamic disease (secondary hypothyroidism?), certain drugs (see Table 11.1).
  - If fT_4 concentration is normal, consider sick euthyroid/non-thyroid illness, subclinical hyperthyroidism, particularly if clinically hyperthyroid, certain drugs, such as glucocorticoids and dopamine that may affect TSH, fT_3 toxicosis (fT_3 concentration is raised).
  - If fT_4 concentration is high, consider hyperthyroidism (see Box 11.2), drugs such as amiodarone (see Table 11.1), iodine excess, hyperemesis gravidarum, molar pregnancy, activating TSH receptor mutations.

CASE 4

A 45-year-old man was on the coronary care unit the day after an acute myocardial infarction. One of his doctors thought that he looked hypothyroid and requested thyroid function tests, the results of which were as follows:

Plasma thyroid-stimulating hormone (TSH) < 0.05 mU/L (0.20–5.0)
Free thyroxine (fT_4) 10.1 pmol/L (12–25)
Free tri-iodothyronine (fT_3) 1.4 pmol/L (3–7)

On repeating the tests 3 months later at a follow-up appointment in the medical out-patient department, the following results were obtained:

Plasma TSH 2.3 mU/L (0.20–5.0)
Free T_4 18.1 pmol/L (12–25)
Free T_3 4.5 pmol/L (3–7)

DISCUSSION

The first set of results could indicate hypothyroidism due to pituitary or hypothalamic defects (secondary hypothyroidism), that is, low TSH and 'normal' fT_4 and fT_3 concentrations. However, the normalization of the results when the patient was not acutely ill suggested sick euthyroidism or non-thyroidal illness. Beware of requesting thyroid function tests in acutely ill patients.

Table 11.2 Interpretation of thyroid function tests

	Total T_4	Total T_3	fT_4	fT_3	TBG	TSH
Euthyroid	Normal	Normal	Normal	Normal	Normal	Normal
Hyperthyroid	↑	↑	↑	↑	Normal	↓ if primary
						↑ if secondary
T_3 toxicosis	Normal	↑	Normal	↑	Normal	↓
Hypothyroid	↓	↓	↓	↓	Normal	↑ if primary
						↓ if secondary
TBG excess	↑	↑	Normal	Normal	↑	Normal
TBG deficiency	↓	↓	Normal	Normal	↓	Normal
T_4 displacement by drug	↓	Normal	Normal/↓	Normal	Normal	Normal

T_4, thyroxine; T_3, tri-iodothyronine; fT_4, free thyroxine; fT_3, free tri-iodothyronine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

- If the plasma TSH concentration is *high*, look at plasma fT_4:
  - If fT_4 concentration is low, consider primary hypothyroidism (see Box 11.1).
  - If fT_4 concentration is normal, consider compensated hypothyroidism, inadequate thyroid replacement for hypothyroidism, drugs such as metoclopramide or domperidone, or sick euthyroid.
  - If fT_4 concentration is high, consider generalized thyroid hormone resistance, TSH-secreting tumour, interfering assay antibodies.

SUMMARY

- Thyroid-stimulating hormone from the anterior pituitary acts upon the thyroid gland to release two iodine-containing hormones, T_4 and T_3. The latter is more active and can also be produced from T_4 peripherally. These hormones are essential for normal growth and development and increase basal metabolic rate.
- Both T_4 and T_3 are bound to proteins, including TBG, albumin and transthyretin. Only the free or unbound form is physiologically active, although this fraction constitutes less than 1 per cent of the total hormone concentration.
- Thyroid disease is relatively common. Hypothyroidism can be primary or secondary and manifest as weight gain, tiredness and constipation – to name but a few of its clinical features. Hyperthyroidism causes thyrotoxicosis associated with weight loss, sweating and sometimes thyroid eye disease. Both can present with a goitre, although some patients with a goitre may be euthyroid (normal thyroid function tests).