Endocrine system 3: thyroid and parathyroid glands

Key points

- The thyroid is in the neck, just below the Adam's apple, and contains four tiny, independently functioning, parathyroid glands.
- Thyroid follicular cells secrete iodine-rich hormones, T3 and T4, which help regulate metabolism.
- Release of T3 and T4 is modulated by hypothalamus and pituitary gland hormones.
- Hypothyroidism and hyperthyroidism are common thyroid disorders, often treatable with drugs or radioactive iodine therapy.
- Calcitonin produced by the thyroid works antagonistically with parathyroid hormone to maintain calcium homeostasis.

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Abstract

The endocrine system comprises glands and tissues that produce hormones to regulate and coordinate vital bodily functions. This article, the third in an eight-part series on the endocrine system, examines the anatomy and physiology of the thyroid and parathyroid glands, and the pathophysiology associated with some common thyroid diseases.

Citation


In this article...

- How thyroid hormones T3 and T4 act to regulate cellular metabolism
- Clinical features of hypothyroidism and hyperthyroidism
- The role of the thyroid and parathyroid glands in maintaining calcium homeostasis

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His eight-part series on the endocrine system opened with an overview of endocrine glands and the role of hormones as chemical signals that help maintain the homeostatic balance that is essential to health; the remaining articles each explore different major endocrine glands and tissues. The second article in the series focused on the hypothalamus and pituitary gland. In this third article, we explore the anatomy and physiology of the thyroid and parathyroid glands, and the pathophysiology associated with some common thyroid diseases.

Thyroid gland

Anatomy

The thyroid is a bi-lobed gland, often described as resembling a butterfly or bow tie. It is positioned in the neck, between the C5 and T1 vertebrae, just below the thyroid cartilage (Adam's apple) of the larynx. It consists of two major lobes (right and left), which are connected by a smaller piece of tissue called the isthmus; around half of individuals also possess an additional third lobe, usually triangular shaped and known as the pyramidal lobe (Fig 1). The weight of the adult thyroid gland varies between 15g and 30g, and each of the major lobes is around 4cm long and 2cm wide (Benvenga et al, 2018; Dorion, 2017). Embedded in the posterior portion of the thyroid are four tiny parathyroid glands, which function independently of the thyroid (Fig 1).

Histology

The thyroid contains two major populations of endocrine cells:
- Follicular cells – each major lobe of the thyroid consists of smaller lobules that are composed of sac-like follicles (Fig 2). The walls of each follicle primarily consist of cube-shaped cells. These synthesise and secrete iodine-rich hormones that regulate metabolism.
- Parafollicular cells – these are found in much smaller numbers, interspersed between the thyroid follicles, and synthesise calcitonin, a hormone that helps maintain calcium homeostasis.

Thyroid hormones: T3 and T4

The follicular cells of the thyroid produce two iodine-containing hormones, called T3 and T4 (also known as thyroxine). Each
smaller amounts present in potato skins, watercress, kale, green beans, cranberries, strawberries and most types of nut. Many people supplement their iodine intake with combined multivitamin and mineral preparations or iodised table salt. The current recommended daily intake (reference intake) of iodine for adults is 140-150µg, rising to 200µg in women who are pregnant or breastfeeding (Bit.ly/NHSIodine; Bit.ly/BDAIodine).

Around 90% of dietary iodine is rapidly absorbed in the stomach and duodenum before circulating in the blood (Leung et al, 2010). The majority of plasma iodine is taken up by the thyroid gland and any excess is eliminated efficiently by the kidneys. The follicular cells of the thyroid are equipped with transporter proteins in their cell membranes; these facilitate rapid uptake of iodine, which is then joined to a large protein called thyroglobulin. This iodised thyroglobulin is stored and concentrated in the centre of the thyroid follicles, where it forms the major component of a homogenous suspension called colloid (Fig 2).

Thyroglobulin is rich in the amino acid tyrosine, which provides the substrate for the biosynthesis of thyroid hormones T3 and T4. These thyroid hormones are composed of two molecules of tyrosine linked together, containing three (T3) or four (T4) atoms of iodine (Fig 3). When T3 and T4 are required, small droplets of iodised thyroglobulin are taken back into the follicular cells from the central colloid. The thyroglobulin is digested by intracellular enzymes to release individual molecules of T3 and T4 (Benvenga et al, 2018; Leung et al, 2010).

Like all endocrine glands, the thyroid is highly vascularised and T3 and T4 are released directly into the blood. Proportionally, the thyroid gland releases approximately 80% T4 and 20% T3, although it is estimated that T3 has around four times the potency of T4 (Sargis, 2019). Both hormones have very low solubility in the aqueous environment of the plasma so are transported around the body bound to plasma proteins. These include:

- Albumin (the most abundant plasma protein);
- Transthyretin;
- Thyroxine-binding globulin (TBG).

Each of these three plasma proteins is synthesised by the liver, with TBG having the highest binding affinity (Chakravarthy and Ejaz, 2020). T3 and T4 are bound to their plasma protein vehicles but cannot exert any biological effects; however, small amounts of T3 and T4 detach and, once
free, are able to exert their effects.

Free T3 and T4 cross into their target cells and bind to thyroid hormone receptors (THRs) located in the cell nucleus. Both hormones can bind to THRs, but T3 binds with a much greater affinity than T4. Many of the target cells have enzymes, called deiodinases, which rapidly remove an atom of iodine from the T4 molecules, thereby generating greater amounts of the more-potent T3 (Shahid et al, 2020).

**Biological effects of T3 and T4**

Virtualy all human cells and tissues have THRs and can respond to free T3 and T4, which play an essential role in regulating cellular metabolism.

To release the energy needed to drive the biochemical processes necessary to sustain life, cells need to use simple food-derived molecules, such as sugars and fats. The primary – and preferred – energy source for most human cells is glucose, a monosaccharide sugar. In cells, glucose is metabolised in the cytoplasm using specialised organelles called mitochondria. These contain respiratory enzymes, which progressively release energy from the chemical bonds present in glucose molecules, and use this to synthesise the energy storage molecule, adenosine triphosphate (ATP). This process occurs most efficiently in the presence of oxygen (aerobic cellular respiration), with each molecule of glucose (under normal conditions) typically yielding around 29-32 molecules of ATP (Flurkey, 2010).

As a by-product of cellular metabolism, heat is also generated; this is dissipated through the body via circulating blood and other bodily fluids. This heat generation is called thermogenesis and is vital to help maintain the body’s core temperature at around 37°C, the optimal temperature for the functioning of most human enzymes.

The rate at which food-derived molecules, such as fats, proteins and glucose, are metabolised to release energy is largely governed by T3 and T4 levels. In addition to regulating metabolism, T3 and T4 also influence a variety of other physiological processes, including heart and respiratory function, muscle strength, neural function and the level of cholesterol in the blood (Sargis 2019, VanPutte et al 2017).

**Hypothalamic-pituitary-thyroid axis**

The release of T3 and T4 by the thyroid is modulated by hormones produced by the hypothalamus and pituitary gland; this regulatory mechanism is referred to as the hypothalamic-pituitary-thyroid axis (HPT axis).

The hypothalamus continually monitors the concentration of T3 and T4 circulating in the plasma. When levels of T3 and T4 decrease, the hypothalamus synthesises and releases thyrotropin-releasing hormone (TRH). TRH is a small peptide that binds to receptors in the anterior pituitary, initiating the secretion of thyroid stimulating hormone (TSH). TSH (another peptide hormone) circulates in the blood before binding to its complementary receptors on the follicular cells of the thyroid gland, which then release T3 and T4 (Fig 4).

The HPT axis is fine-tuned via continual negative feedback. Increased levels of T3 and T4 circulating in the plasma are detected by the hypothalamus, reducing the secretion of TRH. This reduces the release of TSH by the anterior pituitary gland, thereby reducing the release of T3 and T4 secretion (Chiasera, 2013). Tight homeostatic regulation of the HPT axis usually ensures a relatively stable metabolic rate but thyroid disorders, which can upset homeostasis are common; these are explored below.

**Hypothyroidism**

Hypothyroidism is the term for an underactive thyroid gland and is characterised by a deficiency in levels of circulating T3 and T4. Hypothyroidism is the most common thyroid disorder; UK incidence is around 2%, increasing to 5% in people >60 years, with women five to 10 times more likely to be affected compared with men (National Institute for Health and Care Excellence (NICE), 2019).

The most common form of hypothyroidism is primary hypothyroidism. In areas where the diet is not deficient in iodine, the major form of primary hypothyroidism is an autoimmune disease called Hashimoto’s thyroiditis (Chaker et al, 2017). The precise cause of this disease remains unclear, but it is associated with the production of autoantibodies that bind to the follicular components of the thyroid gland, which are progressively destroyed by the patient’s own immune system. The condition is associated with varying degrees of inflammation of the thyroid, while loss of follicular cells results in reduced secretion of T3 and T4, and a reduced metabolic rate (Machala et al, 2019).

Blood tests usually reveal significantly elevated levels of TSH in patients with Hashimoto’s thyroiditis (Chaker et al, 2017). This is because the low circulating levels of T3 and T4 are detected by the hypothalamus, which releases TRH, initiating the release of TSH from the anterior pituitary. Ageing is often linked to an increase in circulating autoantibodies that react with the follicular cells of the thyroid gland (Calsolaro et al, 2019); this may partially explain the reduction in basal metabolic rate usually observed in old age.

Although the recommended daily intake for iodine is low, many people are deficient in the mineral. In some parts of the UK, and more often in landlocked regions of Africa and Asia, access to iodine-rich marine food sources is limited. This can result in chronic iodine deficiency, which may cause hypothyroidism.

Prolonged iodine deficiency is often associated with a pronounced swelling of the thyroid gland, known as a goitre; this can be disfiguring and visibly stretch the skin at the front of the neck. Worryingly, despite initiatives to improve iodine intake, iodine deficiency is thought to affect around 2 billion of the world’s population (Li and Eastman, 2012).

Insufficient iodine intake during pregnancy can lead to congenital iodine deficiency syndrome (also known as cretinism). Iodine is essential for the central nervous system to develop normally, and deficiency is associated with varying degrees of brain damage. This can result in
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Table 1. Signs and symptoms of hypothyroidism and hyperthyroidism

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
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<tbody>
<tr>
<td>Metabolism</td>
<td>Decreased, with tendency for weight gain; difficulty losing weight; decreased body temperature; cold intolerance; cold hands and feet; shivering; fatigue and lethargy</td>
<td>Increased, with tendency for weight loss; increased body temperature; heat intolerance; increased appetite</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Depression; poor memory; sluggish speech; slow reflexes</td>
<td>Overstimulation; agitation; poor concentration; anxiety; insomnia; nervous tics; mood swings; tremors</td>
</tr>
<tr>
<td>Integumentary system</td>
<td>Dry, scaly skin; decreased sweating, thickened dystrophic nails, coarse hair, hair loss on scalp and eyelids, puffy face</td>
<td>Increased sweating; thinning skin; flushed skin; fine, brittle hair; thin, soft nails; itchy and skin rashes</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Reduced heart rate, increased cholesterol</td>
<td>Tachycardia; arrhythmias; systolic hypertension</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Reduced fertility, decreased libido, heavy and prolonged periods, miscarriage</td>
<td>Irregular/light periods; amenorrhea</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Constipation, goitre, muscle cramps, hoarse voice, joint pain</td>
<td>Increased bowel movements; nausea; exophthalmos (bulging eyes)</td>
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Impaired neurocognitive development, speech and hearing deficits, and muscular and gait problems. Many affected individuals may also display: impaired growth; dry, thickened skin; poor/sparse hair growth; and gastrointestinal problems (Toloza et al, 2020).

Secondary and tertiary hypothyroidism
Occasionally, reduced levels of T3 and T4 are found when the thyroid gland is healthy and receiving a steady supply of iodine. This can occur due to abnormalities affecting the anterior pituitary gland, such as tumours, which reduce the synthesis and release of TSH. Without adequate TSH stimulation, the follicular cells of the thyroid gland release less T3 and T4, and metabolic rate falls; this is referred to as secondary hypothyroidism (Beck-Peccoz et al, 2017).

Even more rarely, damage to the hypothalamus, potentially due to head trauma or surgery, may reduce or stop the release of TRH. This will prevent the release of TSH from the anterior pituitary and lead to reductions in T3 and T4; this is known as tertiary hypothyroidism (Chaker et al, 2017).

Clinical features of hypothyroidism
Unsurprisingly, a reduced metabolic rate means people with hypothyroidism often gain significant weight. As less energy is being released from food, with no decrease in food intake there is a calorific surplus and increased fat deposition. Patients with hypothyroidism also generate substantially less heat through thermogenesis and often complain of feeling cold all the time; other common symptoms of hypothyroidism are highlighted in Table 1.

Unintended weight gain and a reduced core temperature are the classic symptoms of hypothyroidism, and necessitate a full thyroid function evaluation. Fortunately, treatment for the most common forms of hypothyroidism is usually fairly straightforward and relies on taking levothyroxine. This drug is a synthetic form of T4 and is usually taken once a day in tablet form (bit.ly/NHSLevothyroxine). For adult patients beginning levothyroxine treatment, it is advisable to monitor the level of TSH every three months until it has stabilised to within the normal reference range, and then once yearly (NICE, 2019).

Hyperthyroidism
Hyperthyroidism is the term for an overactive thyroid, with consistently elevated secretion of T3 and T4. The most common form of hyperthyroidism is an autoimmune disorder called Graves’ disease; in the UK this affects around 2% of women and 0.2% of men (NICE, 2019).

Graves’ disease is characterised by the production of autoantibodies that bind to the same receptors as TSH. These autoantibodies act as TSH mimics, increasing the release of T3 and T4 beyond their normal physiological concentrations. Although the exact causes are poorly understood, the major risk factors are being female (true for most autoimmune diseases) and a family history of autoimmune disease (Campi and Salvi, 2018). The disease can usually be confirmed by the detection of TSH-receptor autoantibodies in the plasma.

Clinical features of hyperthyroidism
In many ways, the primary symptoms of hyperthyroidism are the opposite of hypothyroidism: an increased secretion of T3 and T4 raises the metabolic rate, which often results in marked weight loss. As food molecules are metabolised more rapidly, there is greater thermogenesis, raising the body’s core temperature and leading to heat intolerance and increased sweating. Other common clinical features of hyperthyroidism are summarised in Table 1.

One of the most dramatic clinical features of Graves’ disease is an accumulation of inflamed, fibrous, fatty tissue behind the eyes, which can cause a prominent bulging of the eyes, called exophthalmus. In severe cases, this may result in progressive eyelid retraction and compressive optic neuropathy, which may affect vision. This collection of clinical features affecting the eyes is known as Graves’ ophthalmopathy and affects around 50% of people with the disease to varying degrees (Al-Sharif and Alsuhaibani, 2017). The perceived disfigurement caused by pronounced exophthalmus can cause emotional distress and impaired psychosocial health. This has led to various surgical interventions aimed at removing excess tissue behind the eye (orbital decompression), which are largely shown to be safe and effective at improving cosmetic appearance (Al-Sharif and Alsuhaibani, 2017).

Transient or mild hyperthyroidism can be treated using the drug carbimazole, which inhibits the addition of iodine to tyrosine residues in the thyroid, thereby reducing the release of T3 and T4. However, in most adults with hyperthyroidism, radioactive iodine (radioiodine) therapy is recommended as a first-line treatment; this provides accurate and targeted therapy as the follicular portions of the thyroid gland...
are so effective at taking up and concentrating iodine. I-131 is an isotope that emits gamma radiation; this damages and kills the follicular cells, leading to a significant reduction in the secretion of T3 and T4. Radioiodine therapy is not used in women who are pregnant or breastfeeding or in male or female patients planning for a pregnancy in the next 4-6 months.

Surgical removal of the thyroid (thyroidectomy) is recommended when thyroid malignancy is suspected or there is significant enlargement of the thyroid tissues and risk of tissue compression. Following radioiodine therapy or thyroidectomy, secretion of T3 and T4 declines, and many patients will develop hypothyroidism. This usually requires levothyroxine therapy, often for the rest of the patient’s life (British Thyroid Association, 2019; NICE, 2019).

**Calcium homeostasis**

Calcium plays many diverse roles in human physiology including:

- Maintenance of bone density and tooth health;
- Triggering of muscle contraction;
- Cell division;
- Secretion from glands;
- Synaptic transmission of nerve impulses;
- Acting as a cofactor for multiple enzymes;
- Haemostasis and blood coagulation.

It is essential that calcium is always freely available and is dissolved in the blood and other bodily fluids at the correct concentration. It is the most tightly regulated of all the major plasma electrolytes, having an incredibly narrow normal range of 2.1-2.6mmol/l (Bazydlo and Needham, 2014). This is achieved primarily through the actions of two antagonistic hormones:

- Calcitonin, produced by the parafollicular cells and calcitonin-like peptides produced by the parathyroid glands;
- Parathyroid hormone (PTH), produced by the parathyroid glands.

**Parafollicular cells and calcitonin**

The parafollicular cells (also known as C-cells) are scattered between the follicles of the thyroid gland in relatively small numbers and make up only around 0.15% of the total thyroid cells (Benvenega et al, 2018). Although the parafollicular cells are an intrinsic part of the thyroid gland, their activity is not regulated by the HPT axis; instead, they act independently, continuously monitoring plasma-calcium concentration. When plasma calcium rises (for example, after eating calcium-rich dairy food, such as cheese) these cells release the peptide hormone calcitonin. The major effect of calcitonin is to reduce the plasma-calcium concentration; this is achieved by two main mechanisms:

- Inhibition of osteoclast activity – bone is a dynamic tissue continually built up by cells called osteoblasts (bone-forming cells) and broken down by cells called osteoclasts (VanPutte et al, 2017). These two groups of cells usually work at similar rates to maintain bone density. The skeleton acts as a calcium reservoir, storing around 99% of the total calcium present in the body. By inhibiting the activity of osteoclasts, calcitonin allows the bone-forming osteoblasts to freely deposit the excess calcium in the bones, normalising plasma-calcium concentration;
- Decreasing tubular re-absorption of calcium by the kidneys – calcitonin inhibits re-absorption of calcium from the renal filtrate into the blood. This allows excess calcium to be rapidly eliminated in the urine, reducing the plasma-calcium concentration (Summers and Macnab, 2017).

**Parathyroid glands**

The parathyroid glands are found in the posterior portion of the thyroid gland (Fig 1). There are usually four, each 3-5mm in diameter, which tend to be oval-to-round in shape and weigh around 35mg (Benvenega et al, 2018; Dorion, 2017). Each parathyroid gland contains a population of cells called chief cells, which synthesise parathyroid hormone (PTH or parathormone).

PTH is a small peptide hormone that primarily works antagonistically to calcitonin to help maintain calcium homeostasis. The chief cells monitor plasma-calcium concentration and release PTH when plasma-calcium levels decrease. PTH enhances osteoclast activity; increasing the breakdown of bone and the release of calcium and phosphate (the two major inorganic mineral components of bone) into the plasma. This begins to increase and normalise the plasma-calcium concentration. As well as stimulating calcium release from the skeletal reservoir, PTH further increases plasma-calcium by enhancing tubular calcium re-absorption in the kidneys (Summers and Macnab, 2017).

**Conclusion**

This article has examined the anatomy and physiology of the thyroid and parathyroid glands, and outlined hypothyroidism and hyperparathyroidism. Part 4 of this series will explore the adrenal glands and the diverse roles they play in human physiology.