

## EVALUATION OF PATIENT WITH THYROID DISORDERS

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The thyroid gland is one of the largest endocrine glands. The thyroid gland is found in the neck, below the thyroid cartilage (which forms the laryngeal prominence, or "Adam's apple"). The isthmus (the bridge between the two lobes of the thyroid) is located inferior to the cricoid cartilage.

The thyroid gland controls how quickly the body uses energy, makes proteins, and controls how sensitive the body is to other hormones. It participates in these processes by producing thyroid hormones, the principal ones being triiodothyronine ( $T_3$ ) and a thyroxine which can sometimes be referred to as tetraiodothyronine ( $T_4$ ). These hormones regulate the rate of metabolism and affect the growth and rate of function of many other systems in the body.  $T_3$  and  $T_4$  are synthesized from both iodine and tyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis.

Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus.

The thyroid gets its name from the Greek word for "shield", due to the shape of the related thyroid cartilage. The most common problems of the thyroid gland consist of an overactive thyroid gland, referred to as hyperthyroidism, and an underactive thyroid gland, referred to as hypothyroidism.

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, lobus dexter (right lobe) and lobus sinister (left lobe), connected via the isthmus. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly to the esophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. It

is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing.

The thyroid gland is covered by a thin fibrous sheath, the capsula glandulae thyroidea, composed of an internal and external layer. The external layer is anteriorly continuous with the lamina pretrachealis fasciae cervicalis and posteriorolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of Berry<sup>1,2</sup>. The thyroid gland's firm attachment to the underlying trachea is the reason behind its movement with swallowing<sup>3</sup>. In variable extent, Lalouette's Pyramid, a pyramidal extension of the thyroid lobe, is present at the most anterior side of the lobe. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament and tubercle.

Between the two layers of the capsule and on the posterior side of the lobes, there are on each side two parathyroid glands.

The thyroid isthmus is variable in presence and size, can change shape and size, and can encompass a cranially extending pyramidal lobe (lobus pyramidalis or processus pyramidalis), remnant of the thyroglossal duct. The thyroid is one of the larger endocrine glands, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy.

The thyroid is supplied with arterial blood from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, branching directly from the brachiocephalic trunk. The venous blood is drained via superior thyroid veins, draining in the internal jugular vein, and via inferior thyroid

veins, draining via the plexus thyroideus impar in the left brachiocephalic vein.

Lymphatic drainage passes frequently the lateral deep cervical lymph nodes and the pre- and paratracheal lymph nodes. The gland is supplied by parasympathetic nerve input from the superior laryngeal nerve and the recurrent laryngeal nerve.

At the microscopic level, there are three primary features of the thyroid<sup>4</sup>

#### (a) Follicles

The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I<sup>-</sup>) from the blood for production of thyroid hormones, but also for storage of iodine in thyroglobulin, in fact iodine is necessary for other important iodine-concentrating organs as breast, stomach, salivary glands, thymus etc. (see iodine in biology). Twenty-five percent of all the body's iodide ions are in the thyroid gland. Inside the follicles, in a region called the follicular lumen, colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called thyroglobulin.

#### (b) Thyroid epithelial cells

The follicles are surrounded by a single layer of thyroid epithelial cells, which secrete T<sub>3</sub> and T<sub>4</sub>. When the gland is not secreting T<sub>3</sub>/T<sub>4</sub> (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.

#### (c) Parafollicular cells

Scattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, parafollicular cells, which secrete calcitonin.

#### Physiology

The primary function of the thyroid is production of the hormones triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), and calcitonin. Up to 80% of the T<sub>4</sub> is converted to T<sub>3</sub> by peripheral organs such as the liver, kidney and spleen. T<sub>3</sub> is several times more powerful than T<sub>4</sub>, which is largely a prohormone, perhaps four<sup>5</sup> or even ten times more active<sup>6</sup>.

#### T<sub>3</sub> and T<sub>4</sub> production and action

Thyroxine (T<sub>4</sub>) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen

peroxide generated by the enzymethyroid peroxidase (TPO)<sup>7</sup> and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming T<sub>4</sub> and T<sub>3</sub> (in T<sub>3</sub>, one iodine atom is absent compared to T<sub>4</sub>), and releasing them into the blood. Deiodinase enzymes convert T<sub>4</sub> to T<sub>3</sub><sup>15</sup>. Thyroid hormone secreted from the gland is about 80-90% T<sub>4</sub> and about 10-20% T<sub>3</sub><sup>5,6</sup>.

Cells of the developing brain are a major target for the thyroid hormones T<sub>3</sub> and T<sub>4</sub>. Thyroid hormones play a particularly crucial role in brain maturation during fetal development<sup>8</sup>. A transport protein that seems to be important for T<sub>4</sub> transport across the blood-brain barrier (OATP1C1) has been identified<sup>9</sup>. A second transport protein (MCT8) is important for T<sub>3</sub> transport across brain cell membranes<sup>9</sup>. Non-genomic actions of T<sub>4</sub> are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV beta3 that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the Na(+)/H(+) exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells, which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some cancers including gliomas. T<sub>4</sub> also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T<sub>4</sub> is critical to cell migration in neurons and glial cells and is important to brain development.

T<sub>3</sub> can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin alpha V beta3.

In the blood, T<sub>4</sub> and T<sub>3</sub> are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T<sub>4</sub> 0.03% and T<sub>3</sub> 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell membrane and bind to intracellular receptors ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$  and  $\beta_2$ ), which act alone, in pairs or together with

the retinoid X-receptor as transcription factors to modulate DNA transcription<sup>1</sup>.

### T<sub>3</sub> and T<sub>4</sub> regulation

The production of thyroxine and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T<sub>4</sub> levels are high<sup>10</sup>. The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as cold exposure (to stimulate thermogenesis). TSH production is blunted by somatostatin (SRH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration.

An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids.

### Disorders

Imbalance in production of thyroid hormones arises from dysfunction of the thyroid gland itself, the pituitary gland, which produces thyroid-stimulating hormone (TSH), or the hypothalamus, which regulates the pituitary gland via thyrotropin-releasing hormone (TRH). Concentrations of TSH increase with age, requiring age-corrected tests<sup>11</sup>. Hypothyroidism affects between three and ten percent of adults, with incidence higher in women and the elderly<sup>12-14</sup>.

There are four main types of thyroid disease:<sup>15</sup>

- Hyperthyroidism -- too much thyroid hormone
- Hypothyroidism -- too little thyroid hormone
- Benign (noncancerous) thyroid disease
- Thyroid cancer

### Hyperthyroidism and Hypothyroidism<sup>16</sup>

Hyperthyroidism is a condition in which the thyroid gland makes too much thyroid hormone. The condition is often referred to as an "overactive thyroid." Hypothyroidism is a condition in which the thyroid gland does not make enough thyroid hormone.

The thyroid gland is located in the front of the neck just below the voice box (larynx). It releases hormones that control metabolism.

Hypothyroidism, or underactive thyroid, is more common in women and people over age 50.

The most common cause of hypothyroidism is thyroiditis. Swelling and inflammation damage the thyroid gland's cells. Causes of this problem include:

- An attack of the thyroid gland by the immune system
- Cold or other respiratory infection
- Pregnancy (often called "postpartum thyroiditis")

Other causes of hypothyroidism include:

- Certain drugs, such as lithium and amiodarone
- Congenital (birth) defects
- Radiation treatments to the neck or brain to treat different cancers
- Radioactive iodine used to treat an overactive thyroid gland
- Surgical removal of part or all of the thyroid gland
- Sheehan syndrome, a condition that may occur in a woman who bleeds severely during pregnancy or childbirth and causes the destruction of the pituitary gland

### Anaplastic thyroid cancer<sup>17</sup>

Anaplastic thyroid carcinoma is a rare and aggressive form of cancer of the thyroid gland. Causes

Anaplastic thyroid cancer grows very rapidly and is an invasive type of thyroid cancer. It occurs most often in people over age 60. The cause is unknown.

Anaplastic cancer accounts for only about 1% of all thyroid cancers.

- Symptoms
- Cough
- Coughing up blood
- Difficulty swallowing
- Hoarseness or changing voice
- Loud breathing
- Lower neck lump, which often grows quickly

### Chronic thyroiditis (Hashimoto's disease)<sup>18</sup>

Chronic thyroiditis is swelling (inflammation) of the thyroid gland that often results in reduced thyroid function (hypothyroidism).

### Causes

Chronic thyroiditis or Hashimoto's disease is a common thyroid gland disorder. It can occur at any age, but is most often seen in middle-aged

women. It is caused by a reaction of the immune system against the thyroid gland.

The disease begins slowly. It may take months or even years for the condition to be detected. Chronic thyroiditis is most common in women and in people with a family history of thyroid disease. It affects between 0.1% and 5% of all adults in Western countries.

Hashimoto's disease may, in rare cases, be related to other endocrine (hormonal) disorders caused by the immune system. Hashimoto's disease can occur with adrenal insufficiency and type 1 diabetes. In these cases, the condition is called type 2 polyglandular autoimmune syndrome (PGA II). Less commonly, Hashimoto's disease occurs as part of a condition called type 1 polyglandular autoimmune syndrome (PGA I), along with

- Adrenal insufficiency (poor function of the adrenal glands)
- Fungal infections of the mouth and nails
- Hypoparathyroidism (underactive parathyroid gland)

#### Symptoms

- Constipation
- Difficulty concentrating or thinking
- Dry skin
- Enlarged neck or presence of goiter
- Fatigue
- Hair loss
- Heavy and irregular periods
- Intolerance to cold
- Mild weight gain
- Small or shrunken thyroid gland (late in the disease)

Other symptoms that can occur with this disease

- Joint stiffness
- Weight gain (unintentional)
- Swelling of the face

#### Goiter – simple<sup>19,20</sup>

A goiter is an enlargement of the thyroid gland. It is not cancer.

#### Causes

There are different kinds of goiters.

- A simple goiter can occur for no known reason, or when the thyroid gland is not able to produce enough thyroid hormone to meet the body's needs. The thyroid gland makes up for this by becoming larger.
- Toxic nodular goiter involves an enlarged thyroid gland that contains a small, rounded growth or growths

called nodules. These nodules produce too much thyroid hormone. Iodine is needed to produce thyroid hormone.

- Simple goiters may occur in people who live in areas with iodine-poor soil. People in these areas might not get enough iodine in their diet.
- The use of iodized table salt in the United States today prevents a lack of iodine in the diet.

In most cases of simple goiter the cause is unknown. Sometimes, certain medications such as lithium or aminoglutethimide can cause a simple goiter.

Simple goiters are also more common in:

- Anyone over age 40
- People with a family history of goiter
- Females.

#### Symptoms

The main symptom is a swollen thyroid gland. The size may range from a single small nodule to a large neck lump.

Some people with a simple goiter may have symptoms of an underactive thyroid gland.

Rarely, the swollen thyroid can put pressure on the windpipe and food pipe (esophagus), which can lead to:

- Breathing difficulties (may rarely occur with very large goiters)
- Cough
- Hoarseness
- Swallowing difficulties

#### Thyroid function tests (TFTs)

Thyroid function tests (TFTs) is a collective term for blood tests used to check the function of the thyroid<sup>21</sup>.

TFTs may be requested if a patient is thought to suffer from hyperthyroidism (overactive thyroid) or hypothyroidism (underactive thyroid), or to monitor the effectiveness of either thyroid-suppression or hormone replacement therapy. It is also requested routinely in conditions linked to thyroid disease, such as atrial fibrillation and anxiety disorder.

A TFT panel typically includes thyroid hormones such as thyroid-stimulating hormone (TSH, thyrotropin) and thyroxine (T4), and triiodothyronine (T3) depending on local laboratory policy.

Test	Abbreviation	Normal ranges <sup>22, 23</sup>
Serum thyrotropin/thyroid-stimulating hormone	TSH	0.3–3.0 µU/ml
Free thyroxine	FT <sub>4</sub>	7–18 ng/l = 0.7–1.8 ng/dl
Serum triiodothyronine	T <sub>3</sub>	0.8–1.8 µg/l = 80–180 ng/dl
Radioactive iodine-123 uptake	RAIU	10–30%
Radioiodine scan (gamma camera)	N/A	N/A - thyroid contrasted images
Free thyroxine fraction	FT4F	0.03–0.005%
Serum thyroxine	T <sub>4</sub>	46–120 µg/l = 4.6–12.0 µg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT4I	4–11
Free triiodothyronine I	FT <sub>3</sub>	230–619 pg/d
Free T3 Index	FT3I	80–180
Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 µg
TRH stimulation test	Peak TSH	9–30 µIU/ml at 20–30 min.
Serum thyroglobulin I	Tg	0-30 ng/m
Thyroid microsomal antibody titer	TMAb	Varies with method
Thyroglobulin antibody titer	TgAb	Varies with method

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