College of Pharmacy

Fifth Stage

Clinical Chemistry

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Lecture 8

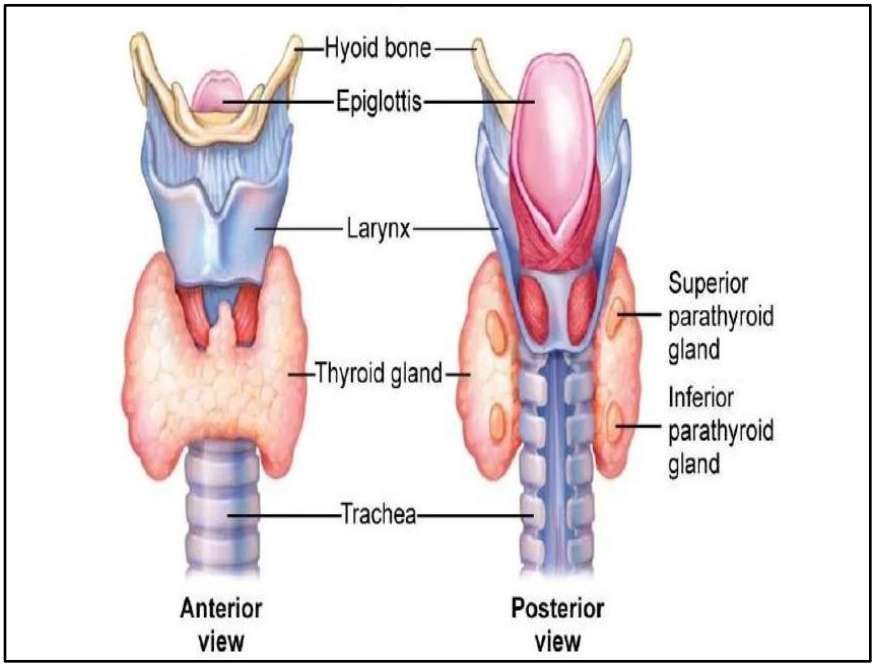
Thyroid Gland

Lecture: 8 **Dr. Maytham Ahmed**

Thyroid Gland

The thyroid gland secretes three hormones: thyroxine (T_4) and triiodothyronine (T_3), both of which are iodinated derivatives of **tyrosine**. The third hormone is calcitonin. The T_4 and T_3 are produced by the follicular cells but calcitonin is secreted by the C cells (parafollicular cells). About 10 times more T_4 than T_3 is formed, with most of the T_3 being formed by **de-iodination** in the peripheral tissues liver, kidneys and muscle.

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.

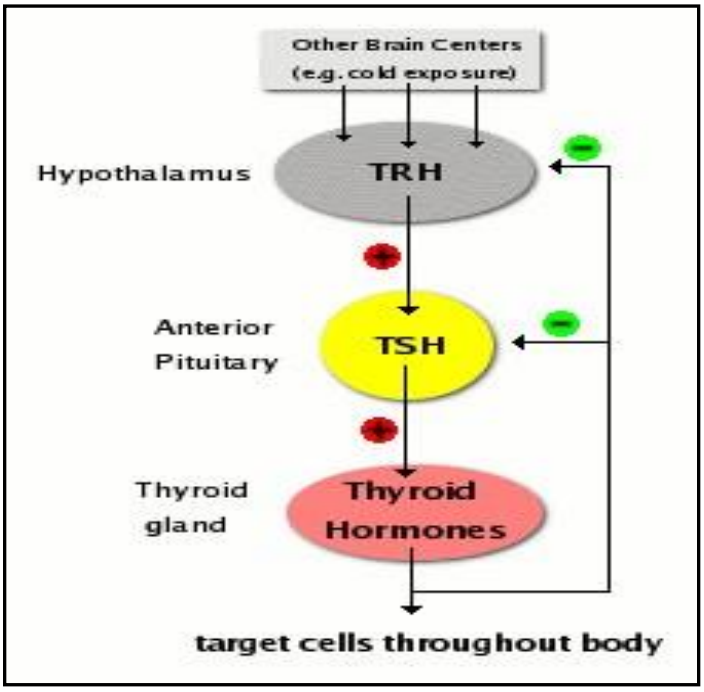


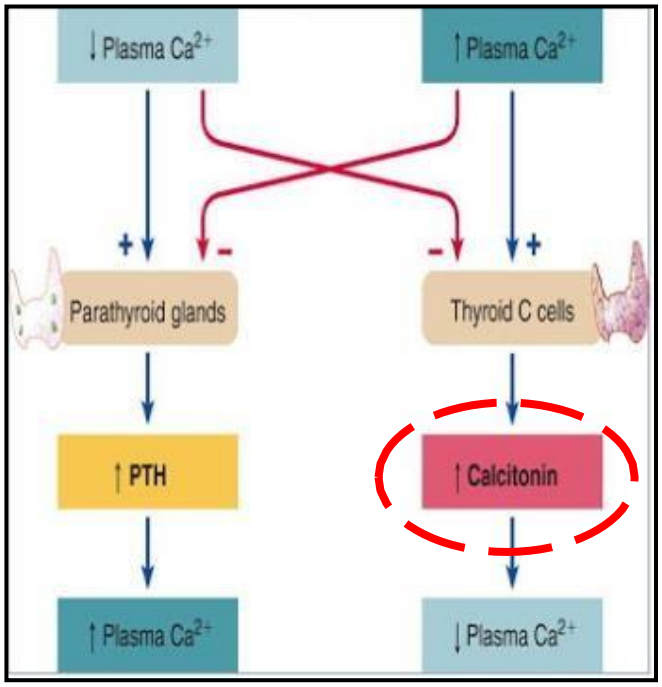
Action of thyroid hormones

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 (**TSH**) which is a **pituitary trophic hormone** stimulates the synthesis and release of thyroid hormones from the thyroid gland. TSH secretion from the anterior pituitary gland is controlled by **thyrotrophin-releasing hormone** (**TRH**) from the **hypothalamus** and also controlled by negative feedback by the circulating concentrations of 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.

Thyroid function tests (TFT)

Laboratory tests of thyroid function are required to assist in the **diagnosis** and **monitoring of thyroid disease**. 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. Plasma **TSH assays** are used as **first-line** assays for thyroid function assessment.

1- Plasma thyroid-stimulating hormone (**TSH**).

2- Plasma total thyroxine (**Total T_4**) or free thyroxine (**fT_4**) assays.

3- Plasma total tri-iodothyronine (**Total T_3**) or free tri-iodothyronine (**fT_3**).

4- Thyrotrophin-releasing hormone test (**TRH test**).

5- Other tests of thyroid function include measurement of **various antibodies** such as

A) Thyroid-stimulating immunoglobulin (**TSI**) antibodies that bind to and stimulate the TSH receptor (Graves' disease).

B) Anti-thyroid peroxidase (**anti-TPO**), anti-thyroglobulin (**anti-Tg**) or **TSH receptor blocking antibodies**.

Drug effects on thyroid function tests

Drugs may alter plasma T_4 and T_3 concentrations as appeared in Table 1

Table 1 Drug effects on thyroid function tests

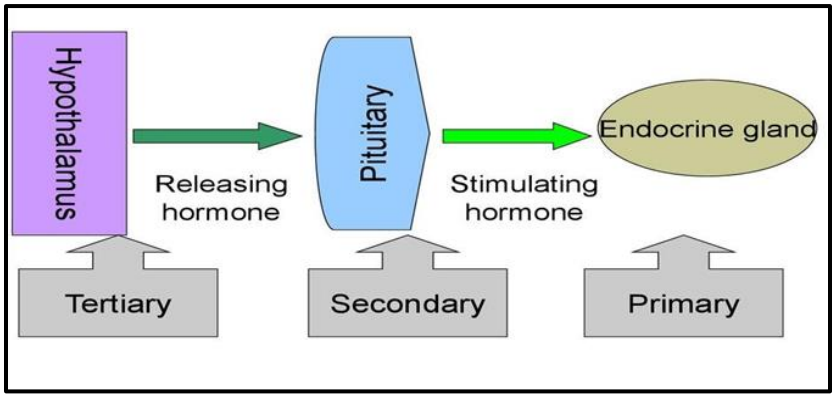
Drug	T_4	fT_4	T_3	fT_3	Remarks
Amiodarone	↑	Normal or ↑	Normal	Normal	Blocking T_4 to T_3 conversion
Androgens	↓	Normal	↓	Normal	Reduced TBG
Carbamazepine	↓	↓	Normal	Normal	Increased T_4 to T_3 conversion
Carbimazole	↓	↓	↓	↓	Therapeutic if thyrotoxic
Lithium	↓	↓	↓	↓	Lithium may inhibit iodination
Estrogens	↑	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.

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.

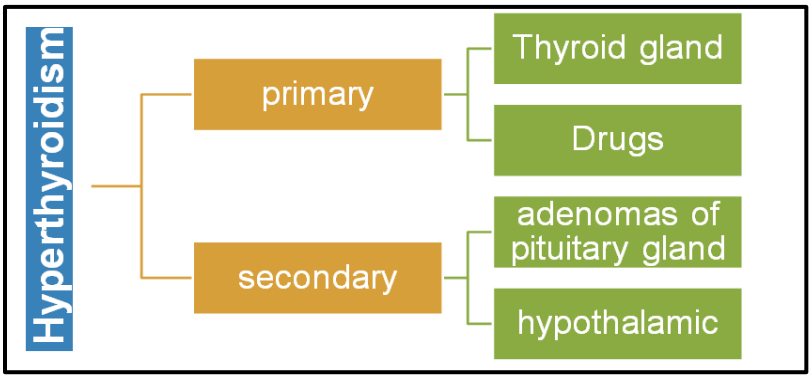
The levels of disorders



Disorders of the thyroid

Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism causes **sustained high** plasma concentrations of **T_4** and **T_3**. The plasma **fT_4** and **fT_3** concentrations are clearly high and the TSH concentration is suppressed in clinically thyrotoxicosis patients.



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.

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 goiter. It is an autoimmune thyroid disease characterized by a variety of circulating antibodies.

Hypothyroidism

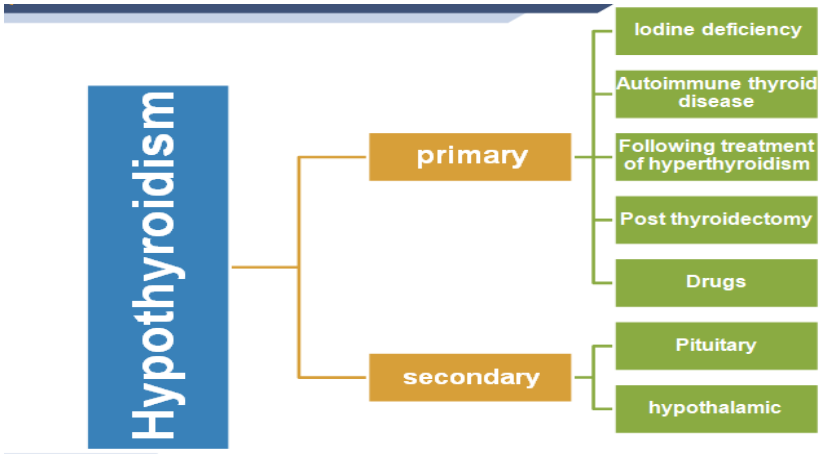
Hypothyroidism is caused by suboptimal circulating concentrations of thyroid hormones. It becomes more prevalent with age, affecting about 6 per cent of people over 60 years, and is more common in women.

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.

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**.

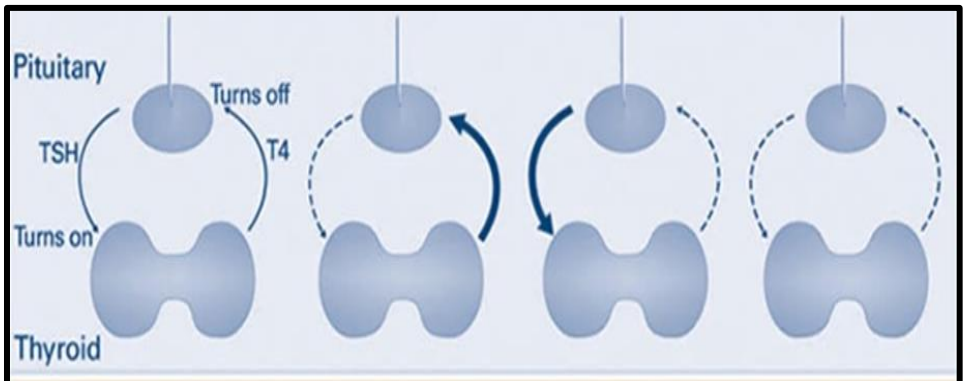
Hashimoto's thyroiditis, an autoimmune condition, has been mentioned as a cause of hypothyroidism.



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.

Goiter: enlargement of the thyroid, can occur in patients with hyperthyroidism, hypothyroidism and euthyroid individuals (euthyroid goiter).

Interpretation of thyroid function tests (TFT)



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low