**Thyroid Gland**

Thyroid gland is a part of the body’s endocrine system. It is the largest organ specialized for endocrine function in human body. It is a butterfly- shaped gland fig (1). It is an organ with many veins, anchored around the front of the throat near the voice box.

In mammals, thyroid hormones are essential for normal growth and maturation. Therefore, thyroid hormones are major anabolic hormones.

Dietary intake, mainly in the form of iodide of about 500µg per day, is typical. To maintain normal thyroid hormone secretion, 150 µg is the minimal intake necessary. Ι- is the form absorbed from the small intestine.

**Organization of the thyroid gland**

1. The functional unit is the follicle.
2. The lumen is filled with thyroglobulin, to which are covalently bound large numbers of thyroid hormone molecules.
3. Surrounding the lumen are the follicle cells, which function to both synthesize and release thyroid hormones.

These relationships are schematically represented in figure (2).

**Synthesis, structure, and secretion of thyroid hormones**

**Synthesis of thyroid hormones**

**Iodide transport**

Iodine uptake is via a sodium/potassium pump powered. This pump can raise the concentration of Ι- within the cell to as much as 250 times that of plasma. The pump can be blocked by anions like perchlorate and thiocyanate, which compete with Ι.

**Thyroglobulin synthesis**

A high molecular weight protein (300,000 daltons) is synthesized in ribosomes in the endoplasmic reticulum, and packaged into vesicles in the Golgi apparatus. The thyroglobulin then enters the lumen via exocytosis.

**Oxidation of Ι- to Ι°**

The enzyme, thyroperoxidase (TPO) catalyzes oxidation. Peroxidase also catalzes iodination and coupling.

**Iodination**

The catalyst for this reaction is peroxidase. The initial products of iodination are mono- and diiodotyrosine (MIT nd DIT) respectively, with the latter from predominating, except when iodine is scarce.

Large amounts of iodine will inhibit thyroid hormone synthesis by suppressing peroxidase (wolff-chaikoff effect). The normal thyroid will eventually escape this suppressive effect off elevated iodine. An abnormally functioning thyroid will often not escape and thyroid hormone synthesis remains depressed.

**Coupling**

Peroxidse also promotes the coupling of iodinated tyrosine in the thyroglobulin molecule. When two DITs couple, tetraiodothyronine (T4) is formed. When one DIT and one MIT combine, triiodothyronine (T3) is formed. When iodine is aboundant, mainly T4 is formed. But when iodine becomes scarce, the production of T3 increases.

**Structure of thyroid hormones**

The chemical structures of T4,T3, and reverse T3 (rT3) are shown in fig(3).

**Secretion of thyroid hormone**

The thyroglobulin is broken into free amino acids, some of which are T4, T3, DIT, and MIT. T3 and T4 are secreted into the blood, with the T4:T3 ratio being a high as 20:1 and in an iodine deficient state more of the hormone can be released as T3.

Along with thyroid hormones a small amount of thyroglobulin is also released into the circulation. Its release is increased in a number of states including thyroiditis, nodular goiter, and by cancerous thyroid tissue. After the surgical removal of cancerous thyroid tissue, any residual thyroglobulin in the circulation indicate cancerous cells are still present.

**Deiodination**

Removes the iodine from iodinated tyrosines (DIT and MIT) but not from the iodinated thyronines (T3 and T4). The iodine is then available for resynthesis of hormone. (individuals with a deficiency of this enzyme are more likely to develop symptoms of iodine deficiency.)

**Transport of thyroid hormones in blood**

There is an equilibrium between bound and free circulating thyroid hormone in the bloodstream. About 70% of the circulating thyroid is bound to thyroid-binding globulin (TBG). The remainder of the bound protein is attached to albumin.

Also, T4 has higher affinity for binding proteins; therefore, it binds more tightly to protein than does T3, and consequently has a greater half-life than T3. Most circulating thyroid hormone is T4.

T4 half-life = 6 days

T3 half-life = 1 day

**Activation and degradation of thyroid hormones**

T3 and T4 bind to the same nuclear receptor but T3 binds with 10 times more affinity than T4. Thus, because it has greater affinity for receptor, T3 is the more active from T4.

Many target tissues can regulate conversion of T4 to either T3 or Rt3, thereby locally controlling hormone activity. In addition, even though the thyroid releases some T3 into the circulation, most of the circulating T3 is derived from the peripheral conversion of T4 into T3 and its release again into the circulation (Kidney, Liver, and Skeletal muscle).

Certain clinical states are associated with a reduction in the conversion of T4 into T3 , often with an enhanced conversion of T4 into rT3 (low T3 syndrome). Such states would include fasting, medical and surgical stresses, catabolic disease, and even excess secretion of cortisol could be included here. The result is a reduction in metabolic rate and a conservation of energy resources.

**Physiologic action of thyroid hormones**

1 Metabolic rate

Thyroid hormones increase metabolic rate, as evidenced by increased O2 consumption and heat production. Thyroid hormones increase the activity of the membrane-bound Na/K-ATPase in many tissues.

2- Growth and maturation (T4 and T3 Anabolic hormones).

Fetal growth rates appear normal in the absence of thyroid hormone production (if the fetus is hypothyroid). However, without adequate thyroid hormones during the perinatal period, abnormalities rapidly develop in nervous system maturation.

Synapses develop abnormally and there is decreased dendritic branching and myelina- tion. These abnormalities lead to mental retardation.

These neural changes are irreversible and lead to cretinism unless replacement therapy is started soon after birth.

1. **Lipid metabolism**

Thyroid hormone accelerates cholesterol clearance from plasma. Thyroid hormones are required for conversion of carotene to vitamin A, as a consequence, hypothyroid individuals can suffer from night blindness and yellowing of the skin.

1. CHO Metabolism

Thyroid hormones increases the rate of glucose absorption from the small intestine.

**Cardiovascular effects**

Thyroid hormones have positive inotropic and chronotropic effects on the heart. The increased contractility is partly direct and partly indirect: they increase the number and affinity of β-adrenergic receptors in the heart, thereby increasing the sensitivity to catecholamines. Acting on the SA node they directly increase heart rate.

Thyroid hormones in the normal range are required for optimum cardiac performance.

**Control of thyroid hormone secretion**

Thyrotropin-releasing hormone (TRH) provides a constant and necessary stimulus for TSH secretion. In the absence of TRH the secretion of TSH (and T4) decreases to very low levels. The target tissue for TSH is the thyroid, where it increases the secretion mainly of T4.

Negative feedback of thyroid hormones is exerted mainly at the level of the anterior pituitary gland.

Because the main circulating form is T4, it is T4 that is responsible for most of the negative feedback.

As long as circulating free T4 remain normal, changes in circulating T3 have minimal effects on TSH secretion. However TSH secretion increases if there is a significant drop in circulating free T4, even in the presence of an increase in circulating T3.

**Overall effects of TSH on the thyroid**

TSH tends to rapidly increase (within minutes or an hour) all steps in the synthesis and degradation of thyroid hormones, including:

1. Iodide trapping
2. Thyroglobulin synthesis and exocytosis into the follicular lumen.
3. Secretion of T4 into the blood.
4. Increased blood flow to the thyroid gland.

**TESTS OF THYROID FUNCTION**

1-Determining the serum TSH is the first step in evaluating thyroid function.

2-Secondly, free T4 (FT4) measurement are now readily available and would confirm an initial conclusion based on the TSH measurement.

3- Thirdly, a TRH stimulation is not usually necessary, but would differentiate secondary from tertiary hypofunction.

1. Autoimmune thyroid disease is easily detected by measuring circulating antibodies. Most notably are the TPO antibodies, which are elevated in Hashimoto thyroiditis (hypothyroidism) and Graves’ disease (hyperthyroidism).
2. Additional antibodies are those against thyroglobulin and the TSI antibodies that sitmulate the TSH receptor in Graves’ disease.

**Pathologic changes in thyroid hormone secretion**

In most cases, if iodine is deficient in the diet but not absent, the individual will remain euthyroid but will develop a Goiter.

**Primary hypothyroidism**

Most common cause is Hashimotos thyroiditis, an autoimmune destruction of the thyroid with lymphocytic infiltration; TPO antibodies.

TSH, FT4 ; in subclinical hypothyroidism the TSH is on the high side of normal and the FT4 is on the low side of normal.

Decreased basal metabolic rate and oxygen consumption.

Plasma cholesterol and other blood lipids tend to be elevated.

Increased TRH drives a hyperprolactinemia. In women it may result in amenorrhea. In men infertility .

Inability to convert carotene to vitamin A may cause yellowing of the skin and night blindness.

Decreased food intake but individuals tend to be overweight.

**Treatment**

Replacement doses of T4. The goal is to give enough T4 to normalize serum TSH.

Because metabolism of T4 decreases and the plasma half-life increases with age, higher doses of T4 are required in younger individuals.

In women beyond menopause, overdosing with T4 can contribute to the development of osteoporosis.

**Primary hyperthyroidism (Graves’s disease)**

Thyrotoxicosis by definition is the clinical syndrome whereby tissues are exposed to high levels of thyroid hormone (hyperthyroidism).

The most common cause of thyrotoxicosis is Graves’ disease, a primary hyperthyroidism.

Graves’ disease is an autoimmune problem in which one antibody is directed against the thyroid receptor. It is referred to as the thyroid stimulating antibody (TSI or TSH-R).

In addition TPO antibody and those against thyroglobulin are also found in Graves’ disease.

FT4, TSH, decreased serum cholesterol, increased metabolic rate and heat production. Individuals tend to seek a cool environment.

Weight loss with increased food intake. Protein wasting, and muscle weakness.

Cardiac output, contractility, and heart rate are increased with possibly palpitations and arrhythmias (increased β-adrenergic stimulation).

**Goiter**

A goiter is simply an enlarged thyroid and does not designate functional status. A goiter can be present in hypo-, hyper-, and euthyroid states.

There is no correlation between of thyroid size and function.