THYROID HORMONES

T3 and T4 hormones are secreted from the thyroid gland. The thyroid gland located immediately below the larynx on each side of the trachea. One of the largest endocrine glands. Normally weighing : 15-20 gms in adults.

The thyroid secretes 2 significant hormones

1. **Thyroxine and**
2. **Tri Iodo Thyronine commonly called T4 and T_3 respectively.**

Both of these hormones have the profound effect of increasing the metabolic rate of the body.

Thyroid secretion is controlled primarily by thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland.

The thyroid gland also secretes Calcitonin, an important hormone for calcium metabolism.

Synthesis and secretion of the thyroid hormones

About 93% of the metabolically active hormones secreted by the thyroid gland is thyroxine T_4 and 7%. Triiodo thyronine T_3. However almost all the thyroxine is eventually concentrated to T3 in the tissues, so that both are functionally important.

The functional of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. T_3 is about 4 times as patent as T4 but it is present in the blood in much smaller quantities and persists for much shorter time then does T_4.

PHYSIOLOGICAL ANATOMY OF THYROID GLAND

The thyroid gland is composed of large no. of closed follicles, 100-300 mm in diameter, filled with secretary subs called colloid and lined with cuboidal epithelial cells that secrete into the interior of the follicles.

The major constituent of colloid is the large glycoprotein Thyroglobulin which contains the thyroid hormones within its molecules. Once the secretion has entered the follicles it must be absorbed back through the follicular epithelium into the blood before it can function in the body.

The thyroid gland has a blood flow about 5 times the wt. of the gland each min. which is a blood supply as great as that of any other area of the body.

Iodine is required for the formation of thyroxine:

To form normal quantities of thyroxine about 50 mg of ingested iodine in the form of iodides are required each year or about 1mg/week. To prevent iodine deficiency common table salt is iodised with about 1-part sodium iodide to every 1 lac part sodium chloride.

Iodides ingested only are observed from the GI tract into the blood in about the same manner as chlorides.

Normally most of them are rapidly excreted by the kidneys but only after about 1/5 are selectively removed from the circulating blood by the cells of the thyroid gland and used for the synthesis of the thyroid hormones.

Iodide Pump

The I stage in the formation of thyroid hormones is the transport of iodised from the blood into the thyroid glandular cells. The basal membrane of thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called iodide trapping.

In a normal gland the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active this concentration ratio can rise as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors. The most important being the concentration of TSH (Thyroid stimulating hormone).

Formation of secretion of thyroglobulin by the thyroid cells

The thyroid cells are typical protein secreting glandular cells. The ER and golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin with a molecular weight of about 335000. Each molecule of thyroglobulin contains about 70 Tyrosine amino acids.

They are the substrates that combine with iodine to form the thyroid hormones. Thus the thyroid hormones form with in the thyroglobulin molecule i.e. T3 and T4 hormones formed from the tyrosine amino acids remain part of the Thyroglubulin molecule during synthesis of the thyroid hormones and even after words as stored hormones in the follicular colloid.

The binding of iodine with the thyroglubulin molecule is called organization of the thyroglobulin oxidized iodine even in the

molecular form well bind directly but very slowly with the amino acids tyrosine.

In the Thyroid cells however, the oxidized iodine is associated with an iodinase enzyme that causes the process to occur within sec. of min. therefore, almost as rapidly as the thyroglobulin molecule is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle iodine binds with about 1/6 of the tyrosine amino acids within the thyroglobulin molecules.

Tyrosine is first oxidized to Mono Iodo Tyrosine (MIT) and then to Di-iodo Tyrosine (DIT) then during the next few minute or hrs. and even days more and more of the iodo tyrosine residues become coupled with one another.

The major hormonal product of the coupling run is then molecule thyroxine that remains part of the thyroglobulin molecule. One molecule of the mono-iodo tyrosine couples with one molecule of Di-iodo tyrosine to form Tri-iodo thyronine which represents about 1/15 of the final hormone.

The thyroid gland is unique among the endocrine gland. It has ability to store large amount of hormones. After synthesis of the thyroid hormone has run its course each thyroglobulin molecule contains upto 30 thyroxine molecules. In this form the thyroid hormones are stored in the follicles in an amount to body with its normal requirements of thyroid hormones for 2-3 months. Therefore, when synthesis of thyroid hormone cases, the physiological effects of deficiency are not observed for several months.

Thyroglobulin itself is not release into the circulating blood in measurable amounts instant T3 and T4 must first to done a form the thyroglobulin molecules and then these free hormones are released.

The process occurs as follows :-

The optical surface of the thyroid cell sends out pseudo pass extension that closed around small portion of the colloid to form pinocytic vesicles that enter the apex of the thyroid cell. The lysosomes in the

cytoplasm immediately fused with these vesicles to form digestive vesicles containing digestive enzyme from the lysosome mixed with colloid multiple protinases among the enzymes digit the thyroglobulin molecules and release T4 and T3 in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries thus the thyroid hormonal are released into the blood.

CHEMISTRY & NORMAL PHYSIOLOGY OF THYROID

- The normal daily intake of iodine is 100-200 μg.
- It is absorbed mainly in small intestine and transported in the plasma in loose attachments to the protein.
- About 2/3 of the ingested iodine is excreted by the Kidneys and remaining 1/3 is taken up by the thyroid gland.
- TSH of pituitary gland stimulates iodine uptake by the glands.
- Within the thyroid, iodine is oxidized and transfer to tyrosine molecule in the thyroglobulin by peroxidases. Thus reaction stimulated of TSH.
- Iodination of tyrosine leads to the formation of MIT & DIT.

- **About 80% of iodine stored by thyroid gland is thyroxine (T4) and 20% is probably T3. Conversion of inorganic iodine to T4 and T3 takes about 48 hrs.**
- **The release of T4 and T3 takes place by a secretion process including microtubules and microfilaments, hydrolysis of thyroglobulin by a protease which is stimulated by TSH.**
- **Within the plasma T3 and T4 are transported almost entirely in association with thyroxine binding globulin (TBG) and thyroxine binding pre-albumin when the binding capacities of these proteins are exceeded, the hormones then bind to serum albumin. These hormones can be measured as protein bound iodine (PBI).**
- **T3 is 3 to 5 times more active then T4 and has a more rapid onset of action. Both T4 and T3 are metabolized in the peripheral tissues by deamination and decarboxylation. They control following actions:**

- As a catalyst for the oxidative runs and regulation of metabolic rates in the body.
- Enhance oxygen uptake, lipolysis and decrease circulating cholesterol.
- Accelerate anabolism by causing an increase in RNA and protein synthesis which precede basal metabolic rate (BMR).
- Increases ATP utilization
- De-iodination of T3 and T4 may occur in peripheral tissues. The liberated iodine is then excreted in urine.
- In the liver T4 and T3 rapidly conjugate with gluaronic acid and the conjugate are then excreted into the bite. Part of the conjugate may be reabsorbed in the small intestine and then it is excreted in the urine.

The general effect of thyroid hormones is to activate nuclear transcription of large no. genes. Therefore in virtually all of protein enzymes, structural proteins, transport proteins and agar subs are synthesized. The net result is generalized including in functional activity throughout the body. The thyroid hormones including the metabolic activities of almost the tissues of body.

The BMR can inc. upto 60-100% above normal when large quantities of hormones are secreted. The rate of utilization of foods for energy is greatly accelerated.

THYROID DISORDER

The thyroid disorders fall into following main categories

- Enlargement of gland, goiter
- Tumours of the gland.
- Abnormal secretion of thyroid hormones i.e. T3 and T4.

GOITER :

An enlarged thyroid gland or without nodules is called a goiter. A nodule is the enlargement of a part of gland. Multiple nodules may be as much as 100 times the size of the normal thyroid gland.

Any regulation in the rate, or any region of the thyroid should be tested for cancer by ultrasound and by scanning techniques.

- **Simple Goiter**

  In this condition there is enlargement of the thyroid gland and deficient secretion of T3 and T4 inspite of elevated TRH and TSH.

There is diffuse or nodular hyperplasia of the gland. Sometimes the extra thyroid tissue is able to maintain normal hormonal levels. Myxedema develops when deficiency of T3 and T4 occurs after normal mental and physical development is complete.

<u>Underline causes of simple goiter are :</u>
Persistent Iodine Deficiency
Genetic Abnormality
Interference of contain drugs and chemicals such as para-amino salicycic acid, sulphonyl urease, resorcinol etc.

Note : In simple goiter, the level of T3 and T4 is decreased and TRH, TSH level is increased.

MYXEDEMA :

This condition is commonly found in elderly and incidences are where common in females that mammal. Low T4 and T3 level results in an abnormally low metabolic rate and lack of response demand for including energy.

Eg. During exercises.

Mental and physical processes become slower and there is reduced heat production with feeling of cold.

The various causes of myxodema are:

- ➔ Severe prolong iodine deficiency.
- ➔ Deficiency of TRH & TSH
- ➔ Surgical removal of excess thyroid tissues.
- ➔ Administration of excess antithyroid tissue.
- ➔ Autoimmune thyroiditis.

AUTOIMMUNE THYRODITIS

In the condition there is auto immunity to T3, T4 and thyroglobulin and thyroid gland cell. The Abs prevent synthesis and release of hormone causing myxedema.

The variants of this disease are :

Primary myxedema & focal thyroiditis.

TUMOURS OF THE THYROID GLAND

Benign Tumours

Benign tumours are simple and multiple adenomas with thyrotoxicosis may develop if the adenoma secretes hormones. The tumours have tendency to become malignant specially in elderly.

Malignant Tumours

These are relatively rare and the type of cell varies. Thyroid cancer is one of the softest among cancer. In this condition the patient is treated by the required hormones, in the form of drugs for the rest of the life.

HYPERTHYROIDISM

There are two conditions

i) Thyrotoxicosis
ii) Toxic Goiter

This conditions arises due to excessive secretion of T3 and T4 by the thyroid gland. The main effects are due to including metabolic rate. The elevated levels of T3 and T4 cause:

a) Cardinal Arrethemia : Since the heart tries to supply extra O2 and nutrition to the hyperactive blood cells.
b) Including Gluconeogenesis from body proteins to provide extra energy this leads to loss of weight, muscle waisting and weakness.
c) Decreased Glucose tolerance
d) Excessive Heat production, due to including metabolic rate.
e) Physical restlessness and mental excitability.

Enlargement of thyroid gland may develop single or multiple hormone secreting nodules or secretary cells.

Thus, the various symptoms, includes nervousness, excessive sweating, fatigue, loss of weight, including body temp., including heart rate, protrusion of the eye balls.

Hyperthyroidism can be treated by surgery or by ANTI THYROID called GOITROGENS.

GRAVE'S DISEASE :

This is the most common cause of thyrotoxicosis there is diffuse hyperplasia of the thyroid gland with excess secretion of T3 and T4. It is caused by an auto immune reaction to the thyroid tissue and thyroglobulin resulting into development of antibodies which mimic the action of TSH by releasing high levels of T3 and T4 which depress secretion of TRH from the hypothalamus and TSH from the anterior pituitary gland.

Grave's disease has been found more commonly in women than in man.

In men, untreated hyperthyroidism is known to cause disturbances in sex & fertility. Female, suffering from delayed or less menstrual periods and unexplained fertility or miscarriages should be tested for HYPOTHYROIDISM. During pregnancy both the mother and foetus require an optimum level of T3 and T4.

Deficiency of thyroid hormones can cause irreversible damage to the physical and mental growth of the foetus.

TSH receptors are int. on thyroid cells which sense and bind with TSH molecules. In autoimmunity, the receptor antibodies bind with receptors are do not allow TSH to perform its function. This may also result in HYPOTHYROIDISM.

In hyperthyroidism, T3 and T4 levels are high while TSH is low.

Some individuals are more likely then others to suffer from thyroid related diseases. They are :

- **Thos who have enraged thyroid gland.**
- **Women's above 40 years of age.**
- **Women who have abnormalities in menstrual cycle history.**
- **Women who have recently given birth.**
- **Those who have lost or gained more than 2 kg. increase or lost 2 or more Kgs. in 2-3 months.**
- **Those who feel exhausted & fatigue.**
- **Those who have too low or too high pulse rate.**
- **Those suffering from infertility.**
- **Those with family history of thyroid disease.**
- **Those having high or low cholesterol.**