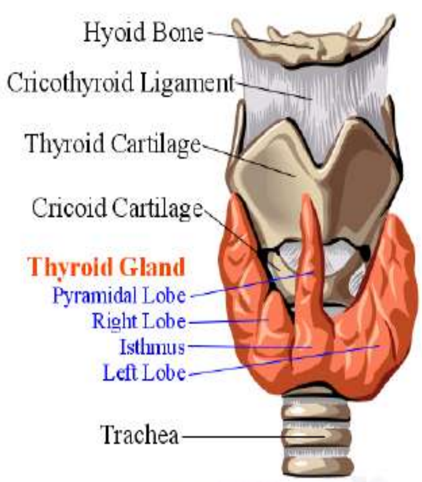
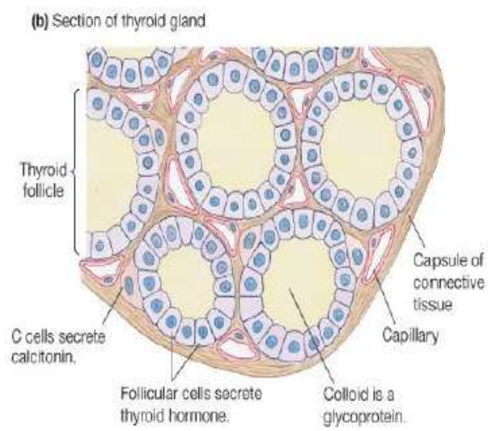
Thyroid gland

The **thyroid gland** is a butterfly-shaped endocrine gland located anterior to the trachea, just inferior to the larynx (fig1). The gland weighs 10–25 g and consists of a right and left lobe connected by the isthmus. It is one of the highly vascularized organ receive about 120 ml of blood per minute. Each of the thyroid gland on its posterior side embedded with parathyroid gland. The cellular composition of the thyroid gland is diverse, including the following:

- Follicular (epithelial) cells, involved in thyroid hormone synthesis
- Endothelial cells lining the capillaries that provide the blood supply to the follicles
- Parafollicular or C cells, involved in the production of calcitonin, a hormone involved in calcium metabolism.



Thyroid gland



Thyroid follicle

The thyroid follicles are the structural and functional units of a thyroid gland. The follicular cells are the lining cells of a thyroid follicle. These are spherical. These follicular cells are the derivates of the endoderm and synthesize and secrete **thyroxine,** which is also called **tetraiodothyronine (T_4)** along with a small quantity of **triiodothyronine (T_3),** are the thyroid hormone. In between these thyroid follicles or within the wall of the thyroid follicles, we find the small **C cells**, also known as **Parafollicular cells.** C cells secrete polypeptide hormone known as **calcitonin**. The calcitonin helps in depositing calcium and phosphate in skeletal and other tissues including blood.

The hyphothalamic-Pituitary-thyroid axix.

Thyrotrophic releasing hormone (TRH) is synthesized in paraventricular nucleus of the hyphothalamous. TRH is a tripeptide amide (pyro-Glu-His-Pro-NH2) derived from a large precursor protein, prepro-TRH (ppTRH), by posttranslational processing by prohormone convertase enzymes. Nerve terminals of the hypophysiotropic neurons releases TRH and researches anterior pituitary thyrotrophs via hyphophyseal portal system.

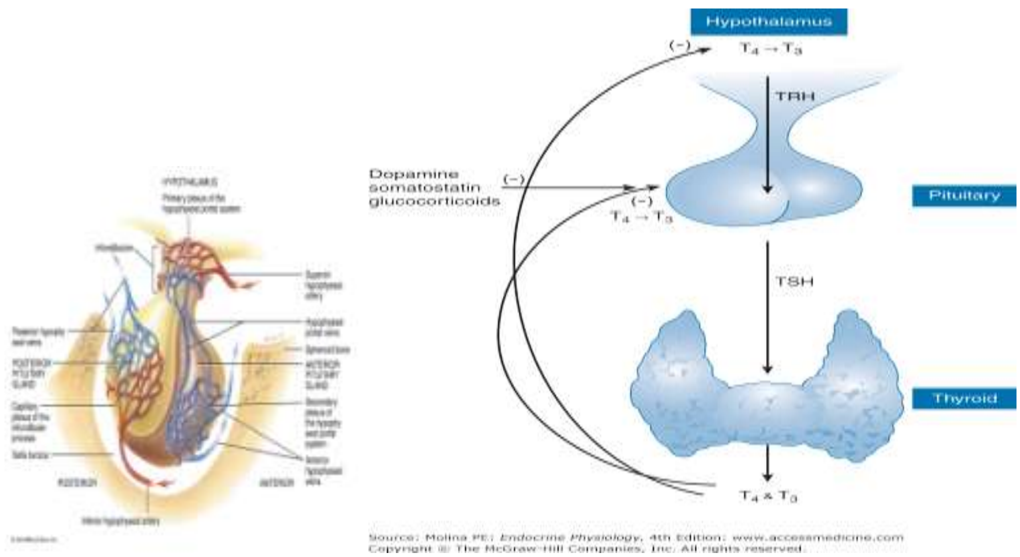


Fig: Hyphophyseal portal system and T_4 and T_3 inhibit the secretion of TSH both directly and indirectly by inhibiting the secretion of TRH.

- TRH binds on the anterior pituitary thyrotrophic G-protein coupled receptor, leading to increased release of calcium from endoplasmic reticulum results in increased cytoplasmic calcium concentration, which intern results in exocytosis of Thyroid Stimulating Hormone (TSH). TSH enters into the systemic blood circulation reaches thyroid gland and regulates synthesis of T_3 and T_4 hormones from thyroid follicle cells.

Biosynthesis of T_3 and T_4

TSH act on thyroid follicular cells through G protein coupled receptor results in the activation of PKA and PKC. PKA and PKC mediated up regulation of pendrin, anoctamin (Ca^{2+} activated chloride transmembrane channel protein) and voltage-gated chloride channel, Thyroglobulin (a rich tyrosine containing globular protein), Thyroid peroxidase , sodium–iodide symporter, deiodinases, dual-function oxidase (DUOX2) and DUOX1) etc are essential for biosynthesis of Thyroid hormone.

- Iodide is initially absorbed in the gastrointestinal tract and enters the systemic circulation; upon reaching the thyroid gland, iodide traverses the basolateral plasma membrane and enters the cytoplasm of thyroid follicular epithelial cells via the activity of the sodium–iodide symporter.
- Pendrin (multifunctional anion exchanger) , anoctamin (Ca^{2+} activated chloride transmembrane channel protein) and voltage-gated chloride channel 5 (CLCN5) are involved in efflux of iodide from apical membrane of the follicular cells cytoplasm to the lumen of the thyroid follicles.

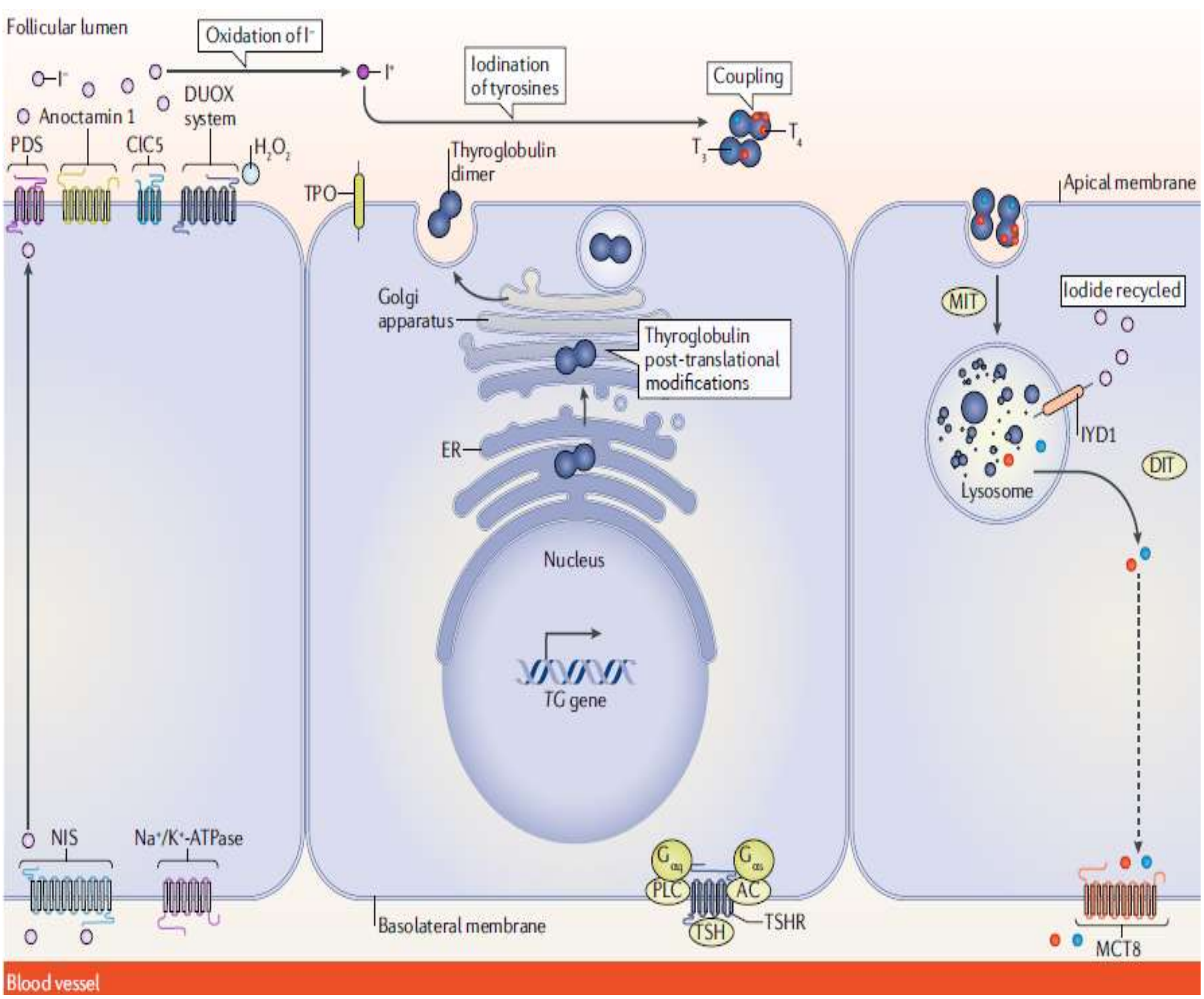
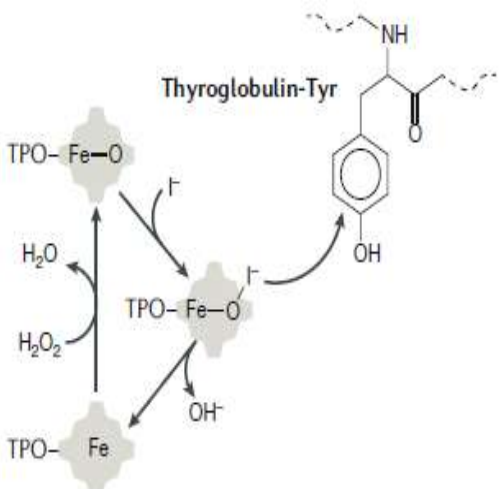


Fig Overview of de novo thyroid hormone biosynthesis.

AC, adenylyl cyclase; ER , endoplasmic reticulum; PLC, phospholipase C.TSHR-TSH receptor

- Thyroidal uptake of iodide is increased by iodide efflux across the apical membrane into the follicular lumen,
- The apical thyroid follicular cells are capable of expressing dual-function oxidase (DUOX2) and DUOX1) which are upregualted by the TSH action on thyroid follicular cells, which are belongs to NADPH oxidase family generates H_2O_2.
- The availability of H_2O_2 at the apical membrane of thyroid follicular cells enables membrane bound thyroid peroxidase (TPO) to catalyse the oxidation of iodide.
- In the presence of oxidized I^- and H_2O_2, TPO catalyses the iodination of thyroglobulin tyrosine residues, beginning with the molecules that are closest to the apical plasma membrane.



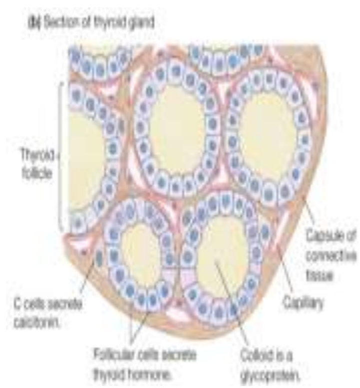


Fig: Oxidation of Iodine by TPO in the apical membrane of thyroid follicular cells

Oxidized iodide is then organified into selected tyrosyl residues of thyroglobulin. I

- At the time of iodination, selective di-iodotyrosine (DIT) and mono-iodotyrosine (MIT) residues of thyroglobulin can undergo the coupling reaction to initiate formation of T4 and T3.
- The transfer of an iodophenoxyl ring from a donor MIT (iodinated thyroglobulin) to an acceptor DIT residue within thyroglobulin, yielding T3.

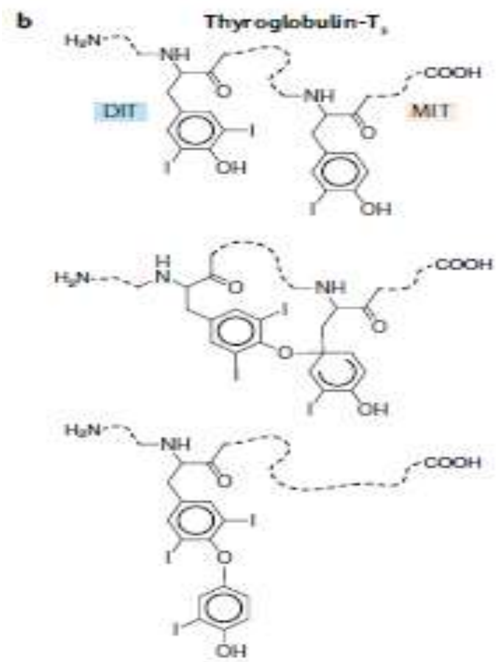


Fig: Transfer of an iodophenoxyl ring from a donor MIT (mono iodinated TG) to acceptor DIT (di iodinated TG) residue within thyroglobulin, yielding T3

- Coupling of DIT residue to an acceptor DIT residue within thyroglobulin, yielding T4

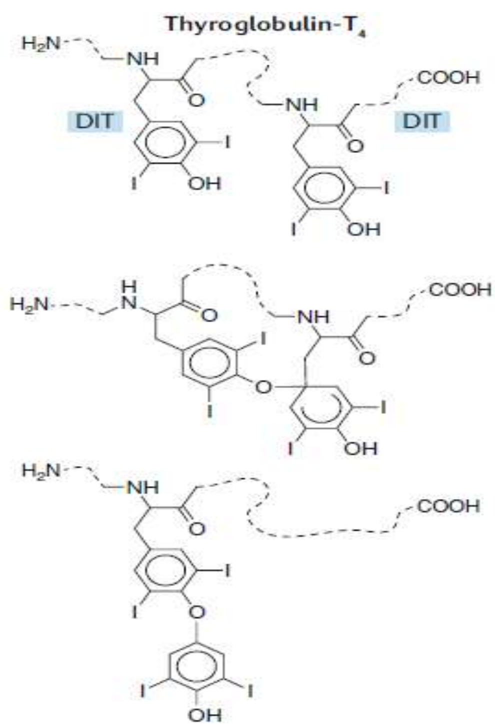
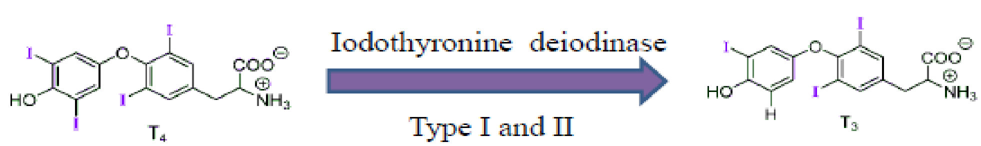
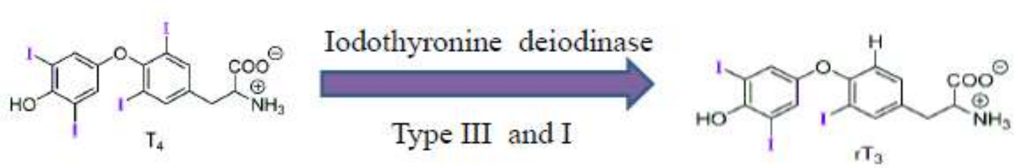


Fig: Coupling of DIT residue to an acceptor DIT residue within thyroglobulin, yielding T4

- Follicular thyroglobulin is re-internalized into the thyrocytes via endocytosis, which promotes the thyroglobulin proteolysis that liberates thyroid hormones from the polypeptide backbone,
- The released T3 and T4 are secreted into the bloodstream via MCT8 a basolateral plasma membrane transporters.
- The I^{-} contained within uncoupled MIT and DIT is recycled by iodotyrosine dehalogenase 1.
- In healthy humans, only ~21% of daily T3 production is originally derived from thyroidal secretion. T3 can be generated from T4 in the cells of the as kidney and as well as in thyroid follicles , by the actions of type 1 iodothyronine deiodinases.
- Transport proteins, such as thyroglobulin (TBG) and transthyretin (TTR), transport thyroid hormones T3 and T4 to target cells based on metabolic and/or developmental needs .
- Upon reaching target cells, deiodination by the iodothyronine deiodinase (Dio) family of selenoproteins modulates Thyroid hormones.
- Deiodination of the outer (phenolic) ring by type 1 and II iodothyronine deiodinases (ORD) produces active $T_{3.}$
- 

- While inner-ring deiodination (IRD) of T_4 by Type III (Dio3, and Dio1 to a lesser extent) T_3 produces the inactive metabolite 3,3′,5′-triiodothyronine or reverse T_3 (rT_3



- Dio3 also lowers T_3 concentrations through conversion to 3,3′-diiodothyronine (T_2).

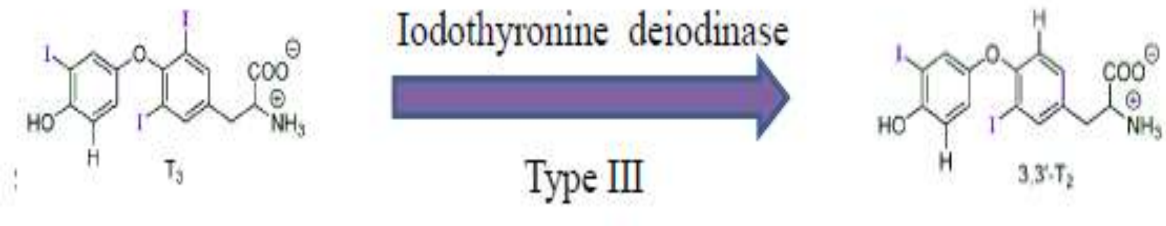


Fig: Deiodination/metabolism of thyroid hormone by deiodinase

Physiological functions of thyroid hormones

- Thyroid hormones are essential for normal development, growth, and metabolism.
- All cells in the body are targets for thyroid hormones.
- Thyroid hormone stimulates basal metabolic rate.
- Required for GH and prolactin production and secretion
- Required for GH action
- Increases intestinal glucose reabsorption (glucose transporter)
- Increases mitochondrial oxidative phosphorylation (ATP production)
- Increases activity of adrenal medulla (sympathetic; glucose production)
- T3 increases the synthesis of Na^+/K^+ pumps, markedly increasing ATP consumption.
- Increase mitochondrial size, number and key enzymes
- T3 also acts on mitochondria to increase ATP synthesis
- The resulting increased metabolic rate increases thermogenesis (heat production).
- Regulate the glomerular filtration rate

Effects of Thyroid Hormones on the Reproductive System

- Required for normal follicular development and ovulation in the female
- Required for the normal maintenance of pregnancy
- Required for normal spermatogenesis in the male

Effects of Thyroid Hormones on the Nervous System

- Critical for normal CNS neuronal development
- Enhances wakefulness and alertness
- Enhances memory and learning capacity

- Required for normal emotional tone
- Increase speed and amplitude of peripheral nerve reflexes

Effects Thyroid Hormones in Growth and Tissue Development

- Increase growth and maturation of bone
- Increase tooth development and eruption
- Increase growth and maturation of epidermis, hair follicles and nails
- Increase rate and force of skeletal muscle contraction
- Inhibits synthesis and increases degradation of mucopolysaccharides in subcutaneous tissue

Effects of Thyroid Hormones on Intermediary Metabolism

- Increase glucose absorption from the GI tract
- Down-regulate insulin receptors

Effects of Thyroid Hormones on the Cardiovascular System

- Increase force of cardiac contractions
- Increase stroke volume
- Increase Cardiac output
- Up-regulate catecholamine receptors.

Thyroid Hormone Actions which Increase Oxygen Consumption

- Increase mitochondrial size, number and key enzymes
- Increase plasma membrane Na-K ATPase activity
- Increase futile thermogenic energy cycles
- Decrease superoxide dismutase activity.

Disorders of the Thyroid Gland

Thyroid hormones are essential for the growth and development of many target tissues, including the brain and skeleton. Abnormalities of thyroid gland function in infancy and childhood result not only in the metabolic consequences of thyroid dysfunction seen in adult patients, but in unique effects on the growth and /or maturation of these thyroid hormone-dependent tissues as well. Newborn infants with congenital hypothyroidism frequently have hyper bilirubinemia, and delayed skeletal maturation, reflecting immaturity of liver and bone, respectively, and they are at risk of permanent mental retardation if thyroid hormone therapy is delayed or inadequate.

Hypothyroidism

Hypothyroidism is a condition in which thyroid gland doesn't produce enough of T_3 and T_4 hormones. In the early stage of development of Hypothyroidism there were no noticible symptoms. Over the time, untreated hypothyroidism leads to various health problems, such as obesity, joint pain, infertility, heart diseases etc. Accurate thyroid function tests are available to diagnose hypothyroidism.

Hypothyroidism signs and symptoms may include.

- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Muscle weakness
- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods
- Slowed heart rate
- Depression
- Impaired memory
- Enlarged thyroid gland (goiter)

Hypothyroidism may be caused by **Iodine deficiency,** disease/disorder affecting any part of the **hypothalmic-pituitary-thyroid axis.**

Iodine deficiency

Worldwide, iodine deficiency is the leading cause of hypothyroidism. Iodine is a key component of thyroid hormones and its deficiency results in 'endemic' goitres.

Secretion of thyroid hormone by the thyroid gland is tightly regulated by the hypothalamic–pituitary axis. The hypothalamus secretes thyrotropin releasing hormone (TRH), which in turn regulates the release of TSH from the anterior pituitary. The TSH, in a potent negative-feedback system, regulates the release of thyroid hormone from the thyroid gland.

Primary	Secondary	Tertiary
Failure of the Thyroid gland	Reduced output of TSH from pituitary cells	Reduced output of TRH from Hypothalamus

Primary hypothyroidism

The majority of cases of hypothyroidism are caused by disease intrinsic to the gland itself. This is termed primary hypothyroidism. In primary hypothyroidism, due to lack of negative feedback from thyroid hormones we can find increased TSH.

Secondary hypothyroidism

Rarely disease, Thyrotrophs of the anterior pituitary may produce or release low levels of TSH. It is most frequently caused by pituitary adenomas. In these conditions, we can find reduced levels of thyroid hormone accompanied by reduced TSH. In even rarer cases the TSH level is normal (or high) but the structural abnormalities cause the hormone to have less biological activity.

Tertiary hypothyroidism

Rare disease, reduced synthesis of TRH from hypothalamic neurons or reduced release of TRH from hypophyseal portal system In this condition, we can find expected reduced levels of thyroid hormone accompanied by reduced TSH and TRH.

Hashimoto's Thyroiditis.

Thyroiditis - Thyroiditis is the swelling, or inflammation, of the thyroid gland and can lead to over- or under-production of thyroid hormones.

Hashimoto thyroiditis is an autoimmune disease that destroys thyroid cells by antibody-mediated immune processes. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. The pathology of the disease involves the formation of serologically antithyroid antibodies, especially against thyroperoxidase (anti-TPO) and antithyroglobulin (anti-Tg) and more rarely TSH-stimulation blocking antibody (TSBAb), correlate positively with an increased inflammatory reaction in the thyroid and with the development of hypothyroidism. The most common laboratory findings show an elevated thyroid-stimulating hormone (TSH) and low levels of free thyroxine (fT4).

Treatment with synthetic thyroid hormone is usually advised and practiced. Almost all cases of hypothyroidism are irreversible and need to be treated. The treatments consist of replacing the thyroid hormone. Most of the time this is successfully done by using one daily dose of oral levothyroxine (Synthroid, Levoxyl, etc). The doctor will periodically measure the thyroid-stimulating hormone level to guide the treatments.

Hypothyroidism

- Early onset: delayed/incomplete physical and mental development
- Later onset (youth): Impaired physical growth
- Adult onset (myxedema) : gradual changes occur. Tiredness, lethargy, decreased metabolic rate, slowing of mental function and motor activity, cold intolerance, weight gain, goiter, hair loss, dry skin. Eventually may result in coma.

Many causes (insufficient iodine, defect in synthesis of TPO, NIS, presence of TPO antibodies, lack of hormone receptors, lack of Thyroid hormone binding globulin etc.)

Goiter

A goiter simply refers to enlargement of the thyroid gland. A goiter may be associated with hyperthyroidism or hyphothyroidism, it may contain one or several nodules that can be cancerous in some cases. Most individuals who have a goiter will not be aware of its presence until it gets to a palpable or visible size. Iodine deficiency was the main cause of goiter in the earlier, and it still one of the main cause in underdeveloped country with low supliment of Iodine in the diet.

Iodine is a key ingredient in the synthesis of thyroid hormones and also a major factor in the regulation of thyroid function. At the cellular level, iodine has been shown to inhibit multiple signaling pathways of thyroid cells, including cAMP and PIP_2. Iodine not only reduces the expression of thyroid-specific proteins such as NIS but also has been shown to alter the TSH/TSHr signaling pathway.

How is Hypothyroidism Related to Goiter?

- During iodine deficiency, thyroid hormone production decreases.
- This results in increased TSH release (less negative feedback).
- TSH acts on thyroid, increasing blood flow, and stimulating follicular cells and increasing colloid production, leads to enlargement of thyroid gland, the follicles are filled with colloidal thyroglobulin.

Congenital hypothyroidism

Simple goiter

Hyperthyroidism

Graves' Disease

Graves' disease is an autoimmune disorder. The hyperactivity of the thyroid gland is due to the presence of thyroid-stimulating antibodies, and these are now known to recognize and activate the thyroid-stimulating hormone receptor (TSHR). These TSHR-stimulating antibodies increase the growth and the function of the thyroid follicular cells leading to the excessive production of thyroid hormones (both T3 and T4). If left untreated, hyperthyroidism may cause weight loss, emotional liability (uncontrollable crying, laughing, or other emotional displays), depression, and mental or physical fatigue.

Graves' disease and hyperthyroidism share many of the same symptoms. These symptoms may include:

- hand tremors
- weight loss
- rapid heart rate (tachycardia)
- intolerance to heat
- fatigue
- nervousness
- irritability
- muscle weakness
- goiter (swelling in the thyroid gland)
- diarrhea or increased frequency in bowel movements
- difficulty sleeping

The cause of Graves' disease is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the TSH receptor.

How is Goiter Related to Hyperthyroidism

- Due to excessive stimulation by TSH (thyroglobulin production, enlarged follicles…).

In this case, excessive stimulation of the thyroid gland by TSH/TSH mimic molecule result in thyroid hormone secretion, since iodine is available.

References

1. Aleksandra Pyzik, Ewelina Grywalska, Beata Matyjaszek-Matuszek, and Jacek Roliński.2015 Immune Disorders in Hashimoto's Thyroiditis: What Do We Know So Far?. Journal of Immunology Research , 2015.
2. Cintia E. Citterio, Héctor M. Targovnik and Peter Arvan. The role of thyroglobulin in thyroid hormonogenesis. Nature Reviews Endocrinology
3. Huibin Huang, Lijun Chen, Bo Liang, Huiyao Cai, Qingyan Cai, and Yaxiong Shi 2016. Upregulation of TSHR, TTF-1, and PAX8 in Nodular Goiter Is Associated with Iodine Deficiency in the Follicular Lumen. International Journal of Endocrinology Volume 2016, Article ID 2492450, 6 pages.

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