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Recent advances in the treatment of thyroid disorder

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Abstract

Thyroid gland is a part of the body's endocrine system. It is the largest organ specialized for endocrine function in human body. The gland is essential to normal body growth in infants and childhood. It absorbs iodine from the diet and releases thyroid hormones-iodine- containing compounds that help govern the rate of body's metabolism (its total processes) controlling body temperature, and regulating protein, fat and carbohydrate catabolism in all cells. Thyroid disorders and classification of thyroid disorders (hyperthyroidism & hypothyroidism). Medications (anti-thyroid drugs) used for thyroid disorders and side-effects, symptoms of overdose of anti-thyroid drugs. Epidemiology of thyroid (spread and study of thyroid disorder).

Keywords

Thyroid gland, thyroid hormone, embryology, histology, thyroid disorders, antithyroid drugs.

INTRODUCTION

A butterfly-shaped organ. The thyroid gland is located anterior to the trachea, just inferior to the larynx. The medial region called as isthmus is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands. Parathyroid glands are located at posterior surfaces. The tissue of the thyroid gland is composed of thyroid follicles. The follicles are made up of a central cavity which is filled with a sticky fluid called colloid. Colloids are surrounded by a wall of epithelial follicle cells. The colloid is the centre of thyroid hormone production, and it is dependent on the hormones' essential and unique component called iodine.

Thyroid Gland

- The thyroid gland is located in the neck where it wraps around the trachea.
- (a) Anterior (front) view of the thyroid gland.

- (b) Posterior (back) view of the thyroid gland.
- (c) The glandular tissue is composed primarily on thyroid follicles. The larger parafollicular cells often appear within the matrix of follicle cells.

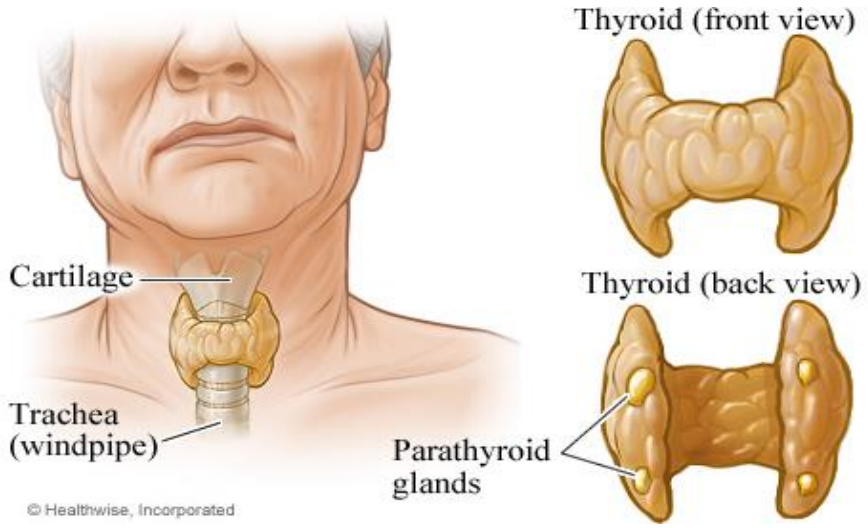


Fig: 1 Thyroid gland

Thyroid Hormones

- Thyroid hormone is the hormone that controls body's metabolism, the process in which the body transforms food into energy. The two main hormones of thyroid gland releases – thyroxine (T4) and triiodothyronine (T3) collectively make up thyroid hormones.

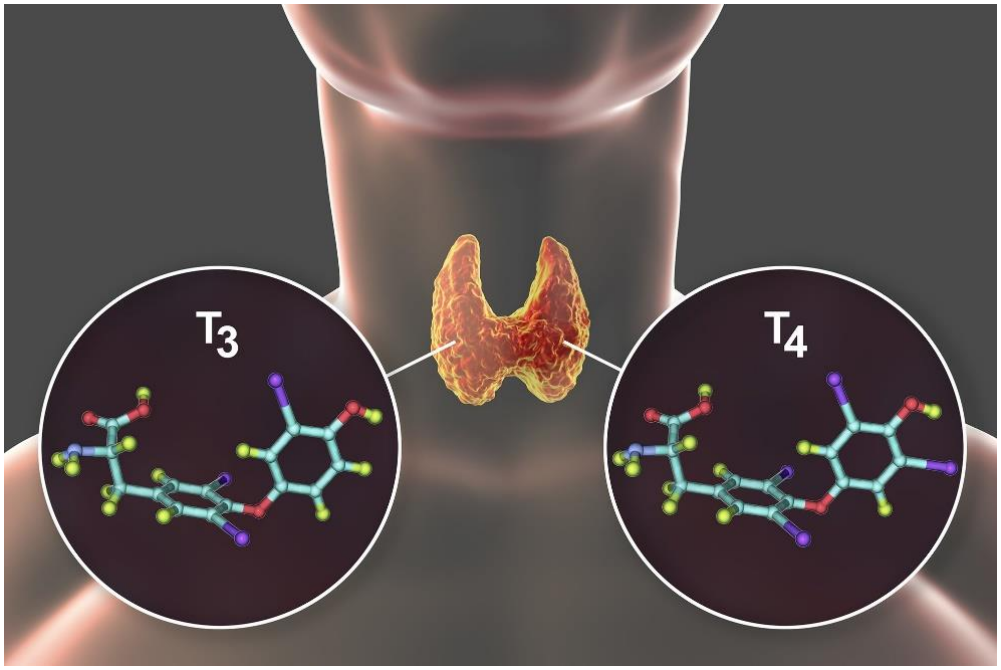


Fig:2 Thyroid hormones

Classification of thyroid hormone

- The two main hormones of the thyroid gland releases are – thyroxine (T4) and triiodothyronine (T3).

Epidemiology

- The incidence of thyroid disorder in hospitalised patients in Japan is estimated to be 0.2 per 1,00,000 per year with more than 10% mortality., overall incidence of hyperthyroidism is estimated to between 0.05% and 1.3%, with majority of cases being subclinical in terms of presentation. Among hospitalised thyrotoxicosis patients, the incidence of thyroid storm has been noted to be <10%. The mortality of thyroid storm without treatment ranges between 80% and 100%; with treatment the figure is between 10% and 50%. Multiple organ failure was reported to be the most common cause of death in thyroid storm, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation hypoxic brain syndrome and sepsis. The mortality rate in the group with a total bilirubin level >3mg/dL is significantly higher.
- Incidence of women 66.4% and 33.6% in men, 15% of cases occur in patients older than 60 years of age. In India a large number of people suffer from thyroid disorders. Previous studies reveal that almost 42 million Indians suffer from thyroid disorders. Unfortunately, awareness about the disease is low. A recent study across 8 cities of India revealed 11% of the urban population with women being 3 times more prone to the disease than men.

Anatomy

The thyroid gland is a butterfly-shaped organ composed of bulbous right and left lobes connected in the midline by a thin structure called the isthmus. It is located in the neck. The thyroid wraps around the anterior trachea directly inferior to the larynx, at the level of the C5 through T1 vertebrae. On average, it measures 5 cm in height, 5 cm in width, and weighs 20-30 g in adults, and slightly heavier thyroids are seen in females. The richly vascular structure of the thyroid receives blood supply predominantly from two sources. The superior thyroid artery, which is the first branch of the external carotid artery, supplies the upper half of the thyroid over 95% of people. The lower portion of the thyroid is most commonly supplied by the inferior thyroid artery, branching from the thyrocervical trunk, itself a branch of the subclavian artery, the inferior thyroid artery may be absent or duplicated. In addition, the thyroid has extensive lymphatic drainage involving multiple levels of lymph nodes including but not limited to the prelingual (or Delphian), pre- and paratracheal, retropharyngeal, retroesophageal, and internal jugular lymph nodes. This becomes very important in the staging of thyroid carcinoma, which is careful in lymph node dissection. It may be necessary in the search for metastases.

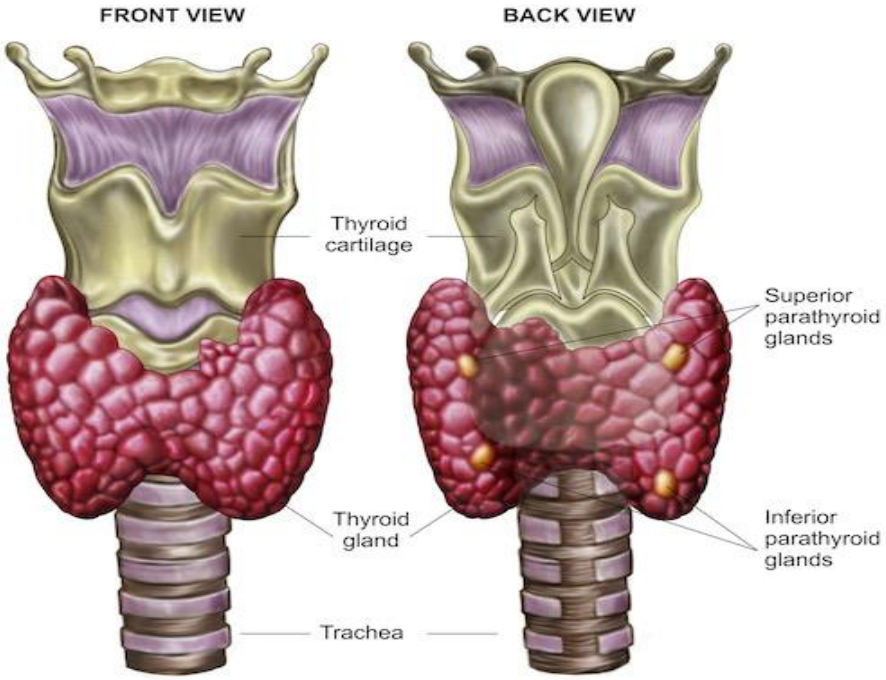


Fig: 3 Anatomy of Thyroid gland

The thyroid hormones regulate vital body functions, including:

- Breathing
- Heart rate
- Central and peripheral nervous systems
- Body weight
- Muscle strength
- Menstrual cycles
- Body temperature
- Cholesterol levels
- The thyroid gland is about 2-inches long and lies in front of the throat is below the prominence of thyroid cartilage sometimes called the Adam's apple. The thyroid has two sides called lobes that lie on either side of the windpipe, and it is usually connected by a strip of thyroid tissue known as an isthmus. Some people do not have an isthmus, and instead have two separate thyroid lobes.

Embryology

The thyroid gland is the first endocrine organ which forms during foetal development. It begins to develop at four weeks gestation as an epithelial diverticulum arising from the foregut endoderm near the base of the primitive tongue. Which extends progressively, inferiorly starts fifth week of the foetus develops. It reaches its final shape and relative size by seven weeks gestation. The connection between the thyroid and the fore-gut, called the thyroglossal duct. Later regresses in normal development; if this regression does not occur, a thyroglossal duct cyst may form. The most common congenital anomaly of the thyroid, thyroglossal duct cysts are seen in 7% of

adults, appearing as 2-3 cm fusiform or spherical nodules in the midline neck, which move upon swallowing. Histologically, the cyst lining varies based on location; superiorly, the lining is stratified squamous, and inferiorly, it is thyroid epithelium. Thyroglossal duct cysts may become infected and rarely, squamous cell and/or thyroid carcinoma may arise from the cyst lining. The thyroglossal duct may also leave behind an anatomic remnant known as the pyramidal lobe, which is a third, narrow thyroid lobe extending superiorly from the isthmus in 18-60% of people. Finally, due to the thyroid's intimate association with branchial structures during development, several clinically insignificant anatomic variations can occur, including intrathyroidal ectopic thymus, parathyroid gland, salivary gland, and cartilage.

Normal Histology

The normal thyroid is comprised of numerous follicles surrounded by a fibrous capsule, which forms septa that divide the parenchyma into multiple lobules. The septa also contain the nerves and blood vessels supplying each lobule. Each lobule contains 20-40 round follicles, 200μm in average diameter and lined by simple, flat & low columnar epithelium, depending on the state of functional activity; the more active the follicle, the taller the follicular epithelium. Follicular cells have uniform dark, small nuclei that are centrally located, and some have abundant granular cytoplasm, this variant known as Hurtle cells. Sanderson pollsters, which are small follicles extending into the central spaces of larger follicles, can be seen scattered throughout the thyroid, and should not be mistaken for papillary structures. Follicles contain colloid and a viscous material composedpredominantly the thyroid hormone precursor protein thyroglobulin. The normal thyroid gland contains up to three months' worth of thyroglobulin stored within colloid. The final cell type of the thyroid is the parafollicular, or cell, a derivative of the neural crest by way of the ultimobranchial body. Parafollicular cells form clusters – within and in between follicles, and are found in highest concentration within the mid- and upper portions of the lobes. These cells form and secrete calcitonin, thereby participating in calcium homeostasis.

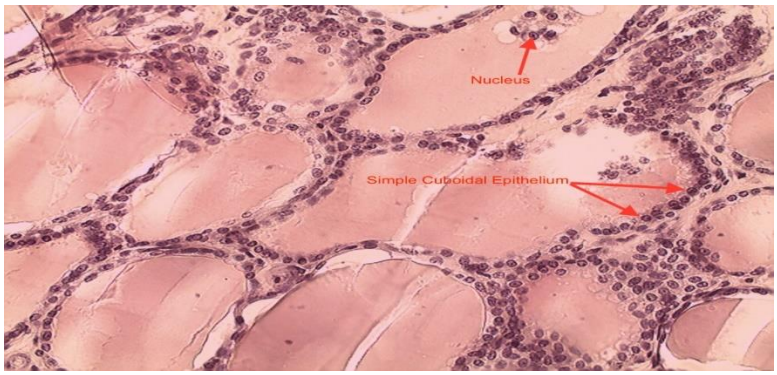


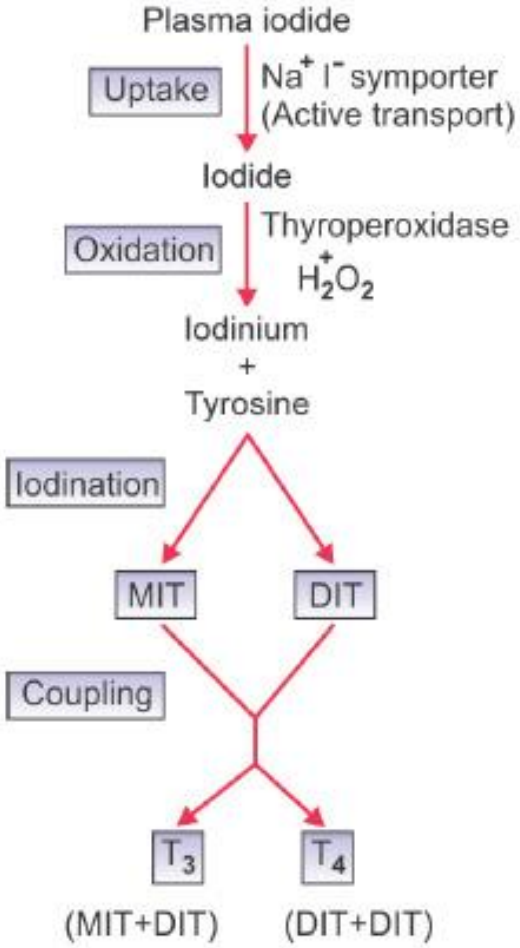
Fig:4 Histology of Thyroid gland

Synthesis and Release of Thyroid Hormones

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones' assembly:

1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I^-) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.
2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions ($2\ I^-$) results in iodine (I_2), which passes through the follicle cell membrane into the colloid.
3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodine's. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is triiodothyronine (T_3), a thyroid hormone with three iodine's. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as thyroxine (T_4), a thyroid hormone with four iodine's.
4. These hormones remain in the colloid centre of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T_3 and T_4, which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T_3 and T_4 remains unbound. This free T_3 and T_4 can cross the lipid bilayer of cell membranes and can be taken up by cells. The remaining 99 percent of circulating T_3 and T_4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T_3 and T_4 begin to decline, bound T_3 and T_4 are released from these plasma proteins and readily cross the membrane of target cells. T_3 is more potent than T_4, and many cells convert T_4 to T_3 through the removal of an iodine atom.



Regulation of TH Synthesis

The release of T_3 and T_4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). The low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4. The levels of TRH, TSH, T_3, and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH.

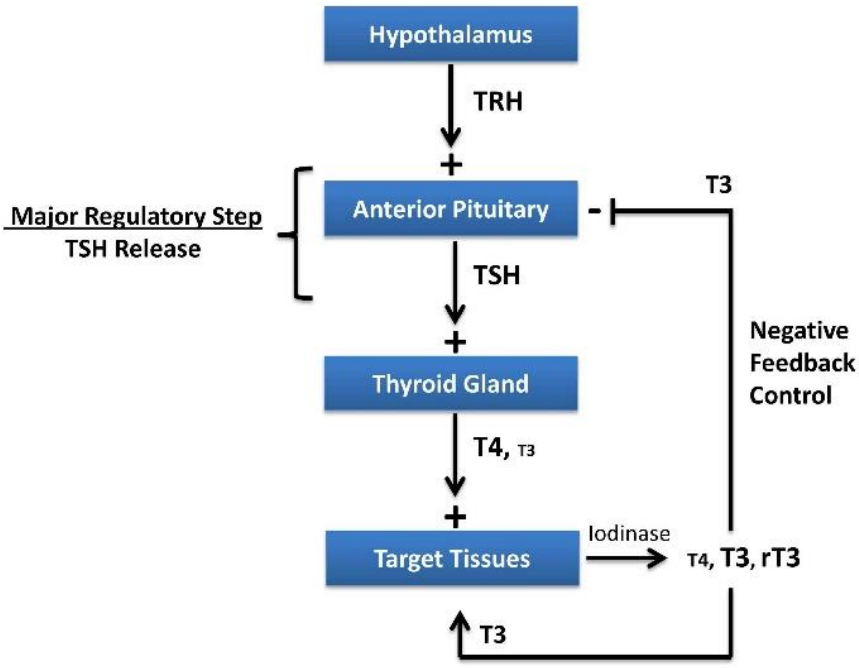
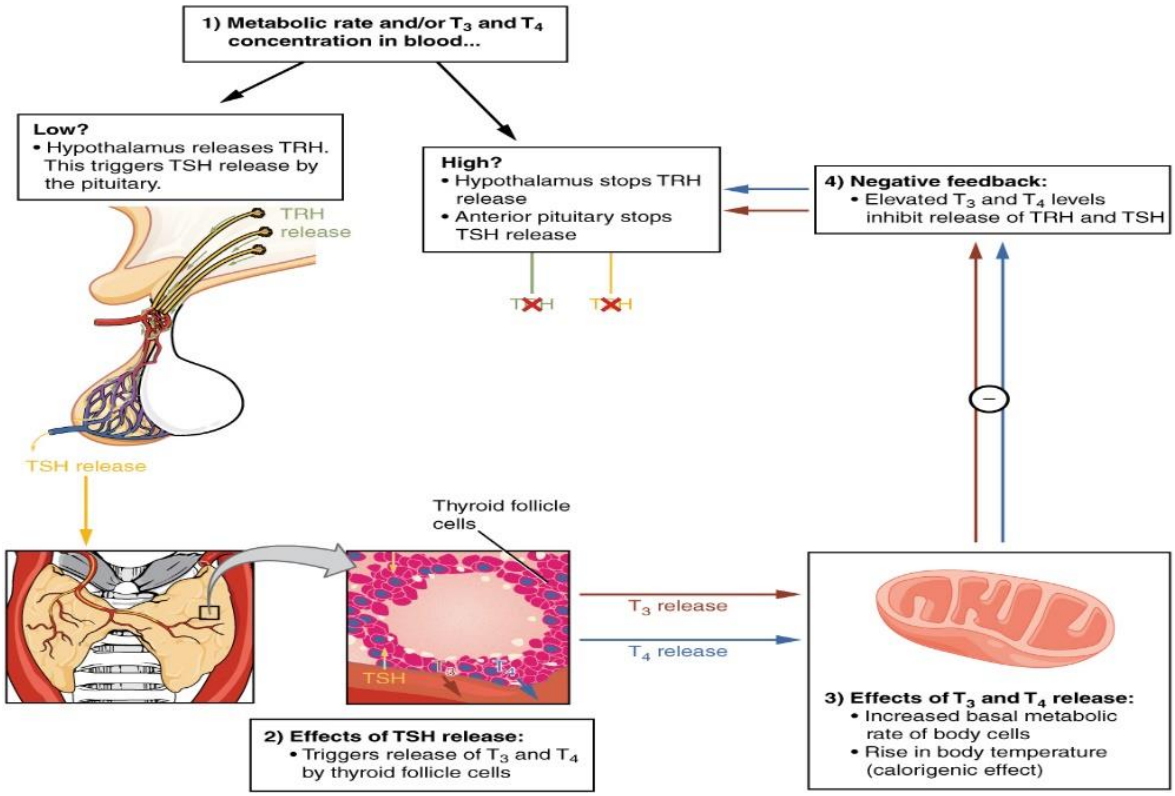


Fig: 6 Regulation of thyroid hormone

Classic Negative Feedback Loop

- A classic negative feedback loop controls the regulation of thyroid hormone levels.



Functions of Thyroid Hormones

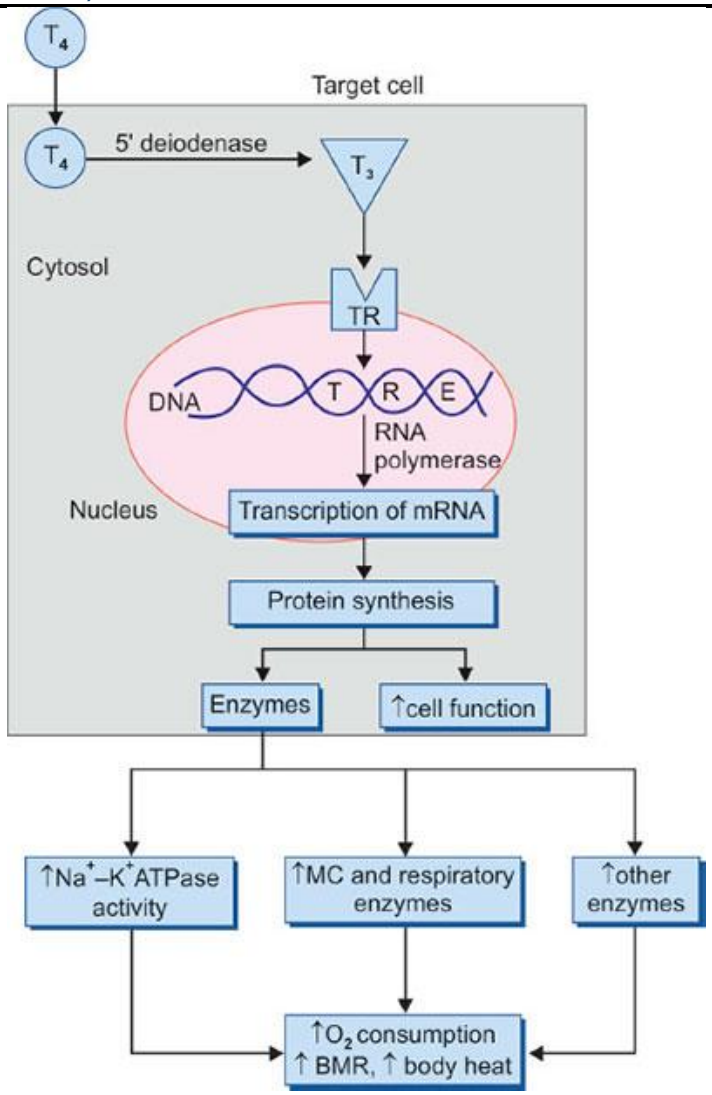
- The thyroid hormones, T_3 and T_4, are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T_3 and T_4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the

use of oxygen to produce ATP. In addition, T_3 and T_4 initiate the transcription of genes involved in glucose oxidation. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a by-product of these reactions. This so-called calorigenic effect (calor- = "heat") raises body temperature.

- Adequate levels of thyroid hormones are also required for protein synthesis and for foetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T_3 and T_4 hormones are excessive, this effect accelerates the heart rate, strengthen the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions.

Mechanism of Action of Thyroid hormones.

- The thyroid hormones have on these diverse functions are primarily mediated through binding of T3 and T4 to specific nuclear receptor sites. The nuclear action of T3 results in organ-specific increases and decreases of specific mRNAs, leading to alteration in the level of the corresponding proteins.
- Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic activity in adults; they also affect the function of virtually every organ system. Thyroid hormones must be constantly available to perform these functions. To maintain their availability, there are large stores of thyroid hormone in the thyroid gland. Furthermore, thyroid hormone biosynthesis and secretion are maintained within narrow limits by a regulatory mechanism that is very sensitive to small changes in circulating hormone concentrations.
- Thyroid hormone, in the form of triiodothyronine (T3), acts by modifying gene transcription in virtually all tissues to alter rates of protein synthesis and substrate turnover. These actions are the net result of the presence of T3 and of multiple other factors that amplify or reduce its action. Thyroid hormone action is recognized to occur by direct binding of thyroid hormone receptor (TR) to DNA, referred to as Type 1, but can be due to indirect binding of TR to DNA (type 2) or even without DNA binding (type 3). Extranuclear actions of T4 and T3 have been increasingly recognized and are mediated by interactions with membranes receptors, organelles, and components of the signal transduction system (type 4).



Metabolism

- The predominant circulating TH is the pro-hormone T4, which can be converted to the biologically more potent hormone, T3. TH metabolism is mediated by three iodothyronine deiodinases. The type 1 and type 2 enzymes (D1 and D2) convert T4 to T3 by catalysing removal of a 5′-iodine atom. By contrast, the type 3 enzyme (D3) irreversibly removes a 5-iodine atom from either T4 or T3 to generate the inactive metabolites 3,3′,5′-L-triiodo-thyronine (reverse T3, rT3) and 3,3′-diiodothyronine (T2), respectively. D1 is not expressed in skeletal cells, indicating D1 does not influence T3 action on bone directly. D2 is restricted to mature primary osteoblasts but is undetectable in chondrocytes and osteoclasts.
- The cellular influx as well as efflux of iodothyronines is known to be mediated by several specific membrane transporter proteins including the monocarboxylate transporters 8 and 10 (MCT8 and MCT10), sodium dependent organic anion co-transporting polypeptide 1 (OATP1), the sodium taurocholate co-transporting polypeptide (NTCP) and the L-type amino acid transporter 1 (LAT1) and LAT2. A study by Capello *et al* revealed that MCT8, LAT1 and LAT2 are expressed in the skeletal tissues of mice as well as in osteoblastic MC3T3-E1 cells. Thus, the intra-cellular levels of the active hormone, T3, and its availability to nuclear TH receptors (TRs) are determined by the relative activities of D2 and D3 as well as expression levels of TH transport proteins.

TH receptor/ TH action

- The major action of TH is exerted through nuclear TH receptors (TRs), which are ligand-inducible transcription factors. Based on chromosomal localization and amino acid homology, two classes of TRs, α and β, have been identified. Due to differential splicing of these two genes, multiple TRs are generated as α1, α2, α3, β1, β2, and β3, as well as three truncated forms, Δa1, Δa2, Δβ. The α2 and α3 isoforms of all the truncated receptors are non-T3 binding proteins that function as antagonists of TH signalling. TRa1 and TRβ1 are expressed in virtually all tissues, but their abundance and roles differ, depending on the developmental stage of the organism and on the particular tissue type. TRa1 is more abundantly expressed in heart, brain, and bone, while TRβ1 is more highly expressed in liver and pituitary. By contrast, expression of TRβ2 is restricted to the hypothalamus and pituitary where it mediates inhibition of TRH and TSH expression and the cochlea and retina where it regulates sensory organ development and TRβ3 is expressed in kidney, liver, and lung. Thus, TH action in target tissues is determined in part by the types and abundance of TH receptors present.
- In the nucleus, TRs form homodimers with another TR or heterodimers with retinoid X receptors (RXR) and bind to specific TH response element sequences (TREs) located in promoter regions of T3-target genes and regulate their expression in a ligand-dependent manner. Unliganded TRs bind TREs in T3 target genes and mediate transcriptional repression. Co-repressor proteins such as nuclear receptor corepressor protein/silencing mediator of retinoid and TH receptors are recruited to the RXR-TR heterodimer in the absence of T3 and inhibit target gene expression. T3 binding displaces the co-repressor, allowing co-activator proteins such as CBP/p300, pCAF, and SRC-1 to interact with the RXR-TR heterodimer and activate gene transcription in a hormone-dependent manner.
- Besides the genomic actions of T3, nongenomic mechanism of TH analogues is recognized to have downstream consequences at the level of specific gene transcription. The nongenomic mechanisms of TH are known to be initiated at the plasma membrane, in the cytoplasm or in the intracellular organelles, such as mitochondria. At the membrane level, TH may interact with integrin Av/β3 to activate ERK1/2 which culminates in regulation of ion transport systems or cell proliferation. The relative contribution of nongenomic mechanisms in mediating TH effects on skeletal development is yet to be determined.

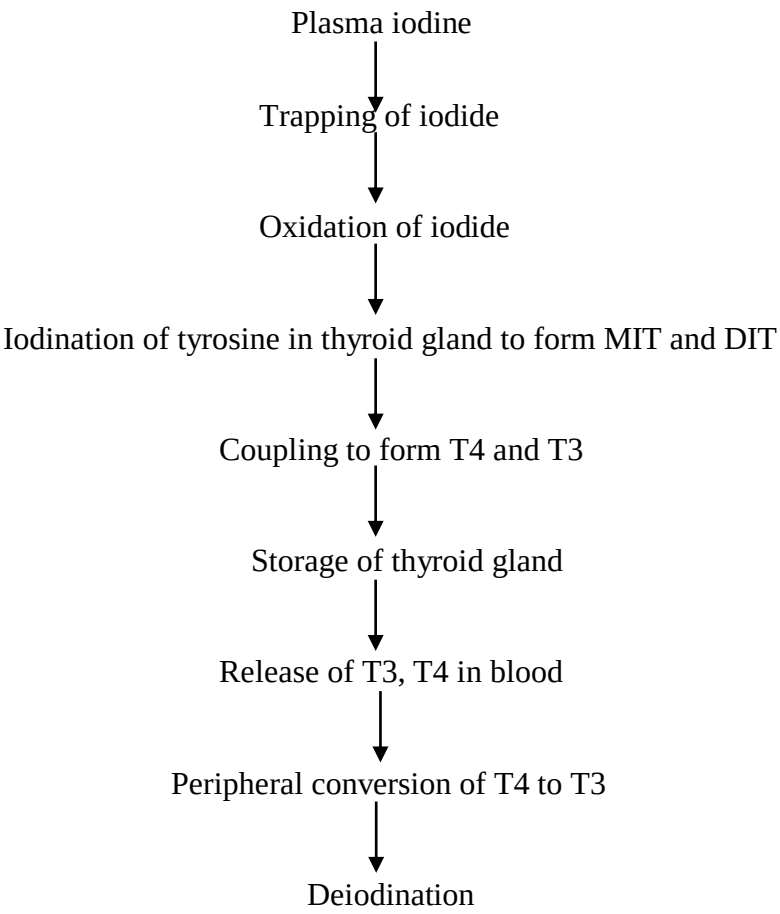
Thyroid disorder

- Thyroid disorders are of two types: hyperthyroidism and hypothyroidism. In these conditions thyroid hormone (TH) concentration only confirm the diagnosis. However, in many patients the signs or symptoms can be nonspecific, vague or mild, especially in females. In these conditions, clinicians have to rely on the laboratory for assistance in the diagnosis of thyroid disorder. All organ systems are affected by thyroid hormones. Thyroid hormone increase metabolic rate, heart rate, and vertical contractility, as well as muscle and central nervous system (CNS) excitability. Two major types of thyroid hormones are tri-iodothyronine (T3) and thyroxine (T4) released in the ratio of 20:1, respectively. Peripherally, T3 is converted to the active T4, which is three to four times more better than T4.

Hypothyroidism:

- Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones. There is a generalized slowing down of metabolic process. Most common cause of hypothyroidism is excess iodine can transiently inhibit iodine organification and thyroid hormone synthesis. Hypothyroidism is by lack of thyroid hormones. It is a common endocrine disorder caused by autoimmune thyroiditis [Hashimoto thyroiditis], iodine deficiency or following surgery or radioiodine therapy. In primary hypothyroidism TSH will be elevated and fT4 and fT3 are decreased. Primary hypothyroidism is caused by conditions namely Grave's disease and multinodular goitre, or toxic nodule in which TSH is usually very low for the clinical features help to separate these three conditions. Similarly, features of hypothyroidism may be seen in patient getting treatment for hyperthyroidism, patient who had undergone total thyroidectomy along with patient who had history of radiation. Rare conditions like congenital condition when thyroid tissue is absent, thyroid digenesis, iodine transport defect, intake of goitrogens (broccoli, cabbage) may also lead to hypothyroidism.

PATHOPHYSIOLOGY OF HYPOTRHYROIDISM:



Symptoms of hypothyroidism:

- The symptoms of hypothyroidism depend on the severity of the condition. Problems tend to develop slowly, often over several years.
- The symptoms of hypothyroidism, such as fatigue and weight gain. But the metabolism in the body continues to slow, it may develop more-obvious problems.

Hypothyroidism symptoms may include:

- Tiredness
- More sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarse voice
- Coarse hair and skin
- Muscle weakness
- Muscle aches, tenderness and stiffness
- Menstrual cycles that are heavier than usual or irregular
- Thinning hair
- Slowed heart rate, also called bradycardia
- Depression
- Memory problems

Causes of Hypothyroidism:

Hypothyroidism happens when the thyroid gland doesn't make enough hormones. Conditions or problems that can lead to hypothyroidism include:

- **Autoimmune disease:** The most common cause of hypothyroidism is an autoimmune disease called Hashimoto's disease. Autoimmune diseases happen when the immune system makes antibodies that attack healthy tissues. Sometimes that process involves the thyroid gland and affects its ability to make hormones.

- **Thyroid surgery:** Surgery to remove all or part of the thyroid gland can lower the gland's ability to make thyroid hormones or stop it completely.

- **Radiation therapy:** Radiation used to treat cancers of the head and neck can affect the thyroid gland and lead to hypothyroidism.

- **Thyroiditis:** Thyroiditis happens when the thyroid gland becomes inflamed. This may be due to an infection. Or it can result from an autoimmune disorder or another medical condition affecting the thyroid. Thyroiditis can trigger the thyroid to release all of its stored thyroid hormone at once. That causes a spike in thyroid activity, a condition called hyperthyroidism. Afterward, the thyroid becomes underactive.

- **Medicine:** A number of medicines may lead to hypothyroidism. One such medicine is lithium, which is used to treat some psychiatric disorders.

Other causes:

- **Problems present at birth:** Some babies are born with a thyroid gland that doesn't work correctly. Others are born with no thyroid gland. In most cases, the reason the thyroid gland didn't develop properly is not clear. But some children have an inherited form of a thyroid disorder. Often, infants born with hypothyroidism don't have noticeable symptoms at first. That's one reason why most states require new born thyroid screening.

- **Pituitary disorder:** A relatively rare cause of hypothyroidism is the failure of the pituitary gland to make enough thyroid-stimulating hormone (TSH). This is usually because of a noncancerous tumour of the pituitary gland.
- **Pregnancy:** Some people develop hypothyroidism during or after pregnancy. If hypothyroidism happens during pregnancy and isn't treated, it raises the risk of pregnancy loss, premature delivery and preeclampsia. Preeclampsia causes a significant rise in blood pressure during the last three months of pregnancy. Hypothyroidism also can seriously affect the developing foetus.
- **Not enough iodine:** The thyroid gland needs the mineral iodine to make thyroid hormones. Iodine is found mainly in seafood, seaweed, plants grown in iodine-rich soil and iodized salt. Too little iodine can lead to hypothyroidism. Too much iodine can make hypothyroidism worse in people who already have the condition. In some parts of the world, it's common for people not to get enough iodine in their diets. The addition of iodine to table salt has almost eliminated this problem in the United State

Risk factors

- Family history of thyroid disease.
- An autoimmune disease, such as type 1 diabetes or celiac disease.
- Received treatment for hyperthyroidism.
- Received radiation to the neck or upper chest.
- Thyroid surgery.

Complications and other related diseases

Hypothyroidism that isn't treated can lead to other health problems, including:

- **Goitre:** Hypothyroidism may cause the thyroid gland to become larger. This condition is called a goitre. A large goitre may cause problems with swallowing or breathing.

- **Heart problems:** Hypothyroidism can lead to a higher risk of heart disease and heart failure. That's mainly because people with an underactive thyroid tend to develop high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol.

- **Peripheral neuropathy:** Hypothyroidism that goes without treatment for a long time can damage the peripheral nerves. These are the nerves that carry information from the brain and spinal cord to the rest of the body. Peripheral neuropathy may cause pain, numbness and tingling in the arms and legs.

- **Infertility:** Low levels of thyroid hormone can interfere with ovulation, which can limit fertility. Some of the causes of hypothyroidism, such as autoimmune disorders, also can harm fertility.

- **Birth defects:** Babies born to people with untreated thyroid disease have a higher risk of birth defects compared with babies born to mothers who do not have thyroid disease. Infants with hypothyroidism present at birth that goes untreated are at risk of serious physical and mental development problems. But if the condition is diagnosed within the first few months of life, the chances of typical development are excellent.

- **Myxoedema coma:** This rare, life-threatening condition can happen when hypothyroidism goes without treatment for a long time. A myxoedema coma may be triggered by sedatives, infection or other stress on the

body. Its symptoms include intense cold intolerance and drowsiness, followed by an extreme lack of energy and then unconsciousness. Myxoedema coma requires emergency medical treatment.

Diagnosis of hypothyroidism

- Blood tests to check for thyroid or pituitary problems. In kids already diagnosed with thyroid or pituitary problems, those tests are used to guide treatment.
- Commonly ordered thyroid blood tests include:
- **T4 test:** This is done to measure the blood level of the hormone T4 (thyroxine). It might be done in one or both of the following ways:
- Total T4, which measures the entire amount of thyroxine in the blood, including the amount attached to blood proteins that help to carry the hormone through the bloodstream free T4, which measures only the thyroxine that's not attached to proteins. This is the part of T4 in the blood that affects how the body's cells work.
- The results of the T4 blood tests can help diagnose hyperthyroidism or hypothyroidism and guide treatment.
- **TSH test:** A thyroid stimulating hormone (TSH) test can help, tell how well the thyroid is working. If a thyroid disease prevents the gland from making enough thyroid hormone, the pituitary gland releases more TSH into the blood. If the thyroid is making too much thyroid hormone, the pituitary releases less TSH, which can lower the levels of TSH in the blood.
- **T3 total test:** The T3 total test measures the other major thyroid hormone in the blood. It often helps to diagnose hyperthyroidism.
- **Thyroid antibodies test:** Hashimoto's thyroiditis is an autoimmune condition in which the immune system attacks the thyroid gland. To diagnose it, to check for high levels of antibodies that are sign of the immune system's attack on proteins in the thyroid gland. Usually, two types of thyroid antibodies are measured: thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPO).

Treatment of Hypothyroidism

- Treatment for hypothyroidism usually includes taking the thyroid hormone medicine levothyroxine (Levo-T, Synthroid, others) every day. This medicine is taken by mouth. It returns hormone levels to a healthy range, eliminating symptoms of hypothyroidism.
- It'll likely start to feel better one or two weeks after begin the treatment. Treatment with levothyroxine likely will be lifelong. Because the dosage that need can change, by checking the TSH level every year.

Finding the right dosage

- To find the right dosage of levothyroxine, firstly check the level of TSH about 6 to 8 weeks after start taking the medicine. It needs another blood test to check TSH again six months later. Too much levothyroxine can cause side effects, such as:
    - Tiredness
    - Increased appetite
    - Sleep problems
    - Shakiness
    - Pounding of the heart, sometimes called heart palpitations
- Levothyroxine typically causes no side effects when used in the correct dose. If change in brands of the medicine, as the dosage may need to change.
- If the person suffering with coronary artery disease or severe hypothyroidism, then start treatment with a smaller amount of medicine and then slowly increase the dosage. This allows the heart to adjust to the rise the body's metabolism.

Taking levothyroxine correctly

- Levothyroxine is best taken on an empty stomach at the same time every day. Ideally, it takes the hormone in the morning, and then wait 30 to 60 minutes before eat or take other medicine. If the patient takes the medicine at bedtime, wait to take it until at least four hours after the last meal or snack.
- Don't skip doses or stop taking the medicine because feel better. If they do, it's likely that the symptoms of hypothyroidism will slowly return. If miss a dose of levothyroxine, take two pills the next day.
- Some medicines, supplements and even some foods may affect the body's ability to absorb levothyroxine. If eat large amounts of soy products, or if typically eat a high-fibre diet. Also, if take other medicines, especially:
    - Iron supplements or multivitamins that contain iron
    - Aluminium hydroxide, which is found in some antacids
    - Calcium supplements

HYPERTHYROIDISM:

- Hyperthyroidism, also called overactive thyroid, is when the thyroid gland makes more thyroid hormones than the body needs. The thyroid is a small, butterfly-shaped gland in front of the neck. Thyroid hormones control the way the body uses energy, so they affect nearly every organ in body, even the way the heart beats. With too much thyroid hormone, many of the body's functions speed up.
- In females with hyperthyroidism hormonal changes effecting reproductive system may occur. Have reported that androstenedione and testosterone production increases in hyperthyroidism and subsequently this leads to elevation of estrone and oestradiol. Both this mechanism and decreases metabolic clearance of oestrogen lead to higher plasma oestrogen levels in females with hyperthyroidism. Infertility incidence is about 5-8% in females with hyperthyroidism.

PATHOPHYSIOLOGY OF HYPERTHYROIDISM

Hyperthyroidism characterised by loss normal regulatory control of thyroid hormone secretion.

↓

Increase sympathetic nervous system activity.

↓

Alteration secretion and metabolism of hypothalamic pituitary and gonadal hormone.

↓

Excessive amount of thyroid hormone stimulates the cardiac system and increases the adrenergic receptors.

↓

Tachycardia and increases cardiac output, stroke volume and peripheral blood flow.

↓

Negative nitrogenous balance, lipid depletion and the resultant state of nutritional deficiency.

↓

Causes Hyperthyroidism.

Symptoms of Hyperthyroidism

- Hyperthyroidism sometimes looks like other health problems. That can make it hard to diagnose. It can cause many symptoms, including:

- Losing weight without trying
- Fast heartbeat, a condition called tachycardia
- Irregular heartbeat, also called arrhythmia
- Pounding of the heart, sometimes called heart palpitations
- Increased hunger
- Nervousness, anxiety and irritability

- Tremor, usually a small trembling in the hands and fingers
- Sweating
- Changes in menstrual cycles
- Increased sensitivity to heat
- Changes in bowel patterns, especially more-frequent bowel movements
- Enlarged thyroid gland, sometimes called a goitre, which may appear as a swelling at the base of the neck
- Tiredness
- Muscle weakness
- Sleep problems
- Warm, moist skin
- Thinning skin
- Fine, brittle hair

Causes of Hyperthyroidism

Medical conditions and situations that can cause hyperthyroidism include:

- **Graves' disease**: In this disorder, the immune system attacks the thyroid. This makes the thyroid create too much thyroid hormone. Graves' disease is a hereditary condition (passed down through a family). If a member of the family has Graves' disease, there's a chance other in the family could have it, too. It's more common in people assigned female at birth than people assigned male at birth. Graves' disease is the most common cause of hyperthyroidism, making up about 85% of cases.
- **Thyroid nodules**: A thyroid nodule is a lump or growth of cells in the thyroid gland. They can produce more hormones than the body needs. Thyroid nodules are rarely cancerous.
- **Thyroiditis**: Thyroiditis is inflammation of the thyroid gland, which may be painful or painless (silent). It may happen within a year of delivering a baby (postpartum thyroiditis). After you experience of thyroiditis, the thyroid may be unable to recover, which would lead to hypothyroidism.
- **Consuming excess iodine:** If there is any risk for hyperthyroidism and consume too much iodine (through your diet or medications), it can cause the thyroid to produce more thyroid hormone. Iodine is a mineral that the thyroid uses to create thyroid hormone. Receiving intravenous iodinated contrast (iodine "dye") may also cause hyperthyroidism. Amiodarone, a medication that contains a high amount of iodine, may also cause hyperthyroidism.

Risk factors

Risk factors for hyperthyroidism include:

- Hereditary of thyroid disease, particularly Graves' disease.
- Chronic illnesses, including pernicious anaemia and primary adrenal insufficiency.
- A recent pregnancy, which raises the risk of developing thyroiditis.

Complications and other related diseases

Hyperthyroidism can lead to the following complications.

Heart problems

Some of the most serious complications of hyperthyroidism involve the heart, including:

- A heart rhythm disorder called atrial fibrillation that increases the risk of stroke.
- Congestive heart failure, a condition in which the heart can't circulate enough blood to meet the body's needs.

Brittle bones

Untreated hyperthyroidism can lead to weak, brittle bones. This condition is called osteoporosis. The strength of bones depends, in part, on the amount of calcium and other minerals in them. Too much thyroid hormone makes it hard for the body to get calcium into bones.

Vision problems

Some people with hyperthyroidism develop a problem called thyroid eye disease. It's more common in people who smoke. This disorder affects the muscles and other tissues around the eyes.

Symptoms of thyroid eye disease include:

- Bulging eyes
- Gritty sensation in the eyes
- Pressure or pain in the eyes
- Puffy or retracted eyelids
- Reddened or inflamed eyes
- Light sensitivity
- Double vision
- Eye problems that go untreated may cause vision loss

Discoloured, swollen skin

- In rare cases, Graves' disease develops Graves' dermopathy. This causes the skin to change colours and swell, often on the shins and feet.

Thyrotoxic crisis

This rare condition also is called thyroid storm. Hyperthyroidism raises the risk of thyrotoxic crisis. It causes severe, sometimes life-threatening symptoms. It requires emergency medical care. Symptoms may include:

- Fever
- Fast heartbeat

- Nausea
- Vomiting
- Diarrhoea
- Dehydration
- Confusion
- Delirium

Diagnosis of Hyperthyroidism

Hyperthyroidism is diagnosed with a medical history, physical exam and blood tests. Depending on the results of the blood tests, If may need other tests too.

Medical history and physical exam: During the exam, health care provider may check for:

- Slight tremor in your fingers and hands
- Overactive reflexes
- Rapid or irregular pulse
- Eye changes
- Warm, moist skin

Health care provider also examines the thyroid gland as swallow to see if it's larger than usual, bumpy or tender.

- **Blood tests:** Blood tests that measure the hormones T-4 and T-3 and thyroid-stimulating hormone (TSH) can confirm a diagnosis of hyperthyroidism. A high level of T-4 and a low level of TSH is common in people with hyperthyroidism.
- Blood tests are particularly important for older adults because they may not have classic symptoms of hyperthyroidism.
- Thyroid blood tests may give false results if you take biotin. Biotin is a B vitamin supplement that also may be found in multivitamins. Tell your health care provider if you are taking biotin or a multivitamin with biotin. To make sure your blood test is accurate, your health care provider may ask you to stop taking biotin 3 to 5 days before the test.

If blood test results show hyperthyroidism, your health care provider may suggest one of the following tests. They can help find out why your thyroid is overactive.

Radioiodine scan and uptake test: For this test take a small dose of radioactive iodine called radioiodine, to see how much of it collects in the thyroid gland and where it collects in the gland.

If the thyroid gland takes in a high amount of radioiodine that means the thyroid gland is making too much thyroid hormone. The most likely cause is either Graves' disease or overactive thyroid nodules.

If the thyroid gland takes in a low amount of radioiodine, that means hormones stored in the thyroid gland are

leaking into the bloodstream. In that case, it's likely causing thyroiditis.

Thyroid ultrasound: This test uses high-frequency sound waves to make images of the thyroid. Ultrasound may be better at finding thyroid nodules than are other tests. There's no exposure to radiation with this test, so it can be used for people who are pregnant or breastfeeding, or others who can't take radioiodine

Treatment of Hyperthyroidism

There are several treatments available for hyperthyroidism. The best approach is depends on the age and health. The underlying cause of hyperthyroidism and how severe it makes a difference too. The personal preference also should be considered to decide on a treatment plan. Treatment may include:

Anti-thyroid medicine: These medications slowly ease symptoms of hyperthyroidism by preventing the thyroid gland from making too many hormones. Anti-thyroid medications include methimazole and propylthiouracil. Symptoms usually begin to improve within several weeks to months.

Treatment with anti-thyroid medicine typically lasts 12 to 18 months. After that, the dose may be slowly decreased or stopped if symptoms go away and if blood test results show that thyroid hormone levels have returned to the standard range. For some people, anti-thyroid medicine puts hyperthyroidism into long-term remission. But other people may find that hyperthyroidism comes back after this treatment.

Although rare, serious liver damage can happen with both anti-thyroid medications. But because propylthiouracil has caused many more cases of liver damage, it's generally used only when people can't take methimazole. A small number of people who are allergic to these medicines may develop skin rashes, hives, fever or joint pain. They also can raise the risk of infection.

Beta blockers: These medicines don't affect thyroid hormone levels. But they can lessen symptoms of hyperthyroidism, such as a tremor, rapid heart rate and heart palpitations. Sometimes, health care providers prescribe them to ease symptoms until thyroid hormones are closer to a standard level. These medicines generally aren't recommended for people who have asthma. Side effects may include fatigue and sexual problems.

Radioiodine therapy: The thyroid gland takes up radioiodine. This treatment causes the gland to shrink. This medicine is taken by mouth. With this treatment, symptoms typically lessen within several months. This treatment usually causes thyroid activity to slow enough to make the thyroid gland underactive. That condition is hypothyroidism. Because of that, over time, if may need to take medicine to replace thyroid hormones.

Thyroidectomy: This is surgery to remove a part or all of the thyroid gland. It is not used often to treat hyperthyroidism. But it may be an option for people who are pregnant. It also may be a choice for those who can't take anti-thyroid medicine and don't want to or can't take radioiodine therapy.

Risks of this surgery include damage to the vocal cords and parathyroid glands. The parathyroid glands are four tiny glands on the back of the thyroid. They help control the level of calcium in the blood.

People who have a thyroidectomy or radioiodine therapy need lifelong treatment with the medicine levothyroxine (Levoxyl, Synthroid, others). It supplies the body with thyroid hormones. If the parathyroid glands are removed during surgery, medicine also is needed to keep blood calcium in a healthy range.

Medications used for Thyroid disorders

- Our thyroid gland is a butterfly-shaped gland that is located just below the Adam's apple, along the front of the windpipe. Even though thyroid hormones are made in the thyroid gland, the production of these hormones is regulated by another hormone, called thyroid stimulating hormone (TSH), which is made by the pituitary gland (a pea-shaped organ found at the base of the brain). If thyroid hormone levels are low, then our metabolism and many other body functions slow down
- Thyroid drugs (thyroid hormones) are used to supplement low thyroid levels in people with hypothyroidism.
- Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormones to meet the needs of the body. Doctors may use the term "an underactive thyroid gland" to describe hypothyroidism.
- Another condition, called hyperthyroidism, is when the thyroid produces too much thyroid hormone. Although hyperthyroidism seems to be the opposite of hypothyroidism, the link between them is complex, and one can led to the other in certain circumstances.
- Thyroid drugs are used to treat hypothyroidism, also referred to as an underactive thyroid.
- Even though the thyroid produces two hormones, T3 and T4, T4 is most commonly prescribed to treat hypothyroidism.

Thyroid hormone preparations can be divided into two categories:

- Natural preparations derived from animal thyroid
- Synthetic preparations manufactured in a laboratory.

Natural preparations include desiccated thyroid and thyroglobulin.

- The most common medication used for supplementation is synthetic thyroxine, also called levothyroxine. This is identical to the T4 hormone. T4 is converted into T3 in the body.
- Liothyronine (T3, also called triiodothyronine) is another thyroid hormone that may be prescribed to people who are unable to properly convert T4 into T3.
- Liotrix is a combination of levothyroxine (T4) and liothyronine (T3) in a 4:1 ratio. Although the ratio remains the same, there are multiple strengths of this medication, so ensure you receive the correct dose. It is important that levothyroxine is taken on an empty stomach at least 30 to 60 minutes before breakfast

to ensure that it is absorbed properly. It should be taken with a big glass of water, and spaced apart by at least four hours from antacids or supplements such as calcium or iron.

Side-effects

- Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, they may need medical attention.
- Check with the doctor immediately if any of the following side effects occur:

Ingredients	Brand name examples
levothyroxine	Levoxyl, Synthroid, Tirosint, unithroid
liothyronine	Cytomel, Triostat
liotrix	Thyroral-1
Thyroid desiccated	Armour thyroid

Less common

- Cough
- fever or chills (continuing or severe)
- general feeling of discomfort, illness or weakness
- hoarseness
- mouth sores
- pain, swelling, or redness in joints
- throat infection

More common

- Fever (mild and temporary)
- skin rash or itching

Rare

- black, tarry stools
- blood in urine or stools
- increase in bleeding or bruising
- increase or decrease in urination
- numbness or tingling of fingers, toes, or face
- pinpoint red spots on skin
- shortness of breath

- swelling of feet or lower legs
- swollen lymph nodes
- swollen salivary glands

Symptoms of overdose

- Changes in menstrual periods
- coldness
- constipation
- dry, puffy skin
- headache
- listlessness or sleepiness
- muscle aches
- swelling in the front of the neck
- unusual tiredness or weakness
- weight gain (unusual)

Unwanted side effects: Some side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

Less common

- Dizziness
- loss of taste (for methimazole)
- nausea
- stomach pain
- vomiting

PATIENT CARE IN THYROID DISORDER

Once the diagnosis of Grave's disease with hyperthyroidism has been established, the patient should be given a complete explanation of the illness and options for treatment. The goal is to involve the patient as a partner in the medical decision-making process and care, rather than have the endocrinologist dictate the choice of therapy. Patients who elect to receive, radioactive iodine should be given an explanation of the treatment, and a consent form for such therapy should be signed. After receiving radioactive iodine, patients should be given an instruction sheet that itemizes appropriate precautions and explains follow-up Management. The radioactive iodine uptake should be assessed before treatment to ensure adequate uptake at the time of therapy, to rule out the presence of a variant of thyroiditis or iodine contamination, and to help determine the dose of radioactive iodine. A thyroid scan is also useful in distinguishing toxic nodular goitre and toxic adenoma from Graves' disease. Typically, toxic

nodular goitre is more resistant to radioactive iodine and frequently necessitates use of a larger dose. ß Adrenergic antagonists provide symptomatic relief and can be administered before radioactive iodine is given. Because patients with hyperthyroidism may be relatively resistant to the effects of ß adrenergic blocking agents, larger and more frequent doses may be necessary. The dose of these drugs can be tapered and discontinued once the patient no longer has hyperthyroidism. In addition, in severe thyrotoxic states, adjuvant treatment can include organic or inorganic iodides and anti-thyroid drugs after radioactive iodine therapy. After treatment with radioactive iodine, patients should have follow-up examinations at frequent intervals (varying from 4 to 6 weeks, but individualized for each case) until they are euthyroid and their condition is stable. Most patients will require full thyroid hormone replacement therapy. Patients usually become hypothyroid within 3 months and could begin receiving partial replacement doses of levothyroxine approximately 2 months after receiving radioactive iodine. This schedule is determined by laboratory testing and clinical evaluation. At this time, the patient's thyroid status is quickly changing from euthyroid to hypothyroid, and the TSH level may not be a good indicator of function because it fails to increase quickly. From 2 weeks to several months may elapse before TSH responsiveness is recovered, and free thyroid hormone estimate tests are more accurate than TSH values during this interval. When the condition of patients has stabilized, the frequency of visits and re-evaluations can be extended. A common schedule for follow-up consultations is at 3 months, at 6 months, and then annually, but this can be modified on the basis of the physician's judgment.

Conclusion

Finally, The **thyroid**, or **thyroid gland**, is an endocrine gland in vertebrates. In humans, it is in the neck and consists of two connected lobes. The lower two thirds of the lobes are connected by a thin band of tissue called the thyroid isthmus. The thyroid is located at the front of the neck, below the Adams apple. Microscopically, the functional unit of the thyroid gland is the spherical thyroid follicle, lined with follicular cells (thyrocytes), and occasional parafollicular cells that surround a lumen containing colloid. The thyroid gland secretes three hormones: the two thyroid hormones – triiodothyronine(T3) and thyroxine(T4) – and a peptide hormone, calcitonin. The thyroid hormones influence the metabolic rate and protein synthesis and growth and development in children. Calcitonin plays a role in calcium homeostasis. Secretion of the two thyroid hormones is regulated by thyroid-stimulating hormone (TSH), which is secreted from the anterior pituitary gland. TSH is regulated by thyrotropin releasing hormone (TRH), which is produced by the hypothalamus.

Thyroid disorders include hyperthyroidism, hypothyroidism, thyroid inflammation(thyroiditis), thyroid enlargement (goitre), thyroid nodules, and thyroid cancer. Hyperthyroidism is characterized by excessive secretion of thyroid hormones: the most common cause is the autoimmune disorder grave's disease. Hypothyroidism is characterized by a deficient secretion of thyroid hormones: the most common cause is iodine deficiency. In iodine-deficient regions, hypothyroidism secondary to iodine deficiency is the leading cause of preventable intellectual disability in children. In iodine-sufficient regions, the most common cause of hypothyroidism is the autoimmune disorder Hashimoto's thyroiditis.

An increase or decrease in the thyroid hormone secretion leads to different clinical and pathological changes. Causes, pathogenetic mechanisms and symptoms finding of hyperthyroidism and hypothyroidism. More research

is needed to understand effect of treatment of subclinical thyroid dysfunction and screen-detected, undiagnosed over thyroid disease.

The pathology of the thyroid gland presents the pathologist with a particular set of diagnostic problems. If best practice and the minimum data set guidelines are adhered to, the correct diagnosis should be reached in most cases. Newer techniques such as immunocytochemistry can certainly be helpful in more difficult cases but, as in all areas of pathology, histological features take precedence and good communication with the relevant clinical colleagues is paramount.

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