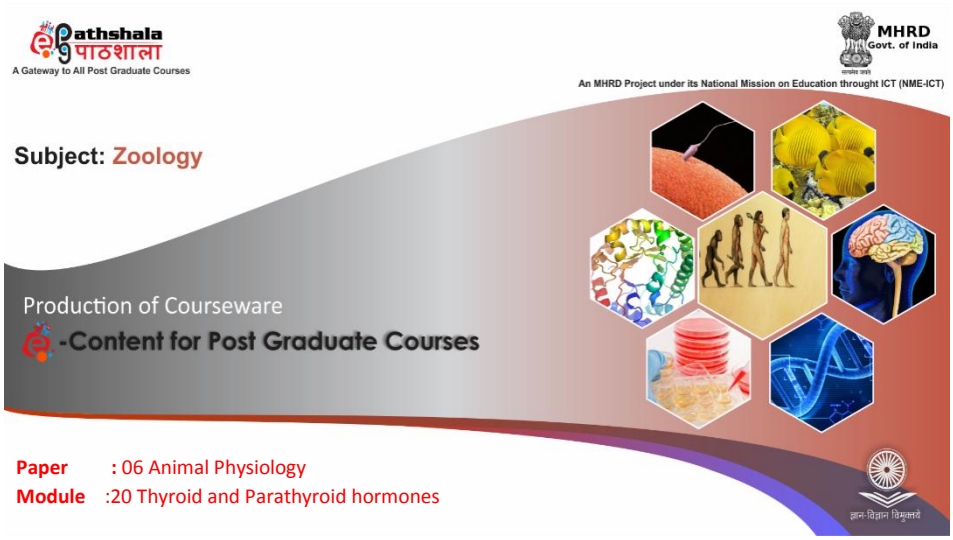

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ZOOLOGY

Animal Physiology

Thyroid and Parathyroid Hormones

Description of Module	
Subject Name	ZOOLOGY
Paper Name	Zool 006 Animal Physiology
Module Name/Title	Neuro-endocrine Physiology
Module Id	M20 Thyroid and Parathyroid Hormones
Keywords	Thyroid gland, colloid filled follicles, follicular cells, thyroid hormone, parafollicular cells, calcitonin, thyroxine, triidothyronine, thyroglobulin, parathyroid gland, chief cells, parathyroid hormone, calcium homeostasis

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PART A - THYROID HORMONE

1. Learning Outcomes

After studying this module, you shall be able to understand,

- The location, structure, and anatomy of thyroid gland.
- Synthesis, regulation, and mechanism of the thyroid hormones.
- Various functions of the thyroid hormone
- Disorders associated with any impairment in the functioning of the gland.
- Causes, symptoms and treatment for various disorders associated.

2. Introduction

The nomenclature of the thyroid gland comes from its close relation to the **thyroid cartilage** (derived from Greek word *thyreoeides* meaning shield-shaped) and it protect the vocal cords.

Also thyroid gland clasps anterior and lateral surface of pharynx, larynx, and trachea "like a shield".

It is a one of the largest pure endocrine, brownish-red gland located immediately below the larynx (housing voice box) on each side of and anterior to the trachea. It is the only gland that consists of two lobes attached together by an isthmus (Figure.1). Contrary to most of the endocrine glands having cells, tissues, or organs arranged in cords or clumps, thyroid has its cells arranged into spherical structures, called follicles. It is highly vascularized gland and has rich network of capillaries that allows easy passage of thyroid hormones into the blood.

The weight of the gland varies form 15 to 20 grams in adults and secretes two major hormones, **thyroxine** (T4), and **triiodothyronine** (T3), collectively called thyroid hormone. Both of these hormones modulate energy utilization, heat production, and facilitate growth. Imbalance in the level of thyroid hormones leads to several disorders. **Calcitonin**, an important hormone for the maintenance of calcium homeostasis is also synthesized by parafollicular cells of the thyroid gland.

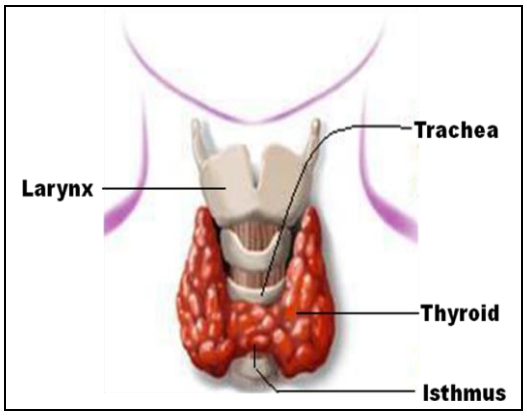


Figure 1. Location of thyroid gland – Consists of two lobes on either side of the trachea below larynx

3. Structure and Anatomy of Thyroid Gland

The butterfly-shaped **thyroid gland** is located against and around the front of the larynx (behind the thyroid cartilage) and trachea composed of two pear shaped, right and left **lateral lobes,** one on either side of the trachea. The right lobe (lobus dexter) is often larger than left

(lobus sinister) and are connected by an **isthmus.** Thyroid cartilage lies just above the gland and behind the Adam's apple. Each lobe is 50-60 mm long, with the superior poles extending to the thyroid cartilage, and the lower poles diverge laterally at the level of fourth to sixth tracheal rings. Small, **pyramidal-shaped lobe** (Lalouette's pyramid) sometimes extends upward from the isthmus towards the hyoid bone to which it may be attached by a fibromuscular band.

The gland has its own double layered thin fibrous capsule and is enclosed by an envelope of pretracheal fascia, attaching the gland to the cricoid cartilage and upper tracheal rings (**suspensory ligament of Berry**). This arrangement causes the thyroid to move up and down with larynx during swallowing. The inner layer of the fibrous capsule enters the gland to form septa and divide the gland into microscopic lobules. Four parathyroid glands, two on each side, lie on each side at the back of the thyroid lobes.

It is highly vascularized gland and receives 80–120 mL of blood per minute. Each thyroid lobe is supplied by a superior and an inferior thyroid artery and drained by three veins (Figue.2):

1. **superior thyroid veins** - drain superior poles
2. **middle thyroid veins** - drain lateral parts
3. **inferior thyroid veins** - drain inferior poles

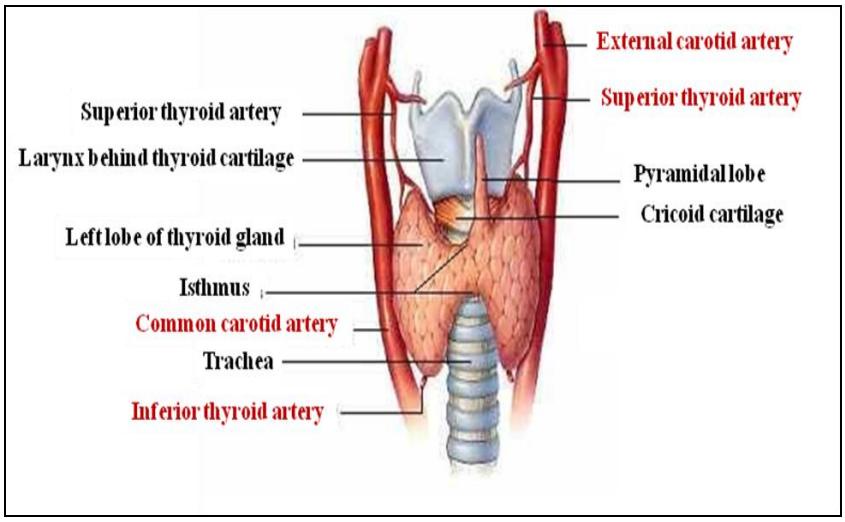


Figure 2. Structure and Blood Supply to the Thyroid Gland

Anatomy

Spherical colloid filled follicles of variable size are the characteristic identification feature of thyroid gland. Follicles (100 to 300 micrometers in diameter) are structural and functional units of the thyroid gland, and lined by **follicular cells** also known as principal cells. Follicular cells rest on a basement membrane and are responsible for the secretion of thyroid hormone (T_3 and T_4). They synthesize, release and store their product in the lumen of follicles as **acidophilic colloid** and secret the thyroid hormone to the blood stream when stimulated by thyroid stimulating hormone (TSH) from the anterior pituitary. Follicular cells are normally cuboidal in shape but become columnar when stimulated & squamous when inactive.

Besides follicular cells, the gland also contains large, pale-staining interfollicular cells, **parafollicular cells** or **C cells** located within the follicular epithelium as single cells or as cell clusters adjacent the follicles. They synthesize and secrete the hormone **calcitonin/thyrocalcitonin,** responsible for calcium metabolism & homeostasis in the body.

Thyroid gland is further divided into various lobules by the connective tissue septa that extend from the capsule of the gland. These septa also serve as conduits for blood vessels, lymphatic vessels, & nerves.

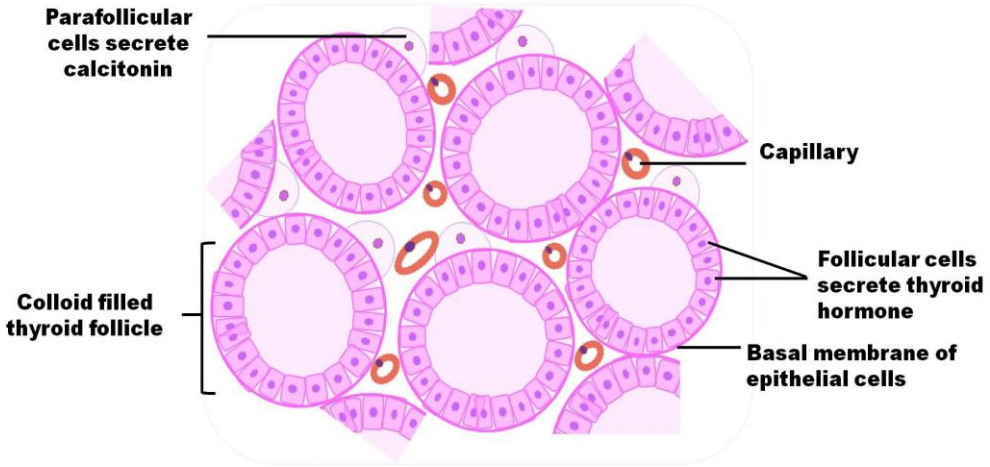


Figure 3. Detailed Microscopic Section of Thyroid Gland
(Source: Author)

4. Thyroid Hormone

Thyroid gland synthesizes primarily two iodine-containing hormones, **thyroxine (T_4)** and **triiodothyronine (T_3)** along with a peptide hormone **calcitonin**. T_4 and T_3 hormones have same qualitative functions however they differ in rapidity and intensity of action. T_3 is the active hormone and three to four times more potent than thyroxine. Besides its high metabolic effect, only 7% of the total hormone is secreted as T_3 and remaining 93% as T_4 because the latter has longer half-life. Contrary to high level of T_4 in the blood, almost all of it is converted to T_3 before acting on the genes of target cells by removal of one iodide because intracellular receptors for thyroid hormone have very high affinity for T_3. Therefore, T_3 is the functional form of thyroid hormone in the cells and also produced by deiodination of T_4 in liver, kidney, brain and pituitary.

4.1. Synthesis of thyroid hormone

1. Iodide trapping – Synthesis and secretion of thyroid hormone takes place in the follicular cells of thyroid follicles. Iodides ($\mathbf{I^-}$) taken orally are absorbed through gastrointestinal tract into the blood and the circulating iodide is further co-transported with sodium ions ($\mathbf{Na^+}$) through the basal membrane to the cytoplasm of follicular cells using **sodium- iodide symporter**. The thyroid gland can actively concentrate 30-times more iodide against its concentration gradient in blood (recommended minimum intake is 150 µg/day).

2. Synthesis of thyroglobulin – Thyroglobulin (TG) a glycoprotein (MW – 660 kDa), is synthesized like any other secretory protein in the rough endoplasmic reticulum and glycosylated in Golgi apparatus of follicular cells. The thyroglobulin molecules are then packed into the secretory vesicles and delivered to the follicular lumen through exocytosis. The glycoprotein contains about 70 tyrosine amino acids that are major substrates to combine with iodine to form the thyroid hormones.

3. Oxidation of iodide and organification – Iodide ions are not capable of combining with tyrosine amino acids therefore, oxidized rapidly to the iodine free radicals at the lumen surface of the follicular cells. The enzyme **thyroid peroxidase** (TPO) synthesized in the follicular cells catalyzes the oxidation of iodide ions ($\mathbf{2I^- \longrightarrow I_2}$) and incorporation of activated

iodine molecules to the phenolic rings of one sixth of the tyrosine amino acid within the thyroglobulin a process known as **organification**.

Iodine molecules are added at the 3' and 5' positions to form diiodotyrosine (DIT) and only at the 3' position to produce monoiodotyrosine (MIT).

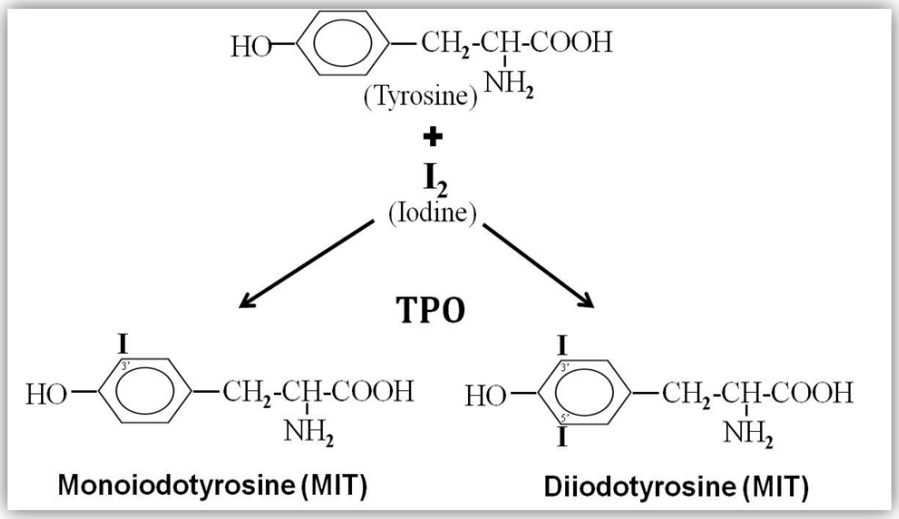
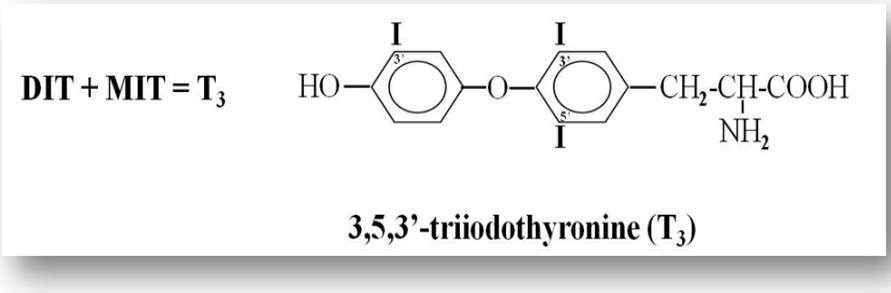
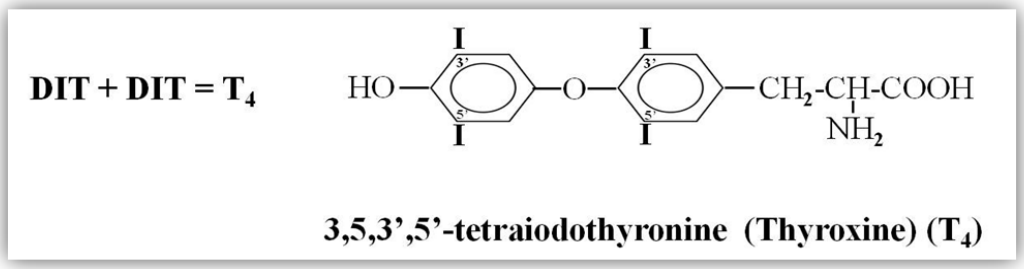


Figure 4. Organification of the tyrosine amino acid in the presence of enzyme TPO to synthesize monoiodotyrosine and diiodotyrosine

4. Coupling – In the coupling reaction mediated by enzyme TPO, phenolic ring of MIT or DIT is removed from the remainder of its tyrosine and coupled to another DIT on the thyroglobulin molecule. This forms a bound thyroid hormone residue. If two DIT molecules are coupled, the result is thyroxine (T_4) and if one MIT and one DIT are coupled, the result is triiodothyronine (T_3) that remains as a part of thyroglobulin in colloid.



(A)



(B)

Figure 5. Coupling reaction to synthesize T_3 (A) and T_4 (B) catalyzed by enzyme TPO

5. Storage: Each thyroglobulin molecule contains approximately 30 T_4 molecules and a few T_3 molecules and they can be stored in this form for 2 to 3 months.

6. Release of thyroid hormone into the circulation:

Thyroxine and triodothyronine are cleaved from the thyroglobulin before getting secreted to the blood stream. The coupled thyroglobulins in the colloid are engulfed by apical surface of the follicular cells to form pinocytic vesicles. These vesicles then fuse with lysosomes and acted upon by proteases, cleaving off molecules of T_3 and T_4. Being lipid soluble T_3 and T_4, enter the blood stream by diffusion. Thyroid gland release three T_4, T_3, and reverse T_3 (inactive form of T_3) to the circulation.

Role of Deiodinases

Besides being synthesized by coupling of DIT and MIT, circulating T_3 (3,5,3',-triiodothyronine) is also derived from 5'-deiodination of circulating T_4 (3,5,3',5'-tetraiodothyronine) in the peripheral tissues by the reaction catalyzed by enzyme **deiodinases.** Deiodination at inner ring produces hormone, reverse T_3 (3,3,5'-triiodothyronine), an isomer of T_3 and biologically inactive enzyme.

The follicular cells contain an enzyme "**deiodinase**" that remove the iodide from inactive iodotyrosine, MIT & DIT, allowing the freed iodide to be recycled for synthesis of more hormone because only 25% of DIT & MIT give rise to thyroid hormones. Thus, deiodinases helps in metabolism of thyroid hormone

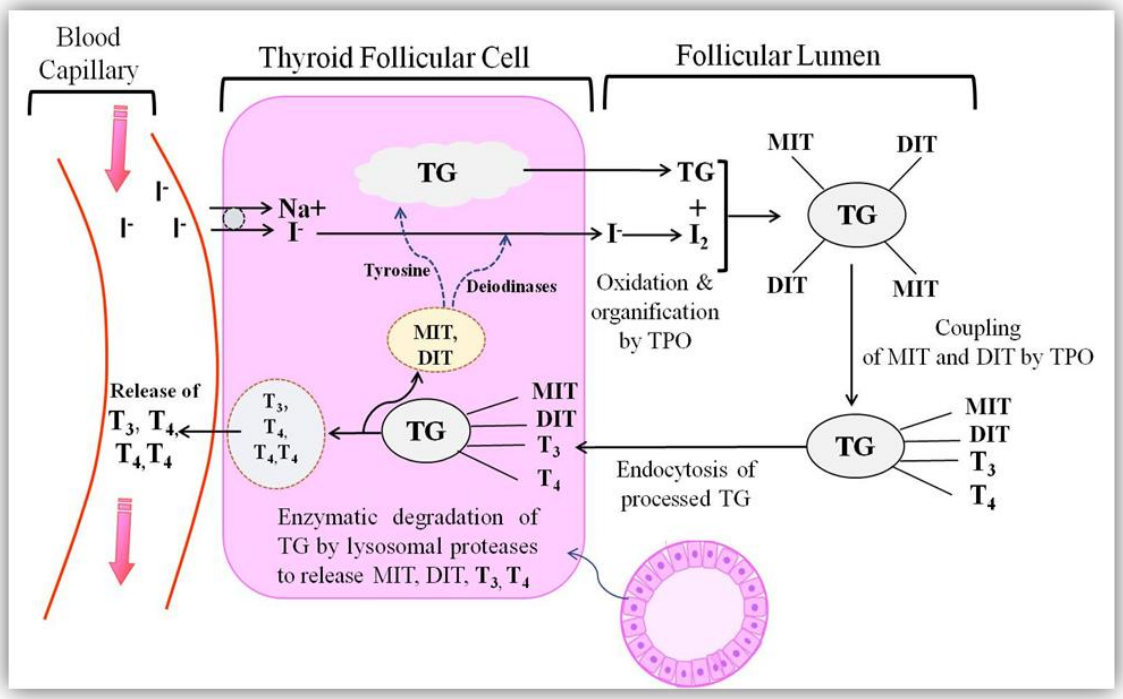


Figure 6. Pathway for Synthesis and Release of Thyroid Hormone

(**Source**: Author)

4.2. Transport of thyroid hormones

Thyroid hormones circulate in blood in an inactive form, bound to 3 different plasma proteins synthesized by the liver.

a. Thyroxine binding globulin (TBG) - 75%

b. Thyroxine binding pre-albumin (TBPA)/Transthyretin – 10-15%

c. Plasma albumin (serum albumin) - 7%

T_3 has less affinity for the plasma proteins and binds loosely with them, so that it releases quickly. Therefore, T_3 acts on the target cells immediately and T_4 acts slowly. Only very little T_3 (0.25-0.3%) & T_4 (0.03%) are carried in the blood in the free active form.

4.3. Regulation of Thyroid Hormone

To maintain the normal levels of metabolic activity, it is important to maintain right amount of thyroid hormone in the blood and this regulation is achieved by **thyroid stimulating hormone** (TSH) also known as **thyrotropin** released by the anterior pituitary in response to

TRH (thyrotropin [=TSH] releasing hormone) from hypothalamus. Low blood levels of T_3 and T_4 or low metabolic rate stimulate the release of TRH and then TSH. TSH stimulates the follicular cells by binding to TSH receptors present on the basal membrane thereby activating "second messenger system" of the cell. Association of TSH with the receptors increases cAMP formation and cAMP further acts as a second messenger to activate protein kinase, and cause multiple phosphorylations to increase the secretion of thyroid hormones by follicular cells. TSH influence almost all the functions of follicular cells (increases DNA replication, transcription, translation and cell division, and increases the amount of RER and other cellular machinery required by follicular cells for protein synthesis) and fall into different categories depending on the time taken to respond:

1) **short term effects** (minutes): increased phagocytosis and proteolysis of thyroglobulin to release T_3 and T_4 within 30 minutes.

2) **intermediate term effects** (hours): increase the activity of iodide pump, iodine trapping and activation of iodine, hydrogen peroxide generation, TG synthesis and transport, T_3:T_4 ratio and recovery of iodide from free MIT and DIT by thyroid deiodinases.

3) **long term effects** (days to weeks): thyroid hypertrophy and hyperplasia.

The basic control mechanism of TSH production is the negative feedback action of thyroid hormone on the anterior pituitary and, to a lesser extent, the hypothalamus. Constant concentration of free thyroid hormones in the circulating body fluids (elevated level of T_3) inhibits release of TRH and TSH (**negative feedback inhibition**).

Conditions that increase ATP demand—a cold environment, hypoglycemia, high altitude, and pregnancy—also increase the secretion of the thyroid hormones.

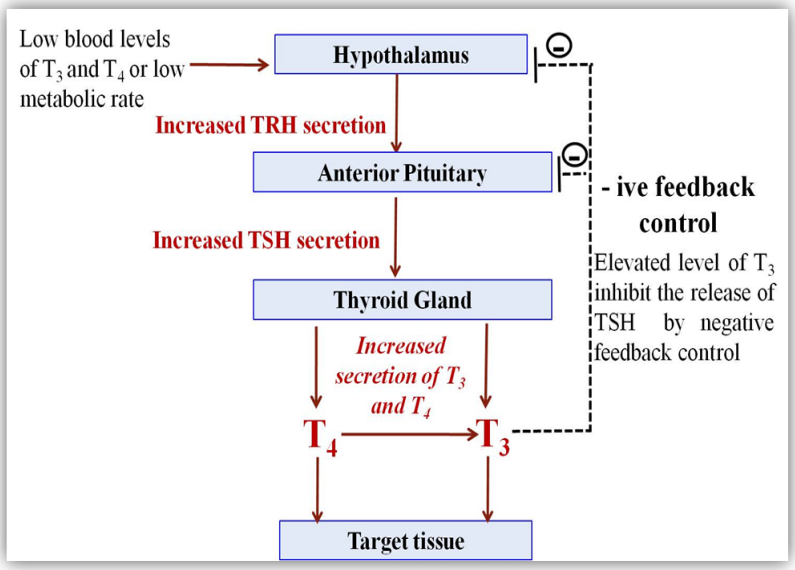


Figure 7. Hypothalamic-pituitary-thyroid axis showing regulation of synthesis and release of thyroid hormones. (**Source:** Author)

4.4. Mechanism of Action of Thyroid Hormone

On the basis of receptor localization, the mechanism of hormone action is categorized into two categories:

- Hormones that binds to intracellular receptors follow genomic pathway of action
- Hormone that binds to cell surface receptors follow non genomic pathway of action

4.4.1. Genomic Action

TH receptors are present in the nuclei of most of the cells of the body, unlike receptors for many other hormones, whose distribution is more limited. Before acting on the genes T_4 is deiodinated to T_3 with help of cytoplasmic enzyme **iodinase**. Thyroid hormone (T_3) exerts its effect by increasing the synthesis of various proteins at molecular level by directly combining with the high affinity nuclear thyroid hormone receptors on DNA (either as heterodimer with retinoid X receptor or as homodimer). T_3 with bound receptors recognise thyroid response elements (TRE) in the promoter of target gene and activate the expression of respective genes to synthesize RNA and protein. The increased level of proteins further facilitates the

enzymatic and other functions to suffice the increased demand for growth, development and metabolism.

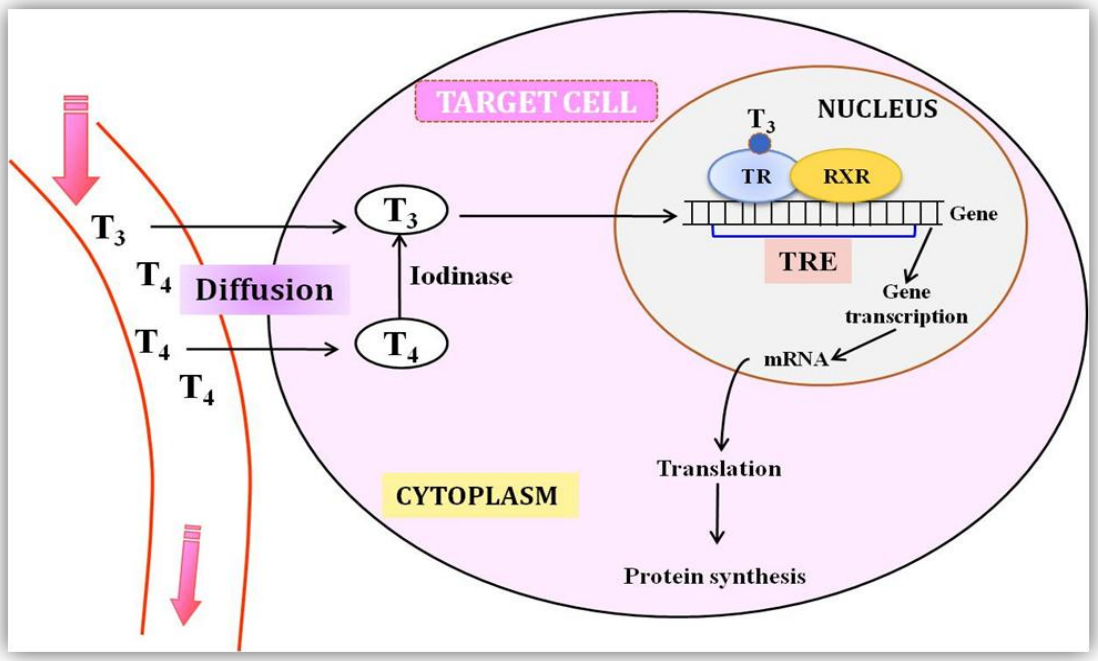


Figure 8. Molecular Mechanism of Action of Thyroid Hormone on Target Cell

(**Source:** Author)

4.4.2. Non-genomic Action

Besides having genomic actions, thyroid hormone has many fast non genomic actions on the target cells mediated by receptors present on plasma membrane, mitochondria or cytoplasm. The binding of hormone with receptor activate cyclic-AMP or the protein kinase signalling cascades resulting in microfilament organization, mitochondrial cytochrome-c-oxidase activity, cell growth, cell proliferation, angiogenesis and thermogenic responses.

4.5. Functions of thyroid hormone

The thyroid hormones (T_3 and T_4) have a wide range of effects on the human body and are required for homeostasis of all the cells. Thyroid hormones target virtually all the tissues of the body and broadly they have two major functions:

1. an increase in overall metabolic rate
2. stimulate growth and development

Effect of thyroid hormone on growth and development

The proper development during gestational period is the critical determinant in overall growth of an individual. Thyroid hormone starts manifesting its effect from early stage of development by promoting growth of the brain and central nervous system. Untreated congenital hypothyroidism or chronic hypothyroidism during fetal development, infancy or childhood causes severe mental retardation and incomplete growth.

Also, together with human growth hormone, insulin, and other growth factors, thyroid hormones accelerate body growth, particularly the growth of the nervous system, and skeletal systems throughout life.

Metabolic effects of thyroid hormones

Thyroid hormones increase basal metabolic rate (BMR) of almost all body tissues (except brain, retina, spleen, lungs, gonads, and lymphocytes). The rate of cellular oxygen consumption increases under standard or basal conditions for ATP production.

Thyroid hormone stimulates the absorption, uptake and cellular metabolism of carbohydrates, lipids, and proteins to maintain metabolic rate at a high level. Protein synthesis is stimulated (at low levels of thyroid hormone) to attain body growth and oxidation of glucose and fatty acids increases for ATP production. Lipids are mobilized rapidly from the fat tissues. The blood cholesterol, phospholipids, and triglycerides are significantly decreased and level of free fatty fatty acids increases in plasma due to increased thyroid hormone.

Synthesis of Sodium-potassium pumps/calorigenic effect

Thyroid hormones stimulate synthesis of additional sodium-potassium pumps (Na^+/K^+ ATPase) to maintain normal resting membrane potential, which use large amounts of adenosine triphosphate (ATP). About $1/3^{rd}$ of all ATP is used by these pumps. As ATP consumption increases the number and activity of mitochondria also increases, which in turn increases the rate of formation of ATP to energize cellular function. The resulting increased turnover of ATP, increases thermogenesis or heat production and the phenomenon is called the **calorigenic effect.** Because of this important role in temperature maintenance normal mammals can sustain freezing temperatures.

Besides performing these three basic functions thyroid hormone influences diverse functions and organ system in the body as outlined:

1.	**Thyroid Hormone Influences Cardiovascular Hemodynamic**	Increase blood flow and cardiac output Increase heart rate Increase heart strength Normal arterial pressure Increase respiration (to sustain increased demand of oxygen)
2.	**Effect on Gastrointestinal tract**	Increase gut motility Increase secretion of the digestive juices. Hyperthyroidism often results in diarrhea. Lack of thyroid hormone can cause constipation.
3.	**Effect on the Function of the Muscles**	Increases breakdown of protein Skeletal maturation at the growth plate; osteoblast differentiation and proliferation, and chondrocyte maturation leading to bone ossification Hyperthyroidism leads to muscle tremor.
4.	**Effect on adipose tissue**	Lipolysis
5.	**Effect on Sleep**	Normal level of thyroid hormone required for sleep. Extreme somnolence is characteristic of hypothyroidism
6.	**Effect on Other Endocrine Glands.**	Because of its direct control on growth and development of an individual thyroid hormone indirectly affect other endocrine glands as it increases the need of tissues for the hormone. Increased rate of glucose metabolism causes corresponding increase in insulin secretion form pancreas.
7.	**Effect of Thyroid Hormone on Sexual Function**	Have pronounced effect on menstrual cycle, libido and maintenance of pregnancy.

Table 1. Functions of Thyroid Hormone

4.6. Function of Calcitonin

Calcitonin was purified in 1962 by **Copp and Cheney**. Calcitonin is a 32-amino-acid polypeptide with a molecular weight of 3700 Dalton and a disulfide bridge between residues 1 and 7; is synthesized by parafollicular cells in response to high blood calcium level. Calcitonin lowers blood calcium level by inhibiting the number and activity of **osteoclasts**, the bone resorption cells. It also inhibits reabsorbtion of calcium and phosphate ions in the renal tubules therefore, increased excretion through urine. The production and release of calcitonin is completely independent of pituitary gland and depends only on level of calcium in blood.

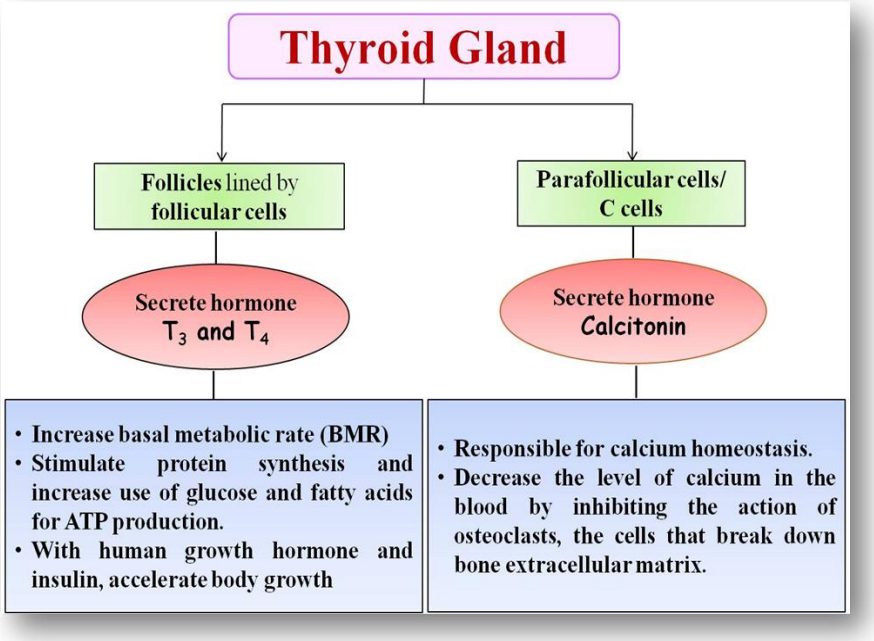


Figure 9. Overview of Thyroid Gland
(**Source:** Author)

5. Disorders associated with thyroid gland functioning

Endocrine disorders associated with thyroid gland have high prevalence in India especially in females. According to a report about 42 million people suffers from thyroid disease with iodine deficiency being a major causative factor.

Because of high prevalence it is important to discuss the various disorders, causes and symptoms. Thyroid diseases are broadly divided into two classes:

- **Hypothyroidism** (hyposecretion of TH)
- **Hyperthyroidism** (hypersecretion of TH)

5.1. Hypothyroidism

Hypothyroidism in fetal life, infants and children is known as **cretinism,** causes mental retardation and stunted growth. At birth, the child with congenital hypothyroidism is normal because it was supplied with some (but usually not enough) maternal thyroid hormone, but

after birth, the baby becomes sluggish showing symptoms of retarded growth. Oral thyroid hormone treatment is prescribed soon after birth and continued for life.

Hypothyroidism in **adults** results in a severe condition with almost total lack of thyroid hormone function, known as **myxedema**. Myxedema is characterized by **edema** i.e. accumulation of interstitial fluid (hyaluronic acid and chondroitin sulfate bound with protein form excessive tissue gel) which is immobile, causes the facial tissue to swell and puffy. Oral thyroid hormone therapy help reduce the symptoms.

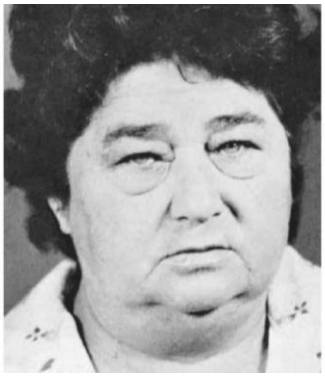


Figure.10. *Patient with Myxedema*

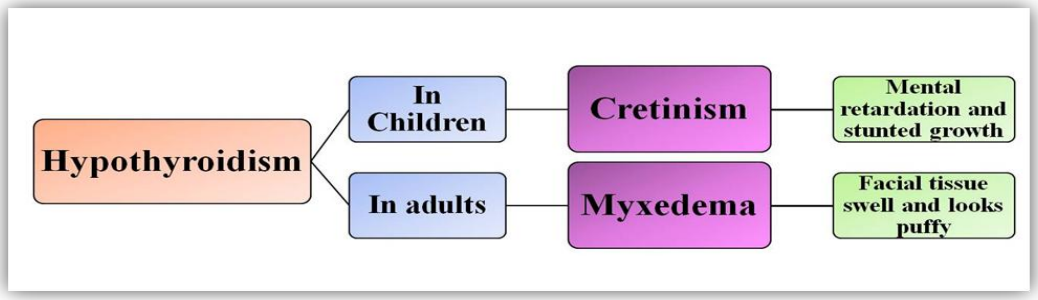


Figure 11. Disorders Associated with Hypothyroidism
(**Source**: Author)

The main causes for hypothyroidism are classified into two categories:

- **Primary**
- **Secondary**

5.1.1. Primary Causes of Hypothyroidism

95% of hypothyroidism cases are **primary defects** caused by damage or functional loss of thyroid tissue or iodine deficiency.

- **Hashimoto's Disease** – Autoimmune disease against the thyroid gland leads to "**autoimmune thyroiditis**" means thyroid inflammation. Thyroid-attacking antibodies, including thyroid peroxidase antibodies (**TPO**) and thyroglobulin antibodies (**TgAb**) are synthesized by body's own immune system and attack the thyroid gland. Progressive deterioration leads to fibrosis of the gland and finally low secretion of thyroid hormone. Increased risk of thyroid nodules, goiter (an enlarged thyroid), and thyroid cancer are associated with the disease.

  Daily replacement with T_4 restores the normal level of TSH in blood and usual treatment for autoimmune thyroiditis.

- **Endemic colloid thyroid goiter** - Iodine deficiency is often associated with enlargement of thyroid gland and one of the causes for **endemic colloid thyroid goiter.** Insufficient intake of iodine ameliorates the synthesis and in turn low levels of circulating hormone. Therefore negative feedback to the hypothalamus and pituitary leads to increased synthesis of TRH and TSH level respectively. Elevated plasma TSH levels over stimulates the gland to produce thyroglobulin colloid into the follicles. Due to accumulated thyroglobulin the gland grows larger and larger (10 to 20 times) because the synthesized thyroglobulin cannot be utilized for T_4 and T_3 production due to lack of iodine. Iodine supplement in the diet causes reversibility of normal functioning.

Post-surgical hypothyroidism, radioactive iodine treatment (cancer) hypothyroidism, congenital hypothyroidism (baby born without a thyroid gland or with a malformed gland), drug- and supplement-induced hypothyroidism, thyroid hormone resistance, radiation induced hypothyroidism *etc*. are the other possible primary cause for hypothyroidism.

5.1.2. Secondary Causes of Hypothyroidism

Defect in the functioning/communications of the pituitary gland and the hypothalamus leading to deficient secretion of TSH and TRH respectively.

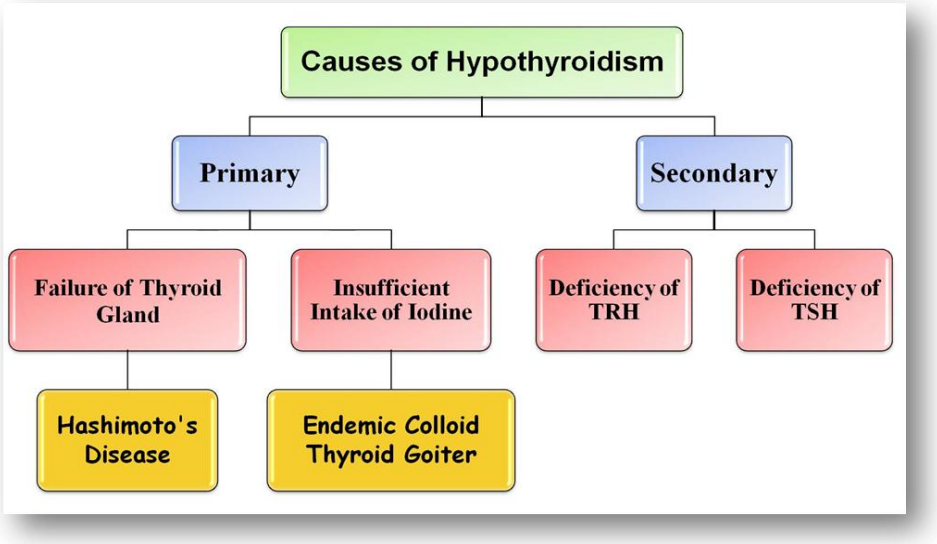


Figure 12. Causes of Hypothyroidism

(**Source**: Author)

5.1.3. Symptoms of Hypothyroidism

Hypothyroid disorders are characterized by mental and physical slowness, cold intolerance, weight gain, decrease in basal metabolic rate, decreased cardiac function, hypertension, hypercholesterolemia, and is associated with increased risk for development of atherosclerosis.

5.2. Hyperthyroidism

Hyperthyroidism or **thyrotoxicosis** is caused by elevated levels of thyroid hormones and reflected by hyperactivity of the thyroid gland caused by Graves' disease, toxic adenoma, multinodular goiter, or thyroiditis.

- **Graves' Disease -** Disease is seven to ten times more common in females than in males, before the age of 40. It is an autoimmune disorder where antibodies that mimic the action of thyroid-stimulating hormone (TSH) are produced by the body. These antibodies are known as **thyroid-stimulating immunoglobulin (TSI).** TSI continually stimulate the thyroid gland hypertrophy and produce thyroid hormones. Increased thyroid hormone by

negative feedback suppress the level of TSH, therefore Graves' disease is characterized by elevated levels of T_3 and T_4 with low TSH. Hypertrophy of gland leads to development of goitre.

The presence of a goiter does not distinguish between hypothyroidism and hyperthyroidism, because both types of disease can result in thyroid hypertrophy.

One third of Graves' disease is often accompanied by **exophthalmos**, an autoimmune-induced inflammation of the tissue behind the eyes resulting in protrusion of the eyes; autoimmune attack on the ocular tissue occurs leading to impaired vision.

- **Thyroid Adenoma -** Thyroid adenoma (tumor) develops in the thyroid tissue and secretes large quantities of thyroid hormone by suppressing the secretory function of the gland because increased thyroid hormone from the adenoma inhibit the production of TSH pituitary gland.
- **Toxic Multinodular Goiter -** Functional multiple nodules develop and produce elevated level of thyroid hormone and hypertrophy of the gland.
- **Thyroiditis -** Inflammation of thyroid gland leads to thyroiditis and caused by antibody attack on thyroid gland.

5.2.1. Symptoms of Hyperthyroidism

Heat intolerance, weight loss, increased appetite, insomnia, nervousness, hyperactivity, restlessness, tachycardia and cardiac arrhythmia, and weight loss due to increased BMR are common symptoms of hyperthyroidism. Some of these symptoms are due to increased sensitivity to catecholamines. High levels of thyroid hormone increase chances of myocardial infarction, increase risk for osteoporosis, and may increase insulin requirements in diabetics.

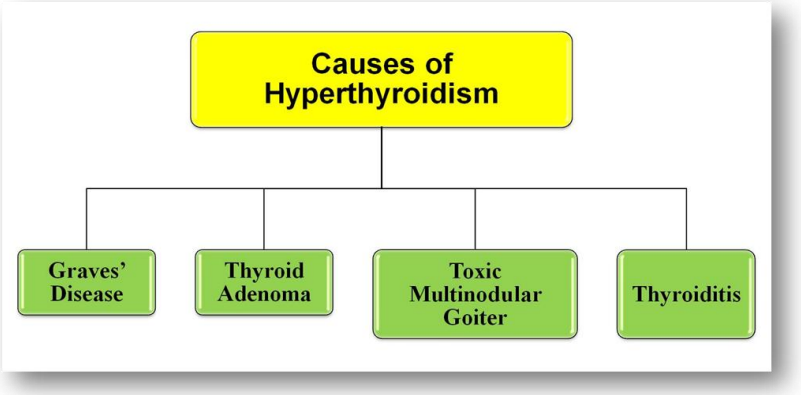


Figure 13. Causes of Hyperthyroidism

(**Source**: Author)

5.2.2. Treatment

- **Antithyroid drug treatment**—Antithyroid drugs, including methimazole (tapazole), carbimazole (neo-mercazole), and propylthiouracil (PTU), can slow down the thyroid's production of thyroid hormone.
- **Radioactive iodine treatment (RAI)**—Given in a single dose, either in a capsule or drink, it enters the thyroid, radiates thyroid cells, and damages and kills them. This shrinks the thyroid, slows down its function, and reverses hyperthyroidism.
- **Thyroid surgery/thyroidectomy**—In some cases, this is performed as a treatment for Graves' disease and hyperthyroidism, especially for people who cannot tolerate antithyroid drugs or are pregnant and RAI is not an option.

6. Summary

- Thyroid gland is a unique endocrine gland having cells arranged in the form of follicles located in lower neck below larynx.
- The main function of thyroid gland is to secrete thyroid hormones, T_4 and T_3 along with calcitonin.
- Thyroid hormones are synthesized in the colloid filled follicles by trapping iodine from circulation under the stimulation of TSH released from anterior pituitary.

- Although T_4 is synthesized in larger amount, ultimately converted to T_3 in the cytoplasm of the target cells because it is the biologically active form of thyroid hormone with very short half-life. T_3 shows its effect after binding to thyroid hormone receptors present in the nucleus and increasing the expression of various proteins.
- Thyroid hormones are required for normal growth & development, maturation of CNS, and to maintain basal metabolic rate.
- Disorders associated with thyroid gland have high prevalence in India especially in females. Iodine deficiency in the dietary intake is the major causative factor affecting all the age groups. Because of high prevalence it is important to study the various disorders, causes and symptoms of thyroid gland disorders.

PART B - PARATHYROID HORMONE

1. Learning Outcomes

After studying this module, you shall be able to understand,

- The location, structure, and anatomy of parathyroid gland.
- Structure, synthesis, and control of the parathyroid hormone.
- Functions of the parathyroid hormone
- Effect of parathyroid hormone on various tissues.
- Disorders associated with any impairment in the functioning of the gland.

2. Introduction

Calcium homeostasis is maintained by a highly intricate and complex endocrine system in all vertebrates involving parathyroid hormone (PTH), calcitonin and calcitriol. Parathyroid hormone is secreted by four parathyroid glands, two on each side at the posterior surface of the lateral lobes of the thyroid gland, each having mass of about 40 mg. The size of the gland resembles a rice grain, usually about 6 mm long and 3 to 4 mm wide, and 1 to 2 mm anteroposteriorly. The parathyroid gland plays a critical role in monitoring the level of extracellular calcium levels and maintaining the level in precise range by secreting PTH. The role of parathyroid hormone in maintaining calcium homeostasis was studied in 1909.

3. Histology of Parathyroid Gland

Parathyroid gland depicts presence of two kinds of cells arranged into cords or clumps, surrounded by reticular connective tissue framework. **Principal** or **chief cells** are small, more in number, and secret **parathyroid hormone** (PTH). Oxyphil cells are highly eosinophilic, larger, and less in number as compared to chief cells with unknown function.

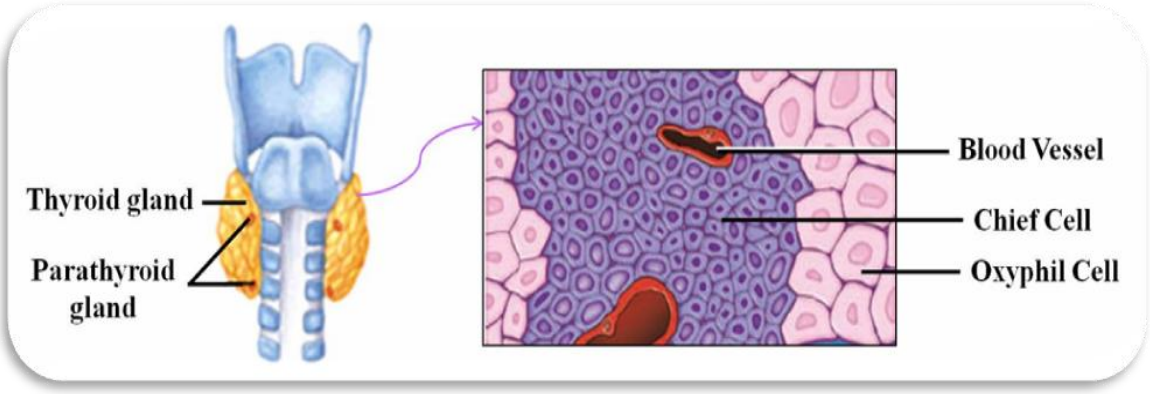


Figure 1. Location and Structure of Parathyroid Gland

4. Parathyroid Hormone

PTH is a glycoprotein made of 84-amino acids arranged in a linear polypeptide (MW – 9500 Da) with a half-life of 2-4 minutes. Along with **calcitonin** (CT), 1,25-dihydroxycholecalciferol {$1,25(OH)_2D_3$}/**calcitriol**, PTH maintain the level of calcium and phosphorus in plasma through its action on intestine, kidney, and bone.

Maintenance of adequate levels of plasma calcium (8.5 and 10.5 mg/dL) is required for normal neuromuscular function, bone mineralization, and many other physiological processes like cell division, cell adhesion, plasma membrane integrity, protein secretion, glycogen metabolism, and coagulation.

50% to 60% calcium is bound to circulating proteins or complexed with anions such as citrate and phosphate. The remaining ionized (unbound or "free") calcium is the portion responsible for controlling the physiologic processes listed above.

4.1. Structure and Processing of Parathyroid Hormone

Parathyroid hormone is translated as **pre-prohormone** in the chief cells of parathyroid gland having 25 AA pre sequences, 6 AA pro sequence, and 84 AA mature PTH sequence. Pre sequence is cleaved during the transport of the polypeptide across endoplasmic reticulum (ER) and required as a signal sequence. Pro sequence helps in efficient ER transport of polypeptide and protein folding and cleaved by trypsin-like protease in the golgi apparatus. The mature parathyroid hormone of 84 amino acids is further packed in secretory vesicles

and released when required. In the liver, PTH is metabolized into active N-terminal component (AA; 1-34) and in-active C-terminal fraction (AA; 35-84).

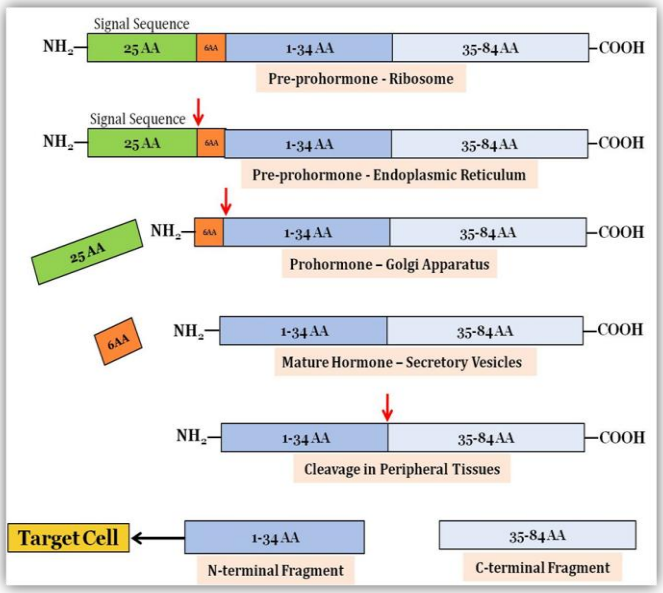


Figure 2. Structure and processing of Parathyroid Hormone

(Source: Author)

4.2. Functions of Parathyroid Hormone

Parathyroid hormone is secreted as mature hormone of 84 amino acids in the circulation. However, before acting on the target cells it is cleaved in the liver and kidney into active amino terminal fragment and inactive carboxy terminal fragment. Amino terminal fragment increases the concentration of calcium after binding to:

- Type 1 parathyroid hormone receptor located in bone, kidney, and intestine.
- Type 2 parathyroid hormone receptor located present in the CNS, pancreas, testis, and placenta.

The major function of PTH is to increase calcium levels and decrease phosphate levels in extracellular fluid by:

- Increasing the bone resorption by activating osteoclasts and further release of calcium and phosphate into the circulation.
- Stimulating distal convoluted tubule of the kidney to reabsorb calcium and PCT to increase phosphate secretion.

- Increasing conversion of 25-hydroxycholecalciferol (calcidiol) to 1,25-dihydroxy cholecalciferol (calcitriol; active form of vitamin D) in the kidney catalyzed by the enzyme 1α-hydroxylase.
- Indirectly acting on intestine through calcitriol to stimulate increased absorption of calcium and phosphates.

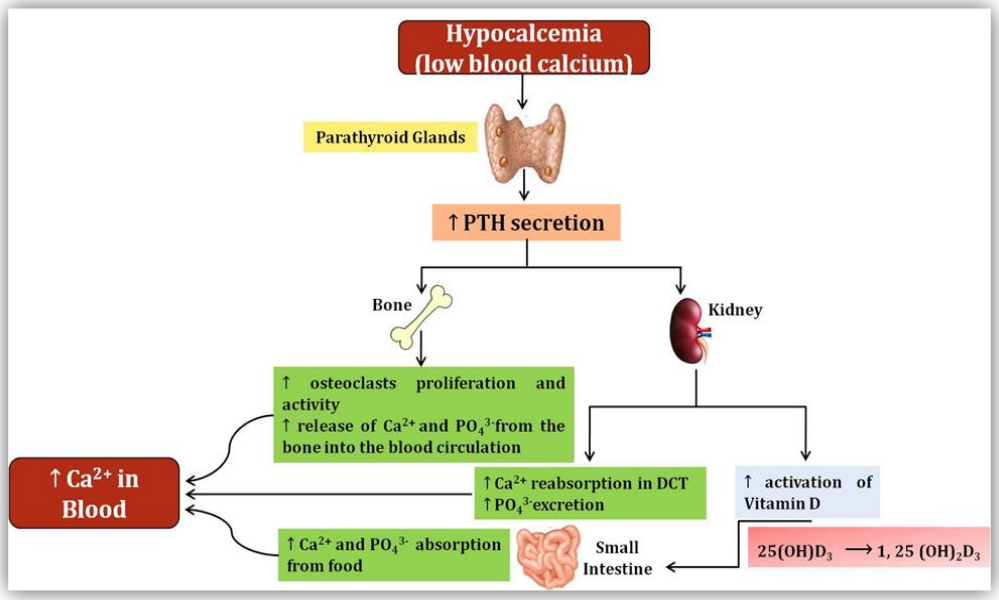


Figure 3. Functions of Parathyroid Hormone

((Source: Author**)**

4.3. Effect of Parathyroid Hormone on Bone

PTH has two effects on bone to increase the concentration of calcium in extracellular fluid:

1. Rapid phase (1-3hrs) leads to **osteocystic osteolysis** or activation of osteocytes for the transfer of calcium from bone fluid to extracellular fluid via activity of osteocytes without any decrease in the bone mass. Studies have shown that inter-connected network of osteoblasts and osteocytes spreads though out the bone and on the surface of the bone. This extensive, long, and filmy process is called ***osteocytic membrane system*** and separates the bone from extracellular fluid. The fluid filled between osteocytic membrane and extracellular

fluid is known as **bone fluid** responsible for release of calcium ions during osteocystic osteolysis.

Low calcium level in the extracellular fluid activates parathyroid gland to release PTH. The association of PTH to its receptors present on the osteocytic membrane system increases the activity of calcium pump resulting in diffusion of calcium phosphate salts from bone fluid to the osteocytic membrane. Then the calcium pump on the other side of the cell membrane transfers the calcium ions to the extracellular fluid.

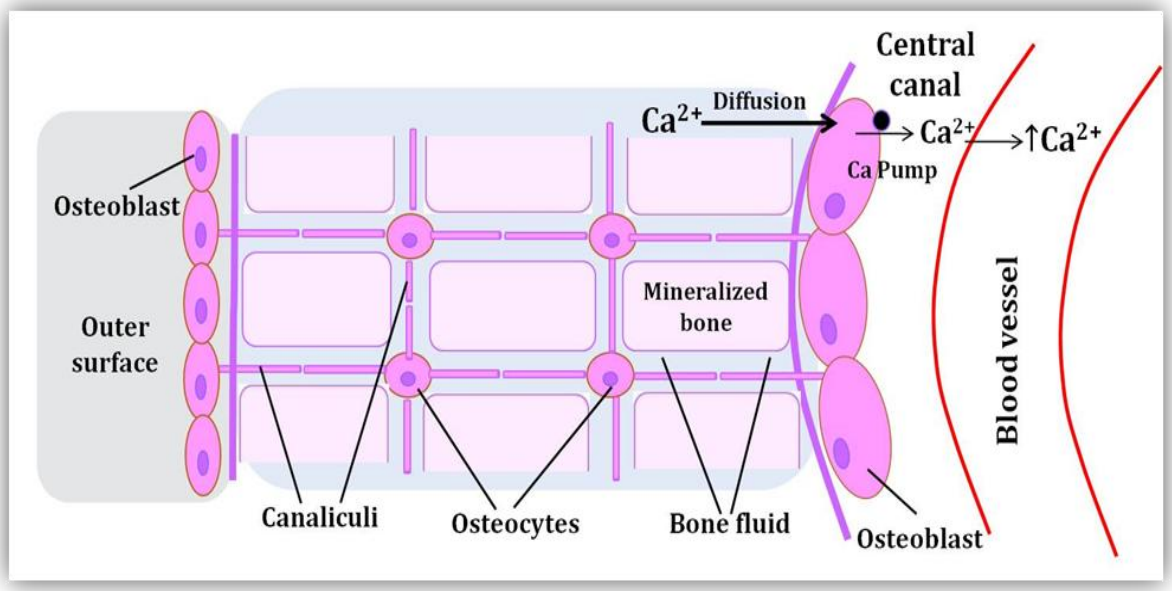


Figure 4. ***Osteocytic membrane system*** **-** In rapid phase calcium is moved from bone fluid via PTH activated calcium pump located on the osteocytic membrane system. (**Source**: Author)

2. Slower phase (12-24hrs) – **osteoclastic osteolysis** leads to proliferation of osteoclasts to promote reabsorption of the bone. Increased level of PTH as stimulated by continued hypocalcemia causes hypertrophy and hyperplasia of osteoclasts. The increases activity of osteoclast thus enhances bone resorption to mobilize calcium, magnesium and inorganic phosphate from mineralized bone into the plasma.

Increased PTH for longer duration causes osteoclastic resorption of bone leading to soft bones and further secondary stimulation of the osteoblast attempt to correct the weakened

state. Therefore, the late effect is ultimately enhancing both osteoblastic and osteoclastic activity.

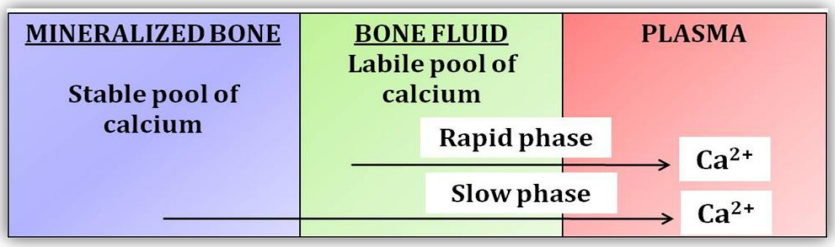


Figure.5. Mobilization of Calcium ion from bone in rapid and slow phase

(Source: Author**)**

4.4. Effect of Parathyroid hormone on Kidney

Parathyroid hormone acts on the distal convoluted tubules and collecting ducts to increase calcium and magnesium reabsorption. Also it increases the excretion of phosphate, sodium and bicarbonate by its action on proximal convoluted tubule (PCT). PTH by increasing the activity of 1α- hydroxylase facilitates the production of 1, 25-$(OH)_2$-Vit D in PCT. The increased calcitriol further acts on small intestine to increase calcium and phosphate ion absorption. Calcitriol also acts on osteoblast to produce paracrine signals which further activate osteoclasts to resorb calcium from bone matrix.

4.5. Effect of Parathyroid hormone on Intestine

PTH indirectly affects the function of intestine through calcitriol. Kidneys under PTH influence form the hormone calcitriol, resulting in increased calcium and phosphate absorption from the gastrointestinal tract into bloodstream. The increased absorption is achieved by increase in activity of sodium-calcium antiporter activity and synthesis of calcium binding proteins called **calbindins**.

4.6. Control of PTH Secretion

The major factor controlling the secretion of PTH is change in concentration of extracellular calcium ion as observed in cases of pregnancy, rickets, and lactation leading to hypertrophy

of parathyroid gland. Besides this, the change in normal levels of vitamin D and phosphate also leads to functional regulation of parathyroid gland as shown in table:

STIMULUS	EFFECT
Decreased Serum Calcium	↑PTH
Increased Serum Phosphate	↑PTH
Decreased Serum Calcitriol	↑PTH

Table.1. Control of Parathyroid hormone secretion

4.6.1. Control by Calcium - Concentration of extracellular calcium ion is the major regulator for PTH synthesis, secretion and degradation. Chief cells have cell surface calcium-sensing receptors (CaSR), to monitor the fluctuation in extracellular concentration of calcium. In the conditions of hypocalcemia CaSR is inactive, causing increased transcription of the gene encoding PTH, enhanced stability of PTH mRNA, and secretion of PTH by fusion of vesicles with plasma membrane. Hypercalcemia activates CaSR and suppresses the synthesis and secretion of PTH.

CaSR is a typical G-protein coupled receptor that activates phospholipase C and inhibits adenylate cyclase. It increases the intracellular Ca^{2+} concentration via generation of inositol phosphates and decreases cAMP which prevents exocytosis of PTH from secretory granules.

4.6.2. Control by Vitamin D - Deficiency of vitamin D also leads to increased secretion of PTH and associated with decreased hydroxylase activity, ↓absorption of calcium ion and ↓phosphate secretion in renal tubules. The resultant hypocalcemia thus stimulates parathyroid gland to secrete PTH. The suppression of PTH secretion is achieved by binding of calcitriol to vitamin D receptor located on chief cells and this receptor complex further binds to transcriptional repressor of PTH gene.

It has been reported that vitamin D and calcium act co-ordinately to inhibit the transcription of PTH gene and parathyroid cell proliferation.

4.6.3. Control by Phosphate - Increased level of phosphate in serum leads to hyperphosphatemia (in case of renal failure) leads to hyperplasia of parathyroid gland. Excess phosphate ions present in serum binds with calcium resulting in hypocalcemia, thus stimulating parathyroid gland to secrete and release PTH.

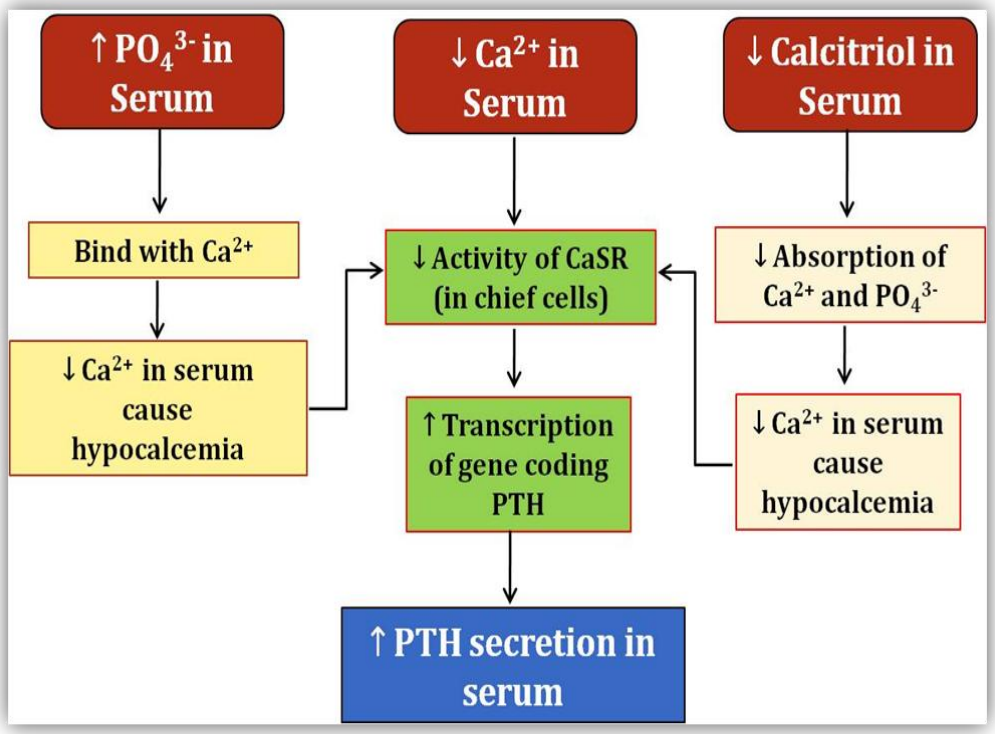


Figure 6. Control of PTH Secretion by calcium, phosphate and calcitriol

(**Source**: Author)

5. Role of Calcitonin in Calcium Homeostasis

Calcitonin is a physiologic antagonist of PTH and synthesized by parafollicular cells of thyroid gland in response to increased concentration of circulating calcium and phosphate ion. Inhibit the activity of osteoclasts *via* increased cAMP concentrations in cytosol to decrease the translocation of calcium from the bone along with inhibitory effect on renal tubules to reabsorb calcium ion.

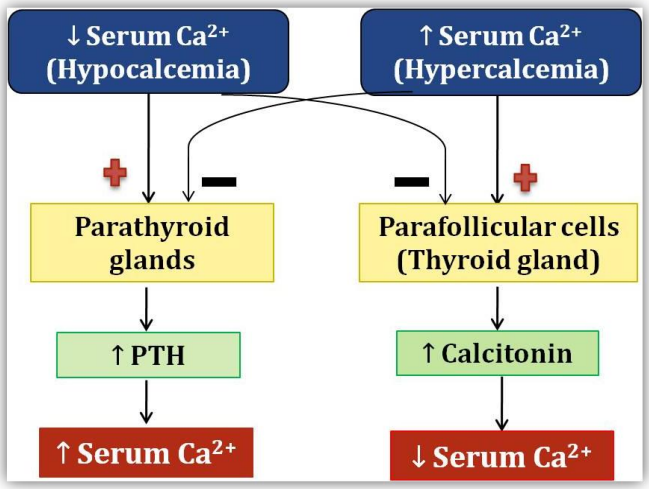


Figure.7. Calcium homeostasis by PTH and Calcitonin

6. Pathophysiology of Parathyroid Hormone

Disorders associated with parathyroid gland are divided into two categories:

- Hypoparathyroidism – too little parathyroid hormone
- Hyperparathyroidism – higher levels of parathyroid hormone

6.1. Hypoparathyroidism

Low levels of PTH in circulation leads to deficiency of blood calcium (hypocalcemia), due to its reduced effect on osteoclasts activity and vitamin D synthesis in the kidney. The low level of blood calcium causes hyper-reflexia, spontaneous depolarization of nerve and muscle fibers (hypocalcemia increases the neuronal sodium permeability with resultant influx of sodium moving the resting potential closer to threshold). The increased excitability of nerves and muscles leads to twitches, spasms, and tetany of skeletal muscle (eg. tetanic spasm of laryngeal muscles, carpopedal spasm).

The **primary cause** of hypoparathyroidism is removal of the gland during thyroid surgery and thus low level of PTH.

In case of **pseudohypoparathyroidism**, the level of PTH is normal in circulation but target tissues become resistant to its effect and therefore symptoms of hypoparathyroidism are apparent.

Increased supplement of calcium and vitamin D in diet or direct administration helps in the treatment of hypoparathyroidism.

6.2. Hyperparathyroidism

Also known as disease of "Bones, Stones, Abdominal groans" and causes increased level of circulating calcium in blood by increasing the activity of osteoclasts and synthesis of calcitriol. The concentration of phosphate ions get depressed because of increased renal excretion of phosphate. Excessive resorption of bone matrix causes the bones to become soft and easily fractured. High blood calcium level promotes formation of kidney stones. Fatigue, depression of CNS and PNS, personality changes, lethargy, muscle weakness, constipation, abdominal pain, peptic ulcer, lack of appetite, and depressed relaxation of the heart during diastole are also seen in patients with hyperparathyroidism.

6.2.1. Primary hyperparathyroidism

The primary cause is benign tumor (adenoma) of one of the four parathyroid glands usually having high prevalence in women because increased demand for calcium during pregnancy and lactation to support the developing child activate the parathyroid glands and therefore prone to the tumor development. Adenoma secretes high level of PTH and not controlled by negative feedback of extracellular calcium. The patients can be treated by surgical removal of the gland.

Continuous increase in the level of PTH causes high level of extracellular calcium as well as phosphate, probably because of inability of kidneys to excrete out huge amount of phosphate absorbed from bones by the osteoclasts. These ions combine together to form crystals of calcium phosphate and begin to get deposited throughout the body having fatal affects as they can impair the functioning of alveoli of the lungs, tubules of the kidneys, thyroid gland, acid-producing area of the stomach mucosa, and walls of the arteries. Crystals of calcium phosphate tend to precipitate in the kidney, forming kidney stones. Probability to develop osteoclast tumor also increases.

6.2.2. Secondary hyperparathyroidism

Hyperparathyroidism is associated with hypocalcemia rather than hypercalcemia to restore normal levels of calcium in plasma. Deficiency of vitamin, failure to absorb vitamin D in intestine or inability of kidney to convert vitamin D to active form is the possible causes for hypocalcemia. Increased PTH restores the normal levels of calcium by increasing the bone resorption.

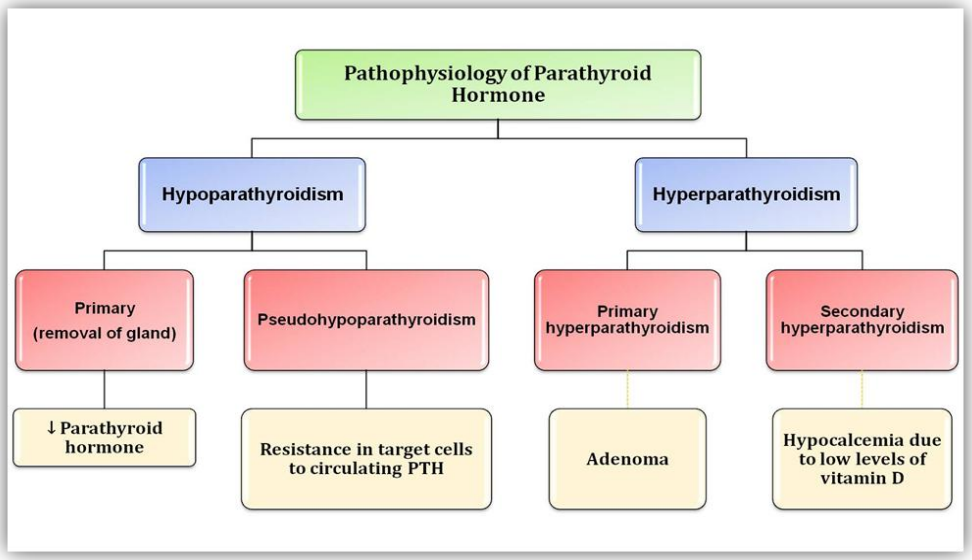


Figure.8. Pathophysiology of parathyroid hormone

(**Source**: Author)

7. Summary

- Parathyroid glands are the endocrine glands located behind the thyroid gland in the neck.
- Chief cells of the gland synthesize hormone parathyroid hormone (PTH) responsible for calcium homeostasis.
- PTH increases the level of calcium in serum by increasing the bone resorption, reabsorption of calcium in the renal tubules, and absorption in small intestine.

- Hypocalcemia in the circulation inhibits the calcium sensing receptors located on the chief cells, thereby increasing the expression of genes responsible for PTH synthesis.
- Hypoparathyroidism leads to decrease in free calcium level increases the neuronal sodium permeability with resultant influx of sodium moving the resting potential closer to threshold thus, fall in free calcium results in over excitability of nerves and muscles.
- On the other hand hyperparathyroidism leading to hypocalcemia depresses neuro-muscular excitability and bones become soft.