THE THYROID GLAND: FUNCTIONS, DISORDERS, AND ADVANCEMENTS IN TREATMENT

Mrs. R. Kavitha[1*] Mr. P. Kanish kumar[2] Mr. G. Madhan Kumar [3] Mr. V. Vasudevan[4]

[1] Assistant professor, JKKMMRF'S Annai JKK Sampoorani Ammal College of Pharmacy, Vattamalai, Komarapalayam (Po) – 638183, Namakkal District.

[2,3,4] JKKMMRF'S Annai JKK Sampoorani Ammal College of Pharmacy, Vattamalai, Komarapalayam (Po) – 638183, Namakkal District.

Abstract

The thyroid gland is a butterfly-shaped endocrine gland located in the front of the neck, just below the Adam's apple. It produces hormones such as thyroxine (T4) and triiodothyronine (T3), which regulate metabolism, growth, and energy balance in the body. Proper functioning of the thyroid is essential for maintaining body temperature, heart rate, and overall health. The thyroid gland regulates the body's metabolism by releasing the hormones thyroxine (T4) and triiodothyronine (T3). These hormones control how the body uses energy, influencing processes like heart rate, body temperature, and digestion. The gland also works with the pituitary gland to maintain hormonal balance for normal growth and development. Thyroid gland disorders occur when the gland produces too much hormone (hyperthyroidism) or too little hormone (hypothyroidism). Common conditions include goiter, thyroid nodules, Hashimoto's thyroiditis, and Graves' disease. These disorders can lead to symptoms such as weight changes, fatigue, mood disturbances, and altered heart rate. Advanced treatments for thyroid disorders include radioactive iodine therapy, targeted drug therapy, and minimally invasive or robotic thyroid surgery. Hormone replacement therapy with levothyroxine is also widely used to restore normal metabolism after thyroid removal or in hypothyroidism. The thyroid gland regulates many body systems with the help of the hypothalamus and pituitary gland, and imbalances in its hormones can lead to disorders like hypothyroidism from Hashimoto's thyroiditis or hyperthyroidism from Graves' disease. Doctors often use thyroid-stimulating hormone (TSH) tests, which are cost-effective and efficient, to detect and manage these conditions early.

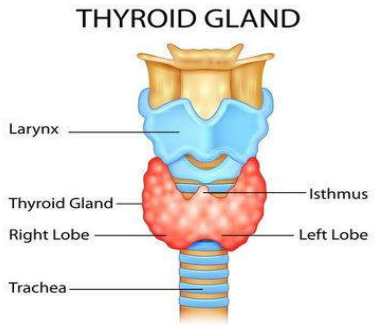
Keywords: *Thyroid Stimulating Hormone, Hypothyroidism, Hyperthyroidism, Hashimoto's thyroiditis, Graves' disease.*

1. Introduction:

Thyroid disorders are the most common type of endocrine diseases around the world. In India alone, about 42 million people are affected. A recent survey by the Indian Thyroid Society found that one in every ten Indians has hypothyroidism. Hypothyroidism affects 11%

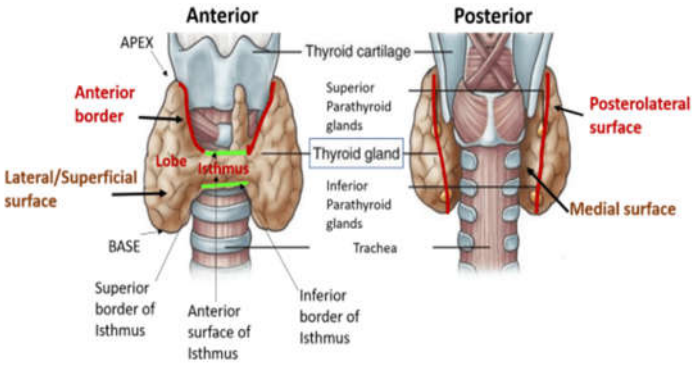
of people in India, which is much higher than 2% in the UK and 4.6% in the US. Among all thyroid problems, hypothyroidism which means the thyroid isn't working properly, is the most common. Congenital thyroid issues, which are present from birth, are much less common. Hypothyroidism in new born and pregnant women can lead to serious problems like mental development issues and problems with brain growth. Hypothyroidism is also linked to changes in the body's immune responses, an increase in harmful chemicals in the brain, and problems with how signals are sent in different parts of the brain.

It also causes lower levels of protective chemicals inthe body and more damage from harmful su bstances. Thyroid disorders can happen to people of all ages, genders, and places. If left untreated these conditions can lead to serious health problems like high cholesterol, high blood pressure, heart issues, trouble getting pregnant, and depression.



2.Anatomy and physiology of thyroid gland:

- 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.
- 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 gm in adults, with slightly heavier thyroids seen in women.
- A richly vascular structure, the thyroid receives its 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 in over 95% of people.



3.Development of Thyroid gland:

- Embryology the thyroid gland is the first endocrine organ to form during fetal 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 starting at week five as the foetus develops.
- It reaches its final shape and relative size by seven weeks gestation.
- 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.

4.Functions of thyroid hormones:

Thyroid hormones regulate your body's metabolic rate, controlling the speed at which your organs work and how food is converted into energy.

Metabolism:

Thyroid hormones increase your basal metabolic rate (BMR), which is the amount of energy your body uses at rest. This affects how quickly your body processes food and uses energy.

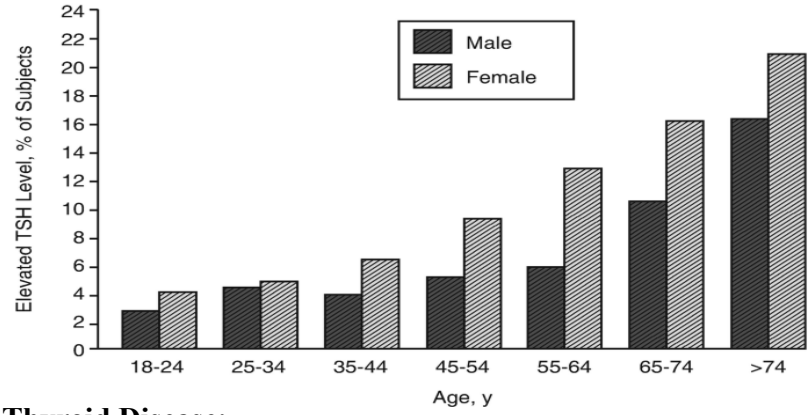
Body Temperature:

By stimulating your metabolism, thyroid hormones help regulate your body's temperature, making you feel warmer or colder if levels are abnormal.

Muscle Control: They affect how muscles contract and the speed at which they move.

5. Epidemiology:

- Thyroid disease is some of the most common problem related to the endocrine system around the world. About 5to10 percent of people globally have some kind of thyroid issue. Women are 5 to 10 times more likely to have thyroid problems than men.
- The chance of having a thyroid disease goes up as you get older. Thyroid disease is a big problem all over the world, but how common it is can change depending on where you live and who you are.



6. Types of Thyroid Disease:

1. Hypothyroidism

Hypothyroidism is defined as failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body. Untreated hypothyroidism can contribute to hypertension dyslipidemia infertility cognitive impairment and neuromuscular dysfunction. Hypothyroidism does not produce thyroid hormone its termed as underactive thyroid.

There are three types of hypothyroidism:

Primary hypothyroidism

Primary hypothyroidism is a common type of hypothyroidism. It is due to decreased the secretion of T4 and T3 from the thyroid. Serum T4 and T3 levels are low and thyroid stimulating hormone (TSH) is decreased.

Central hypothyroidism

Secondary hypothyroidism occurs when the hypothalamus produces insufficient Thyrotropin releasing hormone (TRH) or pituitary produces insufficient TSH. Sometimes deficient TSH secretion due to deficient TRH secretion it is termed as hypothyroidism. Tertiary hypothyroidism results from hypothalamus disorders

Subclinical hypothyroidism

Subclinical hypothyroidism is elevated from TSH in patients with absent or minimal symptoms of hypothyroidism and normal serum level of thyroxine (T4). Subclinical hypothyroidism dysfunction is relatively common; it occurs in about 15% of older woman and 10% of older men in those with underlying Hashimoto thyroiditis.

2. Hyperthyroidism

Hyperthyroidism is a condition where the thyroid gland produces and releases too many thyroid hormones into the bloodstream. These hormones primarily thyroxine (T4) and triiodothyronine (T3) regulate the body's metabolism so an excess leads to an overactive metabolism. This can cause a range of symptoms affecting various bodily functions. Hyperthyroidism is otherwise called as the overactive thyroid.

There are classified upon three types:

Primary hyperthyroidism

Grave disease

This is the most common cause of hyperthyroidism affecting primarily women under 40. It's an autoimmune condition where the body produces antibodies that stimulate the thyroid gland to produce excess hormones.

Secondary hyperthyroidism

This is a rare form caused by lesions in the pituitary gland (which produces TSH) or the hypothalamus (which regulates the pituitary).

Subclinical hyperthyroidism: Mild Subclinical Hyperthyroidism: TSH levels are low but still detectable, typically between 0.1 and 0.4 mIU/L. Severe Subclinical Hyperthyroidism: TSH levels are suppressed below 0.1 mIU/L. 12

7. Thyroid disorders:

1. **Hypothyroidism**

Hypothyroidism comes in many forms, but congenital hypothyroidism is especially important. It needs to be diagnosed early so that treatment can be started quickly, which helps prevent brain damage.

Studies from Mumbai show that congenital hypothyroidism is common in India. It happens in 1 out of every 2640 babies which is more common than the worldwide average of 1 in 3800 people. In India there's often a delay in diagnosing this condition. Hypothyroidism can also happen in children. A study from Mumbai looked at 800 kids with thyroid problems, and 79% of them had hypothyroidism.

Hyperthyroidism:

The occurrence of hyperthyroidism has been looked at in many studies. In one study from Cochin 1.6% of people in a community survey had subclinical hyperthyroidism and 1.3% had overt hyperthyroidism. In another study done in a hospital with women from Pondicherry 0.6% had subclinical hyperthyroidism and 1.2% had overt hyperthyroidism. Over a third of the hyperthyroid cases found in the community had positive result.

Goiter and Iodine Deficiency:

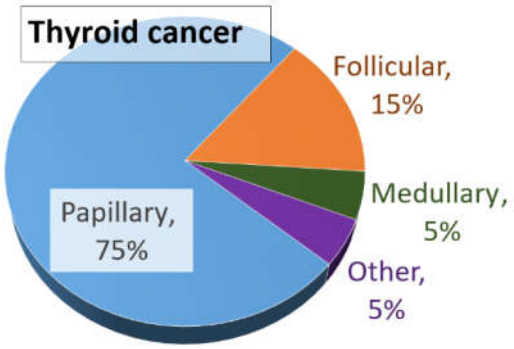
Recent population studies have shown that about 12% of adults have a palpable goiter. Autoimmune thyroid disease is probably commoner than iodine deficiency as a cause of goiter in areas that are now iodine sufficient. However, given that iodine deficiency is a problem in India, the importance of iodine deficiency cannot be underestimated in the Indian context.

Autoimmune Thyroiditis:

Autoimmune Thyroiditis in India Population studies have suggested that about 16.7% of adult subjects have anti-thyroid peroxidase antibodies and about 12.1% have antithyroglobulin (TG) antibodies. In this same study of 971 subjects, when subjects with abnormal thyroid function were excluded, the prevalence of anti TPO and anti TG antibodies was 9.5% and 8.5%.

Thyroid Cancer and India:

Thyroid Cancer and India the Indian Council of Medical Research established the National Cancer Registry Program and the NCRP has collected the data of more than 3,00,000 cancer patients between the periods 1984 and 1993. Among these patients, the NCRP noted 5614 cases of thyroid cancer, and this included 3617 females and 2007 males. The six centers involved in the studies were at Mumbai Delhi Thiruvananthapuram Dibrugarh Chandigarh and Chennai. Among them, Thiruvananthapuram had the highest relative frequency of cases of thyroid cancer among all cancer cases enrolled in the hospital registry, 1.99% among males and 5.71% among females. The nationwide relative frequency of thyroid cancer among all the cancer cases was 0.1% 0.2%. The age-adjusted incidence rates of thyroid cancer per 100,000 are about 1 for males and 1.8 for females as per the Mumbai Cancer Registry, which covered a population of 9.81 million subjects. The histological types of thyroid cancer were studied in a Hospital Cancer Registry of 1185 “new cases” of thyroid cancer. The commonest cancer type was papillary, followed by follicular cancer.



8. Thyroid Disease Causes and Risk Factors:

Thyroid disease is caused by over or underproduction of thyroid hormones. An overproduction of thyroid hormones is called hyperthyroidism, and an underproduction of thyroid hormones is called hypothyroidism.These conditions can occur because of problems such as inflammation of the thyroid nodules that develop on the thyroid gland autoimmune disorders, and exposure to radiation.

9. Causes of Hyperthyroidism: Hyperthyroidism occurs when the thyroid overproduces thyroid hormones. This can happen due to inflammation in the thyroid called thyroiditis, which causes the thyroid to create excess hormones.

Causes of Hypothyroidism

Hypothyroidism and the diseases associated with it happen when the thyroid doesn't produce enough thyroid hormone, which also results in a lack of energy. Causes of hypothyroidism include an autoimmune disorder such as Hashimoto's disease. This is a condition in which the body attacks the thyroid and causes it to produce fewer thyroid hormones.

Risk Factors:

Some people are at higher risk of developing thyroid problems than others. Your risk can be affected by things like genetics, your gender, and your lifestyle habits.

Genetics: Conditions like Hashimoto's disease and Graves' disease can be hereditary. Aside from family history there are several other risk factors for both hypothyroidism and hyperthyroidism, some of which (including gender and pregnancy) overlap.

Hypothyroidism Risk Factors:

- Age and gender (women over 60 at high risk)
- Preexisting condition (autoimmune disease such as type 1 diabetes or celiac)
- Pituitary gland disorder
- Pregnancy (women who are pregnant or who have had a baby in the past six months at high risk)

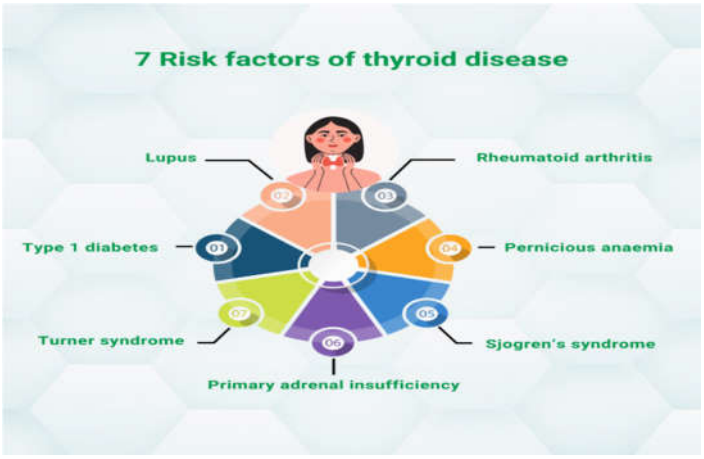
Hyperthyroidism Risk Factors:

- Gender (females at higher risk)
- Family or personal history of autoimmune disorders (celiac, lupus, rheumatoid arthritis)
- Past trauma to thyroid gland
- Current or recent pregnancy
- Smoking
- Recent use of iodine contrast (such as that used in CT scans)

Lifestyle Risk Factors

There are certain lifestyle factors that increase the risk of thyroid disorders. They include:

- Smoking, as tobacco contains substances that affect the thyroid gland, causing inflammation and interfering with the absorption of iodine as well as the production of thyroid hormones.
- Injury or trauma to the thyroid.
- History of certain medication use in high amounts, such as lithium (used in many mood stabilizers).



10. Signs and symptoms seen with hyperthyroidism and Hypothyroidism:

- Hyperthyroidism Hypothyroidism
- Heat intolerance Cold intolerance
- Flushed skin Dry skin
- Increase appetite Lethargy
- Muscle wasting Generalized weakness
- Weight loss Weight gain
- Exophthalmos
- Heart palpitations
- Tachycardia Bradycardia
- Shortness of breath Heart enlargement
- Restlessness Apathy

- Nervousness Mental sluggishness
- Fatigue Mental retardation

11. Etiology:

A. Hypothyroidism: The most common cause of hypothyroidism in adults may be summarized as follows

1. Autoimmune [Hashimoto thyroiditis]: In some people bodies the immune system that protects body from invading infections can mistake thyroid gland cells. Enzymes are left to them. This are more common in women than men. Autoimmune thyroiditis can begin suddenly or it can develop slowly overs years. These are the most common forms are Hashimoto thyroiditis and atrophic thyroiditis.

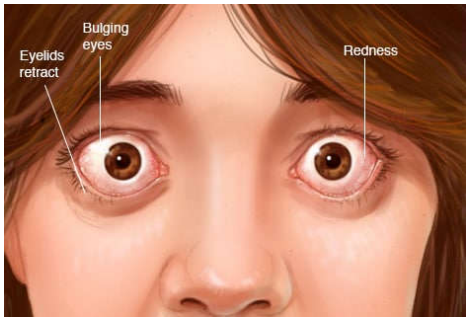
2. Thyroiditis: Thyroiditis is an inflammation of thyroid gland, usually caused by an auto immune attack or viral infection. Thyroiditis can make thyroid dump its whole supply of stored thyroid hormone into blood at once, so it can underactive thyroid.

3. Iodine intake: The thyroid gland has iodine to make thyroid hormone. Iodine comes to body in food and travels through the blood to thyroid. Keeping thyroid hormone production in balance requires the right amount of iodine. Taking in too much iodine can cause or woman hypothyroidism.

B. Hyperthyroidism

Hyperthyroidism, or overactive thyroid, occurs when the thyroid gland produces too much thyroid hormone. Several factors can cause this, with **Graves' disease** being the most common. Other causes include thyroid nodules thyroiditis excessive iodine intake and certain medications.

1.Graves' disease: This autoimmune disorder is the most frequent cause of hyperthyroidism. In Graves' disease the immune system mistakenly attacks the thyroid gland causing it to produce excessive amounts of thyroid hormone. Symptoms include anxiety heat intolerance muscle weakness and an enlarged thyroid (goitre). The condition can also affect other organs, causing thyroid eye disease (TED) with bulging eyes and skin changes like pretibial dermopathy. Treatment is necessary to manage the symptoms and prevent serious complications.



2. Thyroid nodules: These are lumps or growths on the thyroid gland. While usually begin some nodules can become overactive and produce excess thyroid hormone. These are sometimes referred to as hot nodules.

3. Thyroiditis: This refers to inflammation of the thyroid gland. Inflammation can cause the gland to release stored thyroid hormone into the bloodstream, leading to a temporary state of hyperthyroidism.

4. Excessive iodine intake: The thyroid gland needs iodine to produce thyroid hormones. However, consuming too much iodine either through diet or medications, can overstimulate the gland and lead to hyperthyroidism.

5. Medications: Certain medications such as those used to treat heart conditions can sometimes have hyperthyroidism as a side effect.

6. Pituitary adenomas: These are benign tumours on the pituitary gland that can stimulate the thyroid to produce more hormones.

7. Gestational thyroiditis: A temporary form of hyperthyroidism that can occur during pregnancy, particularly in women with hyperemesis gravidarum or multiple gestation.

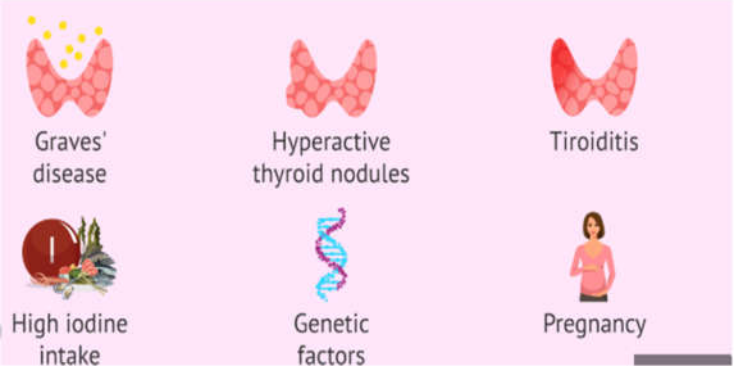


Figure – causes of Hyperthyroiditis

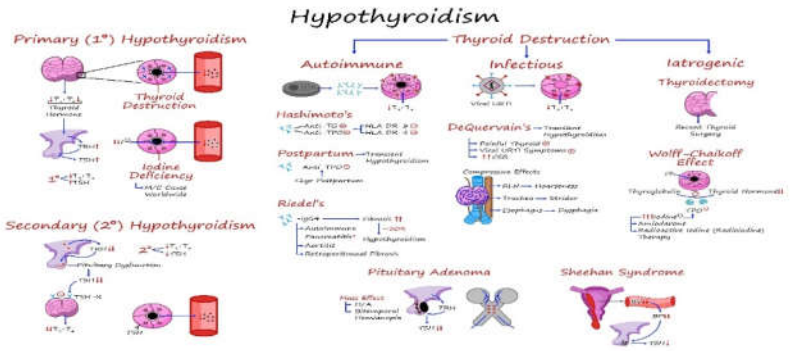


Figure – causes of Hypo thyroiditis

12. Pathophysiology: The thyroid is a butterfly-shaped gland located in the front of the neck just above the trachea. It weighs approximately 15 to 20 grams in the adult human. The thyroid produces and releases into the circulation at least two potent hormones, thyroxine (T4) and triiodothyronine (T3), which influence basal metabolic processes and/or enhance oxygen consumption in nearly all body tissues. **Complication:** Thyroid issues can happen when the thyroid is not working properly, either too slowly (hypothyroidism) or too quickly(hyperthyroidism). Hypothyroidism can cause several problems.

Goiter: This is when the thyroid becomes swollen, which might make it hard to swallow or breathe.

Myxedema coma: This is a rare but serious condition that happens when hypothyroidism is not treated. It affects many organs, causes very low body temperature slow breathing, and can lead to a coma.

13. Test and diagnosis:

Diagnosis of Hypothyroidism

Hypothyroidism is diagnosed primarily through blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine (T4) levels. A diagnosis is confirmed with elevated TSH and low T4 levels, indicating the thyroid isn't producing enough hormone. A healthcare provider will also consider your medical history, physical exam findings, and possibly antibody tests to determine the cause.

Blood tests

- **TSH tests**: This is the standard initial test. The Pituitary gland produces TSH to stimulate the thyroid gland to make thyroid hormones (T4). If the thyroid isn't making enough, the pituitary will release more TSH resulting in high TSH levels.
- **T4 tests**: A blood test for T4 (thyroxine) is also performed.
- **Confirming Diagnosis**: Hypothyroidism is diagnosed if the TSH level is high and the T4 level is low.

3. Additional tests:

- **Thyroid antibody tests**: To check for autoimmune thyroid disease such as Hashimoto's thyroiditis the most common cause of hypothyroidism.
- **Thyroid ultrasound**: May be used in children or to visualize the thyroid gland and lymph nodes.
- **Nuclear medical scan**: In children, this test can assess how well the thyroid tissue absorbs iodine to make hormones.

Diagnosis of hyperthyroidism: Hyperthyroidism, or overactive thyroid, is diagnosed through a combination of physical exams blood tests and sometimes imaging tests. The diagnosis confirms excessive thyroid hormone production and identifies the underlying cause.

1. Thyroid blood tests

- These tests measure the levels of thyroid hormones in the blood.
- **TSH (Thyroid Stimulating Hormone):** A low TSH level is a key indicator of hyperthyroidism, as it means the pituitary gland is trying to suppress thyroid hormone production.
- **T4 (Thyroxine) and T3 (Triiodothyronine):** These are the main thyroid hormones, and elevated levels confirm hyperthyroidism.
- **Thyroid antibody tests:** These can help identify Graves' disease, a common cause of hyperthyroidism.

14. Treatment:

1. Hypothyroidism:

- Treatment for hypothyroidism usually includes taking the thyroid hormone medicine levothyroxine (Levo-T, Synthroid, others) every day.
- The medication for hypothyroidism is levothyroxine, a synthetic thyroid hormone that replaces what your thyroid gland can no longer produce. It is usually taken daily in a pill form, though liquid and soft gel options are also available. Your doctor will monitor your blood tests to ensure you are on the correct dose to control your symptoms and prevent serious side effects.

How its take,

Empty stomach: Take the medication daily, usually in the morning.

Wait before eating: Wait at least 45 minutes before eating, drinking coffee, or taking other medications.

Do not take other supplements: Do not take calcium, iron, or gastric tablets for up to 6 hours after taking levothyroxine, as they can interfere with absorption. Hypothyroidism is second only to diabetes mellitus as the most common endocrine disorder in the United States, and its prevalence may be as high as 18 cases per 1,000 persons in the general population. The disorder becomes

increasingly common with advancing age, affecting about 2 to 3 percent of older women, because hypothyroidism is so common, family physicians need to know how to diagnose the disorder and select appropriate thyroid hormone replacement therapy.

Treatment of hyperthyroidism:

Hyperthyroidism treatments include anti-thyroid drugs (like methimazole), radioactive iodine therapy, and surgery (thyroidectomy) to reduce or remove the thyroid glands hormone production. Beta-blockers are also used to control symptoms like a rapid heartbeat and tremors, but they don't address the underlying cause. The choice of treatment depends on the cause, severity, and individual patient factors.

METHIMAZOLE (anti-thyroid drugs)

How its work: These medications prevent the thyroid gland from producing too much thyroid hormone.

Common drugs: Methimazole is the most common first choice, while propylthiouracil may be used in the first trimester of pregnancy or if methimazole cannot be tolerated.

Duration of action: Treatment can last 12 to 18 months, and sometimes results in a long-term remission, but hyperthyroidism can return.28**.** Hyperthyroidism is a commonly found endocrine pathology, with a prevalence of 2 % in women and 0.2 % in men, and an incidence of 20 / 1 000 000 / year in general population, with a male / female ratio of 1 / 5 –7.29.

15. Drug details:

Thyroid drugs, also known as thyroid hormones are used to help people with hypothyroidism, which is when the thyroid gland doesn't make enough of these hormones. Doctors sometimes call this condition an underactive thyroid. The thyroid is a butterfly-shaped gland located just below the Adam's apple, in front of the windpipe. Even though the thyroid makes thyroid hormones, the body uses another hormone called TSH (thyroid stimulating hormone) to control how much is made.

Thyroid hormone medications come in two main types:

- Natural preparations taken from animal thyroid glands, like desiccated thyroid and thyroglobulin

- Synthetic preparations made in a lab, such as levothyroxine (also called thyroxine or T4).

  It is similal to T4, which the body converts into T3. Some people may need liothyronine (T3 or triiodothyronine) if they can't properly change T4 into T3. Liotrix was a medication that had both levothyroxine (T4) and liothyronine (T3) in a 4:1 ratio.

Ingredients	**Brand name examples**
levothyroxine	Levoxyl, Synthroid, Unithroid
liothyronine	Cytomel, Triostat
thyroid desiccated	Armour-thyroid

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.

16. Conclusion: The thyroid gland is a complex organ that plays a major role in controlling many body systems and processes. It works closely with the hypothalamus and pituitary gland to keep hormone levels in the blood within a normal range. If thyroid hormone levels get too high or too low, it can cause problems like hypothyroidism or hyperthyroidism, which can be caused by different factors. The most common causes are Hashimoto's thyroiditis, which leads to an underactive thyroid, and Grave's disease, which causes an overactive thyroid. Labs are important in diagnosing and managing thyroid issues because tests for TSH can find problems before symptoms show up. Now, doctors often focus on TSH tests instead of full thyroid panels because this method is more cost-effective and efficient for treating thyroid conditions.

REFERENCE:

1. American Academy of Clinical Endocrinologist. American Association of Clinical Endocrinologist medical guidelines for clinical practice for the evaluation and treatment of hyper thyroidism and hypothyroidism. Endocr. Pract. 2002, 8, 457-469

2. Vanderpump MPJ. The epidemiology of thyroid diseases. In: Braverman LE, Utiger RD (eds). Werner and Ingbar's the Thyroid: A Fundamental and Clinical Text, 9th edn. JB Lippincott-Raven: Philadelphia, 2005,398–496
3. Hall JE and Guyton AC. (2011) Textbook of Medical Physiology. Twelfth Edition. Elsevier Saunders.
4. Waugh A and Grant A. (2004) Anatomy and Physiology. Ninth Edition. Churchill Livingstone.
5. Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull. 2011; 99:39–51.
6. Wassner AJ, Brown RS. Congenital hypothyroidism: recent advances. Curr Opin Endocrinol Diabetes Obes. 2015; 22:407–12.
7. Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med. 2012; 172:799–809
8. Vanderpump MP, Lazarus JH, Smyth PP, et al. Iodine status of UK schoolgirls: a cross-sectional survey. Lancet. 2011; 377:2007–12.
9. Devdhar M, Ousman YH, Burman KD. Hypothyroidism. Endocrinol Metab Clin North Am. 2007;36(3):595-615, v.
10. Phillip R Orlander, MD, FACP, Divisions of Endocrinology, Diabetes and Metabolism. Hypothyroidism (Hypothalmic- pituitary- Thyroid axis)2022: (1,2).
11. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-1421.
12. Biondi B, Cooper DS. Subclinical Hyperthyroidism. N Engl J Med. 2018 Jun 21;378(25):2411-2419.
13. Impiombato F.S., Parks L.A.M. & Coon H.G. (1980) Culture of hormone-dependent functional epithelial cells from rat thyroids. *Proc Natl Acad Sci U S A.* Vol.77, pp.3455–3459.
14. Casey B.M., Dashe J.S., Wells C.E., McIntire D.D., Leveno K.J., Cunningham F.G. Subclinical hyperthyroidism and pregnancy outcomes. Obstet. Gynecol. 2006; 107:337–341. doi: 10.1097/01.AOG.0000197991.64246.9a.
15. Kim D. The Role of Vitamin D in Thyroid Diseases. *Int J Mol Sci*. 2017 Sep 12. 18 (9):
16. Gosi SKY, Kaur J, Garla VV. Subclinical Hypothyroidism. *StatPearls*. 2024 Feb 15.

17. 17. Gossage A, Munro D. The pathogenesis of Graves' disease. Clin Endocrinol Metab. (1985) 14:299–330. 10.1016/S0300-595X(85)80036-0.
18. 18. American Thyroid Association. Hyperthyroidism Assesed . 2024
19. 19. Arafah, B.M. (2001). Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N. Engl. J. Med., 344(23), 1743-1749.
20. 20. Bastenie, P.A. Vanhaelst, L. and Neve, P. (1967). Coronary artery disease in hypothyroidism. Observations in preclinical myxoedema.The Lancet, 290(7528),1221-2.
21. 21. Klein I, Ojamaa K, Thyroid hormone and the cardiovascular system. N Eng J Med2001;344(7) 501-509.
22. 22. Paparella R, Menghi M, Micangeli G, Leonardi L, Profeta G, Tarani F, Petrella C, Ferraguti G, Fiore M, Tarani L. Autoimmune Polyendocrine Syndromes in the Pediatric Age. Children (Basel). 2023 Mar 19;10(3)
23. 23. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab. 2001;86(10):4585–4590.
24. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017 Oct;13(10):610-622.
25. 25. Slatosky J, Shipton B, Wahba H. Thyroiditis: differential diagnosis and management [published correction appears in Am Fam Physician 2000;62:318]. Am Fam Physician 2000;61:1047-52.