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Understanding thyroid disorders

Priyanka Gurung
College Student, Department of Pharmacy, RK University, Rajkot, Gujarat, India
Email: pgurung807@gmail.com

Abstract:

Thyroid disorders appear to be a widespread and diverse group of medical conditions affecting millions of individuals of all age group worldwide. This abstract provides an outline of thyroid disorders, summarizing their crucial aspect including prevalence, epidemiology, treatment approaches and preventive measures. A thyroid disorder occurs mainly due to the dysfunction of the thyroid gland, an essential endocrine gland responsible for the metabolism of the body, i.e. the ways in which the body uses the energy. Hyperthyroidism and hypothyroidism are the two main disorders where hyperthyroidism is characterized by rise of thyroid hormone level and hypothyroidism is characterized by low level of thyroid hormone secretion. Symptoms including enlarged thyroid gland, weight loss, hair loss, fatigue, heat sensitivity and mood swings are seen in people with hypothyroidism. Similarly, hypothyroid patient are seen to have intolerance to cold, weight gain, depression, coarse hair and myasthenia. Many factors contribute to the disorders, Hashimoto's thyroiditis and Graves' disease being the main ones. With these autoimmune conditions, iodine deficiency or over sufficiency, pregnancy, genetic factor and some medical conditions also leads to the thyroid dysfunction.

Being on medication and with adaptation of a right lifestyle, thyroid hormone balance can be restored. Hormone replacement therapy is considered for hypothyroidism, where a tablet such as levothyroxine is used to replace the thyroxine hormone, which the thyroid is not able to produce sufficiently. In case of hyperthyroidism, medication which suppresses hormone production, radioactive iodine therapy or with surgical removal of thyroid are the choices of treatment.

It is important to have necessary knowledge about a disease for treatment as well as for awareness. Having a basic understanding about the causes, treatments and preventive measures are essential for the patients to address their concerns.

Keywords:

Thyroid disorders, hormone production, radioactive iodine therapy, Hyperthyroidism, hypothyroidism

1. Introduction:

The thyroid gland is the small, butterfly-shaped endocrine gland located below the below the Adam's apple. It is made up of the right and the left lobe, which are joined by a small bridge of thyroid tissue called the isthmus.

The thyroid gland creates two hormones and secretes these hormones into the systemic circulation. The two hormones which are thyroxin (T4) and triiodothyronine (T3), are important for the body to carry out various cell metabolism. Thyroxin (T4) contains 4 atoms of iodine while triiodothyrodine (T3) have three iodine atoms. T3 is mainly responsible for the activity of all the cells and tissues of our body. T4 is converted into the biologically active T3 hormone and is secreted from the thyroid gland. (Medlineplus, 2023)

How the hormone affects the functions of the cells and tissues?

If the thyroid hormones are produced more than the required amount, the cells and the tissues work faster than normal. This leads to hyperthyroidism, an overactive thyroid. Due to the excess secretion of the thyroid hormone or thyroxin, the metabolism increases, resulting in the increased activities of the cells and organs.

Table. 1: Causes and symptoms of hyperthyroidism

Causes	Symptoms
• Graves' disease which is the most common cause of hyperthyroidism • Thyroiditis- Inflammation of the thyroid due to some medicines, viral infections or after pregnancy • Excess intake of thyroid hormone medication • Non-cancerous growths of thyroid gland and pituitary gland • Some tumors of the testes and ovaries	○ Goiter or enlarged thyroid gland ○ Bulging eyes in case of Grave's disease ○ Palpitations(Tachycardia and irregular heart rate) ○ Hand tremors ○ Warm skin and excessive sweating ○ Loose nails ○ Hives(Urticaria) ○ Hair loss or thinning ○ Weight loss ○ Redness of eyes, dryness and vision problems ○ Nervousness, anxiety and irritability ○ Mood swings ○ Insomnia

• Excess intake of iodine • Overactive thyroid nodules(Toxic nodular goiter or multinodular goiter)	○ Fatigue ○ Heat sensitivity ○ Diarrhea ○ Needing to pee frequently ○ Persistent thirst

2. Hypothyroidism:

In case if the hormones are not secreted enough, it leads to an underactive thyroid which is known as the hypothyroidism. The activities of the cells and organs slow down. The symptoms are not observable in the early stages of the disease. If the hypothyroidism is left untreated, it causes complications such as high cholesterol and heart disease.

Types of hypothyroidism:

1. Primary hypothyroidism: most common type and is caused when the thyroid gland itself is impaired.
2. Secondary hypothyroidism: caused when the pituitary gland is impaired
3. Tertiary hypothyroidism: caused due to the impairment of hypothalamus.
4. Subclinical or underactive hypothyroidism: early form of thyroid failure
5. Congenital hypothyroidism: hypothyroidism in infants

2.1. Other thyroid related conditions or diseases:

2.1.1. Thyroid eye disease:

It is an autoimmune disorder which causes the inflammation of the eye muscles, the fatty tissue and the connective tissue behind it causing the redness and swelling of the eyes. It is often associated with Grave's disease and causes the similar symptoms that the Grave's disease has on the eyes.

2.1.2. Hashimoto's thyroiditis (Most common cause of hypothyroidism):

An autoimmune disorder where the body's own immune system attacks and slowly destroys the thyroid gland. It is also known as chronic lymphocytic thyroiditis and is most common in middle-aged women.

Table. 2: Causes and symptoms of hypothyroidism

Causes	Symptoms
○ Hashimoto's Thyroiditis (Most common) ○ Thyroid surgery where removal of a part or a whole of thyroid gland lowers the secretion of the hormone or completely inhibits the hormone. ○ Radiation therapy used for the treatment of cancers on the head and neck ○ Thyroiditis ○ Medicines used for heart disease, bipolar disorder and cancer like lithium, amiodarone, nitroprusside, sulfonylurea and etc. ○ Congenital thyroidism (Genetic) ○ Iodine deficiency ○ Pituitary and hypothalamus disorder ○ Low libido ○ Pregnancy	• Fatigue • Sensitivity to cold • Constipation • Dry skin (Xerosis or Xerodema) • Weight gain • Bloated face • Hoarse or husky voice • Coarse hair and skin. • Mysthenia (Muscle weakness) • Muscle aches (Myalgia), tenderness and stiffness(Spasticity) • Menstrual cycles that are heavier than usual or irregular. • Hair fall • Bradycardia (slow heart rate) • Depression • Memory problems

2.1.3. Grave's disease (most common cause of hyperthyroidism):

An autoimmune disorder where the immune system attacks and slowly destroys the thyroid gland and causes excessive secretion of hormone. It is hereditary and most common in women between the ages of 20 and 30.

2.1.4. Goiter:

Non-cancerous swelling or enlargement of the thyroid gland caused due to iodine deficiency in diet. It is more common people older than 40 years. Mild goiter does not show any symptoms. However, depending on the size of the goiter, it can cause symptoms like tightness of the neck, difficulty in breathing and swelling, coughing and wheezing, and hoarse voice

2.1.5. Thyroid nodules:

Solid or fluid filled lumps which forms in the thyroid gland. A 2015 study reported that about 1% of men and 5 % of women in iodine-sufficient countries have thyroid nodules that are large enough to feel. It is not dangerous but can be cancerous in rare cases. Thyroid nodules don't usually cause symptoms but its enlargement can result in swelling in the neck causing difficulties in breathing and swallowing, pain and also goiter.

2.1.6. Thyroid cancer:

Growth of cancerous (malignant) cells in the thyroid gland. Thyroid cancer is generally treatable with a high cure rate. However, if the cancerous cell spreads to other parts of the body, it causes symptoms like fatigue, anorexia, sudden weight loss, nausea and vomiting.

2.1.7. Postpartum thyroiditis:

Inflammation of the thyroid gland in women in the first year after the delivery of the baby. Postpartum thyroiditis first leads to hyperthyroidism and then eventually leads to hypothyroidism. It is also an autoimmune disease and is relatively rare and temporary condition, affecting only 5% of the women.

2.2. Risk factors:

People are generally at a higher risk of developing a thyroid disorder under the following conditions:

- Family history of thyroid disease
- Diagnosed with diseases like pernicious anemia, Type-1 Diabetes, primary adrenal insufficiency, lupus, rheumatoid arthritis, Sjogren's syndrome and Turner syndrome
- High intake of iodine or intake of medication high in iodine like amiodarone
- Older than 60, especially in women
- Treatment for past thyroid conditions or cancer such as thyroidectomy or radiation (Myoclinic, 2022)

2.3. Preventive measures:

1. Quit smoking
2. Limit or avoid soy intake as it interferes with the absorption of the medication.
3. Use of thyroid collar during X-ray to provide protection to the thyroid gland from radiation.

4. Take selenium supplements as it is required for antioxidant function and for the metabolism of thyroid hormones.
5. Regular checkups. (Amstrong, 2020)

3. Epidemiology:

Iodine is the most essential components which results in the occurrence of thyroid disorders and Epidemiology studies suggests that the prevalence of thyroid disorders depends solely on the availability of iodine in dietary meals and hence varies worldwide. Studies have shown that even in the areas with enough supply and availability of iodine, hypothyroidism is still observed between 1% and 2%. It was found to be 10 percent more common in older women than in men. Hyperthyroidism was also found to be more common in women by 10% than in men, its prevalence being between 0.5 % and 2%. Thyroid nodules are detected clinically in 1% of men and 5% of women, with the frequency increasing with age and more common in iodine-deficient populations. Congenital hypothyroidism affects about one new born in 3500-4000 births in areas where iodine was available. Subclinical hypothyroidism was found in approximately 10% of the population and subclinical hyperthyroidism was found in 1% of the population.

Among the thyroid disorders, hypothyroidism is seen to be more common than hyperthyroidism and other thyroid dysfunctions, worldwide with approximately 80% being diagnosed with hypothyroidism and 20% being diagnosed with hyperthyroidism. In addition, 5% of the people with diabetes were found to be more vulnerable to be diagnosed an onset of thyroid disorder and 50% of the children with the family history of a thyroid disorder was found to be diagnosed with the disease by the age of 40. (The epidemiology thyroid disorders, 2011)

4. Pathophysiology:

Hypothalamus which is known as the mastergland, detects the level of thyroid hormone in the blood. In case of low level of hormone, the hypothalamus releases thyroid regulating hormone (TRH) which stimulates the anterior pituitary gland to release thyroid stimulating hormone (TSH). TSH then stimulates the thyroid gland. Thyroid gland is made of thousands of follicles (small spheres) lined with follicular cells. A protein called thyroglobuline is found inside the the follicle. TSH converts thyroglobuline to iodine containing hormones (T_3 and T_4). The

hormones are released into the blood stream form the gland, where they bind to the circulating plasma protein. These hormones then control the metabolism of the body (metabolic rate).

Some hormones remain in an unbound state in the blood and its concentration gradually increases leading to thyrotoxicosis. T3 and T4 enter the cells. T4 is converted to the biologically active T3 by the enzyme 5' Deiodinase. T3 increases the basal metablic rate (BMR), producing more protein and using more energy, eventually resulting to the hyperactivity of the thyroid gland. Cardiac output is increased, bone absorption is stimulated, sympathetic nervous system is activated, alertness and breathing rate is also increased, heart rate is increased(Tachycardia) and dilated pupil is also observed along with other symptoms. Grave's disease, the most common cause of hyperthyroidism lies in the secretion of thyroid stimulating antibodies (TSI) that attacks the thyroid follicular cells resulting in the excessive uncontrolled release of thyroxine. Opthalmopathy and skin manifestations are also caused due to the TSI. (Hyperthyroidism, 2020)

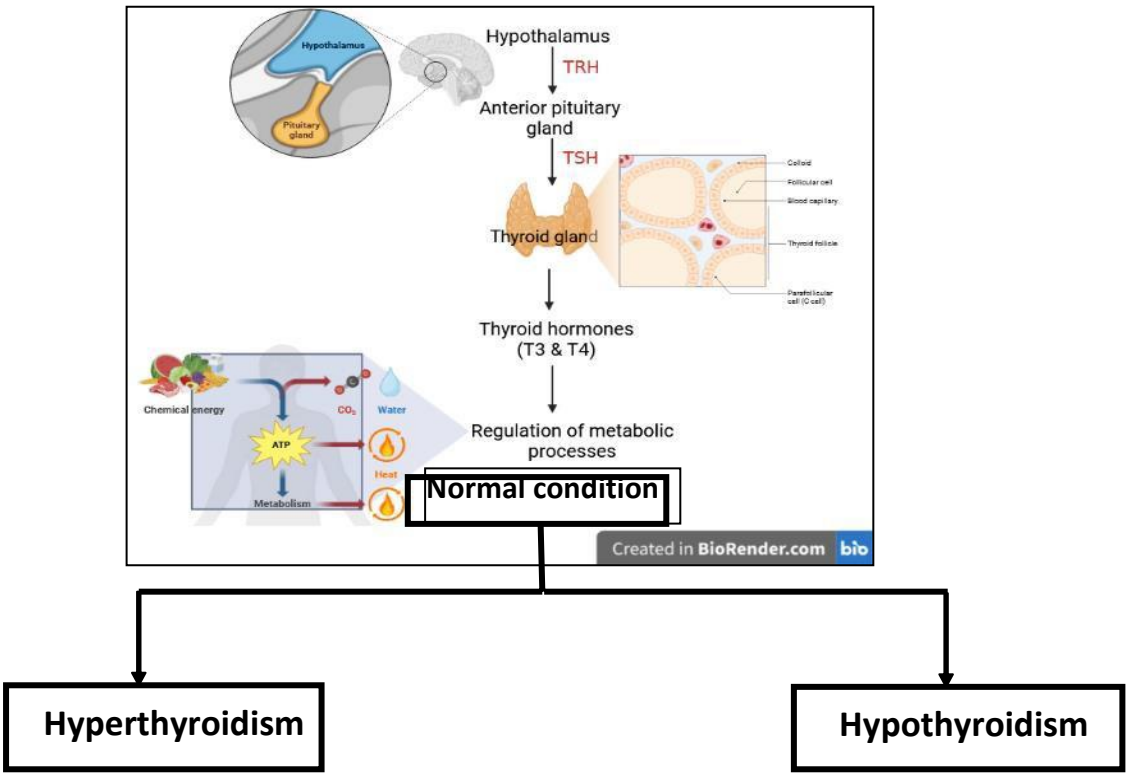

Figure. 1: Flowchart for pathophysiology of hypothyroidism and hypothyroidism; Novel Drug Target (Laura C Lane, 2020)

The destruction of the thyroid gland which is known as the primary hypothyroidism mainly causes the hypothyroidism in addition to the secondary and tertiary hypothyroidism. Due to this, the thyroid hormone secretion is reduced and on the other hand, secretion thyroid stimulating hormone by the pituitary gland is increased. TSH stimulates hypertrophy and

hyperplasia of the thyroid gland along with the activity of 5'-deiodinase activity, increasing the T3 production. As a result, the basal metabolic rate decreases along with the following changes: (Philip R Orlander, 2022)

- Decreased contractility (Cardiomyopathy)
- Pericardial effusion
- Disturbed lipid metabolism
- Accumulation of mucoploysaccharide- thickened skin
- Disturbed reproductive cycle
- Sleep apnoe- lack of ventilation
- Reduced erythropoietin level- reduced bone marrow function

Targeted disease	**Drug used**	**Mechanism of Action**
Grave's disease	Rituximab (RTX)	-used to treat lymphoproliferative malignancies such as lymphoma and usedin autoimmune disease over the past decades. -causes depletion of B lymphocytes (anti-CD20 monoclonal antibody).
	Iscalimab (CFZ533) Immunosupressive therapy	• Anti- CD40 monoclonal antibody • Targets the CD40-CD154 co-stimulatory pathway which results in reduced B cell activation signaling. • It is a non-consumable immunoglobulin silencing antibody designed to block CD40 receptor interactions without removing CD40-expressing cells
	Efgartigimod and Rozanolixizumb	• Targets neonatal immunoglobulin receptor(FcRn) • FcRn is associated with the long life of IgG antibodies such as TRAb (TSH receptor antibody)

		• FcRn prevents degradation of IgG and maintains its level via receptor-mediated internalization and recycling of IgG • In FcRn therapy, antibody catabolism is accelerated and circulating pathogenic TRAb level is reduced. • Efgartigimod is a humanized igG-1 derived Fc fragment and Rozanolixizumb is a humanized anti- FcRn monoclonal antibody, both of which blocks FcRn-IgG interaction
	TSHR antagonist (Antag-3, VA-K-14, S37a, K1-70)	• Antag-3 inhibits TSH-stimulated cyclic adenosine phosphate (cAMP) production and reduces thyroid hormone levels. • TSHR antagonist compound, VA-K-14 and S37a, identified by high throughput library screening, can both inhibit TSH expression and TRAB-induced signaling. • K1-70(TSHR-blocking antibody), which could completely inhibit the elevation of serum thyroxine, suggesting a potential therapeutic effect for Grave's disease with high serum TRAB level. Specific immunotherapy against TSHR involves the use of drugs with a broad immunosuppressive effect and thus has the potential for infectious side effects.
	Teprotumumab (Tepezza)	• IGF-1R(Growth factor 1 receptor) inhibitor • Considerable evidence shows that IGF-1R is involved in the development of goiter. Teprotumumab is the only FDA approved treatment for goiter as IGF-1R plays an important role in the pathogenesis of goiter

Treatments:

Table. 3: Novel Drug Targets for Hyperthyroid Grave's Disease

Treatment	Formulation/Drug used	Mechanism of Action	Adverse effects
Levothyroxine	Levoxyl, Synthroid, and Unithroid.	It works as a replacement for the thyroid hormone, thyroxine in cases of primary, secondary and tertiary hypothyroidism, where the deficiency of thyroxine is observed. First line therapy	Its overdose leads to effects similar to the symptoms of hyperthyroidism: **i)** weight loss despite increased appetite **ii)** heat intolerance and excessive sweating **iii)** headache, nausea, vomiting **iv)** hyperactivity **vi)** anxiety, anxiousness, irritability, mood swings **vii)** insomnia
Liothyronine	Cytomel	Exact mechanism of action is unknown but it exerts its metabolic effects through the control of DNA transcription and protein synthesis. Best for short term suppression of TSH and has shorter life span(24 hours)	i) Cardiotoxicity ii) Temporary hair loss, iii) Headache **iii)** Mood swings **iv)** Increased sweating and sensitivity to heat v) Diarrhea **vi)** Irregular menstrual cycle **vii)** Fatigue **viii)** Trouble breathing and some allergic

			reactions
Liotrix	Thyrolar	Synthetic combination or preparation of levothyroxine sodium and liothyronine in the ratio of 4:1 and has shorter life span. Rapid onset of action Preferred in patient with altered subtypes of tyope II deiodinase Treats enlarged thyroid gland (goiter) and thyroid cancer.	Causes side effects similar to the symptoms of hyperthyroidism.
Natural thyroid products	(Desiccated thyroid) Armour thyroid and Nature-Throid	Natural product prepared from animal thyroid glands, usually a pig's gland It provides or replaces thyroid hormone.	Severe allergic reactions like hives, difficulty in breathing, swelling of face, lips, tongue or throat

Table. 4: Treatment approaches for hypothyroidism (Laura P. Stegall, 2014)

Treatment	**Formulations/drugs**	**Mechanism of action**	**Adverse effects**
Antithyroid drugs or thioamides	Propylthiouracil, methima zole, carbimazole	-Inhibits iodination of tyrosine residues to thyroglobuline. -Also inhibits coupling of iodotyrosine residues to form T3 and T4. -They do not affect	1. Gastrointestinal intolerance 2. Skin rashes, itching, allergic reactions Joint pain 3. Loss or graying of hair Loss of taste

		the thyroid hormone level in the blood. Thiouracil is the only drug among the three which inhibits the conversion of T4 to T3 and reduces the T3 level in blood (preferred in thyroid storm).	Fever 6. Hepatic failure(in rare cases) 7. Hypothyroidism and goiter in cases of overtreatment. 8. A very rare and serious side effect is agranulocytosis (decreased WBC) due to suppression of bone marrow.
Iodines or iodides		Fastest acting inhibitor of thyroid. It interferes the iodination of tyrosil and thyronil residues of thyroglobulin resulting in reduced synthesis of thyroid hormone It also interferes with sodium iodide symporter by inhibiting its own transport	(In iodine sensitive patient) 1. swelling of eyelids and lips 2. fever 3. Joint pain 4. Thrombocytopenia (Reduced platelet count) 5.Lymphadenopathy (swelling of lymph nodes) 6. Petechiaes (Pinpoint round spots on skin) 7. Iodism due to chronic overdose
Radioactive iodine	Given in the form of oral solution of sodium salt of I^{131}.	The β-particles emitted by the radioactive iodine salts destroy the follicular cells of the	1. Dryness of eyes and mouth 2. Sore throat

		thyroid gland. Radioactive iodine is absorbed by the thyroid gland and slowly Destroys them. It has no side effects on other tissues.	3. Change in taste 4. Hypothyroidism as the thyroid gland Will be destroyed 5.contraindicated in pregnant (risk of miscarriage) and young patients(risk of thyroid cancer)
Beta blockers	Propronalol	Counteracts the effects of thyroid hormone on the peripheral tissues and reduces the symptoms of hypothyroidism such as: - Anxiety - Palpitation - Tachycardia - Tremors - Nervousness and sweating - High blood pressure	Contraindicated in pregnancy and in patients withasthma, chronic pulmonary disease and congestive heart failure.
Thyroid surgery or thyroidectomy		A part or the entire thyroid gland is surgically removed and it is preferred in: - Pregnant	Causes complication such as: 1. Disruption of the surrounding tissues 2. Damage to the

		women - Children showing major adverse effects antithyroid medications. Patient with enlarged thyroid gland causing difficulty in breathing and swallowing	nerves supplying the vocal cords 3. Damage or accidental removal of parathyroid gland which results in hypocalcemia. Difficulty in swallowing and neck pain

5. Conclusion:

Thyroid hormones produced by the thyroid gland plays an important role in controlling metabolism of the body. With the right level of thyroid hormone secretion, the body also functions or carries out metabolism at the right pace. Hypothalamus detects the level of the thyroid hormones in the blood and accordingly signals the anterior pituitary gland to release the thyroid stimulating hormone which then stimulates the thyroid gland to either release more thyroid hormone or less thyroid hormone in order to maintain the normal level. Thyroid disorders are usually caused when the level of the hormones in the blood deviates significantly from the normal level. When the thyroid gland makes hormones in the excessive amount, it leads to the hyperthyroidism with symptoms such as fatigue (due to excess utilization of energy), faster heart rate, weight loss and anxiety. On the other hand, when the thyroid gland is not able to make the hormones or produces less amount of hormone then it leads to hypothyroidism causing symptoms such as tiredness, weight gain, intolerance to cold and also hair loss. In addition to the iodine intake being one of the causes of the disorder, hyperthyroidism and hypothyroidism are also caused by other conditions. Thyroid disease affects people of all age but it is more common in women. Hypothyroidism is the common thyroid disorders seen in approximately 80% of the patient. Medications such as levothyroxine, liothyronine and liotrix are used for hypothyroidism. For hyperthyroidism, thioamine, iodides, radioactive iodine and beta blockers are used. A part or a full thyroid gland is also surgically removed in critical conditions. With the advancement of the medical science, new treatment have also been discovered and implemented recently. Thyroid disorders can create a series of

complication which affects the whole body. Understanding the risk factors can provide an early prevention of the disease and further development of the disease.

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