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Original Article

Physiological aspects of thyroid disorders: Anatomy, Hormones, Diagnosis and Management

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Abstract: The thyroid is a butterfly-shaped gland located in the front of the neck. Its primary function is to produce triiodothyronine hormones (T3) and thyroid hormone (T4). Thyroid hormones play a role A vital role in normal growth and metabolism. For thyroid disorders (TH) A significant impact on individuals' health and lives Thyroid disorders are of two types: hypo- or hyperactivity, and may also be accompanied by benign or malignant tumors. Thyroid hormones play an important role in the human body, including the T4 hormone, whose role is responsible for basic metabolic activity, and the T4 hormone, whose role includes growth and metabolism, in addition to regulating body temperature and heart rate. Thyroid hormones are essential for the normal functioning of physiological systems and are therefore. Knowing which factor (whether genetic or environmental) alters levels of thyroid-stimulating hormone (TSH) and thyroid hormones is crucial. Genetic factors contribute up to 65% of interindividual differences in TSH and thyroid hormone levels, but many environmental factors can also affect thyroid function.Thyroid diseases are the second most common disorder in the endocrine system, affecting many body systems such as the heart, blood vessels, nervous system, kidneys, digestive system, reproductive system, and other systems. It is one of the most common medical conditions, especially in women. Thyroid disorders are detected using blood tests to determine the type of gland disorder, and these tests determine the best of the thyroid hormones. This is done by measuring the hormones TSH, T4, and T3. When these hormones decrease, hypothyroidism occurs, and vice versa, that is, when they rise, hyperthyroidism occurs according to the rate. It is natural to measure these hormones, and in addition to doctors using a medical history, physical examination, and biopsy to determine whether the tumor is malignant or benign, the study therefore aimed to gain detailed knowledge of the definition of the gland and its anatomical structure in terms of structure, hormones, function, and methods of diagnosis and treatment for the purpose of becoming familiar with this gland and its physiological role. In the human body.

Treatments depend on the specific form of thyroid disorder in terms of severity, disease symptoms, and level of infection. These options include medications, radioactive iodine, and surgery (glandectomy).We have concluded from our study that the thyroid gland is one of the most important glands in the human body, and any defect in it affects the functions of many body organs.

Thyroid hormones help in the processes of metabolism, digestion, brain development, and muscle growth. When these hormones are produced in high quantities Or in low quantities, it will lead to a defect in the efficiency of the gland's work, which leads to causing many diseases. The rate of women suffering from thyroid disorders is greater than men. Any dysfunction in the thyroid gland and its hormones causes obesity and polycystic ovary syndrome in women.To avoid thyroid disorders, it is recommended to..Eat foods that contain iodine, such as fish and dairy, stop smoking, drink water and fluids in sufficient quantities, exercise. If you have an underactive thyroid, one of the methods of prevention is to avoid following a diet that contains sugars, trans fats, and processed foods. Avoid eating too much. Of foods rich in compounds that inhibit iodine uptake in the thyroid gland. In patients suspected of having hyperthyroidism, a blood TSH and fT4 test should be performed, obtained in the initial evaluation. Patients with overt hyperthyroidism should be treated with any of these Medications, from the following modalities: ATDS, RAI therapy, or thyroidectomy. Antithyroid medications should be the first line of treatment and the primary treatment for subclinical hyperthyroidism, whatever its causes. ATD is chosen as the primary treatment for GD, and should To be medicine It lasts for approximately 12-18 months, then stops if TSH levels are normal in that time.

Keywords: Thyroid Disorders, Physiological aspects, Anatomy, Hormones, Diagnosis, Management

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1.Introduction:

The thyroid gland including two lobes lying on each side of the trachea produce hormones thyroid hormones can "target ,influence and alter the metabolism of approximately every cell in the body "so that the thyroid gland becomes one of the "largest and most sensitive" endocrine glands in the body. [Ploski R. *et al*., 2019]is a vital butterfly-shaped endocrine gland situated in the lower part of the neck. It is present in front and sides of the trachea, inferior to the larynx. It plays an essential role in the regulation of the basal metabolic rate (BMR), and stimulates somatic and psychic growth, besides having a vital role in calcium metabolism. It is a gland consisting of two lobes, the right and the left lobes joined together by an intermediate structure, the isthmus. Sometimes a third lobe called the pyramidal lobe projects from the isthmus. It has a fibrous/fibromuscular band, i.e., levator glandulae thyroideae running from the body of the hyoid to the isthmus.(Zoeller,*et al.*, 2020) The lobes are 5 x 2.5 x2.5 cm in dimension and weight around 25 gm. It extends from the fifth cervical to the first thoracic vertebrae. The lobes extend from the middle of the thyroid cartilage to the fifth tracheal rings. The isthmus is 1.2 x 1.2 cm in dimensions and extends from second to third tracheal rings. It grows larger in females during the period ofmenstruation and pregnancy.Hormones are chemical substances that help control certain cells and organs. Adrenaline and dopamine are active in many physical and emotional responses, including fear, excitement, and pleasure. Other hormones from this gland also help regulate metabolism, which is the process by which calories and oxygen are converted into energy. Thyroid stimulating hormone(TSH) synthesis in the anterior pituitary is stimulated by" thyrotropin-releasing hormone (TRH) and inhibition by thyroid hormone in a classical endocrine negative- feedback loop binds to the TSH receptor" in the thyroid gland, stimulating the production of "thyroglobulin, thyroid peroxidase, sodium iodide symporter (NIS) protein, and thyroxin(Das DK.2020). Thyroid gland secreting hormones thyroxin (T4) and triiodothyronine (T3) which control the body's metabolic rate and the rate of energy production, so "thyroid function regulates a wide array of metabolic activities".(Qureshi *et al*.,2020)

Thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3), have important roles in cellular and neuronal development, the maturation of bone, growth, metabolism, intracellular protein trafficking modulation, and regulating

production of red blood cells by genomic or non-genomic actions(Zoeller,*et al.*, 2020). Plasma thyroid hormones concentrations are controlled by thyroid hormone axis which included to hypothalamus paraventricular nucleus, anterior pituitary, and thyroid gland.Thyroid hormones are necessary for the normal functioning of physiological systems.(Pyo .*et al*., 2018)Therefore, knowledge of any factor (whether genetic, environmental or intrinsic) that alters the levels of thyroid-stimulating hormone (TSH) and thyroid hormones is crucial. Genetic factors contribute up to 65% of interindividual variations in TSH and thyroid hormone levels, but many other factors can also influence thyroid function. Such factors include demographic factors (age and sex (Chaker *et al*., 2016), intrinsic factors (microbiota, stress), usage of medicaments [Montanelli L *et al.,* 2018] and various environmental factors (Gruppen E. *et al*.,2020).

Environmental Factors That Influence TSH and Thyroid Hormone Levels:

Smoking:Most studies investigating the influence of smoking on TSH and thyroid hormone levels have observed a decrease in TSH levels and an increase in T3 and T4 levels in smokers (Kadkhodazadeh H. *et al*.,2020)

Alcohol Consumption: Alcohol has been shown to have a toxic effect on thyroid cells, which is considered to be the cause of decreased thyroid volume in alcoholics (Balhara Y.2019)

Body Mass Index:The majority of studies that investigated the influence of body mass index (BMI) on TSH and thyroid hormone levels reported a positive correlation between BMI values and TSH (Lundbäck V. *et al.*,2020) and fT3 levels (Habib A.*et al.,* 2020)Diet: diet can alter TSH and thyroid hormone levels.

Aim of the study

Identifying the disease, its causes, methods of diagnosis and treatment, and how to prevent infection with the disease.

1-Thyroid gland

The thyroid, or thyroid gland, is an endocrine gland in vertebrates. In humans, it is in the neck and consists of two connected lobes. The lower two thirds of the lobes are connected by a thin band of tissue called the isthmus (pl.: isthmi). The thyroid gland is a butterfly-shaped gland located in the neck below the Adam's apple. Microscopically, the functional unit of the thyroid gland is the spherical thyroid follicle, lined with follicular cells (thyrocytes), and occasional parafollicular cells that surround a lumen containing colloid. The thyroid gland secretes three hormones: the two thyroid hormones – triiodothyronine (T3) and thyroxine (T4) – and a peptide hormone, calcitonin. The thyroid hormones influence the metabolic rate and protein synthesis and growth and development in children. Calcitonin plays a role in calcium homeostasis.Secretion of the two thyroid hormones is regulated by thyroid-stimulating hormone (TSH), which is secreted from the anterior pituitary gland. TSH is regulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus.(Boron WF,2021)

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

1.2-Definition of Thyroid gland

Thyroid gland: A gland that makes and stores hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. Thyroid hormones are essential for the function of every cell in the body. They help regulate growth and the rate of chemical reactions (metabolism) in the body. Thyroid hormones also help children grow and develop.

The thyroid gland is located in the lower part of the neck, below the Adam's apple, wrapped around the trachea (windpipe). It has the shape of a butterfly: two wings (lobes) attached to one another by a middle part called the isthmus.

The thyroid uses iodine, a mineral found in some foods and in iodized salt, to make its hormones. The two most important thyroid hormones are thyroxine (T4) and triiodothyronine (T3). Thyroid stimulating hormone (TSH), which is produced by the pituitary gland, acts to stimulate hormone production by the thyroid gland. The thyroid gland also makes the hormone calcitonin, which is involved in calcium metabolism and stimulating bone cells to add calcium to bone.

1.3-Anatomy of the Thyroid Gland

The right and left lobes of the thyroid are connected at the midline by the isthmus of the gland. (Shen W, Duren M, *et al* ,2017) A pyrami- dal lobe may extend superiorly from the isthmus or from the medial portions of the left or right lobes. The thyroid extends from the level of the fifth cervical ver- tebra to the first thoracic vertebra. The gland weighs about 30 g, being somewhat heavier in females than in males (Shaheen OH ,2018). The thyroid is surrounded by a sleeve of pretracheal fascia sometimes called the perithyroid sheath. Posteriorly, a thickening of this fascia attaches the gland to the cricoid cartilage. This fascia is the lat- eral ligament of the thyroid (ligament of Berry).

The anterior surface of the thyroid is related to the deep surface of the sternothyroid, sternohyoid, and omohyoid muscles (Figs. 1). Where these muscles are absent in the midline, the isthmus of the gland is subcutaneous. Laterally the gland is related to the carotid sheath, which contains the common carotid artery, the internal jugular vein, and the va- gus nerve. Posteriorly, the superior parts of the lobes of the thyroid are related to the longus colli and lon- gus capitis muscles.(Skandalakis JE ,2020)Medially, the superior part of the thyroid is related to the larynx and laryngopharynx, which includes the cricothyroid and inferior pharyn- geal constrictor muscles and the thyroid and cricoid cartilages. Medially, the inferior part of the thyroid is related to the trachea and the esophagus. The isthmus of the thyroid lies anterior to the second and third tracheal rings.(Sturniolo G,2019)

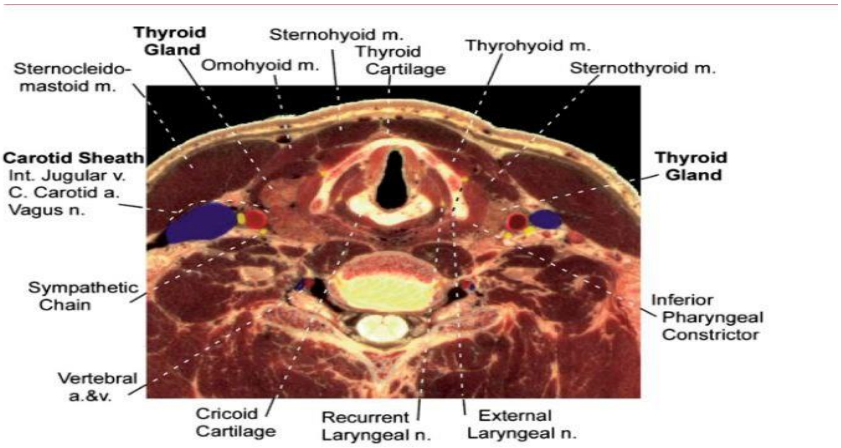

Fig. 1 Thyroid gland and its relations at the level of the thyroid cartilage.(Sturniolo G,2019)

1.4-Thyroid hormones and their effects

Thyroid hormone (thyroxine) or T4 is the main hormone produced by the gland, and is responsible for basic metabolic activity. This hormone is found in the blood and bound to a protein called thyroxine-binding globulin

(TBG- Thyroxine Binding globulin)

Free thyroxine (FT4 - Free T4) is the only one that can enter cells and cause metabolic activity.(Wilkinson *et al*.,2015)

The main function of the thyroid gland is to produce thyroid hormones that contain iodothyronine (triiodothyronine), calcitonin (T4), and triiodothyronine (T3).(Refetoff *et al*.,2018)

Thyroid hormones are created from iodine and tyrosine. The T3 hormone is known by this name because it contains three atoms of iodine per molecule, while the T4 hormone contains four atoms of iodine per molecule.

Thyroid hormones have a wide range of effects on the human body, including:(Suzuki *et al*.,2019)

Metabolic Effects Thyroid hormones increase basal metabolic rate and affect all tissues of the body.Almost all

thyroid hormones affect appetite, absorption of substances, and bowel movement and increase absorption. In the gastrointestinal tract, the absorption and breakdown of glucose by cells is synthesized and thyroid hormones stimulate the breakdown Fats, and increase the number of free fatty acids. Despite their increase in free fatty acids, thyroid hormones reduce cholesterol levels, and this may be due to their increase in the rate of cholesterol absorption. In the gall vesicle

Cardiovascular Effects Thyroid hormones increase the rate and force of the heartbeat. Increases respiratory rate, oxygen uptake and consumption, and increases mitochondrial activity. Together, these factors increase blood flow and body temperature Evolutionary influences.(Liu *et al*.,2018) Thyroid hormones play an important role in normal development. They increase the growth rate of young people, and developing brain cells are a major target of thyroid hormones. Thyroid hormones play a particularly important role in brain maturation during fetal development and the first few years of life after birth.(Peeters *et al*.,2019)

Thyroid hormones also play a role in maintaining normal sexual functions, sleep, and thinking patterns. The sexual effects of thyroid hormones include sexual desire and regular menstruation.(Liu *et al.,*2019)

After secretion, a very small amount of thyroid hormones circulates freely in the blood. Most of them are bound to binding globulin With thyroxine (about 70%), thyroxine-binding protein (10%), albumin (15%). 0.03% of freely circulating T4 and 0.3% of T3 have hormonal activity. In addition, more than 85% of 13 in the blood is produced after conversion of T4 by iodothyronine deiodinase in the body's organs(Gionfra *et al.,*2019)

Thyroid hormones act after crossing the cell membrane and binding to the intercellular nuclear thyroid hormone receptor (TR). 201-TR-1 TR and TR-B2, which bind to hormone response elements and transcription factors to modulate DNA transcription in addition For these effects on DNA, thyroid hormones act within the cell membrane or within the cytoplasm through interactions with... Enzymes(Gionfra *et al.,*2019).

2-Thyroid disorders

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

2.1-Hypothyroid Disorders

Hypothyroid disorders are characterized by mental and physical slowness, cold skin, mild weight gain (although usually not obesity), and decrease in basal metabolic rate. Hypothyroid status also results in decreased cardiac function which can lead to congestive heart failure. Hypothyroidism can lead to both hypertension and hypercholesterolemia, and is associated with increased risk for development of atherosclerosis.

In addition to treatment for the underlying disorder, it is usually necessary to supplement with exogenous thyroid hormone. Poor compliance has been observed, especially in adolescents; this can result in developmental abnormalities.

Severe (non-thyroid) illness may reduce T3 levels to apparent hypothyroid levels (a phenomenon known as euthyroid sick syndrome). In many cases, however, these patients are not, in fact, hypothyroid, and upon resolution of the illness, the thyroid hormone levels return to normal.(Korevaar *et al*.,2017)

2.1.1. Cretinism: Hypothyroid conditions during fetal development result in impairment of growth and brain functioning. The hypothyroidism may be due to iodide deficiency or to congenital defects, such as lack of TSH receptor. The result is amentally retarded, dwarfed newborn.(Taylor *et al*.,2018)

2.1.2.Goiter: The thyroid is capable of massive increases in size, resulting in a visually obvious bulge in the neck. Goiter formation usually results from excessive stimulation of the thyroid by TSH .In hypothyroid conditions, this is usually due to low thyroid hormone production, as a result of iodide deficiency (fairly common in the developing

world, but rare in the United States due to sodium iodide supplementation of table salt) or from goitrogens, which are usually compounds that interfere with iodide uptake. Goitrogens are found in high concentrations in turnips and related vegetables (excessive consumption of which can result in goiter formation, although the goitrogens can be inactivated by cooking). Another type of goitrogen is a compound that stimulates hepatic clearance of thyroid hormone. As with other thyroid conditions, goiters are much more common in women .(Korevaar *et al*.,2017)

2.1.3.Congenital goiter: Defects in thyroglobulin synthesis or structure, or in iodide incorporation (probably as a result of TPO defects) cause neonatal goiter and hypothyroidism. In some cases increased T3 synthesis leads to low euthyroid status, allowing essentially normal growth, but not alleviating the mental symptoms. Defects in TG may result in the presence of proteins iodinated on tyrosine and histidine in urine (in the absence of TG, TPO uses a variety of other proteins as substrates). In some cases the defect alters the three-dimensional structure of the TG protein, and therefore although iodination is normal, coupling is inhibited.(Korevaar *et al.*,2017)

2.1.4Excess iodide: Paradoxically, too much dietary iodide can result in decreased thyroid hormone production, although the thyroid usually compensates. However, the fetus responds to excess iodide by shutting down thyroid hormone production, resulting in goiter, hypothyroid disorders, and problems during labor.(Nyström *et al*.,2020)

2.1.5.Idiopathic myxedema: Myxedema, a condition of puffy skin characteristic of hypothyroidism, is in some cases not associated with any obvious cause. One possible cause is the presence of antibodies that act as antagonists rather than the agonist-type action of TS Ab (Taylor *et al*.,2018)

2.1.6.Hashimoto's syndrome: Hypothyroidism can result from an autoimmune attack on the thyroid (as with all autoimmune disorders, this is much more common in women than in men). It is often subclinical, especially in early stages, due to compensating hypertrophy and hyperplasia of undamaged thyroid tissue, and to increases in secretion of T3 (i.e. an increased T3:T4 secretion ratio). The disorder generally progresses from normal T3/low T4/high TSH, to low T3/low T4/very high TSH, with enlarged thyroid and myxedema. There is some evidence that some types of thyroid-destructive autoimmune attack can be stimulated by environmental insults such as exposure to polyhalogenated biphenyls, and that some types of infection can trigger Hashimoto's disease in susceptible individuals. Autoimmune attack on the thyroid may be associated with other autoimmune disorders, such as Addison's disease and Type I diabetes mellitus.(Dutta *et al*.,2021)

2.2-Generalized resistance to thyroid hormone

Rare individuals exhibit resistance to thyroid hormone due to a genetic defect in the thyroid hormone receptor-gene. In autosomal recessive cases, the disorder is due to a gene deletion. In autosomal dominant cases, the disorder is due to a point mutation that results in decreased affinity for thyroid hormone. GRTH is a disorder characterized by elevated free and (usually) total T3 and T4 levels, with either normal or high levels of TSH. The normal levels are probably a consequence of the fact that the thyroid has become sufficiently hyperplastic as to be capable of producing elevated levels of thyroid hormone from normal levels of TSH. Although some have claimed that the disorder is asymptomatic, most individuals present with somatic abnormalities suggestive of hypothyroid status, as well as low IQ, dyslexia, short stature, and low BMR. About 50% of affected individuals also exhibit attention deficit disorder and hyperactivity. However, individuals diagnosed with attention deficit disorder usually do not have GRTH.(Dutta *et al.*,2021)

2.3 -hyperactive of thyroid gland :

Hyperthyroidism occurs when the thyroid gland produces a large amount of the hormone thyroxine. Hyperthyroidism may cause increased metabolism, resulting in unintended weight loss and rapid, irregular heartbeat.

There are many ways to treat hyperthyroidism. Doctors use antithyroid medications and radioactive iodine to slow the production of thyroid hormone. Sometimes, treatment includes surgery to remove all or part of the thyroid gland. Although hyperthyroidism can be dangerous if ignored, most people respond well Once the condition is diagnosed and treated.(Gerstein *et al.*,2018)

2.4 -Graves' disease (exophthalmic goiter):

It is a disorder of the immune system that results in increased production of thyroid hormones.

Hyperthyroidism is one of the common causes.

Thyroid hormones affect many body systems, so the symptoms and signs of Graves' disease may vary greatly. Although Graves' disease may affect anyone, it is more common among women and people under the age of 40.(Dutta *et al*.,2021)The primary goals of treatment are to reduce the amount of thyroid hormones the body produces and reduce the severity of symptoms.(Yafit *et al*.,2019)

the reasons : Graves' disease, exophthalmos, is caused by a defect in the body's immune system. The reason behind this defect is not known.(Gerstein *et al.*,2018)

The immune system usually produces antibodies designed to target a specific virus, bacteria, or other foreign substance. in Graves' disease (exophthalmic goiter) - for reasons that are not well understood - the immune system produces an antibody to one part of Cells in the gland that produce thyroid hormone.(Lazarus *et al.*,2020)

Thyroid function is usually regulated by a hormone secreted by a small gland at the base of the brain (pituitary gland). And it works Graves' goiter associated antibody) - thyrotropin receptor antibody (TRAD) - same Regulatory action of the pituitary hormone. This means that the lyotropin receptor antibody (TRAb) overrides the normal regulation of the thyroid gland, causing increased secretion of thyroid hormones.(Gerstein *et al.*,2018)

2.5 -Thyrotoxic Nodule

An autonomously functioning thyroid nodule may cause thyrotoxi- cosis with typical hyperthyroid symptoms. Physical examination re- veals a thyroid nodule, and findings specific to Graves' disease are absent. The diagnosis is confirmed with elevated FTI (or free T4), low TSH, and a hot nodule on radioiodine scan. Fine-needle aspira- tion is indicated if the nodule is not hot on nuclear medicine scan, as with other nontoxic nodules.(Yafit *et al*.,2019)

Treatment is with ablation or occasionally surgery. Antithy- roid medications are not usually indicated for thyrotoxic nodules. Hy-pothyroidism following ablation is less common than with Graves' disease, although a 40% long-term prevalence of hypothy-roidism has been reported.Indications for surgery include a thyro-toxic nodule that is very large or progressively enlarging or other signs suggestive of thyroid cancer.(Dutta *et al*.,2021)

The nodule may persist after ablation treatment, and ongoing mon- itoring by physical examination is needed to identify any increase in size. Should the nodule or adjacent tissue enlarge, further evaluation for possible thyroid cancer is required. Periodic monitoring for pos- sible hypothyroidism also is necessary.(Lazarus *et al*.,2020)

2.6 -Thyroiditis

Thyroiditis is defined as an inflammatory process involving the thy- roid gland. This inflammation may cause thyrotoxicosis due to un- regulated release of thyroid hormone from an injured gland. There are several types of thyroiditis, each with a different clinical picture.Subacute painful (granulomatous) thyroiditis is probably caused by a viral infection and is the thyroiditis that most commonly results in thyrotoxicosis. Patients present with an exquisitely tender, firm, asymmetric nodular thyroid gland. They have symptoms of neck pain, a flulike syndrome, and symptoms of thyrotoxicosis. The erythrocyte sedimentation rate is elevated, and antithyroid antibodies are absent. These patients usually go through four phases: (1) hyperthyroidism lasting 3 to 6 weeks; (2) euthyroid status for a few weeks; (3) hy-pothyroidism lasting weeks to months; and (4) euthyroid state again (Andersen *et al*.,2020)

Subacute painless (lymphocytic) thyroiditis is an autoimmune pro- cess that may cause thyrotoxicosis. Physical examination usually re- veals a mildly enlarged thyroid gland that is somewhat firm and non- tender, although nearly 50% of patients have no goiter.(Stagnaro *et al.*,2019) Antibodies to thyroid peroxidase are present in about 50% of patients. These patients may go through the same four phases as subacute painful thyroiditis, but the euthyroid phase preceding hypothyroidism may be brief or absent. Some patients do not return to euthyroid status after hypothyroidism occurs and require chronic thyroid hormone replacement.(Tanaka *et al.*,2020)

Acute thyroiditis, caused by a bacterial infection, is a rare condi- tion in developed countries because of the availability of antibiotic therapy (Andersen *et al.*,2020)

2.7-Thyroid Cancer

Four cell types of thyroid cancer are possible, each with a consider- ably different natural course and prognosis:

1. Papillary carcinoma accounts for 60% to 80% of all thyroid cancer. The tumor is slow-growing, and there is good long-term survival if surgical removal is performed while the cancer is still confined to the thyroid gland. Papillary carcinoma spreads by lymphatic means.

2. Follicular carcinoma accounts for 10% to 15% of all thyroid can- cers. It is slightly more aggressive than the papillary variety and spreads by the hematogenous route. A subcategory of follicular carcinoma is the Hürthle cell type, which is more aggressive and more common in iodine-deficient countries.(Stagnaro *et al*.,2019)

3. Medullary carcinoma accounts for only 2% to 5% of thyroid can-cers. Most of these lesions are sporadic, but some are familial 20% are part of the MEN-II syndrome, which has an autosomal-dominant inheritance pattern. The latter can be identified early with elevated calcitonin levels and genetic testing. Screening with these tests should be performed on all family members if MEN-II or familial medullary carcinoma is diagnosed. If medullary car-cinoma is not diagnosed prior to a palpable mass being present,the cure rate is less than 50%.(Stagnaro *et al*.,2019)

4. Anaplastic thyroid carcinoma is the most aggressive type but ac- counts for only 2% to 7% of cases. It has the worst prognosis of any thyroid cancer, with a median survival time of 4 to 7 months and a 5-year survival rate of only 4%.(Nicholson *et al*.,2021)

5. Surgery is the treatment of choice for all thyroid carcinoma when excision is possible. Controversy remains as to whether total or par- tial thyroidectomy is preferable. Near-total resection is probably the procedure of choice. Radioiodine ablation is recommended for pa- tients with known residual tumor and probably also for those at(Kahaly *et al*.,2018)

2.8-Thyroid Disease During Pregnancy

Both hypothyroidism and hyperthyroidism can complicate preg- nancy. Thyroid-binding globulin increases during pregnancy, and so total T3 and T4 increase as well; hence, tests for these substances are not sufficient to diagnose or follow pregnant patients with thyroid disease. Any use of radioactive iodine is contraindicated during pregnancy.(Kahaly *et al*.,2018) . Hypothyroidism causes anovulation and rarely coincides with pregnancy. When hypothyroidism occurs, it is associated with ges- tational hypertension, premature labor, and low birth weight. Treat- ment consists of replacement with L-thyroxine to maintain the TSH level in the normal range on a sensitive assay. (Nicholson *et al*.,2021) . Hyperthyroidism during pregnancy is caused by the same etiolo- gies as in nonpregnant patients, with Graves' disease being the most common cause. Thyrotoxicosis may lead to spontaneous abortion, stillbirth, neonatal death, and low birth weight. 35.36 Antithyroid drugs (usually propylthiouracil), propranolol, and occasionally thyroid re- section may be used for treatment. (Kahaly *et al*.,2018) . Postpartum thyroiditis is a transient autoimmune thyroid dys- function that occurs within the first postpartum year. It is probably an exacerbation of a preexisting subclinical autoimmune thyroid tis.The true incidence is probably 5% to 10%, although it is fre- quently underdiagnosed.The most common complaints are de- pression, poor memory, and impaired concentration. The clinical course consists of a hyperthyroid phase (which may be absent), fol- lowed by a hypothyroid phase and eventually a return to euthyroid status.The diagnosis is usually made with a sensitive TSH mea- surement. Patients with antibodies to thyroid peroxidase and thy- roglobulin are at increased risk of developing this syndrome. 36 Pa- tients who have one episode of postpartum thyroiditis are at increased risk for recurrence with future pregnancies and may de- velop permanent hypothyroidism.(Korevaar *et al.*,2019)

2.9. Weight gain and the thyroid gland

The relationship between the thyroid gland and weight gain is linked to what is known as hypothyroidism, as it causes a decrease in the metabolism process and thus the inability to lose weight. The metabolism process is also linked to controlling body temperature and heart rate, so a decrease in The efficiency of the gland's work affects the body's burning of calories, and hypothyroidism inhibits the secretion of gland hormones that are important for regulating body processes. The principle of the thyroid gland's work is based on sending hormones that work to regulate the

metabolism process, and therefore hypothyroidism slows down this process and causes(Bavle RM.2019).

3- Diagnosis

When screening for abnormalities of thyroid gland function most doctors will order blood tests that measure the level of TSH (thyroid stimulating hormone) and freeT4. Depending upon the results of these tests and upon the specific thyroid disorder, a number of other tests may be ordered. Some other tests include levels of T3, thyroxine. binding protein, antithyroid antibodies, and serum thyroglobulin. Occasionally tests that evaluate functional responses to stimulation of the thyroid or pituitary glands may be performed. The anatomy of the thyroid gland can be evaluated by a thyroid ultrasound or by a thyroid scan. The scan in done by injecting a minute amount of radioactive iodine into the individual, waiting 30 minutes and then measuring the radioactivity over the thyroid gland (which has the unique capacity of trapping iodine.) The scan produces a picture of the active part of the thyroid gland. A needle biopsy (taking a sample of tissue) or needle aspiration (taking a sample of fluid) from nodules in the thyroid gland can also be done by a physician. (Krassas et al., 2021; van den Boogaard *et al.*, 2020)

3.1.Thyroid Tests

3.1.1TSH Test

A health care provider usually performs the TSH blood test first to check how well the thyroid is working. The TSH test measures the amount of TSH a person's pituitary is secreting. The TSH test is the most accurate test for diagnosing both hyperthyroidism and hypothyroidism. Generally, a below-normal level of TSH suggests hyperthyroidism. An abnormally high TSH level suggests hypothyroidism. (Chiamolera and Wondisford, 2020).

The TSH test detects even tiny amounts of TSH in the blood. Normally, the pituitary boosts TSH production when thyroid hormone levels in the blood are low. The thyroid responds by making more hormone. Then, when the body has enough thyroid hormone circulating in the blood, TSH output drops. The cycle repeats continuously to maintain a healthy level of thyroid hormone in the body. In people whose thyroid produces too much thyroid hormone, the pituitary shuts down TSH production, leading to low or even undetectable TSH levels in the blood. (Visser *et al.*, 2019)

In people whose thyroid is not functioning normally and produces too little thyroid hormone, the thyroid cannot respond normally to TSH by producing thyroid hormone. As a result, the pituitary keeps making TSH, trying to get the thyroid to respond.

If results of the TSH test are abnormal, a person will need one or more additional tests to help find the cause of the problem. (Dentice *et al*., 2019)

3.1.2.T4 Tests

The thyroid primarily secretes T_1 and only a small amount of T3. T, exists in two forms:

1. T_1 that is bound to proteins in the blood and is kept in reserve until needed
2. a small amount of unbound or "free" T4 (FT4), which is the active form of the hormone and is available to enter body tissues when needed

A high level of total T4-bound and FT4 together-or FT, suggests hyperthyroidism, and a low level of total Ta or FT4 suggests hypothyroidism.

Both pregnancy and taking oral contraceptives increase levels of binding protein in the blood. In either of these cases, although a woman may have a high total T level, she may not have hyperthyroidism. Severe illness or the use of corticosteroids-a class of medications that treat asthma, arthritis, and skin conditions, among other health problems-can decrease binding protein levels. Therefore, in these cases, the total T4 level may be low, yet the person does not have hypothyroidism. (Miot *et al.*,2020)

3.1.3.T3 Test

If a health care provider suspects hyperthyroidism in a person who has a normal FT4 level, a T3 test can be useful to confirm the condition. In some cases of hyperthyroidism, FT4 is normal yet free T3 (FT3) is elevated, so measuring

both T4 and T3 can be useful if a health care provider suspects hyperthyroidism. The T3 test is not useful in diagnosing hypothyroidism because levels are not reduced until the hypothyroidism is severe. (McLachlan and Rapoport, 2020)

3.1.4.TSI Test

Thyroid-stimulating immunoglobulin is an autoantibody present in Graves' disease. TSI mimics TSH by stimulating the thyroid cells, causing the thyroid to secrete extra hormone. The TSI test detects TSI circulating in the blood and is usually measured

1. in people with Graves' disease when the diagnosis is obscure
2. during pregnancy
3. to find out if a person is in remission, or no longer has hyperthyroidism and its symptoms(Davies *et al*., 2020).

3.1.5.Antithyroid Antibody Test

Antithyroid antibodies are markers in the blood that are extremely helpful in diagnosing Hashimoto's disease. Two principal types of antithyroid antibodies are

1. anti-TG antibodies, which attack a protein in the thyroid called thyroglobulin
2. anti-thyroperoxidase, or anti-TPO, antibodies, which attack an enzyme in thyroid cells called thyroperoxidase(Davies *et al*., 2020).

3.1.6.Thyroid function testing

serum-based tests available by immunoassay for measuring the concentration of thyroid hormones in the circulation include total (TT_4 and TT_3) and free (FT_4 and FT_3) hormone. In addition, direct measurements of thyroid hormone binding plasma proteins, thyroxine binding globulin (TBG), transthyretin (TTR)/prealbumin (TBPA), and albumin are also available. However, the thyroid test measurement that has the greatest utility for evaluating patients suspected of thyroid disease is the third-generation thyroid stimulating hormone (TSH, thyrotropin) assay. Most third-generation TSH assays today that can reliably detect differences of 0.02 µU/ml or better (interassay imprecision <20 percent) can easily distinguish both hyper- and hypothyroidism from euthyroidism (normal thyroid function).(McLachlan and Rapoport, 2017).

3.1.7.Testing for diagnosis and management of thyroid dysfunction

The most sensitive test in an ambulatory population at risk for thyroid dysfunction is the serum TSH. Serum TSH assays today have sufficient sensitivity and specificity to identify individuals with all forms of thyroid dysfunction in the general population. However, among individuals with serious, acute illness, the serum TSH is less specific for thyroid disease because a serious illness alone can depress TSH secretion. TSH screening of the neonatal population to detect congenital hypothyroidism before it is clinically evident is mandated throughout the United States and in many other countries. (Gu *et al*., 2019).

When an abnormal serum TSH value is obtained, the usual next step is to repeat the measurement of TSH and also measure a serum free T_4. The latter can be performed in several ways and among non-hospitalized individuals, most methods give results that are inversely correlated with the serum TSH result. The most common cause of discordance between the TSH and free T_4 result occurs in patients with subclinical thyroid dysfunction with high or low serum TSH values and a normal serum free T_4 result.

Serum TSH measurements may yield misleading results for individuals with changing levels of thyroid hormones. For example, a serum TSH level may remain high for weeks in hypothyroid patients treated with T_4. Similarly, serum TSH levels may remain low for weeks after the serum T_4 level falls to normal in patients treated for hyperthyroidism. (Thangaratinam *et al*., 2019)

3.2.Diagnosis of Hypothyroidism

Hypothyroidism is a hypometabolic state that results from a deficiency in T_4 and T_3. Its major clinical manifestations are fatigue, lethargy, cold intolerance, slowed speech and intellectual function, slowed reflexes, hair loss, dry skin,

weight gain, and constipation. It is more prevalent in women than men. The most common cause of hypothyroidism is disease of the thyroid itself, primary hypothyroidism.(Gu *et al*., 2019).

The most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease), in which the thyroid is destroyed by antibodies or lymphocytes that attack the gland. Other causes are radioactive iodine and surgical therapy for hyperthyroidism or thyroid cancer, thyroid inflammatory disease, iodine deficiency, and several drugs that interfere with the synthesis or availability of thyroid hormone. Hypothyroidism may also occur rarely (<1 percent of cases) as a result of deficiency of TRH or impaired TSH secretion due to hypothalamic or pituitary disease, respectively. This is known as secondary or central hypothyroidism because of the negative feedback relationship between serum T_4 and T_3 levels and TSH secretion. people with primary hypothyroidism have high serum TSH levels. If an individual has a high serum TSH value, serum free T_4 should be measured. The concomitant finding of a high serum TSH concentration and a low free T_4 level confirms the diagnosis of primary hypothyroidism. People with a high serum TSH concentration and a normal or low-normal serum free T_4 level have, by definition, subclinical hypothyroidism. The diagnosis of secondary hypothyroidism is based on the findings of a low serum free T_4 level and a serum TSH level that is normal or low. People with secondary hypothyroidism are unlikely to be detected by a screening program based on measurements of serum TSH, but the condition is much less common than primary hypothyroidism(Zamocky *et al*., 2020)

3.3.Diagnosis of Hyperthyroidism

Hyperthyroidism is a hypermetabolic state that results from excess production of T_4 and T_3. Its major clinical manifestations are nervousness, anxiety, heart palpitations, rapid pulse, fatigability, tremor, muscle weakness, weight loss with increased appetite, heat intolerance, frequent bowel movements, increased perspiration, and often thyroid gland enlargement (goiter). Most individuals with hyperthyroidism are women.(Gu *et al*., 2019).

The most common cause of hyperthyroidism is Graves' disease, an autoimmune disease characterized by the production of antibodies that activate the TSH receptor, resulting in stimulation of T_4 and T_3 production and enlargement of the thyroid. Other caused of hyperthyroidism are a multinodular goiter, solitary thyroid adenoma, thyroiditis, iodide- or drug-induced hyperthyroidism, and, very rarely, a TSH secreting pituitary tumor.

The diagnosis of hyperthyroidism is based on the findings of a high serum free T_4 level and a low serum TSH concentration. Occasionally, people with hyperthyroidism have a normal serum free T_4 and high serum free T_3 concentrations. These patients have what is called T_3-hyperthyroidism. An increase in serum thyroid hormone binding protein will raise the serum total T_4 level but not free T_4 concentrations. In these patients the serum TSH remains normal. Patients with a low serum TSH concentration and normal serum free T_4 and free T_3 levels have, by definition, subclinical hyperthyroidism. (Krassas *et al*., 2010).

4-Treatment

4.1.Antithyroid medications

- Therapy of Graves' disease is directed toward controlling the effects of excess thyroid hormone and reducing the production of additional hormone. Beta-blockers are especially effective in controlling the tachycardia, tremor, and other symptoms related to excess hormone.(Chopra *et al.*,2019)
- Propranolol is begun at 20 to 40 mg two to four times daily and in-creased every few days until the heart rate is within the normal range. When beta-blockers are contraindicated, diltiazem or cloni-dine may be effective.
- Controlling hormone production may be accomplished with antithyroid medications, radioiodine ablation, or surgery.(Gharib *et al*.,2018)
- Choice of treatment is influenced by the clinical presenta-tion, the age of the patient, and the patient's ability and willingness to comply with a treatment regimen.(Biondi *et al*.,2020)
- Antithyroid medications available in the United States to control thyroid hormone production are methimazole or propylthiouracil. In addition to blocking production of thyroid hormone, these medica-tions may alter the course of the disease via their immunosuppres- sive effects. Reported remission rates

vary widely and are proba- bly higher in patients with less severe hyperthyroidism, short duration of illness, and small goiter. The duration of treatment is usually 6 months to 2 years. The remission rate can be as high as 60% if treat- ment is continued for 2 years. Failure to achieve remission after 2 years of treatment is an indication for alternate therapy. (Gharib *et al*.,2018)

- Initial adult dosage of methimazole is 20 to 30 mg/day divided into two doses. In patients with severe hyperthyroidism and a large goiter, the higher dose is warranted. Euthyroid status, determined clinically and with thyroid function tests (T4 and T3), is usually achieved within 4 to 6 weeks, and the dosage is reduced incremen- tally every 4 to 6 weeks to a maintenance dose of 2.5 to 10 mg/day given in a single dose. TSH is not useful for following the response to treatment, as it may remain suppressed for months after T4 and T3 normalize.(Parkes *et al*.,2021) The initial dose of propylthiouracil is usually 300 mg/day, and maintenance is 50 to 100 mg/day. Both must be divided into three doses. 5.10 Either of these drugs may cause rash, leukopenia, and (rarely) agranulocytosis.
- Patients should be cautioned about these side effects. Methimazole has the advantages of lower risk of agranulo- cytosis, a longer half-life allowing usage on a once-a-day schedule, and more rapid return to euthyroid status. Propylthiouracil may be preferable during pregnancy, lactation or thyroid storm. (Parkes *et al*.,2021) Concomitant administration of thyroxine 100 to 200 µg/day has been proposed to avoid frequent adjustments in antithyroid dosage and possibly reduce recurrence of hyperthyroidism, but data demon- strating the effectiveness of this treatment regimen are limited and have not been reproduced.(Lazarus *et al*.,2019)

4.2. Surgical treatment

- Iodine ablation can be used to permanently destroy thyroid tissue sufficiently to reduce hormone production to normal levels. This method has become the most commonly used initial therapy for Graves' disease in the United States. (Lazarus *et al*.,2019)
- The amount of radiation used can be calculated based on the patient's weight, gland size, and thy- roid uptake. In practice, this method is not strictly used because re- sults are not as precise as desirable. A major disadvantage of this treatment is the high prevalence of hypothyroidism (>90%), which continues to increase with the passage of time. Therefore, a patient's ability to comply with lifelong replacement therapy should be con- sidered when choosing this treatment.(Gharib *et al*.,2018)
- Controversy exists regarding the use of 1311 ablation in children and young adults, owing to the fear of increased risk of thyroid can- cer later in life. Studies to date have not confirmed this increased risk, and use of radioiodine ablation in patients under the age of 20 is common. Pregnancy is a contraindication to (Biondi *et al.*,2020). Patients who are elderly or markedly hyperthyroid should be initially treated with antithyroid drugs because ablation can induce a temporary ex- acerbation of thyrotoxicosis or thyroid storm. Subtotal thyroidectomy is an alternate method of permanently con- trolling thyroid hormone production.(Col *et al.*,2019) This treatment is indicated when the goiter is large, particularly if obstructive symptoms are present.(Gussekloo *et al.*,2019).

Conclusions

1. The thyroid gland is one of the most important glands in the body. Any defect or disorder in it will affect the functions of the body’s organs such as (the heart, nerves, kidneys, digestive system, and reproductive system).
2. The weight of the thyroid gland varies from one person to another depending on the person’s weight, diet, and iodine levels.
3. Women and children are more susceptible to thyroid disorders than men.
4. Any dysfunction in the thyroid gland and its hormones causes obesity and polycystic ovary syndrome.
5. The treatment options depend on the type of disease in terms of tension, and may be with medications, iodine, or surgery.
6. Any increase or decrease in the activity of the thyroid gland, which is represented by hypothyroidism or hyperthyroidism , can lead to cancer.

Recommendations

1. In patients with suspected hyperthyroidism, serum TSH and fT4 should be obtained at the initial evaluation. fT3 should be measured when TSH is suppressed but fT4 is within the normal range
2. Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ATDS, RAI therapy, or thyroidectomy
3. Patients should be informed about the side effects of ATDs and the necessity of informing the physician promptly if they develop pruritic rash, jaundice, acholic stools, or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis
4. If ATD is chosen as the primary therapy for GD, the medication should be continued for approximately 12-18 months, and then discontinued if TSH levels are normal at that time
5. If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice and should be referred to a high- volume thyroid surgeon
6. Treatment if decided, should be based on aetiology and follow the same outlined principles for overt hyperthyroidism
7. Anti-thyroid drugs should be the first-line of treatment and initial treatment for subclinical hyperthyroidism, whatever the aetiology
8. All patients with a suspected thyroid nodule/nodular goitre or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study should undergo a dedicated thyroid/neck US that encompasses the thyroid as well as the central and lateral neck compartments
9. Eat foods that contain iodine, such as fish and dairy.
10. Stop smoking.
11. Drink water and fluids in sufficient quantities.
12. Exercise.
13. If you suffer from hypothyroidism, one of the methods of prevention is to avoid following a diet that contains sugars, trans fats, and processed foods.
14. Avoid eating a lot of foods rich in compounds that prevent the absorption of iodine in the thyroid gland

References

1. Andersen SL, Olsen J, Laurberg P(2020). Antithyroid drug side effects in the population and in pregnancy. J Clin Endocrinol Metab. ;101(4):1606-14.

2. Balhara Y.S., Deb K.(2019) Impact of alcohol use on thyroid function. Indian J. Endocrinol. Metab.;17:580–587. doi: 10.4103/2230-8210.113724.

3. Bavle RM. Orphan annie-eye(2019) nuclei. J Oral Maxillofac Pathol. 2019 May;17(2):154-5. [PMC free article] [PubMed]

4. Biondi B, Palmieri EA, Klain M, et al.(2020) Subclinical hyperthyroidism; clinical features and treatment options. Eur J Endocrinol;152:1-9.

5. Burch HB, Wartofsky L(2020) Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am.;22(2):263-77.

6. Chaker L., Korevaar T.I.M., Medici M., Uitterlinden A.G., Hofman A., Dehghan A., Franco O.H., Peeters R.P. (2016)Thyroid function characteristics and determinants: The Rotterdam study. Thyroid.;26:1195–1204. doi: 10.1089/thy.2016.0133.

7. Chiha M, Samarasinghe S, Kabaker AS(2019). Thyroid storm: An updated review. J Intensive Care Med.;30(3):131-40.

8. Chopra I. Euthyroid sick syndrome: Is it a misnomer? J Clin Endocrinol Metab 2019;82:329-34.

9. Col NF, Surks MI, Daniel GH. (2019)Subclinical thyroid disease. JAMA;291:239-43.

10. Das DK. Psammoma body: a product of dystrophic calcification or of a biologically active process that aims at limiting the growth and spread of tumor? Diagn Cytopathol. 2020 Jul;37(7):534-41. [PubMed]

11. DeLellis RA. Orphan Annie eye nuclei: a historical note. Am J Surg Pathol. 2021 Oct;17(10):1067-8. [PubMed]

12. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al (2019)Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med.,380(14):1316-25.109.

13. Dutta P, Bhansali A, Masoodi S, Bhadada S, Shama N, Rajput R.(2021) Predictors of outcome in myxoedema coma: A study from a tertiary care centre. Crit Care;12(1):1-8.

14. Gerstein HC. Incidence of postpartum thyroid dysfunction in patients with type I diabetes mellitus. Ann Intern Med. 2018;118(6):419-23.115.

15. Gharib H, Tuttle M, Baskin J, et al. (2018)Consensus statement: subclinical thyroid dysfunction: A joint statement on the management from the American Association of Clinical Endocrinologists, the American Thyroid Association and the Endocrine Society. J Clin Endocrinol Metab ;90:581-6.

16. Gionfra F, De Vito P, Pallottini V, Lin HY, Davis PJ, Pedersen JZ, et al. (2019) The Role of Thyroid Hormones in Hepatocyte Proliferation and Liver Cancer. Front Endocrinol 10:532.

17. Gruppen E.G., Kootstra-Ros J., Kobold A.M., Connelly M.A., Touw D., Bos J.H.J., Hak E., Links T.P., Bakker S.J.L.,(2020) Dullaart R.P.F. Cigarette smoking is associated with higher thyroid hormone and lower TSH levels: The PREVEND study. Endocrine.;67:613–622. doi: 10.1007/s12020-019-02125-2.

18. Gussekloo J, van Exel E, de Crein AJ, et al. Thyroid status, disability and cognitive function and survival in old age. JAMA 2019;292:2591-9.

19. Habib A., Molayemat M., Habib A. (2020) Elevated serum TSH concentrations are associated with higher BMI Z-scores in southern Iranian children and adolescents. Thyroid Res.;13:9. doi: 10.1186/s13044-020-00084-9.

20. Kadkhodazadeh H., Amouzegar A., Mehran L., Gharibzadeh S., Azizi F., (2020)Tohidi M. Smoking status and changes in thyroid-stimulating hormone and free thyroxine levels during a decade of follow-up: The Tehran thyroid study. Casp. J. Intern. Med.;11:47–52. doi: 10.22088/cjim.11.1.47.

21. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH.(2018) European thyroid association guideline for the management of graves' hyperthyroidism. Eur Thyroid J.7(4):167-86.

22. Kimura M, Amino N, Tamaki H, et al(2019) . Gestational thyrotoxicosis and hyperemesis gravidarum; possible role for hCG with higher stimulating activity. Clin Endocrinol (Oxf) 2019;38:345-50.

23. Korevaar TIM, Medici M, Visser TJ, Peeters RP. (2017) Thyroid disease in pregnancy: New insights in diagnosis and clinical management [Internet]. Vol. 13, Nature Reviews Endocrinology. Nature Publishing Group; 2017. p. 610–22.

24. Korevaar TIM, Mínguez-Alarcón L, Messerlian C, De Poortere RA, Williams PL, Broeren MA, et al(2018). Association of Thyroid Function and Autoimmunity with Ovarian Reserve in Women Seeking Infertility Care. Thyrnid, 2018;28(10):1349-58.

25. Laurberg P, Nygaard B, Glinoer D, et al. (2020) Guidelines for TSH receptor antibody measurements in pregnancy; results of an evidence-based symposium organised by the European Thyroid Association. Eur J Endocrinol 2020;139:584-6.

26. Lazarus JH, (2020) Premawardhana LDKE. Screening for thyroid disease in pregnancy. J Clin Pathol 2020;58:449-52.

27. Lazarus JH. (2020) Clinical aspects of recurrent postpartum thyroiditis. Br J Gen Pract.;47(418):305-8.116.

28. Lazarus JH. (2019) Thyroid disorders associated with pregnancy. Treat Endocrinol 2019;4:31-41.

29. Liu YC, Yeh CT, Lin KH. (2019) Molecular Functions of Thyroid Hormone Signaling in Regulation of Cancer Progression and Anti-Apoptosis. Int J Mol Sci 20:4986. doi: 10.3390/ijms20204986

30. Lundbäck V., Ekbom K., Hagman E., Dahlman I., Marcus C.(2017) Thyroid-stimulating hormone, degree of obesity, and metabolic risk markers in a cohort of swedish children with obesity. Horm. Res. Paediatr.;88:140–146. doi: 10.1159/000475993.

31. Man saurian,AR.; (2018). The slate of serum lipid profiles in subclinical hypothyroidism .A review of literature .Pak.J.Bio. Sci.; 13 (11):556-62.

32. Mandel SJ, Cooper DS. (2020) The use of antithyroid drugs in pregnancy and lactation. J Clin Endocrinol Metab 2020;86:2354-9.

33. Montanelli L., Benvenga S., Hegedüs L., Vitti P., Latrofa F., Duntas L.H. Drugs and other substances interfering with thyroid function. In: Vitti P., Hegedüs L., editors. (2018) Thyroid Diseases. Endocrinology. Springer; Cham, Switzerland: 2018. pp. 733–761

34. Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR. (2021) Prevalence of postpartum thyroid dysfunction: A quantitative review. Thyroid. 2021;16(6):573-82.

35. Nyström HF, Jansson S, Berg G. (2021) Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2020-2021. Clin Endocrinol (Oxf). 2020;78(5):768–76.

36. Peeters R, Visser T. (2019) Metabolism of Thyroid Hormone. In: Feingold K, editor. Endotext. South Dartmouth: Endotext MDText.com.Inc

37. Ploski R.;Szymanski, K. &Bednarczuk, T. (2019). The genetic Basis of Graves' disease.Curr. Genom. 12:542-563.

38. Premawardhana LDKE, Parkes AB, Ammari F, et al. (2021) Postpartum thyroiditis and long term thyroid status; influence of thyroid peroxidase antibodies and ultrasound echogenicity. J Clin Endocrinol Metab;85:71-5.

39. Pyo JS, Kang G, Kim DH, Park C, Kim JH, Sohn JH.(2018) The prognostic relevance of psammoma bodies and ultrasonographic intratumoral calcifications in papillary thyroid carcinoma. World J Surg. Oct;37(10):2330-5. [PubMed]

40. Qureshi IA, Khabaz MN, Baig M, Begum B, Abdelrehaman AS, Hussain MB. (2020)Histopathological findings in goiter: A review of 624 thyroidectomies. Neuro Endocrinol Lett.;36(1):48-52. [PubMed]

41. Refetoff S. (2018). Thyroid Physiology and Disease: Abnormal Thyroid Hormone Transport. South Dartmouth: MDText.vom, Inc.

42. Shaheen OH (2003) Thyroid surgery. Parthenon Publish- ing, New York

43. Shen W, Duren M, et al (2017) Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg 131:861-867; discussion 867-869

44. Sherman JH, Colborn GL (2018) Absence of the left in- ferior thyroid artery: clinical implications. Clin An16:534-537

45. Skandalakis JE, Carlson GW, et al (2020) Neck. In: Skan-dalakis JE (ed) Surgical anatomy, vol 1. Paschalidis Medi-cal, Athens, pp 3-116

46. Stagnaro-Green A. (2019) Clinical review 152: Postpartum thyroiditis. J Clin Endocrinol Metab.;87(9):4042-7.

47. Sturniolo G, D'Alia C, et al (2019) The recurrent laryngeal nerve related to thyroid surgery. Am J Surg 177:485-488

48. Suzuki S, Nishio S, Takeda T, Komatsu M. (2019) Gender-Specific Regulation of Response to Thyroid Hormone in Aging. Thyroid Res 5:1. doi: 10.1186/1756-6614-5-1

49. Tanaka K, Tanaka H, Kamiya C, Katsuragi S, Sawada M, Tsuritani M, et al. (2020);Beta-blockers and fetal growth restriction in pregnant women with cardiovascular clisease. Cine J. 80(10):2221-6.

50. Taylor PN, Albrecht D, Scholz A, Gutierrez-buey G, Lazarus JH, Dayan CM, et al. (2018)Global epidemiology of hyperthyroidism and hypothyroidism. 2018; May;14(5):301-316. doi: 10.1038/nrendo..18. Epub 2018 Mar 23

51. Wilkinson M, Brown R. (2015)Hormone Synthesis, Storage, Release, Transport, Ans Deactivation. In: Wilkinson M, Brown R, editors. An Introduction to Neuroendocrinology. Cambridge: Cambridge University Press. p. 157–69. doi: 10.1017/CBO9781139045803.00

52. Yafit D, Carmel-Neiderman NN, Levy N, Abergel A, Niv A, Yanko-Arzi R, et al. (2019) Postoperative myxedema coma in patients undergoing major surgery: Case series. Auris Nasus Larynx. Aug;46(4):605-8.117

53. Zhang J, Roggero VR, Allison LA. (2018) Nuclear Import and Export of the Thyroid Hormone Receptor. Vitamins Hormones 106:45–66. doi: 10.1016/bs.vh.2017.04.002

54. Zhu Y, Qiu W, Deng M, Zhu X. (2017) Myxedema coma. Medicine (Baltimore).;96(21):e6952.119

55. Zoeller, TR.; Dowling,AL.; Herzig,CT.(2020). Thyroid hormone ,brai Development and the environment Environ Henlth Perspect; 110:355-361.