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Morphology Aspects of Hypothyroidism

Fernando Candanedo-Gonzalez, Javier Rios-Valencia, Dafne Noemi Pacheco-Garcilazo, Wilfredo Valenzuela-Gonzalez and Armando Gamboa-Dominguez

Abstract

Hypothyroidism is a common endocrine disorder resulting of low levels of thyroid circulating hormones. The prevalence in the general population varies between 0.3% and 3.7%. Presents as clinical or subclinical disease based on presence of symptoms and levels of serum TSH and free thyroxine and T4, respectively. Hypothyroidism has numerous etiologies, some of them are originated on the thyroid itself and some others are of extrathyroid origin, with variable manifestations. Classified as primary, secondary, tertiary and peripheral. Thyroid autoimmune disease is the principal cause. A new class of drugs against cancer, like the anti-CTLA-4 and anti-PD-L1/PD1 therapies have been associated with primary or secondary hypothyroidism. Endocrine disorders can be difficult to diagnose based only on morphological features because endocrine manifestations are caused primarily by a hormonal imbalance. Hypothyroidism may have a higher risk of morbidity and mortality. Finally, myxedematous coma is the main complication of terminal stages hypothyroidism.

Keywords: hypothyroidism, epidemiology, pathophysiology, etiology, pathology, anti-CTLA-4 and anti-PD-L1/PD1 therapies, treatment, prognosis, complications

1. Introduction

1.1 Anatomy

The thyroid gland is a butterfly-shaped organ formed by a right and left lobe connected at the midline by a thin structure called isthmus. Located in the neck, the thyroid covers the anterior side of the trachea underneath the larynx at the vertebral levels of C5 to T1 (**Figure 1A**). The average size of a thyroid gland is of 5 cm height and 5 cm wide and it weighs between 20 and 30 grams in adults (**Figure 1B**), being a little more heavy in women. Is a highly vascular organ, receiving blood supply from two main sources, the superior thyroid artery, branch of the external carotid artery irrigates the superior half of the thyroid in more than 95% of the population, the inferior half is irrigated by the inferior thyroid artery that branches from the thyrocervical trunk which is a branch of the subclavian artery. Furthermore, the thyroid gland has extensive lymphatic drainage that involves multiple levels of

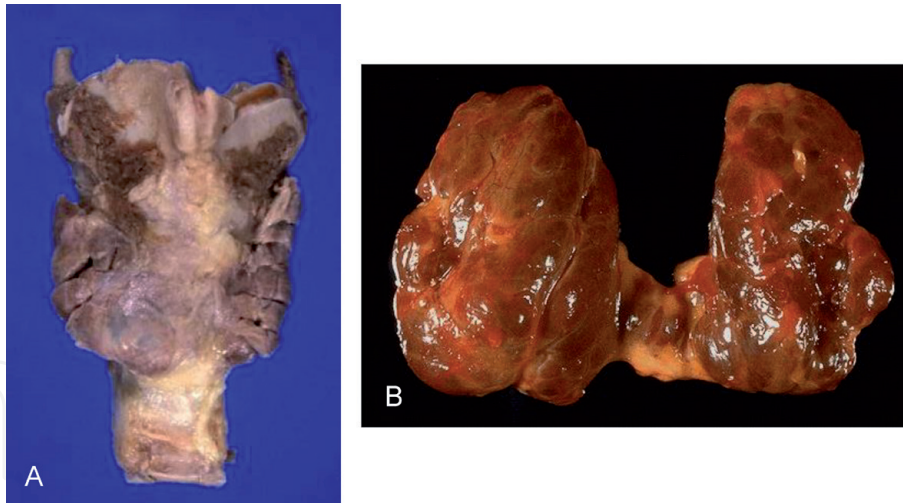


Figure 1.
Thyroid gland: A) butterfly-shaped, located in the anterior side of the trachea underneath the larynx; B) formed by a right and left lobes connected at the midline by a thin structure called isthmus.

lymphatic nodes, including the prelaryngeal, pre and paratracheal, retropharyngeal, retroesophageal and the internal jugular nodes [1].

1.2 Embryology

The thyroid gland is the first endocrine organ that develops during fetal development [2]. It begins to develop during the fourth week of gestation as an epithelial diverticulum arising from the endoderm of the foregut near the base of the primitive tongue, it progressively extending downward starting from week fifth as the fetus develops [2, 3]. It reaches its final shape and size at the end of the seventh week of gestation [2].

1.3 Normal histology

The normal thyroid gland is composed of numerous follicles surrounded by a fibrous capsule that forms septa that divide the parenchyma in multiple lobules. These septa contain nerves and blood vessels that irrigate each lobule. Each lobule

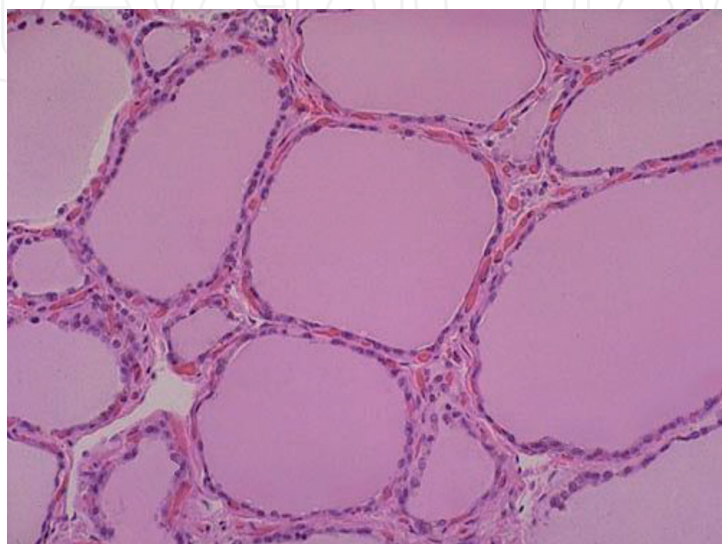


Figure 2.
Normal thyroid gland histology.

contain from 20 to 40 round follicles of 200 μm of diameter on average, these are coated by simple cuboidal epithelium that varies from plane to low according to the current functional activity, when more active the follicle is, taller the follicular epithelium will be. The follicular cells have small, dark and uniform nuclei that are localized at the center of the cell and some of them have an abundant granular and eosinophil cytoplasm, a variant known as Hürthle cells. The follicles contain colloid, a viscous material composed predominantly by the precursor protein of the thyroglobulin (**Figure 2**). The normal thyroid gland contains up to 3 months of thyroglobulin stored in the colloids. Alternating, the parafollicular cells or the C cells, derived from the neural crest through the ultimobranchial body, are found in a higher concentration in the middle and superior portions of the lobes. These cells synthesize and secrete calcitonin, thus participating on calcium homeostasis [4].

2. Definition

Described in 1850, hypothyroidism was the first disorder of endocrine deficiency ever reported [5]. Hypothyroidism is the result of low levels of thyroid circulating hormones. Due to the wide variety of clinical presentations and the lack of specific symptoms, the definition of hypothyroidism is mainly biochemical [6]. Therefore, hormonal levels in overt hypothyroidism are: TSH (Thyroid Stimulating Hormone) >4.8 UI/l, FT4 <13 pmol/l, and in subclinical hypothyroidism are: TSH >4.8 UI/l, FT4: 13–23 pmol/l [7]. Recent research suggests that the superior reference values for serum TSH varies among different age groups [8]. Nevertheless, up to this present day there is no exact definition of a cut point for serum TSH values regarding age in our population [9–12]. According to the moment of clinical presentation, hypothyroidism is divided in congenital or acquired, according to the level of endocrine dysfunction is divided in primary or secondary or central and according to the severity of hypothyroidism is divided in severe or clinic hypothyroidism or in mild or subclinical hypothyroidism [13].

3. Epidemiology

The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the US and between 0.2% and 5.3% in Europe, according to the used definition [6, 10–15]. The National Health and Nutrition Examination Survey found that the prevalence of overt hypothyroidism between people older than 12 years old in the United States is of 0.3% and of subclinical hypothyroidism is of 4.3% [12]. The difference in iodine status affects the prevalence of hypothyroidism, which occurs in population with a relatively high intake of iodine as well as in populations with deficient intake of iodine. The most common cause of thyroid dysfunction is iodine deficiency and it is estimated that 2 thousand millions of people have an insufficient iodine intake [16]. Hypothyroidism is more common in women and the incidence increases with age (>65 years old) and in Caucasian individuals, although data regarding ethnical difference are scarce [6]. Female gender and older age individuals are related to an increase of TSH and prevalence of anti-thyroid antibodies [12]. Among women in reproductive age (12–49 year old), the prevalence of hypothyroidism is of 3.1%. While women older than 80 years old or more, have 5 times more probabilities to suffer from hypothyroidism, compared to the 12–49 year old women population. Hypothyroidism is more frequent among women born with low height and of low body mass index at childhood. However, in countries with good iodine supply, autoimmune disorders are the most common causes of hypothyroidism [12].

3.1 Genetic epidemiology

It is estimated that the heritability of serum levels of TSH and of free thyroxin levels is of 65% and of 23–65% respectively [17, 18]. The results of studies of genome association of all the genome, up to this present day have now explained only but a small proportion of the variability in thyroid function and only three studies have focused on hypothyroidism [19]. The loci that are more consistently implicated in hypothyroidism include genes related to autoimmunity and regulating genes specific to thyroid. The majority of these loci are also related to serum concentrations of TSH within the reference rank [19–23]. Monogenetic disorders that cause congenital hypothyroidism are rare and include TSH resistance (due to an inactivating mutation on the TSH receptor), thyroid digenesis and thyroid dyshormonogenesis.

4. Pathophysiology

To understand better hypothyroidism and its consequences it is important to remember the normal physiology of the thyroid gland. The main function of the thyroid follicular cells is the synthesis of thyroid hormones, tetraiodothyronine or (T₄; 3,5,3',5'-L-tetraiodothyronine) and triiodothyronine (T₃; 3,5,3'-L-triiodothyronine). Iodine is essential for thyroid hormone synthesis. Food and water are the main sources for iodine intake, with a daily supply that ranges from 50 to 300 µg being absorbed in the small intestine. Both thyroid hormones are synthesized by the iodination and condensation of two tyrosine molecules and differ by an iodine atom. The production and release of thyroid hormones is stimulated by the hypothalamus-pituitary axis. The thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates the anterior pituitary gland to release thyrotropin, also called TSH (**Figure 3**) [24]. In response to the stimuli of TSH, the thyroid follicular cells produce thyroglobulin, an inactive protein that is then released from the apical surface into the follicle as a colloid [4]. TSH is released into the bloodstream and it then binds to the thyroid stimulating hormone receptor (TSH-R) in the basolateral surface of the follicular cell of the thyroid gland. The TSH-R is a G-protein coupled receptor and its triggering yields to the activation of the Adenylate Cyclase and of increased levels of intracellular cAMP. An increased cAMP activates the protein kinase A (PKA). PKA phosphorylates different proteins in order to change their functions. The thyroid hormone biosynthesis is made by steps, regulated by enzymes that are stimulated by TSH, these steps are: 1) thyroglobulin synthesis (TG): the thyrocytes in the thyroid follicles produce a protein called thyroglobulin. Thyroglobulin does not contain iodine and is a precursor protein stored in the follicle lumen. Thyroglobulin is produced in the rough endoplasmic reticulum, then the Golgi apparatus packs it up in vesicles and then it enters the follicle lumen by exocytosis. 2) Iodine uptake and transport: the phosphorylation of the kinase A protein increases the activity of the sodium/iodide basolateral symporter protein (Na⁺/I⁻ symporter), driven by the Na⁺ -K⁺ -ATPase to get iodine out of the bloodstream to the thyrocytes. Iodine diffuses from the basolateral surface to the apical surface of the cell, where it transports to the colloid through the pendrin transporter; 3) thyroglobulin iodination: the protein kinase A also phosphorylates and activates the thyroid peroxidase enzyme (TPO). The TPO has three main functions: oxidation, organification and coupling reaction. 4) Oxidation: the TPO uses hydrogen peroxide in order to oxidate iodide (I⁻) to iodine (I₂). NADPH oxidase, an apical enzyme generates hydrogen peroxide for the TPO; 5) Organization: the TPO attaches the remainders of tyrosine from the thyroglobulin with the I₂. It generates

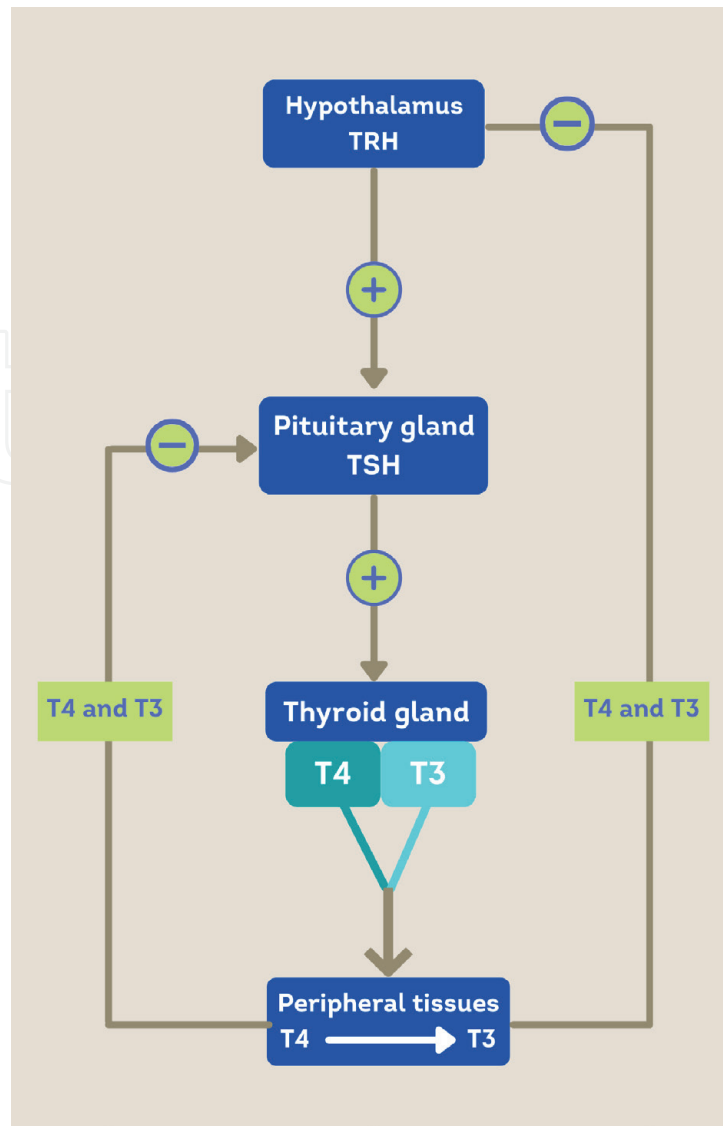


Figure 3.
Normal thyroid physiology.

monoiodotyrosine (MIT) and diiodotyrosine (DIT) (**Figure 4**). MIT has only one remaining tyrosine with iodine and DIT has two remaining tyrosine with iodine; 6) mono and diiodotyrosine attachment; the TPO combines the remainders of iodated tyrosine to produce T3 and T4 [4]. MIT and DIT combine to form T3 and two DIT molecules form T4; 5) Storing: thyroid hormones are attached to TG and are storage in the follicular lumen; and 6) secretion: the iodized thyroglobulin returns to the follicular cell, where the degradation of lysosomic proteases releases T3 and T4 in the fenestrated capillaries. Thyroid hormones travel through the bloodstream united to a binding protein called thyroxin [24]. The thyroxine-binding globuline (TBG), transthyretin (TTR) and albumin are proteins capable to bind to the thyroid hormone, thus becoming able to transport it through the bloodstream to their target sites [25].

Thyroid hormones are important for a variety of functions in the body, including development, growth and increase the basal metabolic rate (BMR) affecting circulation, corporal temperature, gluconeogenesis, lipolysis, proteolysis and glucose absorption [26]. It also increases systolic volume and heart rate, which increases cardiac output. In young populations it boosts growth and leads to bony maturation and the fusion of bone growth plates. It is essential for the maturity of the central nervous system (CNS) during fetal development [24]. All of these biochemical events that make the thyroid gland produce hormones is regulated by a negative feedback

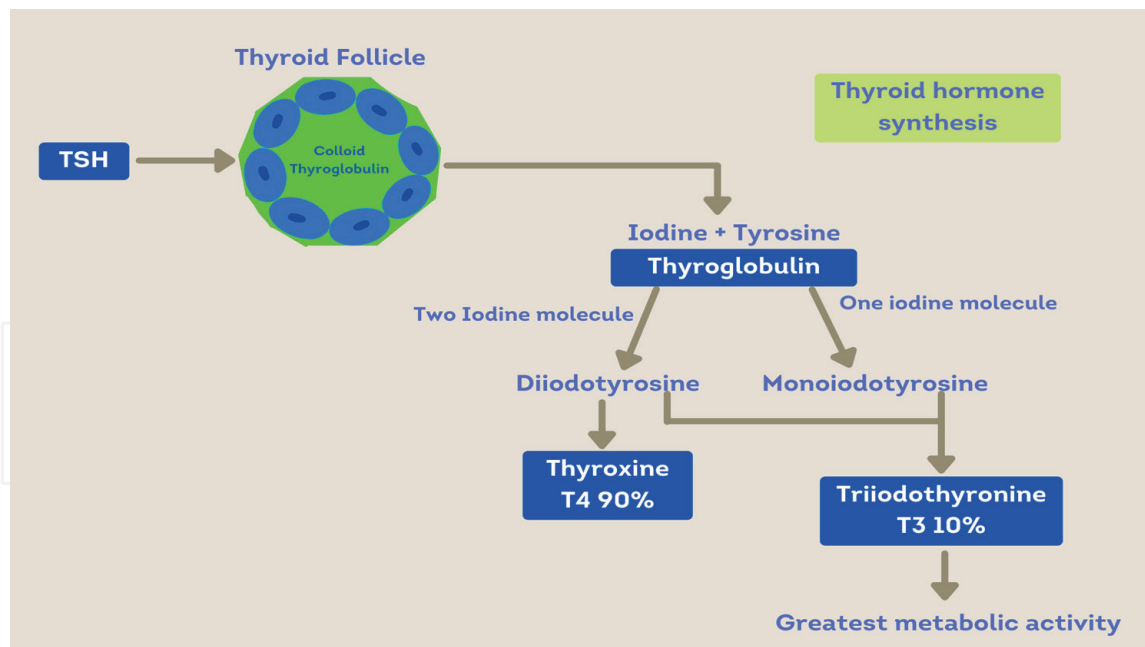


Figure 4.
Thyroid hormone formation.

system in which high levels of thyroid hormones, especially T3, inhibit the release of TSH from the anterior pituitary gland [24]. The counterforces of TRH and T3 allow our body to keep thyroid hormones levels relatively stable in healthy individuals [24]. Although, when alterations occur within this delicate system, severe and even fatal conditions can happen [27]. The most common cause of hypothyroidism is the incapacity of the thyroid gland to produce enough thyroid hormones, nevertheless, with less frequency the hypothalamus and the pituitary can also cause thyroid dysfunction. The half-life of a T4 molecule ranges from 6 to 12 days, in regards to T3 its half-life is of 24 hours, therefore, T4 is significantly more abundant (approximately 100–125 nmol/day) and T3 is found in less quantity, nevertheless T3 is two to tenfold more bioactive [4, 24], to counteract this difference target tissues contain 5'-iodinase, which converts T4 into T3 peripherally through deiodination 5' [4]. The levels of T3 and T4, mostly T3, establish a negative feedback on the production of TRH and TSH. Alterations on the structure and function of any of these organs or axis can result in hypothyroidism. A decline in the production of T4 results in an increased secretion of TSH by the pituitary, which in turn causes hypertrophy and hyperplasia of the thyroid parenchyma, thus leading to an increase in the production of T3 [4].

5. Etiology

Hypothyroidism has numerous etiologies, some of them are originated on the thyroid itself and some others are of extrathyroid origin, with variable manifestations. **Table 1** resumes the principal causes of hypothyroidism. Hypothyroidism can be classified on primary hypothyroidism, secondary (central), tertiary and peripheral. Primary hypothyroidism occurs when the thyroid gland is unable to produce adequate amounts of thyroid hormones. Secondary hypothyroidism occurs when the function of the thyroid gland is normal and the pathology is on the pituitary gland due to a deficiency of TSH. In tertiary hypothyroidism, the pathology is found in the hypothalamus, due to a deficiency of TRH. Central hypothyroidism (secondary and tertiary) and peripheral hypothyroidism are less frequent and represent less than 1% of all cases [28].

1. Primary hypothyroidism	2. Secondary hypothyroidism	3. Tertiary hypothyroidism	4. Euthyroid disease syndrome
a. Biosynthetic defects:	a. Pituitary destruction	a. Hypothalamic destruction	
Innate errors of metabolism			
b. Development abnormalities	i. Neoplasms	i. Neoplasms	
c. Thyroid destruction	ii. Infarct	ii. Granuloma	
ii. Radiation	b. Isolated deficiency of TSH		
iii. Autoimmune thyroiditis			
d. Thyroid tissue replacement			
i. Neoplasms			
ii. Fibrosis			
e. Drug interference in the production and/or secretion of hormones			

Table 1.
Hypothyroidism causes.

5.1 Primary hypothyroidism

Thyroid autoimmune disease is the principal cause of primary hypothyroidism in the United States and in the geographical regions with enough iodine intake [10]. Hashimoto's thyroiditis (HT) is the most frequent etiology in the United States and has a strong association with the development of malignant neoplasms like papillary thyroid carcinoma (PTC) and lymphoma [29].

There are other causes of hypothyroidism induced by drugs, like amiodarone, thalidomide, tyrosine kinase inhibitors (sunitinib, imatinib), stavudine, interferon, rifampicin, ethionamide, phenobarbital, phenytoin, carbamazepine, interleukin-2 and lithium. Therapy with radioactive iodine, thyroid surgery and radiotherapy to the head and neck area may be causes of hypothyroidism. Contrary to the previous, smoking and moderate alcohol consumption are related to a reduced risk of hypothyroidism [10].

Post-partum thyroiditis affects nearly 10% of women and generally occurs between 8 and 20 weeks after birth. Only few women will require hormonal treatment. However, some women have a higher risk of permanent hypothyroidism or recurrent thyroiditis postpartum in future pregnancies. The use of radioactive iodine in the treatment of Graves-Basedow disease generally results in permanent hypothyroidism in approximately 80–90% of patients between 8 and 20 weeks after treatment [10]. Treatment with radiation on the head and neck area can also induce hypothyroidism. A relatively infrequent cause of primary hypothyroidism is sub-acute granulomatous thyroiditis (Quervain's disease), it often arises in middle aged women and it tends to be an auto limited disease. Finally, Down syndrome and Turner syndrome patients have a higher risk of hypothyroidism [10].

5.2 Secondary and tertiary hypothyroidism (central)

Secondary and tertiary hypothyroidism, also known as central hypothyroidism, is caused by a defect in the hypothalamus-pituitary axis. Causes include:

pituitary tumors, tumors that compress the hypothalamus, Sheehan syndrome, resistance to TRH, TSH deficiency, lymphocytic hypophysitis, cerebral radiotherapy, drugs like dopamine, prednisone or opioids [10]. A new class of drugs against cancer, like the anti-CTLA-4 (ipilimumab) and anti-PD-L1/PD1 therapies (pembrolizumab and nivolumab) have been associated with primary or secondary hypothyroidism [30, 31]. In previous years, the use of immune check point inhibitors (ICPi) has improved the treatment and prognosis of different types of cancer. The ICPi are monoclonal antibodies associated with adverse effects pertaining the immune system. Thyroid dysfunction (thyrotoxicosis or hypothyroidism) are among the most common adverse consequences. These monoclonal antibodies inhibit immune checkpoints that are present in the surface of the T cells to assure immune auto-tolerance, which results in an increased T cell capacity to attack cancerous cells. The pathogenesis of the thyroid disorders associated to the use of ICPi is not fully understood. Data from observational studies suggest that thyroid dysfunction induced by ICPi is due to a destructive thyroiditis that can evolve to hypothyroidism. On the other hand, it is proposed that thyroid manifestations in patients with immunotherapy may represent an autoimmune phenomenon. Nevertheless, little is known about thyroid antibodies status during the course of the disease [30, 31].

5.3 Peripheral hypothyroidism

Consumptive hypothyroidism is caused by an aberrant expression of the enzyme type 3 iodothyronine deiodinase (D3), which inactivates thyroid hormones in tumoral tissues. Even when rare, this overexpression can induce severe hypothyroidism. High concentrations of D3 was first described in a newborn with infantile hepatic hemangioma [32], but it can also occur in patients with vascular tumors and tumors of the gastrointestinal stroma [33].

6. Clinical presentation

Classic signs and symptoms of hypothyroidism are bradycardia, weight gain even when reducing food intake, cold intolerance, dry skin, sweat decrease, constipation, alopecia, hyporeflexia, slow talking and lethargy. Nonetheless, it is important to keep high suspicion of hypothyroidism because signs and symptoms can be mild and non-specific. Chronic hypothyroidism also increases total cholesterol and low density lipoprotein and decreases high density lipoproteins, which increases the risk of cardiovascular mortality. Depression is also a common symptom of hypothyroidism and, therefore, it can be found in the medical history of patients that committed suicide [10].

6.1 Subclinical hypothyroidism

A decrease in thyroid function is observed in subclinical hypothyroidism, defined by high levels of TSH and normal levels of free thyroid hormones [34]. Primary hypothyroidism is the most prevalent thyroid dysfunction in elderly population and subclinical hypothyroidism is found nearly in 20% of elderly people [10, 11]. Subclinical thyroid disease during pregnancy can be related to adverse results, including a lower than normal intellectual quotient in the offspring of the pregnant women. It is unknown if the treatment with levothyroxine in women identified with subclinical hypothyroidism or hypothyroxinemia during pregnancy improves cognitive function in their offspring [35].

6.2 Congenital hypothyroidism

Thyroid hormones are extremely important for the correct development of the central nervous system in the fetus. To ensure an adequate availability of thyroid hormones, human chorionic gonadotropin- β (hCG- β) coming from the placenta directly stimulates the maternal thyroid, which increases the production of T3 and T4 during the first trimester. After the first trimester the fetal thyroid converts in the principal source of hormonal thyroid. The placenta also expresses type 3 iodothyronine deiodinase, an enzyme that breaks down T4 into an inverse inactive T3 (rT3), as a protection against excessively high levels of thyroid hormones, however, regardless of this protection, abundant thyroid hormones cross to the fetus [36, 37].

Decreased levels of fetal thyroid hormones during the crucial period of neurologic development drives to severe mental retard, also called cretinism. Therefore, congenital hypothyroidism (CHT) is a pediatric condition that has to be treated with urgency. Other clinical features include musculoskeletal abnormalities, macroglossia and coarse facial features. This condition is irreversible if is not diagnosed early. Even when is not associated to mortality, CHT can be found on fetal and pediatric autopsy for other reasons and must be considered as a differential diagnosis with mental retardation. However, the natural history of CHT has drastically changed in previous years due to newborn screening (NS) programs that consist in detecting this disease in all apparently healthy newborns [36, 37]. In Mexico, the program of NS formally began in 1988 with the emission of the “technical norm 321.4” and in the present its realization is a mandatory action for all health centers that provide child and maternal care, according to the Norma Oficial Mexicana 007-SSA2-1993.5. (Mexican Official Norm 007-SSA2-1993.5) [11, 38].

The main causes that produce CHT are: a) aberrant or incomplete migration of the thyroid bud, which causes the formation of an ectopic gland without lateral lobes, this is also known as a thyroid nodule; b) deficient growth or differentiation that brings about thyroid agenesis or atyriosis, and c) defects on the biosynthesis of thyroid hormones or dyshormonogenesis with or without goiter. The first two entities are grouped under the name of thyroid dysgenesis, which are sporadic and have predominance for the female gender [36–38]. Female predominance is a characteristic particularly interesting in the epidemiology of CHT; although, it is not known if women are more susceptible to develop CHT or if female fetuses with CHT have higher uterine survival compared to masculine fetuses [36]. The molecular mechanisms implicated on thyroid cellular differentiation are not exactly known, yet, some mutations have been described in genes involved in thyroid growth and development, like TTF1, TTF2, PAX8 and TSHR among others [39, 40].

7. Pathology

Endocrine disorders can be difficult to diagnose based only on morphological features because endocrine manifestations are caused primarily by a hormonal imbalance. Nonetheless, anatomical findings, like organomegaly or nodules may suggest anomalies that should encourage further investigation through laboratory tests or microscopic evaluation. Thyroid gland disorders have a wide variety of clinical presentations and can affect many organs and systems.

7.1 Hashimoto's thyroiditis and hypothyroidism

Autoimmune chronic thyroiditis affects from 3 to 5 more times women than men, generally at a median age or older, as well as in children. HT is the most

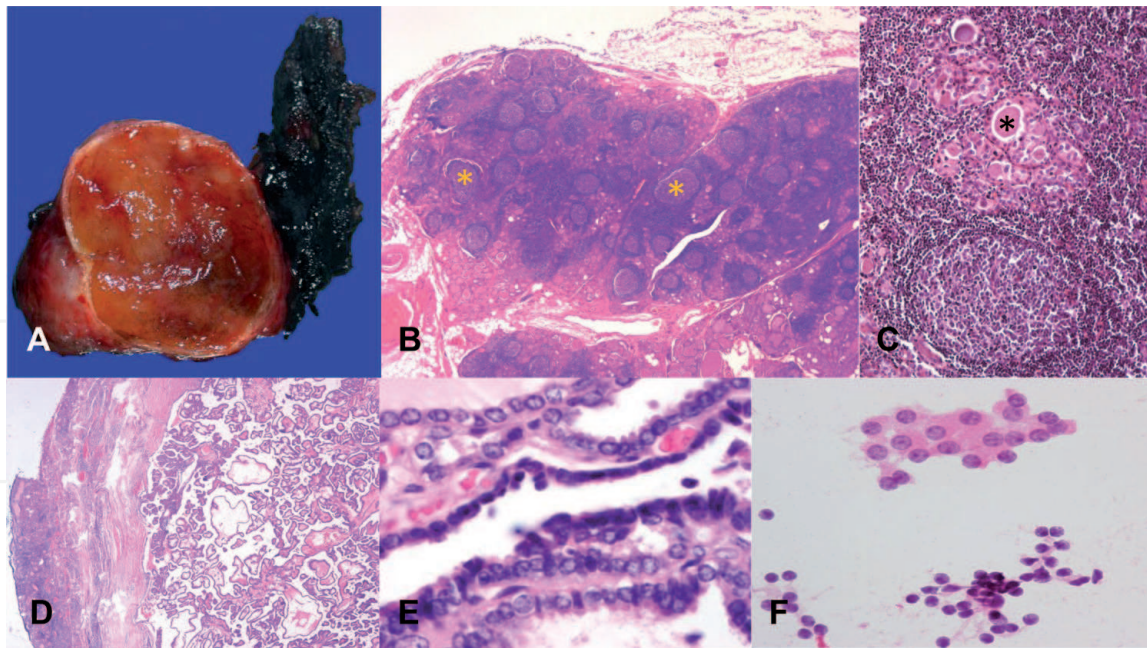


Figure 5. *Thyroid gland: A) product of a hemithyroidectomy with Hashimoto's thyroiditis associated to the presence of a solitary nodule; B) reactive lymphoid infiltrate with lymphoid folliculae with a germinal centers in the thyroid parenchyma (asterisk); C) Hürthle cells (asterisk); D) papillary thyroid carcinoma; E) neoplastic cells with nucleomegaly, open cromatine and nuclear clefts; F) biopsy with fine needle aspiration shows groups of cells with oxyphilic changes (Hürthle cells) and reactive lymphocytes compatible with Hashimoto's thyroiditis.*

common autoimmune disease of the thyroid and is the main cause of autoimmune hypothyroidism. This disease was first described by Hakaru Hashimoto in 1912 as a “lymphomatous stroma” [40]. The global occurrence of HT is estimated to be between 0.3 and 1.5 cases for each 1000 individuals per year; predominantly in the female gender; it has a male-female ratio of 5:20 between the 30 and 50 year old population [41, 42]. There are two different clinical variants: the diffuse form and the nodular form. The nodular form is composed by a heterogeneous thyroid parenchyma that presents fibrosis, sclerosis and calcifications and is mainly associated to neoplasms, particularly PTC (**Figure 5A**). It is characterized by a lymphoid infiltrate capable to destroy the gland (**Figure 5B** and **C**), inducing fibrosis and hypothyroidism as a consequence [29]. Chronic inflammation of the thyroid parenchyma is regulated by an infiltrate of predominantly T lymphocytes [13]. The role of autoimmunity is backed by histological findings of diffuse lymphocytic thyroid infiltration and by specific circulating antibodies in almost all patients. Increased levels of anti-TPO antibodies are found in 95% of cases and anti-thyroglobulin antibodies are found in 60% of cases, these being higher in the atrophic form than in the goiter form of the disease [13]. Treatment is almost always non-surgical, surgery is indicated in cases of glandular enlargement with compressive symptoms, non-satisfactory pharmacological treatment and suspicion of neoplasm degeneration in one or more nodules. The association between HT and PTC, first described by Dailey et al. in 1955 [42, 43], is a controversial matter (**Figure 5D** and **E**).

8. Hypothyroidism detection

Even when there are no established guidelines for thyroid disease detection, the American Thyroid Association recommends to start detection at 35 years old and to continue screening each 5 years. Population with high risk of hypothyroidism include: women older than 60 years old, pregnant women, people with a history of head and neck radiation, patients with autoimmune disease, diabetes type 1,

Patients with 4 or more of the following symptoms	Patients with a history of	Pregnant patients with a history of
Fatigue	Sudden and unexplained thyroid growth	Family history of thyroid disease
Sleepiness	Dementia	Thyroid disease during pregnancy
Cold intolerance	Psychiatric diseases	Type 1 diabetes or autoimmune disease
Goiter	Genetic syndromes	
Dry skin	Neck radiation	Complicated pregnancy
Weight gain	Use of drugs that affect thyroid function	Recurrent miscarriage
Constipation		Menstrual irregularities
	Dermatologic disease	Presence of anti-thyroid peroxidase antibodies
	Hyperlipidemia	
	Cardiovascular diseases	
	Autoimmune disease	
	Hypercholesterolemia	
	Infertility or menstrual irregularities	

Table 2.
Guidelines for plasma TSH measurement and referral to a specialist in cases of hypothyroidism.

positive antibodies against thyroid peroxidase, and people with family history of hypothyroidism [44]. **Table 2** resumes the guidelines for hypothyroidism screening.

9. Treatment

The drug of choice in the treatment of hypothyroidism is the replacement of the thyroid hormones [6, 35, 45].

10. Prognosis

Hypothyroidism may have a higher risk of morbidity and mortality. It can eventually lead to coma or even death. In children, the lack of treatment can provoke severe mental retardation. One of the main causes of death in adults is cardiac failure. With treatment, the majority of patients have a good prognosis and symptoms normally revert within a few weeks or months [46].

10.1 Hypothyroidism complications

Even when is not common, in terminal stages, hypothyroidism, also known as myxedematous coma, is a medical emergency. First described by Sir William Gull in 1873, myxedematous coma has an estimated incidence of 0.22 per million per year [46]. It affects more frequently women older than 60 years old with a large history of hypothyroidism and it tends to occur during cold weather settings. Other triggering factors include infection, cerebrovascular attack, myocardial infarction, traumatism, pregnancy and the use of drugs containing lithium and amiodarone [46].

This affection is associated with a progressive deceleration of physical and mental skills as the disease advances. Initially, symptoms can simulate depression or early dementia, with fatigue, apathy, forgetfulness as the predominant complaints. If not treated, patients can develop severe hypothermia, urinary retention, respiratory depression, bradycardia, hypotension and arrhythmias that include cardiac blocks and torsade de pointes. Torsade de pointes is a non-frequent ventricular tachycardia that is found in a large QT syndrome, caused by an enlargement of the repolarization phase of the action potential. It exists a diffuse deposit of mucopolysaccharides that eventually leads to airway obstruction by affecting tongue and larynx, cardiac tamponade as a result of pericardial effusion and edema without skin and subcutaneous foveae. Electrolyte abnormalities are also produced, specifically hyponatremia and coagulopathies, including the acquired von Willebrand disease, which is associated with an increased mortality [11]. Altered mental state worsens from lethargy to stupor to coma, which increases the risk of aspiration pneumonia, urinary tract infection and sepsis. Mortality in patients with myxedematous coma is estimated to be around 20–25%, which represents a significant improvement respect previous reports of 60–70% due to a better acknowledge and treatment of this disease. Survival rates are worse in elderly patients and in those with severe and or persistent hypothermia, bradycardia, hypotension, lower coma Glasgow score and multiorganic disease. The most common immediate causes of death are sepsis, gastrointestinal hemorrhage secondary to coagulopathy and respiratory insufficiency [10].

11. Directions for future investigation

Even when advances have been made regarding cause detection, knowledge of clinical implications, diagnosis and treatment of hypothyroidism, there are still many questions left without answers regarding diagnosis and treatment. Several risk factors have been identified for abnormal TSH concentrations, concentrations of free thyroxin and thyroid disease, but only a small proportion of these variability is explained. At the moment hypothyroidism diagnosis is based on reference ranks for TSH and free thyroxin. Due to the arbitrary nature of cut points that define mild and overt hypothyroidism, an alternative classification system has been proposed based on thyroid function tests.

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