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Hypothyroidism

Mauricio Alvarez Andrade and Oscar Rosero Olarte

Abstract

Hypothyroidism is a condition that results from thyroid hormone deficiency that can range from an asymptomatic condition to a life-threatening disease. The prevalence of hypothyroidism varies according to the population, from up to 3 to 4% in some populations and in the case of subclinical hypothyroidism up to 5–10%. Clinical symptoms of hypothyroidism are diverse, broad, and non-specific and can be related to many systems, reflecting the systemic effects of thyroid hormones. The severity of the symptoms is usually related to the severity of the thyroid hormone deficit. The most common form of hypothyroidism, primary hypothyroidism, is diagnosed when there is elevation of TSH and decrease in the level of free T4 and Subclinical hypothyroidism is diagnosed when there is an elevation of TSH with normal levels of free T4. The most frequent cause of primary hypothyroidism in populations without iodine deficiency is Hashimoto's thyroiditis or chronic lymphocytic thyroiditis. Iodine deficiency is the main cause of hypothyroidism in populations with deficiency of iodine intake. The treatment of choice for hypothyroidism is thyroxine (T4), which has shown efficacy in multiple studies to restore the euthyroid state and improve the symptoms of hypothyroidism. In subclinical hypothyroidism, the treatment depends on the age, functionality, and comorbidities of the patients. The total replacement dose of levothyroxine in adults is approximately 1.6 mcg/kg; however in elderly patients with heart disease or coronary heart disease, the starting dose should be from 0.3 to 0.4 mcg/kg/day with progressive increase of 10% of the dose monthly.

Keywords: hypothyroidism, autoimmune, Hashimoto's disease, thyroxine, thyroid diseases

1. Introduction

Hypothyroidism is a common disease in many populations, and prevalence varies depending on the sex and the age of the population studied, the iodine status of the population, and the cut points used to define overt and subclinical hypothyroidism [1–11].

Hypothyroidism is 10 times more prevalent in women than in men [2]. It is more prevalent in the elderly people, ranging from 2 to 5% of the population. In iodine-sufficient populations, hypothyroidism ranges from 1 to 2%, while in iodine deficient areas, the prevalence can be as high as 3–4% [2–14]. Prevalence in the USA in the Colorado trial can range from 0.3% and 3.7%, while in Europe can be 0.2 and 5.3% [12].

The prevalence of subclinical hypothyroidism is even higher; in one of the largest studies in the USA, it reaches 9% of the population [12].

2. Physiology

Thyroid word comes from the Greek shield because of its shape. The weight is from 10 to 20 g. Changes of thyroid shape and volume are dependent on age and sex. In the adult population, the usual length is 40–60 mm and the diameter 13–18 mm. The volume is 10–15 ml for females and 12–18 ml for males [15, 16].

The thyroid gland is composed of functional secretory units known as follicles where thyroid hormones are synthesized and storage in the follicular cells and the lumen of the follicles where colloid is stored. The colloid contains high amounts of thyroglobulin (Tg), a 660 kDa glycoprotein, where thyroid hormones are stored [17].

Thyroid hormones are composed by an inner ring, the tyrosine molecule, and the outer ring with a phenyl ring. The active forms of thyroid hormones are thyroxine or T₄, with four iodine atoms, and triiodothyronine or T₃, with three iodine atoms. Under physiologic states, 90% of thyroid gland output is T₄ and 10% is T₃. The half-life of thyroid hormones is of few hours for T₃ and 7 days for T₄ [17].

The follicular cells contain a sodium iodide active symporter responsible for iodine transport against a concentration gradient to synthesize thyroid hormones; it can increase iodine concentration in the follicular cell by more than 20 times above the serum concentration. Iodine is then transported by pendrin in the apical membrane to the colloid in a passive manner [17].

Iodine must be organified to be attached to the tyrosine residues of thyroglobulin. The thyroid peroxidase (TPO) is the enzyme of the selenoprotein group, with hydrogen peroxide organifying iodine to thyroglobulin. Once in the colloid, iodine is organified to thyroglobuline to produce, monoiodothyrosine and diiodothyrosine which finally are coupled to produce T₄ and T₃, this process is catalyzed by the TPO [17].

TPO activity is regulated by iodine concentration and can be blocked by an excess of iodine concentration, which is known as the Wolff-Chaikoff effect and can lead to a temporary hypothyroidism with an escape mechanism. On the other side, an iodine-depleted thyroid gland that is exposed to iodine can increase thyroid synthesis, which is known as the Jod-Basedow effect, and lead to hyperthyroidism [17].

TPO is the enzyme related to autoimmune hypothyroidism as most of the patients have positive anti-TPO antibodies [16, 17].

2.1 Regulation of thyroid hormones production

Thyroid hormone production is regulated by the hypothalamus pituitary axis. At the hypothalamus, thyrotropin-releasing hormone (TRH) is produced. TRH stimulates the pituitary to produce thyroid-stimulating hormone (TSH) [17].

What trigger thyroid hormone synthesis and release is the stimulation of the TSH in the basolateral receptor of the follicular cell, which is a receptor of the seven transmembrane domain G protein-coupled receptors proteins. The effects of the TSH receptor in the follicular cells are derived to the increased concentration in intracellular cyclic adenosine monophosphate (cAMP) that results in increased iodine uptake and increased protein synthesis to enhance the production of thyroid hormones as well as produce a trophic effect at the thyroid gland [17].

3. Definitions

Hypothyroidism is a condition that results from thyroid hormone deficiency which can range from an asymptomatic condition to a life-threatening condition of the patient life [17–19].

Hypothyroidism can be primary due to a decrease in the production of thyroid hormones in the thyroid gland, secondary due to deficit in the production of TSH in the pituitary or tertiary due to a deficit in the production of TRH in the hypothalamus.

3.1 Subclinical hypothyroidism

Subclinical hypothyroidism is a biochemical diagnosis in which there is an elevation of TSH with a normal level of free thyroid hormones in plasma.

4. Manifestations of hypothyroidism

4.1 Adults

Clinical symptoms of hypothyroidism are diverse, broad, and neither sensitive nor specific to make the diagnosis of hypothyroidism and can be related to many systems, reflecting the systemic effects of thyroid hormones. The severity of the symptoms is usually related to the severity of the thyroid hormone deficit.

Systemic symptoms include lethargy, cold intolerance, goiter, and weight gain. At the cardiovascular system hypothyroidism can produce bradycardia, cardiac failure, angina, and pericardial effusion. Gastrointestinal symptoms are constipation and ileus, neuromuscular manifestations include myalgia, hoarse voice, slow relaxing reflexes, depression, emotional lability, psychosis and carpal tunnel syndrome. Hematologic changes include macrocytic anemia, pernicious anemia, and iron deficiency anemia. Skin manifestations include, myxoedema, hair loss, and coarse skin. In the reproductive system menorrhagia and infertility and finally, hyperlipidaemia as the main metabolic manifestation [17–21].

4.2 Myxedema

Myxedema coma is a severe state of hypothyroidism and an endocrine emergency. Manifestations are depressed mental state and hypothermia with a hypometabolic state with bradycardia. Decreased myocardial contractility and pericardial effusion lead to hypotension. Other features are anemia, hyponatremia, and renal dysfunction [22].

4.3 Congenital hypothyroidism

Thyroid hormones are necessary to have a normal neurodevelopment and growth. Symptoms and signs of congenital hypothyroidism are goiter, poor feeding, macroglossia, prolonged jaundice, developmental delay hypothermia, bradycardia, edema, large fontanelles, umbilical hernia, and poor growth [23].

5. Etiology

5.1 Diagnosis

The diagnosis of hypothyroidism is made biochemically. The elevation of TSH levels associated with low levels of free T4 confirms the diagnosis of primary hypothyroidism; in this case it is not necessary to measure levels of free T3 or T3 because in the state of hypothyroidism the peripheral conversion of T4 to T3 is increased so that T4 will be more diminished than T3 [18, 19, 24].

In secondary hypothyroidism, decreased T4 is found, and TSH is low or normal (not elevated), which means that the pituitary is not responding adequately to a deficit of thyroid hormones.

Subclinical hypothyroidism is diagnosed in patients with elevated TSH despite having normal levels of free T4. These patients may or may not be symptomatic [18, 19, 24].

Although the differential diagnosis in hypothyroidism involves multiple pathologies, with symptoms and signs related to hypothyroidism such as anemia and hyponatremia, among others, the differential diagnosis must also be among the various pathologies that produce hypothyroidism that will be discussed in the etiology section [25, 26].

However, it is important to take into account the sick euthyroid syndrome that refers to alterations in thyroid function tests that can be found in patients with critical illness and can vary depending on the severity and duration of the disease.

In laboratory alterations, there is a decrease in T3 and a smaller proportion of T4, due to an increase in the activity of reverse T3. Subsequently, there is a progressive decrease in TSH followed by a progressive elevation and finally normalization of all thyroid function tests once the injury is resolved [25, 26].

6. Differential diagnosis

6.1 Primary hypothyroidism

6.1.1 Chronic autoimmune thyroiditis or Hashimoto's thyroiditis

It is the most prevalent cause of hypothyroidism in iodine-sufficient countries.

Chronic autoimmune thyroiditis can be goitrous or atrophic. Goitrous hypothyroidism is called Hashimoto thyroiditis [27].

More than 90% of patients have elevated anti-thyroglobulin or anti-peroxidase (microsomal antigen) or anti-sodium iodine transporter. Antibodies against thyroid gland produce chronic autoimmune thyroiditis with lymphocytic infiltration and fibrosis, leading to goiter or atrophy of the thyroid gland [27–29].

Women are five times more affected than men. After the age of 45, the rates of hypothyroidism increase [27].

Based on one of the most representative studies of the population of the USA that included 17,353 people, it found a prevalence of 4.6% of hypothyroidism, 0.3% frank hypothyroidism and 4.3% subclinical hypothyroidism [30].

The course of chronic autoimmune thyroiditis is a gradual loss of thyroid function. The spectrum ranges from subclinical hypothyroidism with positive antibodies to frank hypothyroidism, a process that affects approximately 5% patients per year.

The majority of patients present hypothyroidism for life; however it may be transient [28].

The risk factors for Hashimoto's thyroiditis are multiple; the female gender and the older age are two risk factors. There is a genetic factor associated with multiple polymorphisms in human leukocyte antigen (HLA) genes, T cell receptors, and immunomodulatory molecules. Patients with Down or Turner syndrome have a higher prevalence. Chronic autonomic thyroiditis can be part of the autoimmune type 2 polyglandular syndrome, and affected patients are more likely to develop other autoimmune diseases such as diabetes and adrenal insufficiency [27, 31, 32].

6.1.2 Iodine deficiency

Iodine deficiency, defined as the daily intake of less than 100 mcg of iodine, is the most common cause of hypothyroidism worldwide and the most prevalent cause of hypothyroidism in populations with iodine deficiency. As previously described, excess iodine can produce hypothyroidism due to Wolff-Chaikoff effect; however this effect is usually transient [33, 34].

6.1.3 Iatrogenic disease

Post-thyroidectomy state, radioactive iodine therapy for thyroid cancer, or hyperthyroidism and neck radiation at doses greater than 25 Gy are the main causes of iatrogenic hypothyroidism, and as the use of these therapies increases, it becomes a more prevalent etiology [35, 36].

6.1.4 Drugs

Thionamides, lithium, tetracyclines, thalidomide, ethionamide, and iodine-containing drugs like amiodarone can cause hypothyroidism. Tyrosine kinase inhibitors can cause thyroiditis; sorafenib can produce hypothyroidism by increased type 3 deiodination. Immune therapy including pembrolizumab, nivolumab, ipilimumab, alemtuzumab, interleukin 2, and interferon alfa can produce hypothyroidism [37].

6.2 Thyroiditis

6.2.1 Subacute or granulomatous thyroiditis

Subacute or granulomatous thyroiditis is an acute inflammation of the thyroid gland of viral etiology that presents with hyperthyroidism, followed by hypothyroidism and subsequent recovery of thyroid function. Transient hypothyroidism usually lasts from a few weeks to a maximum of 3–6 months and may be permanent in 5% of patients [38, 39].

The presentation consists of acute pain in the thyroid region that increases when swallowing or moving the head and radiates to the jaw. Symptoms may vary depending on whether the patient is in the hyperthyroid, euthyroid, or hypothyroid category [38, 39].

The findings in thyroid gammagraphy are compatible with thyroiditis due to a decrease in iodine uptake diffusely [38, 39].

6.2.2 Silent thyroiditis or postpartum thyroiditis

Silent thyroiditis or postpartum thyroiditis corresponds to a thyroiditis of autoimmune etiology, which occurs in the first year postpartum. It presents with hyperthyroidism in up to 30% of patients, followed by hypothyroidism in up to 50% of patients; however it can only be present as hypothyroidism or hyperthyroidism [40–42].

It is more frequent in patients with type 1 diabetes mellitus and patients with positive anti-peroxidase antibodies. The prevalence can reach up to 17%. It has been associated with deterioration or onset of postpartum depression. Up to 30% of patients remain hypothyroid [40–42].

6.2.3 Infiltrative diseases

Riedel's thyroiditis is a fibrosclerosing thyroiditis of unknown etiology, with a probable primary anti-immune or fibrotic origin similar to retroperitoneal fibrosis, fibrosing mediastinitis, sclerosing cholangitis, and lacrimal fibrosis, among others [43, 44].

Riedel's thyroiditis is characterized by slow, non-painful growth, sensation of pressure in the neck, dysphagia, dysphonia, and hypoparathyroidism. From 30 to 60% of patients present clinical or subclinical hypothyroidism. It is one of the IgG4-related disease varieties, together with Fibrosing hashimoto thyroiditis, IgG4-related Hashimoto's disease, and Graves' disease associated with IgG4 [43–45].

Other infiltrative diseases like hemochromatosis, scleroderma, leukemia, cystinosis, *M. tuberculosis* infection, and *P. carinii* are less frequent causes of hypothyroidism.

6.3 Secondary hypothyroidism

Central hypothyroidism is a much less frequent form of hypothyroidism, with a prevalence of 1:16,000 to 1:100,000 in the general population. It can be congenital or acquired [46].

The causes of acquired central hypothyroidism are usually related to the causes of hypopituitarism like a pituitary sellar region mass, usually a pituitary adenoma, which produces secondary hypothyroidism by thyrotropic cell compression, or tertiary hypothyroidism with decreased production of TRH by the hypothalamus. Other lesions of the sellar region, such as meningiomas, cysts, abscesses, metastasis, craniopharyngiomas, and dysgerminomas, can produce central hypothyroidism [46, 47].

In addition to space-occupying injuries, radiation with doses greater than 40 Gray performed for brain, orbital, or nasal lesions can produce central hypothyroidism [46, 47].

Other less frequent causes of central hypothyroidism are hypophyseal infiltrative pathologies such as haemochromatosis, sarcoidosis or tuberculosis, cranial trauma, Sheehan syndrome, and the use of drugs as checkpoint inhibitors [46, 47].

7. Treatment

7.1 Clinical hypothyroidism

Since the nineteenth century, levothyroxine has been used for the treatment of hypothyroidism. Usually hypothyroidism requires treatment with lifelong hormone replacement with levothyroxine. In a few cases, transient hormonal substitution due to transient secondary hypothyroidism is required, for example, to subacute thyroiditis or drug-induced hypothyroidism [48–50].

The treatment of choice is thyroxine (T4), which has shown efficacy in multiple studies to restore the euthyroid state and improve the symptoms of hypothyroidism [51–54].

The goal of treatment of primary hypothyroidism is to take the patient to the normal range of TSH. However, the normal range of TSH varies depending on the age and population studied. Most people are in the range of 0.5–4.5 mU/L; however as the age of people increases, the normal range of TSH increases, leading to values of up to 7.0 mU/L in those over 90 years. In contrast, most young and healthy patients are in the range of 0.5–2.5 mU/L [50].

For this reason, in the treatment of hypothyroidism, the dose of levothyroxine and the goal of TSH depend on the age of the patient and the comorbidities [49, 50].

Levothyroxine (T4) is a prohormone and requires deionization to T3 which is the active form of thyroid hormone. Levothyroxine is absorbed in the small intestine. The meal affects the time of maximum concentration, which in normal conditions is 2 h. The bioavailability is from 60 to 80%. The metabolism is catabolized by the thyroid deionidase enzyme that removes the iodine from carbon 5 of the outer ring to transform T4 into T3. Approximately half of T4 is deionized to rT3 (inactive form) and half to T3 (active form). Both T3 and reverse T3 are metabolized to diiodothyronine (T2) and monoiodothyronamine (T1) and T2 and T1 reverses [48].

Multiple medications interact with the function or pharmacokinetics of levothyroxine, amiodarone, androgens, calcium carbonate and citrate, carbamazepine, cholestyramine, ferrous sulfate, glucocorticoids, orlistat, phenytoin, proton pump inhibitors, salicylates, sucralfate, and tamoxifen, which are just some of the medications that alter bioavailability, metabolism, protein binding, or hormone levels [48].

The total replacement dose of levothyroxine in adults is approximately 1.6 mcg/kg, given that the body's requirements for thyroid hormones are proportional to weight. In healthy young patients, the starting dose could be 1.6 mcg/kg/day; however in elderly patients with heart disease or coronary heart disease, the starting dose should be from 0.3 to 0.4 mcg/kg/day with a progressive increase of 10% in the dose every 4–6 weeks [50]. Levothyroxine must be taken with empty stomach 30–60 min before the next meal, usually, breakfast.

The thyroid function is monitored with TSH at 4–6 weeks after starting treatment. If the TSH goal is not achieved, the dose of levothyroxine should be adjusted by increasing or decreasing 10% of the dose ideally, especially in older adults [50].

In the case of secondary hypothyroidism, TSH levels are low or inappropriately normal for a low free T4. Therefore, the follow-up is not done with TSH levels but with free T4 levels, to achieve a normal level for the reference range.

7.2 Subclinical hypothyroidism

In the case of subclinical hypothyroidism, the treatment also depends on the age, functionality, and comorbidities of the patients [50].

For patients younger than 75 years, with TSH greater than 10 mU/L, treatment is recommended. However, in those patients with TSH between 4.5 and 10 mU/L, treatment depends on the presence of symptoms and especially the presence of goiter or anti-TPO antibodies, which predict progression to clinical hypothyroidism [54–56].

In patients older than 75 years, treatment depends on the patient's frailty and should be limited to functional patients with TSH greater than 10 mU/L or patients with TSH of 6–10 mU/L in the presence of antithyroid antibodies, symptoms, and concomitant diseases in that they can be impaired by hypothyroidism such as heart failure. Fragile patients, more than 75 years old, may be advisable to be observed without treatment [50].

8. Conclusion

Hypothyroidism is a highly prevalent chronic disease, widely studied by medical science, with a wide spectrum of severity, ranging from subclinical hypothyroidism to the hypothyroid myxedematous state. In some cases of subclinical hypothyroidism, treatment may not be necessary; however in other cases such as in myxedematous states, the treatment may be lifesaving. There are multiple trials

that evaluate the treatment of hypothyroidism in different populations, and there is still controversy regarding the treatment of subclinical hypothyroidism in some populations. It is very important for the primary care physicians to have a broad knowledge of hypothyroidism since they will face hypothyroid patients in the day-to-day clinical practice.

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