

# Definition, Causes, Pathophysiology, and Management of Hypothyroidism

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## ABSTRACT

The thyroid gland produces insufficient amounts of thyroid hormone, which is known as hypothyroidism. It can be primary (caused by an abnormality in the thyroid gland itself) or secondary/central. Between 3.8% and 4.6% of the general population has hypothyroidism. Hypothyroidism can also develop secondary to hypothalamic and pituitary disorders. These endocrine conditions occur primarily in patients who have undergone intracranial irradiation or surgical removal of a pituitary adenoma. Diagnosis of hypothyroidism is not easy because most of the symptoms, especially in mild cases, are nonspecific and are frequently attributed to other causes or to the aging process itself. Levothyroxine dosage selection, patient-appropriate serum thyrotropin (thyroid stimulating hormone) goal selection, and maintenance of that goal are the fundamental components of treating hypothyroidism. Although liothyronine (synthetic T3) has uniform potency, it is more expensive, harder to monitor with standard laboratory testing, and has a higher rate of severe cardiac effects.

**Keywords:** Causes, Definition, Hypothyroidism, Pathophysiology, Management.

## ABBREVIATIONS

AIH: Amiodarone-induced hyperthyroidism; FT3: Free-triiodothyronine; LT4: Levothyroxine; PRL: Prolactin; T4: Thyroxine; T3: Triiodothyronine; TRH: thyroid-releasing hormone; TSH: thyroid-stimulating hormone.

## INTRODUCTION

Thyroid hormone is necessary for healthy growth and brain development, especially in the first few years of life, and hypothyroidism during this time is a major global cause of reversible intellectual disability [1]. A condition known as hypothyroidism occurs when the thyroid gland is unable to produce enough thyroid hormone to meet the needs of peripheral tissues. The thyroid gland itself failing is a defining feature of primary hypothyroidism. Thyroid-stimulating hormone (TSH) secretion increases and serum concentrations of TSH rise when thyroid hormone levels fall. Insufficient stimulation of a structurally normal gland brought on by

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decreased pituitary TSH release (secondary hypothyroidism) or as a result of insufficient hypothalamic thyrotropin-releasing hormone (TRH) release can also result in decreased thyroidal secretion of thyroid hormone. In clinical practice it is not always possible to discriminate between secondary and tertiary hypothyroidism, which are consequently often referred to as 'central hypothyroidism [2]. The thyroid gland produces insufficient amounts of thyroid hormone, which is known as hypothyroidism. It can be primary (caused by an abnormality in the thyroid gland itself) or secondary/central (as a result of hypothalamic or pituitary disease). The grade of primary hypothyroidism known as "subclinical hypothyroidism" is characterized by elevated serum levels of thyroid-stimulating hormone (TSH) and normal levels of free thyroxine (T4) and triiodothyronine (T3). About 2-5% of cases per year may evolve from subclinical to overt hypothyroidism [2]. Between 3.8% and 4.6% of the general population has hypothyroidism. According to the Whickham survey, there are 4.1 hypothyroidism cases per 1000 women and 0.6 cases per 1000 men per year [3]. The thyroid glands inability to produce enough thyroid hormone results in the illness known as hypothyroidism, which has a number of different causes. The overwhelming majority of instances are related to primary thyroid gland failure because of chronic autoimmune (Hashimoto's) thyroiditis, radioactive iodine therapy, or surgery. The focus of the discussion that follows will be primary hypothyroidism [4].

### CAUSES OF HYPOTHYROIDISM

Primary hypothyroidism (95% of cases; thyroid gland failure affects the majority of hypothyroid patients): Iodine deficiency, enzyme defects, thyroid surgery, late-stage invasive fibrous thyroiditis, chronic autoimmune thyroiditis (Hashimoto's disease), irradiation of the thyroid after Graves' disease, iodine deficiency, medication (such as lithium, interferon), and infiltrative diseases (e.g., sarcoidosis, amyloidosis, scleroderma, hemochromatosis). Pituitary or hypothalamic neoplasms, congenital hypopituitarism, pituitary tumors, surgery, external pituitary radiation, autoimmune mechanisms, tuberculosis, and pituitary necrosis (Sheehan's syndrome) are some uncommon causes of secondary hypothyroidism (pituitary failure accounts for 5% of cases). Additionally, abnormalities of the hypothalamus and pituitary gland can lead to hypothyroidism. Patients who have undergone cerebral radiation therapy or surgery

to remove a pituitary adenoma are more likely to develop certain endocrine problems. TSH blood levels can be simply used to identify hypothyroidism. Subclinical hypothyroidism is indicated by a minor increase in TSH levels together with normal T3 and T4 levels, whereas clinical hypothyroidism is indicated by high TSH levels along with low T3 and T4 levels. More people have subclinical hypothyroidism. It may directly cause anovulation or raise prolactin indirectly. If there are no additional independent risk factors, it is crucial to identify, treat, and maintain subclinical hypothyroidism for pregnancy [4]

### CLINICAL MANIFESTATIONS

A lack of vitality, dry skin, aversion to the cold, weight gain, constipation, lethargy, weakness, and weariness. Children's growth delay is one possible symptom. Physical symptoms include periorbital puffiness, coarse skin and hair, bradycardia, and slurred or raspy speech. The majority of patients with pituitary failure (secondary hypothyroidism) have either clinical evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features, or clinical signs of generalized pituitary insufficiency, such as abnormal menses and decreased libido [2].

### PATHOPHYSIOLOGY

TSH, which is created and secreted in the anterior pituitary under activation of thyrotropin-releasing hormone produced in the hypothalamus, directly stimulates thyroid gland hormone synthesis. The thyroid glands metabolism is regulated by a negative feedback regulatory system in people with a healthy hypothalamic-pituitary-thyroid axis. TSH levels are controlled by the pituitary gland in response to feedback from free-thyroxine (FT4) and free-triiodothyronine (FT3) levels, which act as biosensors of thyroid hormone levels. TSH secretion is increased when thyroid hormone synthesis declines. The control system has a rather sluggish response time, and it is possible to detect some discrepancy between the levels of TSH and the plasma thyroid hormone concentrations during non-equilibrium periods, which happen at the beginning of hypothyroidism. For three main reasons, measuring TSH is regarded as the primary test for identifying thyroid illness, specifically overt and subclinical hypothyroidism. First, the concentrations of TSH and FT4 have an inverse log-linear relationship. As a result, minor linear FT4 concentration decreases are accompanied by an

exponential rise in TSH levels. Second, the primary illness of the thyroid gland accounts for the majority of hypothyroidism patients in clinical practice. Thirdly, TSH immunometric tests have sensitivity and specificity of better than 99%. Finding the FT4 level is the second stage in the thyroid problem screening process. When compared to previously used measurements of total T4 or triiodothyronine, FT4 analysis is significantly less expensive [5,6].

### DIAGNOSIS OF HYPOTHYROIDISM

Hypothyroidism is difficult to diagnose because the majority of symptoms, particularly in mild cases, are ambiguous and commonly attributed to other causes or to aging itself. This is a particular issue for elderly people because numerous symptoms, including weariness, loss of focus, dry skin, and many more, are accepted—correctly or incorrectly—as natural aspects of the aging process. Three different clinical conditions hypothyroidism, depression, and presence of

anemia share common and nonspecific symptoms and are each common condition in older people. In community-dwelling persons 65 and older, anemia, as defined by the World Health Organization, occurs more frequently than 10% of the time and is frequently linked to other clinical disorders. Elderly adults frequently experience depressive symptoms or even depression, especially when they also have severe health problems. The differential diagnosis of these three disorders in this situation is essential [6]. The TSH level increasing is the first sign of primary hypothyroidism. Many patients with compensated hypothyroidism have free T4 levels that are within the normal range; however, as the disease worsens, the free T4 concentration falls below the normal range. The T3 concentration is often maintained in the normal range despite a low T4. Patients with decreased T4 levels and inappropriately normal or low TSH levels should be suspected of having pituitary failure (secondary hypothyroidism).

**Table 1.** Laboratory values in hypothyroidism.

TSH level	Free T4 level	Free T3 level	Likely diagnosis
High	Low	Low	Primary hypothyroidism
High (>10 $\mu\text{U per mL}$ )	Normal	Normal	High risk of developing overt hypothyroidism in the future due to subclinical hypothyroidism (10 mU/L)
High (6 to 10 $\mu\text{U per mL}$ )	Normal	Normal	Low risk of developing overt hypothyroidism (6 to 10 mU per L) due to subclinical hypothyroidism
High	High	Low	Amiodarone (Cordarone) effect on T4-T3 conversion; congenital insufficiency of T4-T3-converting enzyme
High	High	High	Resistance to peripheral thyroid hormones
Low	Low	Low	Pituitary thyroid dysfunction or recent thyroxine withdrawal following overuse of replacement therapy

### TREATMENT OF HYPOTHYROIDISM

Levothyroxine (LT4) dose selection, patient-appropriate serum thyrotropin (TSH) goal selection, and maintenance of that desired goal are the fundamentals of treating hypothyroidism. The alleviation of symptoms and prevention of disease progression to myxedema are the two most crucial justifications for treating overt hypothyroidism. The three main goals of treating subclinical hypothyroidism are symptom relief, delaying the onset of overt disease, and possibly averting subclinical disease-related cardiovascular and all-cause death. The majority of individuals with subclinical hypothyroidism have a low risk of consequences, therefore it's probable that the stigma of having a "illness" poses a greater threat to them than the real likelihood of

developing issues. In order to prevent the development of overt disease, subclinical hypothyroidism should also be treated. High TSH levels, particularly when they are 10 IU/L or above, and the presence of antithyroid peroxidase antibodies are the two most significant factors that point to a shift from subclinical hypothyroidism to overt illness. Periodic testing can be used to monitor both measurements every year or every six months.

Levothyroxine sodium: The preferred method of treating hypothyroidism is with levothyroxine sodium. Levothyroxine preparations are produced in a wide range of dosages and enable accurate titration of a patient's needs. For complete replacement, adults with hypothyroidism need about 1.7 microg/kg of body weight each day. Higher doses (up to 4

microg/kg of body weight per day) may be needed in children. Older patients might only require a daily dose of 0.1 microg/kg. Treatment is typically started with full replacement in patients under the age of 50. 0.025 to 0.05 mg of levothyroxine daily, with clinical and biochemical reevaluations at 6- to 8-week intervals, is the recommended starting dosage for patients older than 50 or younger patients with a history of cardiac disease. This dosage should be continued until the serum TSH concentration is normal. Full replacement doses of levothyroxine may be used to treat some people older than 50, such as those who have recently undergone treatment for hyperthyroidism or those who have been known to have hypothyroidism for only a brief period of time, such as a few months. Some medications, such as cholestyramine, ferrous sulfate, sucralfate, and aluminum hydroxide antacids, may prevent the intestines from absorbing levothyroxine. Levothyroxine administration and these drugs should be separated by at least 4 hours. Other medications, particularly the anticonvulsants phenytoin and carbamazepine and the antituberculous medicine rifampin, may speed up the metabolism of levothyroxine, requiring greater dosages of the thyroid hormone. The preferred medication for thyroid hormone replacement and suppressive therapy is levothyroxine (L-thyroxine, T4) because it is uniformly potent, reasonably priced, antigenicity-free, and chemically stable. Levothyroxine should be begun at 50 mcg per day and raised to 100 mcg per day after one month in young patients with long-term conditions and people older than 45 without known cardiac illness [3,6-14].

Liothyronine (synthetic T3) has uniform potency but is more expensive, has a higher risk of severe cardiac effects, and is challenging to monitor with standard laboratory testing [15,16].

Liotrix (synthetic T4:T3 in a 4:1 ratio) is a costly supplement but is pure, reliable, and chemically stable. Extra exogenous thyroid hormone raises the risk of fracture and lowers bone density [17-21].

## CONCLUSION

The inability of the thyroid gland to produce enough thyroid hormone to meet the needs of peripheral tissues is known as hypothyroidism. Failure of the thyroid gland itself is a feature of primary hypothyroidism. More people have subclinical hypothyroidism. It may directly cause anovulation or raise

PRL indirectly. The control system has a rather sluggish response time, and it is possible to detect some discrepancy between the levels of TSH and the plasma thyroid hormone concentrations during non-equilibrium periods, which happen at the beginning of hypothyroidism. Levothyroxine preparations are produced in a wide range of dosages and enable accurate titration of a patient's needs. For complete replacement, adults with hypothyroidism need about 1.7 microg/kg of body weight each day.

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