Hypothyroidism

The Thyroid Produces and Secretes 2 Metabolic Hormones

- Two principal hormones:
- Thyroxine (T4) and triiodothyronine (T3)
- Required for homeostasis of all cells
- Influence cell differentiation, growth, and metabolism
- Considered the major metabolic hormones because they target virtually every tissue

Thyroid-Stimulating Hormone (TSH)

- Regulates thyroid hormone production, secretion, and growth
- Is regulated by the negative feedback action of T4 and T3
- Hypothalamic-Pituitary-Thyroid Axis
- Negative Feedback Mechanism

Carriers for Circulating Thyroid Hormones

- More than 99 of circulating T4 and T3 is bound to plasma carrier proteins
- Thyroxine-binding globulin (TBG), binds about 75
- Transthyretin (TTR), also called thyroxine-binding prealbumin (TBPA), binds about 10-15
- Albumin binds about 7
- High-density lipoproteins (HDL), binds about 3
- Carrier proteins can be affected by physiologic changes, drugs, and disease

Free Hormone Concept

- Only unbound (free) hormone has metabolic activity and physiologic effects
- Free hormone is a tiny percentage of total hormone in plasma (about 0.03 T4 0.3 T3)
- Total hormone concentration
- Normally is kept proportional to the concentration of carrier proteins
- Is kept appropriate to maintain a constant free hormone level

Changes in TBG Concentration Determine Binding and Influence T4 and T3 Levels

- Increased TBG
- Total serum T4 and T3 levels increase
- Free T4 (FT4), and free T3 (FT3) concentrations remain unchanged
- Decreased TBG
- Total serum T4 and T3 levels decrease
- FT4 and FT3 levels remain unchanged

Drugs and Conditions That Increase Serum T4 and T3 Levels by Increasing TBG

- **Drugs that increase TBG**
- Oral contraceptives and other sources of estrogen
- Methadone
- Clofibrate
- 5-Fluorouracil
- Heroin
- Tamoxifen
- **Conditions that increase TBG**
- Pregnancy
- Infectious/chronic active hepatitis
- HIV infection
- Biliary cirrhosis
- Acute intermittent porphyria
- Genetic factors

Drugs and Conditions That Decrease Serum T4 and T3 by Decreasing TBG Levels or Binding of Hormone to TBG

- **Drugs that decrease serum T4 and T3**
- Glucocorticoids
- Androgens
- L-Asparaginase
- Salicylates
- Mefenamic acid
- Antiseizure medications, eg, phenytoin, carbama-zepine
- Furosemide
- **Conditions that decrease serum T4 and T3**
- Genetic factors
- Acute and chronic illness

Typical Thyroid Hormone Levels in Thyroid Disease

- TSH - T4 - T3
- **Hypothyroidism** High – Low - Low
- **Hyperthyroidism** Low - High - High

Hypothyroidism

- **Hypothyroidism** is defined as a deficiency in thyroid hormone secretion and action that produces a variety of clinical signs and symptoms of Hypometabolism.

1. **Overt Hypothyroidism** is defined as an elevated serum TSH concentration (usually above 10 mIU/L) and reduced free Thyroxine concentration (fT4)
2. **Subclinical Hypothyroidism** is defined as serum TSH above the upper reference limit in combination with a normal free Thyroxine (fT4)

Hypothyroidism is defined as failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body. Untreated hypothyroidism can contribute to dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction.

CAUSES OF HYPOTHYROIDISM

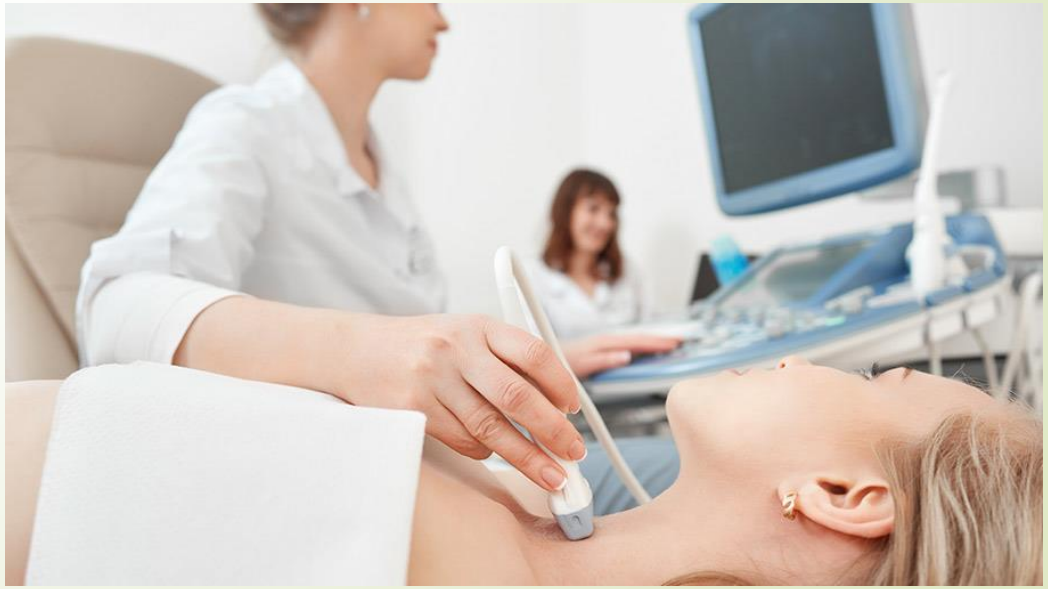
Group	Causes
Primary Hypothyroidism	Iodine deficiency, autoimmune Thyroiditis, previous thyroidectomy, previous radioiodine treatment, previous external beam radiotherapy to the neck. Medication: lithium-based mood stabilizers, Amiodarone, interferon alpha, tyrosine kinase inhibitors such as Sunitinib.
Central Hypothyroidism	Lesions compressing the pituitary (pituitary adenoma, Craniopharyngioma, meningioma, glioma, Rathke's cleft cyst, metastasis, empty sella, aneurysm of the internal carotid artery), surgery or radiation to the pituitary, drugs, injury, vascular disorders (pituitary apoplexy, Sheehan syndrome, subarachnoid hemorrhage), autoimmune diseases (lymphocytic Hypophysitis, Polyglandular disorders), infiltrative diseases (iron overload due to Hemochromatosis or Thalassemia, Sarcoidosis, Langerhans cell Histiocytosis), particular inherited congenital disorders, and infections (tuberculosis, mycoses, syphilis).
Congenital Hypothyroidism	Thyroid Dysgenesis (75%), thyroid Dyshormonogenesis (20%), maternal antibody or radioiodine transfer **Syndromes:** mutations (in GNAS complex locus, PAX8, TTF-1/NKX2-1, TTF-2/FOXE1), Pendred's syndrome (associated with sensorineural hearing loss) **Transiently:** due to maternal iodine deficiency or excess, anti-TSH receptor antibodies, certain congenital disorders, neonatal illness Central: pituitary dysfunction (idiopathic, septo-optic dysplasia, deficiency of PIT1, isolated TSH deficiency)

Autoimmune thyroid disease is the most common etiology of hypothyroidism in the United States.

Clinical symptoms of hypothyroidism are nonspecific and may be subtle, especially in older persons. The best laboratory assessment of thyroid function is a serum thyroid-stimulating hormone test. There is no evidence that screening asymptomatic adults improves outcomes. In the majority of patients, alleviation of symptoms can be accomplished through oral administration of synthetic levothyroxine, and most patients will require lifelong therapy.

Clinical Presentation

Thyroid hormone receptors regulate many key physiologic processes. Consequently, hypothyroidism may result in a myriad of clinical signs and symptoms. The severity of these manifestations generally reflects the degree of thyroid dysfunction and the time course of development of hypothyroidism. Symptoms commonly associated with hypothyroidism are often nonspecific. These include weight gain, fatigue, poor concentration, depression, diffuse muscle pain, and menstrual irregularities. Symptoms with high specificity for hypothyroidism include constipation, cold intolerance, dry skin, proximal muscle weakness, and hair thinning or loss.



Symptoms of hypothyroidism may vary with age and sex. Infants and children may present more often with lethargy and failure to thrive. Women who have hypothyroidism may present with menstrual irregularities and infertility. In older patients, cognitive decline may be the sole manifestation. Examination findings associated with hypothyroidism include but are not limited to goiter, delayed relaxation phase of deep tendon reflexes, thin or brittle hair, dry skin, and peripheral edema

Clinical Features of Hypothyroidism

- Tiredness
- Puffy Eyes
  Enlarged Thyroid (Goiter)
  Forgetfulness/Slower Thinking
  Moodiness/ Irritability
  Hoarseness/Deepening of Voice
  Depression
  Persistent Dry or Sore Throat
  Inability to Concentrate
  Thinning Hair/Hair Loss
  Difficulty Swallowing
  Loss of Body Hair
  Slower Heartbeat
- Dry, Patchy Skin
  Menstrual Irregularities/Heavy Period
  Weight Gain
  Infertility
  Cold Intolerance
- Constipation
  Elevated Cholesterol
  Muscle Weakness/Cramps
  Family History of Thyroid Disease or Diabetes

Common electrocardiography findings include bradycardia, flattened T waves, and low voltage. Patients with severe hypothyroidism may present with pericardial effusion, pleural effusion, megacolon, hemodynamic instability, and coma. The clinical presentation is often confused with septic shock. Myxedema coma, which represents severe physiologic decompensation resulting from hypothyroidism, occurs rarely, with an annual incidence of 0.22 per million. Laboratory findings in hypothyroidism may include hyponatremia, hypercapnia, hypoxia, normocytic anemia, elevated creatine kinase, hyperprolactinemia, and hyperlipidemia.

Hypothyroidism is a clinical disorder commonly encountered by the primary care physician.

Untreated hypothyroidism can contribute to dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction.

The prevalence increases with age and is higher in females than in males. Hypothyroidism may occur as a result of primary gland failure or insufficient thyroid gland stimulation by the hypothalamus or pituitary gland.

Hypothyroidism

Screening and Diagnosis

Family physicians should evaluate for thyroid dysfunction in all patients with symptoms of hypothyroidism. The American Academy of Family Physicians does not recommend screening for hypothyroidism in asymptomatic adults and the U.S. Preventive Services Task Force found insufficient evidence for routine screening in this population.

Screening of asymptomatic patients may be considered in those with risk factors for hypothyroidism, such as a history of autoimmune disease, history of head or neck irradiation, previous radioactive iodine therapy, presence of a goiter, family history of thyroid disease, or treatment with drugs known to influence thyroid function.

The best laboratory assessment of thyroid function, and the preferred test for diagnosing primary hypothyroidism, is a serum TSH test.

If the serum TSH level is elevated, testing should be repeated with a serum free thyroxine (T_4) measurement. Overt primary hypothyroidism is indicated with an elevated serum TSH level and a low serum free T_4 level. An elevated serum TSH level with a normal range serum free T_4 level is consistent with subclinical hypothyroidism. A low serum free T_4 level with a low, or inappropriately normal, serum TSH level is consistent with secondary hypothyroidism and will usually be associated with further evidence of hypothalamic-pituitary insufficiency.

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Treatment

Most patients with hypothyroidism will require lifelong thyroid hormone therapy. The normal thyroid gland makes two thyroid hormones: T4 and triiodothyronine (T3). Although T4 is produced in greater amounts, T3 is the biologically active form. Approximately 80 % of T3 is derived from the peripheral conversion of T4 by deiodinase enzymes. However, because T3 preparations have short biologic half-lives, hypothyroidism is treated almost exclusively with once-daily synthetic thyroxine preparations.

Combination triiodothyronine/thyroxine therapy has no advantages over thyroxine monotherapy and is not recommended. Among patients with subclinical hypothyroidism, those at greater risk of progressing to clinical disease, and who may be considered for therapy, include patients with thyroid-stimulating hormone levels greater than 10 mIU per L and those who have elevated thyroid peroxidase antibody titers.

The starting dosage of levothyroxine in young, healthy adults for complete replacement is 1.6 mcg per kg per day. Thyroid hormone is generally taken in the morning, 30 minutes before eating. Calcium and iron supplements should not be taken within four hours of taking levothyroxine, because these supplements may decrease thyroid hormone absorption. Poor adherence to levothyroxine therapy is the most common cause of persistently elevated TSH levels in patients on adequate doses of thyroid hormone. Levothyroxine dosing for infants and children is also weight-based and varies by age. Dosage should be adjusted based on clinical response and laboratory parameters.

Patients who have difficulty with morning levothyroxine dosing may find bedtime dosing an effective alternative.

OLDER PATIENTS AND PATIENTS WITH ISCHEMIC HEART DISEASE

In older patients and in patients with coronary artery disease, the initial dosage is generally 25 ug or 50 ug daily, with the dosage increased by 25 ug every three to four weeks until the estimated full replacement dose is reached.

Thyroid hormone increases heart rate and contractility, and therefore increases myocardial oxygen demand. Consequently, starting at higher doses may precipitate acute coronary syndrome or an arrhythmia. However, there are no high-quality studies that show that lower starting doses and slow titration result in fewer adverse effects than full-dose levothyroxine replacement in older patients and patients with ischemic heart disease.

PREGNANCY

Thyroid hormone requirements increase during pregnancy. In one prospective study, 85% of pregnant patients required a median increase of 47 % in their thyroid hormone requirements. These increases in levothyroxine dosing were required as early as the fifth week of pregnancy in some patients, which is before the first scheduled prenatal care visit. It is recommended that women on fixed doses of levothyroxine take nine doses each week (one extra dose on two days of the week), instead of the usual seven, as soon as pregnancy is confirmed. Repeat thyroid function tests should be obtained five weeks after the increase in dosage. The increase in thyroid hormone requirement lasts throughout pregnancy.

PATIENTS WITH PERSISTENT SYMPTOMS

A small number of patients with hypothyroidism, mostly women, treated with an adequate dose of levothyroxine will report persistent symptoms such as fatigue, depressed mood, and weight gain despite having a TSH level in the lower half of the normal range. Some patients may have an alternative cause for their symptoms; in these patients, a limited laboratory and clinical investigation is reasonable. Combination T3/T4 therapy, in the form of desiccated thyroid hormone preparations (e.g., thyroid USP, Armour thyroid) or levothyroxine plus liothyronine is sometimes prescribed for patients with persistent symptoms of hypothyroidism.

Numerous medications can affect thyroid hormone levels in patients taking levothyroxine.

Patients on a stable dose of levothyroxine who are then started on a selective serotonin reuptake inhibitor, in particular sertraline (Zoloft), may show a rise in their TSH level and require an increase in their thyroid hormone dose.