THYROID DISORDERS

Thyroid disorders are common. More than 2 billion people, or 38% of the world's population, have iodine deficiency, resulting in 74 million people with goiters (swelling in the neck resulting from an enlarged thyroid gland). Although overt iodine deficiency is not a significant problem in developed countries, a number of common thyroid conditions exist. The most common are hypothyroidism and hyperthyroidism, which often require long-term pharmacotherapy.

❖ Thyroid Hormone Physiology and Biosynthesis

The thyroid gland is the largest endocrine gland in the body, residing in the neck anterior to the trachea between the cricoid cartilage and suprasternal notch. The thyroid gland produces two biologically active hormones, thyroxine (T4) and triiodothyronine (T3).

Thyroid hormones are essential for proper fetal growth and development, particularly of the central nervous system. After delivery, the primary role of thyroid hormone is in regulation of energy metabolism. These hormones can affect the function of virtually every organ in the body.

T4 and T3 are produced by the organification of iodine in the thyroid gland. Iodine is actively transported into the thyroid follicular cells. This inorganic iodine is oxidized by thyroid peroxidase and covalently bound to tyrosine residues of thyroglobulin.

These iodinated tyrosine residues, monoiodotyrosine and diiodotyrosine, couple to form T4 and T3. Eighty percent of thyroid hormone is synthesized as T4 and is stored in the thyroid bound to thyroglobulin. Thyroid hormones are released from the gland when needed, primarily under the influence of TSH (thyrotropin from the anterior pituitary). T4 and T3 are transported in the blood by three proteins, 70% bound to thyroid-binding globulin (TBG), 15% to transthyretin (thyroid-binding prealbumin), and 15% to albumin. T4 is 99.97% protein bound, and T3 is 99.7% protein bound, with only the unbound or free fractions physiologically active. The high degree of protein binding results in a long half-life of these hormones: approximately 7 to 10 days for T4 and 24 hours for T3.

Most of the physiologic activity of thyroid hormones is from the actions of T3. T4 can be thought of primarily as a prohormone. Eighty percent of needed T3 is derived from conversion of T4 to T3 in peripheral tissue under the influence of tissue deiodinases.

The production and release of thyroid hormones are regulated by the hypothalamic–pituitary–thyroid axis. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the release of TSH when there are physiologically inadequate levels of

thyroid hormones. TSH promotes production and release of thyroid hormones. As circulating thyroid hormone levels rise to needed levels, negative feedback results in decreased release of TSH and TRH. Release of TRH is also inhibited by somatostatin and its analogs, and release of TSH can also be inhibited by dopamine, dopamine agonists, and high levels of glucocorticoids.

❖ Patient Assessment and Monitoring

Assessment of patients for thyroid disorders entails a history and physical examination. Various diagnostic tests can be used, including serum thyroid hormone(s), TSH, thyroid antibody levels, and imaging techniques

⇨ TSH Levels

*In most patients with thyroid hormone disorders, measurement of a serum TSH level is adequate for initial screening and diagnosis of hypothyroidism and hyperthyroidism. Serum free thyroxine (FT*4*) and triiodothyronine (FT*3*) levels may be helpful in distinguishing mild (subclinical) thyroid disease from overt disease. TSH for most patients being treated for thyroid disorders should be the mean normal value of 1.5 milli international units/L (mIU/L) or 1.5 micro international units/mL (μIU/mL) (target range, 0.5–4 mIU/L or μIU/mL), although patients must be individually titrated based on resolution of signs and symptoms as well as biochemical tests.*

In patients with primary hypothyroidism or hyperthyroidism resulting from gland dysfunction, there is an inverse relationship between the TSH level and thyroid function. High TSH signifies hypothyroidism (or iatrogenic under-replacement), and low TSH signifies hyperthyroidism (or iatrogenic over-replacement).

⇨ Other Diagnostic Tests

-The radioactive iodine uptake (RAIU) is elevated in those with hyperthyroidism and can aid in identifying thyrotoxicosis owing to non-thyroid gland sources.

-Radionuclide thyroid scans are used in the evaluation of thyroid nodules.

-Antithyroid peroxidase antibodies (anti-TPOAb) and antithyroglobulin antibodies (anti-TGAb) are present in many patients with hypothyroidism. Most patients with Graves disease have TSH receptor-stimulating antibodies (TSHR-SAb) as well as elevated anti-TPOAb and antimicrosomal antibodies.

❖ HYPOTHYROIDISM

Hypothyroidism is the most common clinical disorder of thyroid function. It is the clinical syndrome that results from inadequate secretion of thyroid hormones from the thyroid gland. The vast majority of hypothyroid patients have primary gland failure, but occasional patients have pituitary or hypothalamic failure.

Most studies define hypothyroidism based on a serum TSH level above the upper limit of the laboratory reference range.

In patients with subclinical hypothyroidism and positive anti-TPOAb, 5% per year will progress to overt hypothyroidism. Other risk factors for development of hypothyroidism include the postpartum state, family history of autoimmune thyroid disorders, a previous history of head and neck or thyroid surgery, head and neck irradiation, other autoimmune endocrine disorders such as type 1 diabetes and Addison disease, other non-endocrine autoimmune diseases such as celiac disease and pernicious anemia, history of treatment for hyperthyroidism, treatment with amiodarone or lithium, and an iodine-deficient diet.

Clinical Presentation and Diagnosis of Hypothyroidism[3,6,8–10]

Symptoms

Fatigue	Cold intolerance
Lethargy	Hoarseness
Sleepiness	Dry skin
Mental impairment	Decreased perspiration
Depression	Decreased appetite
Weight gain	Constipation
Menstrual disturbances	Arthralgia
Paresthesia	

Signs

Slow movements	Dry skin
Slow speech	Nonpitting edema (myxedema)
Hoarseness	Hyporeflexia
Bradycardia	Delayed relaxation of reflexes

Screening/Diagnosis

- A TSH level of 4.5 to 10 mIU/L (μIU/mL) may constitute mild or subclinical hypothyroidism.
- A TSH level greater than 10 mIU/L (μIU/mL) signifies overt hypothyroidism.
- The free T_4 level will be normal (0.7–1.9 ng/dL or 9.0–24.5 pmol/L) in mild or subclinical hypothyroidism and low (less than 0.7 ng/dL or 9.0 pmol/L) in patients with obvious signs and/or symptoms.

Common Causes of Hypothyroidism[3,8–11]

Primary Hypothyroidism

Autoimmune thyroiditis (Hashimoto disease)
Iatrogenic (irradiation, surgery)
Drugs (amiodarone, radiocontrast media, lithium, interferon-α, tyrosine kinase inhibitors)
Silent thyroiditis (including postpartum)
Iodine deficiency and excess

Secondary Hypothyroidism

Pituitary disease
Hypothalamic disease

Treatment of Hypothyroidism

⇨ Goals of Treatment

There are three major goals in the treatment of hypothyroidism: replace the missing hormones, relieve signs and symptoms, and achieve a stable biochemical euthyroid state (having normal thyroid gland function).

⇨ Products

Despite the availability of a wide array of thyroid hormone products (synthetic LT4 and T3, combinations of synthetic LT4 and T3, and animal-derived products), it is

clear that synthetic LT4 is the treatment of choice for almost all patients with hypothyroidism. LT4 mimics the normal physiology of the thyroid gland, which secretes mostly T4 as a prohormone. Peripheral tissues convert T4 to T3 as needed based on metabolic demands. If T3 is used to treat hypothyroidism, the peripheral tissues lose their ability to control local metabolic rates. LT4 also has distinct pharmacokinetic advantages over T3. With a 7- to 10-day half-life, LT4 provides a very smooth dose-response curve with little peak and trough effect. In a small number of patients who have impairment of conversion of T4 to T3, addition of T3 may be warranted.

⇨ Bioavailability and Bioequivalence

There is no evidence that one LT4 product is better than another. However, given the evidence that these products do have differences in bioavailability, patients should be maintained on the same LT4 product. Given the generic substitution regulations of most states, this is best accomplished by prescribing a brand-name product or otherwise ensuring the product remains constant and not allowing substitution. If patients are switched to a different product, the prescriber should be notified, and a TSH determination should be done in 6 to 8 weeks to allow dose retitration.

⇨ Dosing

Patients with mild or subclinical hypothyroidism do not need to be started on the full LT4 replacement dose because they still have some endogenous hormone production. Start these patients on 25 to 50 mcg/day and titrate every 6 to 8 weeks based on TSH levels. Over time, it is likely the LT4 dose will need to be increased slowly as the patient's thyroid gland loses residual function.

At the start of therapy and with each change in dose, recheck the TSH in 6- to 8-week intervals. If the TSH is not in the target range (0.5–4 mIU/L or μIU/mL), change the dose by 10% to 20% and then recheck the TSH 6 to 8 weeks later. As the dose is titrated, assess the patient's symptoms.

Monitoring LT_4 Therapy

- Serum TSH
  - Every 6–12 months or if change in clinical status
  - 6–8 weeks after any dose or product change
  - As soon as possible in pregnancy; then monthly
- Same product prescribed and dispensed with every refill
- Watch for mg/mcg dosing errors
- Assess patient's understanding of disease, therapy, and need for adherence and tight control
- Assess for signs and symptoms of over- and undertreatment
- Identify potential interactions between LT_4 and foods and/or drugs

❖ HYPERTHYROIDISM and THYROTOXICOSIS

Hyperthyroidism is much less common than hypothyroidism. Hyperthyroidism is related to excess thyroid hormone secreted by the thyroid gland.

Thyrotoxicosis is any syndrome caused by excess thyroid hormone and can be related to excess hormone production (hyperthyroidism).

Causes of Thyrotoxicosis[33–35]

Primary Hyperthyroidism
Graves disease
Toxic multinodular goiter
Toxic adenoma
Thyroid cancer
Struma ovarii
Iodine excess (including radiocontrast, amiodarone)

Thyrotoxicosis without Hyperthyroidism
Subacute thyroiditis
Silent (painless) thyroiditis
Excess thyroid hormone intake (thyrotoxicosis factitia)
Drug-induced (amiodarone, iodine, lithium, interferons)

Secondary Hyperthyroidism
TSH-secreting pituitary tumors
Trophoblastic (hCG-secreting) tumors
Gestational thyrotoxicosis

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

Clinical Presentation and Diagnosis of Hyperthyroidism[33–35]

Symptoms
- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity, irritability
- Palpitations
- Appetite change (usually increased)
- Weight change (usually weight loss)
- Menstrual disturbances (often oligomenorrhea)
- Diarrhea

Signs
- Hyperactivity
- Tachycardia
- Atrial fibrillation (especially in elderly adults)
- Hyperreflexia
- Warm, moist skin
- Ophthalmopathy, dermopathy (Graves disease)
- Goiter
- Muscle weakness

Screening/Diagnosis
- Low TSH level (less than 0.5 mIU/L or μIU/mL) signifies thyrotoxicosis.
- FT_4 is elevated in overt hyperthyroidism but may be normal in mild hyperthyroidism.
- Increased radioiodine uptake in the thyroid indicates increased hormone production by the thyroid gland.
- Almost all patients with Graves disease will have positive TSHR-SAbs and positive anti-TPOAbs.

Graves Disease

Graves disease is an autoimmune syndrome that includes hyperthyroidism, diffuse thyroid enlargement, exophthalmos and other eye findings, and skin findings. Hyperthyroidism results from the production of TSHR-SAbs in at least 80% of patients with clinical Graves disease. These antibodies have TSH agonist activity,

thereby stimulating hormone synthesis and release. These antibodies cross-react with orbital and fibroblastic tissue, resulting in ophthalmopathy and dermopathy.
Several features of Graves disease are distinct from other forms of thyrotoxicosis. Clinically apparent ophthalmopathic changes are seen in 20% to 40% of patients and include exophthalmos, proptosis, chemosis, conjunctival injection, and periorbital edema. Eyelid retraction causes a typical staring or startled appearance. Patients may complain of vague eye discomfort and excess tearing. In severe cases, the eyelids are unable to close completely, resulting in corneal damage. Treatment of the underlying hyperthyroid state often, but not always, improves the ophthalmopathy.
Dermopathy occurs in 5% to 10% of patients with Graves disease and usually is associated with severe ophthalmopathy. Skin findings include hyperpigmented, non-pitting induration of the skin, typically over the pretibial area (pretibial myxedema), the dorsa of the feet, and the shoulder areas. Clubbing of the digits (thyroid acropachy) is associated with long-standing thyrotoxicosis.

Treatment of Hyperthyroidism

⇨ **Goals of Treatment**

The goals of treating hyperthyroidism are to relieve signs and symptoms, reduce thyroid hormone production to normal levels and achieve biochemical euthyroidism, and prevent long-term adverse sequelae.

⇨ **β-Blockers**

Because many of the manifestations of hyperthyroidism appear to be mediated by the β-adrenergic system, β-adrenergic blockers are used to rapidly relieve palpitations, tremor, anxiety, and heat intolerance.
Because β-blockers do not reduce the synthesis of thyroid hormones, they are used only until more specific antithyroid therapy is effective. Because nonselective agents can impair the conversion of T4 to T3, propranolol and nadolol are preferred. An initial propranolol dose of 20 to 40 mg four times daily should be titrated to relieve signs (target resting heart rate less than 90 beats/min) and symptoms.
β-Blockers should not be used in patients with decompensated heart failure or asthma. A more β-1 specific blocker (eg, metoprolol, atenolol) may be used when a relative contraindication to a β-blocker exists; however, when an absolute contraindication to β-blockers exists, clonidine, verapamil or diltiazem may be used for rate control.

⇨ **Iodide**

Large doses of iodide inhibit the synthesis and release of thyroid hormones. Serum T4 levels may be reduced within 24 hours, and the effects may last for 2 to 3 weeks.

Iodides are used most commonly in Graves disease patients before surgery and to quickly reduce hormone release in patients with thyroid storm.
Potassium iodide is administered either as a saturated solution (SSKI) that contains 38 mg iodide per drop or as Lugol solution, which contains 6.3 mg iodide per drop.
The most frequent toxic effects with iodide therapy are hypersensitivity reactions, "iodism" (characterized by palpitations, depression, weight loss, and pustular skin eruptions), and gynecomastia.

⇨ Antithyroid Drugs

The thionamide agents propylthiouracil (PTU) and methimazole (MMI) are used to treat hyperthyroidism. Carbimazole, an MMI prodrug, is used in some countries (10 mg carbimazole = 6 mg MMI). These drugs inhibit thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin. PTU has the added effect of inhibiting the conversion of T4 to T3. The thionamides also have immunosuppressant effects. In patients with Graves disease treated with thionamides, TSHR-SAb levels and other immune mediators decrease over time. Antithyroid drugs are used as primary therapy for Graves disease or as preparative therapy before surgery or radioactive iodine administration.
The usual starting dose of MMI is 10 to 20 mg/day, and the usual starting dose of PTU is 50 to 150 mg three times daily. Thyroid hormone levels drop in 2 to 3 weeks, and after 6 weeks, 90% of patients with Graves disease will be euthyroid. Thyroid function testing should be performed every 4 to 6 weeks until stable. After the patient becomes euthyroid, the antithyroid drug dose often can be decreased (5–10 mg/day MMI, 100–200 mg/day PTU) to maintain the euthyroid state. Excessive doses of antithyroid drugs will result in hypothyroidism.
Agranulocytosis is one of the most serious adverse effects of antithyroid drugs. Agranulocytosis, thought to be autoimmune, almost always occurs within the first 3 months of therapy, and it occurs suddenly and unpredictably. Patients will present with fever, malaise, and a sore throat, and the absolute neutrophil count will be less than $1000/mm^3$ ($1 \times 109/L$). Patients may develop sepsis and die rapidly. If agranulocytosis occurs, discontinue the antithyroid drug immediately, administer broad-spectrum antibiotics if the patient is febrile, and consider administration of filgrastim.

⇨ Radioactive Iodine

Radioactive iodine, typically ^{131}I, produces thyroid ablation without surgery. ^{131}I is well absorbed after oral administration. The iodine is concentrated in the thyroid gland and has a half-life of 8 days. Over a period of weeks, thyroid cells that have

taken up the ^{131}I begin to develop abnormalities and necrosis. Eventually, thyroid cells are destroyed, and hormone production is reduced.
In most patients, hypothyroidism will develop, and long-term LT4 replacement will be necessary. Because ^{131}I has a slow onset of action, most patients are treated initially with β-blockers and antithyroid drugs to prevent ^{131}I-induced thyroid storm.

⇨ **Surgery**

Subtotal thyroidectomy is indicated in patients with very large goiters and thyroid malignancies and those who do not respond or cannot tolerate other therapies. Patients must be euthyroid before surgery, and they are often administered iodide preoperatively to reduce gland vascularity.