



THYROID GLAND

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ABSTRACT

The thyroid gland secretes thyroxine (T₄) and triiodothyronine (T₃), both of which modulate energy utilization and heat production and facilitate growth. The gland consists of two lateral lobes joined by an isthmus. The weight of the adult gland is 10 to 20 g. Microscopically, the thyroid is composed of several follicles containing colloid surrounded by a single layer of thyroid epithelium. The follicular cells synthesize thyroglobulin, which is then stored as colloid. Biosynthesis of T₄ and T₃ occurs by iodination of tyrosine molecules in thyroglobulin. Dietary iodine is essential for synthesis of thyroid hormones. Iodine, after conversion to iodide in the stomach, is rapidly absorbed from the gastrointestinal tract and distributed in the extracellular fluids. After active transport from the blood stream across the follicular cell basement membrane, iodide is enzymatically oxidized by thyroid peroxidase, which also mediates the iodination of the tyrosine residues in thyroglobulin to form monoiodotyrosine and diiodotyrosine. The iodotyrosine molecules couple to form T₄ (3,5,3',5'-tetraiodothyronine) or T₃ (3,5,3'-triiodothyronine). Once iodinated, thyroglobulin containing newly formed T₄ and T₃ is stored in the follicles. Secretion of free T₄ and T₃ into the circulation occurs after proteolytic digestion of thyroglobulin, which is stimulated by thyroid-stimulating hormone (TSH). Deiodination of monoiodotyrosine and diiodotyrosine by iodotyrosine deiodinase releases iodine, which then reenters the thyroid iodine pool.

KEYWORD: Thyroid Gland, Iodine, Thyroid.

INTRODUCTION

T₄ and T₃ are tightly bound to serum carrier proteins: thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin, and albumin.^[1] The unbound or free fractions are the biologically active fractions and represent only 0.04% of the total T₄ and 0.4% of the total T₃. The normal thyroid gland secretes T₄, T₃, and reverse T₃, a biologically inactive form of T₃.^[5] Most of the circulating T₃ is derived from 5'-deiodination of circulating T₄ in the peripheral tissues. Deiodination of T₄ can occur at the outer ring (5'-deiodination), producing T₃ (3,5,3'-triiodothyronine), or at the inner ring, producing reverse T₃ (3,3,5'-triiodothyronine).^[27]

Hypothalamic thyrotropin-releasing hormone (TRH) is transported through the hypothalamic-hypophysial portal system to the thyrotrophs of the anterior pituitary gland, stimulating synthesis and release of TSH.^[2] TSH, in turn, increases thyroidal iodide uptake and iodination of thyroglobulin, releases T₃ and T₄ from the thyroid gland by increasing hydrolysis of thyroglobulin, and stimulates thyroid cell growth.^[3] Hypersecretion of TSH results in thyroid enlargement (goiter). Circulating T₃ exerts negative feedback inhibition of TRH and TSH release.^[6]

Thyroid hormones increase basal metabolic rate by increasing oxygen consumption and heat production in several body tissues.^[7] Thyroid hormones also have specific effects on several organ systems.^[9] These effects are exaggerated in hyperthyroidism and lacking in hypothyroidism, accounting for the well recognized signs and symptoms of these two disorders.^[10]

Thyroid Evaluation: Thyroid gland function and structure can be evaluated by (1) serum thyroid hormone levels, (2) imaging of thyroid gland size and architecture, (3) measurement of thyroid autoantibodies, and (4) thyroid gland biopsy (by fine-needle aspiration [FNA]).

Total serum T₄ and T₃ measure the total amount of hormone bound to thyroid-binding proteins by radioimmunoassay.^[6] Total T₄ and total T₃ levels are elevated in hyperthyroidism and low in hypothyroidism.^[7] Increase in TBG (as with pregnancy or estrogen therapy) increases the total T₄ and T₃ measured in the absence of hyperthyroidism.^[8] Similarly, total T₄ and T₃ are low despite euthyroidism in conditions associated with low thyroid-binding proteins (e.g., cirrhosis or nephrotic syndrome).^[9] Thus, further tests to assess the free hormone level that reflects

biologic activity must be performed. Free T4 level can be estimated by calculating the free T4 index or can be measured directly by dialysis.^[11]

The free T4 index is an indirect method of assessing free T4.^[12] It is derived by multiplying the total T4 by the T3 resin uptake, which is inversely proportional to the available T4 binding sites on TBG.^[13] Free T4 can be measured directly by dialysis or ultrafiltration.^[14] This is more accurate and is preferred to the free T4 index.^[15] Serum TSH is measured by a third-generation immunometric assay, which employs at least two different monoclonal antibodies against different regions of the TSH molecule, resulting in accurate discrimination between normal TSH levels and levels below the normal range.^[16] Thus, the TSH assay can diagnose clinical hyperthyroidism (elevated free T4 and suppressed TSH) and subclinical hyperthyroidism (normal free T4 and suppressed TSH). In primary (thyroidal) hypothyroidism, serum TSH is supra normal because of diminished feedback inhibition. In secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the TSH is usually low but may be normal. Serum thyroglobulin measurements are useful in the follow-up of patients with papillary or follicular carcinoma.^[17] After thyroidectomy and iodine-131 (131I) ablation therapy, thyroglobulin levels should be less than 2mg/L while the patient is on suppressive levothyroxine treatment. Levels in excess of this value indicate the presence of persistent or metastatic disease.^[18] Calcitonin is produced by the medullary cells of the thyroid. Calcitonin measurements are invaluable in the diagnosis of medullary carcinoma of the thyroid and for following the effects of therapy for this entity.^[20]

Thyroid Imaging: Technetium-99m (99mTc) pertechnetate is concentrated in the thyroid gland and can be scanned with a gamma camera, yielding information about the size and shape of the gland and the location of the functional activity in the gland (thyroid scan).^[21] The thyroid scan is often performed in conjunction with a thyroid uptake assay, usually with iodine-123 (123I), which quantitates thyroid uptake.^[22] Functioning thyroid nodules are called “warm” or “hot” nodules; “cold” nodules are non functioning.^[23] Malignancy is usually associated with a cold nodule; 16% of surgically removed cold nodules are malignant.^[24]

Thyroid ultrasound evaluation is useful in the differentiation of solid from cystic nodules.^[25] It can also guide the operator during FNA of a nodule that is difficult to palpate.^[26]

Thyroid Antibodies: Autoantibodies to several different antigenic components in the thyroid gland, including thyroglobulin (TgAb), thyroid peroxidase (TPO Ab, formerly called antimicrosomal antibodies), and the TSH receptor, can be measured in the serum. A strongly positive test for TPO Ab indicates autoimmune thyroid

disease. Elevated thyroid receptor-stimulating antibody occurs in Graves' disease.^[25]

Hyperthyroidism

Thyrotoxicosis is the clinical syndrome that results from elevated circulating thyroid hormones.^[1] Clinical manifestations of thyrotoxicosis are due to the direct physiologic effects of the thyroid hormones, as well as to the increased sensitivity to catecholamines.^[5] Tachycardia, tremor, stare, sweating, and lid lag are due to catecholamine hypersensitivity.^[6]

Graves' disease, the most common cause of thyrotoxicosis, is an autoimmune disease that is more common in women, with a peak age incidence of 20 to 40 years. One or more of the following features are present: (1) goiter; (2) thyrotoxicosis; (3) eye disease ranging from tearing to proptosis, extraocular muscle paralysis, and loss of sight as a result of optic nerve involvement; and (4) thyroid dermopathy, usually presenting as marked skin thickening without pitting in a pretibial distribution (pretibial myxedema).

Clinical Significance: The common manifestations of thyrotoxicosis are characteristic features of younger patients with Graves' disease.^[9] In addition, patients may present with a diffuse goiter or the eye signs characteristic of Graves' disease.^[7] Older patients often do not manifest the florid clinical features of thyrotoxicosis, and the condition termed *apathetic hyperthyroidism* presents as flat affect, emotional lability, weight loss, muscle weakness, or congestive heart failure and atrial fibrillation resistant to standard therapy.^[10]

Eye signs of Graves' disease may be either a nonspecific manifestation of hyperthyroidism from any cause (e.g., thyroid stare) or may result from Graves' disease due to a specific inflammatory infiltrate of the orbital tissues leading to periorbital edema, conjunctival congestion and swelling, proptosis, extraocular muscle weakness, and or optic nerve damage with visual impairment.^[7]

Pretibial myxedema (thyroid dermopathy) occurs in 2 to 3% of patients with Graves' disease and presents as thickening of the skin over the lower tibia without pitting.^[4] Onycholysis, characterized by separation of the fingernails from their beds, often occurs in Graves' disease.^[9] Thyroid acropachy, or clubbing, may also occur in Graves' disease.^[7]

Treatment: Three treatment modalities are employed to control the hyperthyroidism of Graves' disease.

Antithyroid Drugs: The thiocarbamide drugs propylthiouracil, methimazole, and carbimazole block thyroid hormone synthesis by inhibiting thyroid peroxidase.^[8] Propylthiouracil also partially inhibits peripheral conversion of T4 to T3. Medical therapy must be administered for a prolonged period (12 to 18

months), until the disease undergoes spontaneous remission.^[9] On cessation of medication, only a small percentage of patients (20 to 30%) remain in remission, and the patients who experience relapse must then undergo definitive surgery or radioactive iodine treatment. Side effects of the thiocarbamides include pruritus and rash (about 5% of patients), cholestatic jaundice, acute arthralgias, and, rarely, agranulocytosis (0.5% of patients).^[4] Patients must be instructed to discontinue the medication and consult a physician if they develop fever or sore throat, because these may indicate agranulocytosis.^[7] At the onset of treatment, during the acute phase of thyrotoxicosis, β -adrenergic blocking drugs help alleviate tachycardia, hypertension, and atrial fibrillation.^[5] As the thyroid hormone levels return to normal, treatment with β -blockers is tapered.^[6]

Radioactive Iodine: In terms of cost, efficacy, ease, and short-term side effects, radioactive iodine has benefits that exceed both surgery and antithyroid drugs.^[8] Iodine-131 is the treatment of choice in adults with Graves' disease.^[4] Patients with severe thyrotoxicosis, very large glands, or underlying heart disease should be rendered euthyroid with antithyroid medication before receiving radioactive iodine because ^{131}I treatment can cause release into the circulation of preformed thyroid hormone from the thyroid gland; this can precipitate cardiac arrhythmias and exacerbate symptoms of thyrotoxicosis.^[6] After administration of radioactive iodine, the thyroid gland shrinks and patients become euthyroid over a period of 6 weeks to 3 months. Ten to 20% of patients become hypothyroid within the first year of treatment, and thereafter hypothyroidism occurs at a rate of 3 to 5% per year. Ultimately 50 to 80% of patients become hypothyroid after radioactive iodine treatment. Serum TSH levels should be monitored and replacement with levothyroxine instituted if the TSH level rises.^[3] Hypothyroidism may also develop after surgery or antithyroid medication, mandating lifelong follow-up in all patients with Graves' disease.^[6]

Surgery: Subtotal thyroidectomy is the treatment of choice for patients with very large glands and obstructive symptoms or multinodular glands, or for patients desiring pregnancy within the next year.^[8] It is essential that the surgeon be experienced in thyroid surgery. Preoperatively, patients receive 6 weeks of treatment with antithyroid drugs so that they will be euthyroid at the time of surgery.^[9] Two weeks before surgery, oral saturated solution of potassium iodide is administered daily to decrease the vascularity of the gland. Permanent hypoparathyroidism and recurrent laryngeal nerve palsy occur in less than 2% of patients postoperatively. Ten percent of patients develop recurrent thyrotoxicosis, which should be treated with radioactive iodine.^[10]

Hypothyroidism: Hypothyroidism is a clinical syndrome caused by deficiency of thyroid hormones. In infants and children, hypothyroidism causes retardation of growth and development and may result in permanent

motor and mental retardation.^[4] Congenital causes of hypothyroidism include agenesis (complete absence of thyroid tissue), dysgenesis (ectopic or lingual thyroid gland), hypoplastic thyroid, thyroid dysmorphogenesis, and congenital pituitary diseases. Adult-onset hypothyroidism results in a slowing of metabolic processes and is reversible with treatment.^[7] Hypothyroidism is usually primary (thyroid failure), but it may be secondary (hypothalamic or pituitary deficiency) or due to resistance at the thyroid hormone receptor. In adults, autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of hypothyroidism.^[8] This may be isolated or part of the polyglandular failure syndrome type II (Schmidt's syndrome), which also includes insulin-dependent diabetes mellitus, pernicious anemia, vitiligo, gonadal failure, hypophysitis, celiac disease, myasthenia gravis, and primary biliary cirrhosis.^[9] Iatrogenic causes of hypothyroidism include ^{131}I therapy, thyroidectomy, and treatment with lithium or amiodarone. Iodine deficiency or excess can also cause hypothyroidism.^[10]

Treatment: Patients with hypothyroidism initially should be treated with synthetic levothyroxine. Although T₃ is the more bioactive thyroid hormone, peripheral tissues convert T₄ to T₃ to maintain physiologic levels of the latter.^[7] Thus administration of levothyroxine results in bioavailable T₃ and T₄. A recent study, however, suggested that brain T₄-to-T₃ conversion may be impaired in some patients and that a select group of patients should be treated with both levothyroxine and T₃ (liothyronine).^[8] Because T₃ treatment results in fluctuating blood levels, we recommend that patients be initially treated with levothyroxine, and, if they remain symptomatic despite a normal TSH, then low doses of T₃ given two or three times a day can be added to levothyroxine cautiously.^[9] Levothyroxine has a half-life of 8 days, so it needs to be given only once a day. The average replacement dose for adults is 100 to 150mg/day. In healthy adults, 100mg/day is an appropriate starting dose.^[4] In elderly patients or those with cardiac disease, levothyroxine should be increased gradually, starting at 25mg daily and increasing this dose by 25mg every 2 weeks.^[7] The therapeutic response to levothyroxine therapy should be monitored clinically and with serum TSH levels, which should be measured 6 weeks after a dose adjustment. TSH levels between 0.5 and 2.0mU/L are optimal. Patients with secondary hypothyroidism should be treated with levothyroxine until their free T₄ is in the mid-normal range. Appropriate treatment of these patients will result in suppressed serum TSH levels.^[8]

In patients with myxedema coma, 300 to 400mg of levothyroxine is administered intravenously as a loading dose followed by 50mg daily as well as hydrocortisone (100mg intravenously three times a day) and intravenous fluids.^[3] The underlying precipitating event should be corrected. Respiratory assistance and treatment of hypothermia with warming blankets may be required.

Although myxedema coma carries a high mortality despite appropriate treatment, many patients improve in 1 to 3 days.^[2]

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