

THYROID DISORDERS

Introduction

- The thyroid gland produces two related hormones, thyroxine (T₄) and triiodothyronine (T₃)
- **These hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult**
- Overproduction of thyroid hormones (*thyrotoxicosis*) or hormone deficiency (*hypothyroidism*) occur mainly due to autoimmune disorders or tumor.

Thyroid Hormone Synthesis

- Iodide uptake is a critical first step in thyroid hormone synthesis
- After iodide enters the thyroid, it is trapped and transported to thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide
- The reactive iodine atom is added to selected tyrosyl residues within Tg,
- Thyroid hormones are derived from Tg, a large iodinated glycoprotein.
- Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T₄ and T₃.

Thyroid hormone synthesis

- TSH regulates thyroid gland function through the TSH-R,
- Growth factors that influence thyroid hormone synthesis are insulin-like growth factor I (IGF-1), epidermal growth factor, transforming growth factor (TGF-), endothelins, and various cytokines

Thyroid Hormone secretion and Transport

- T4 is secreted from the thyroid gland in about twentyfold excess over T₃.
- Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin.
- When the effects of the various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T₃ are protein-bound

Table 341-2 Characteristics of Circulating T₄ and T₃

Hormone Property	T₄	T₃
Serum concentrations		
Total hormone	8 µg/dL	0.14 µg/dL
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	$21 \times 10^{-12}\text{M}$	$6 \times 10^{-12}\text{M}$
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 µg/d	32 µg/d
Intracellular hormone fraction	~20%	~70%
Relative metabolic potency	0.3	1
Receptor binding	10^{-10}M	10^{-11}M

Thyroid Hormone Action

- Circulating thyroid hormones enter cells **by passive diffusion** and via specific transporters such as the monocarboxylate 8 (**MCT8**) transporter.
- After entering cells, thyroid hormones act primarily through **nuclear receptors**.
- Thyroid hormones bind with high affinity to nuclear *thyroid hormone receptors* (TRs) α and β .
- **TR α** is particularly abundant in brain, kidneys, gonads, muscle, and heart, whereas **TR β** expression is relatively high in the pituitary and liver.
- The activated receptor can either stimulate gene transcription (e.g., myosin heavy chain) or inhibit transcription (e.g., TSH -subunit gene),

Thyroid Abnormality Evaluation

• **Laboratory Evaluation**

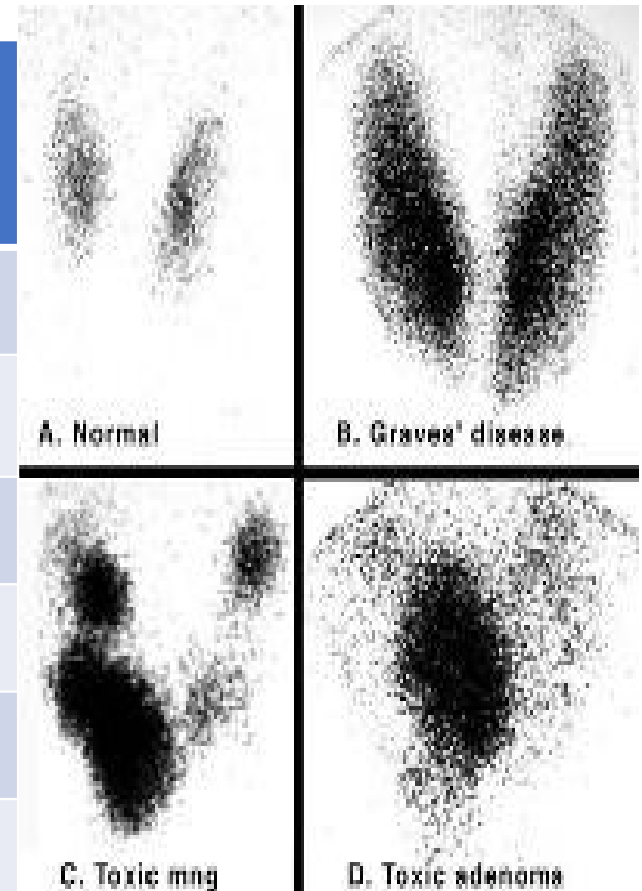
- First determine whether TSH is suppressed, normal, or elevated.
- With rare exceptions , a normal TSH level excludes a primary abnormality of thyroid function.
- Abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH).

• Tests to Determine the Etiology of Thyroid Dysfunction

- Autoimmune thyroid disease is detected most easily by measuring **circulating antibodies against TPO and Tg**.
- **TSI** are antibodies that stimulate the TSH-R in Graves' disease .Other common autoimmune antibodies, as well as anti- thyroid peroxidase (**anti-TPO**) and antithyroglobulin (**anti-TG**) antibodies are also detected.
- **Serum Tg** levels are increased in all types of thyrotoxicosis except **thyrotoxicosis factitia** .

Thyroid scan

Common Forms of thyrotoxicosis	Radioactive iodine uptake over neck
Diffuse toxic goiter (Graves disease)	Increased, homogenous
Toxic multinodular goiter (Plummer disease)	Increased, distorted structure
Thyrotoxic phase of sub acute thyroiditis	Decreased
Toxic adenoma	Increased, focal
Iodide-induced thyrotoxicosis	Variable
Thyrotoxicosis factitia	Decreased



• **Ultrasound**

- Detection of nodules and cysts
- Monitoring nodule size and for the aspiration of nodules or cystic lesions
- Evaluation of recurrent thyroid cancer, including possible spread to cervical lymph nodes.

Hypothyroidism

- Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone.
- It usually is a **primary** process in which the thyroid gland produces insufficient amounts of thyroid hormone. It can also be **secondary**—that is, lack of thyroid hormone secretion due to inadequate secretion of either thyrotropin (thyroid-stimulating hormone [TSH]) from the pituitary gland or thyrotropin-releasing hormone (TRH) from the hypothalamus (**tertiary** hypothyroidism)
- **Iodine deficiency remains the most common cause of hypothyroidism worldwide.**
- In areas of iodine sufficiency, **autoimmune disease** (Hashimoto's thyroiditis) and **iatrogenic** causes (treatment of hyperthyroidism) are most common.

Causes of Hypothyroidism

Primary

Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis

Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation

Drugs: iodine excess (including amiodarone), lithium, antithyroid drugs

Congenital hypothyroidism: absent or ectopic thyroid gland, TSH-R mutation

Iodine deficiency

Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis

Transient

Silent thyroiditis, including postpartum thyroiditis

Subacute thyroiditis

Withdrawal of thyroxine treatment in individuals with an intact thyroid

After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary

Hypopituitarism:

Isolated TSH deficiency or inactivity

Bexarotene treatment

Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Pathophysiology

- Because all metabolically active cells require thyroid hormone, deficiency of the hormone has a wide range of effects. Systemic effects are due to either derangements in metabolic processes or direct effects by myxedematous infiltration (**ie, accumulation of glucosaminoglycans in the tissues**).
- The myxedematous changes in the heart result in decreased contractility, cardiac enlargement, pericardial effusion, decreased pulse, and decreased cardiac output.
- In the GI tract, achlorhydria and decreased intestinal transit with gastric stasis can occur.
- Delayed puberty, anovulation, menstrual irregularities, and infertility are common.

Clinical manifestation of hypothyroidism

- Subclinical hypothyroidism, also referred to as mild hypothyroidism, is defined as normal serum free T4 levels with slightly high serum TSH concentration.
- Symptoms and signs of hypothyroidism are often subtle and neither sensitive nor specific. The diagnosis of hypothyroidism is based on clinical suspicion and confirmed by laboratory testing.

Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

Symptoms

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later oligomenorrhea or amenorrhea)
- Paresthesia
- Impaired hearing

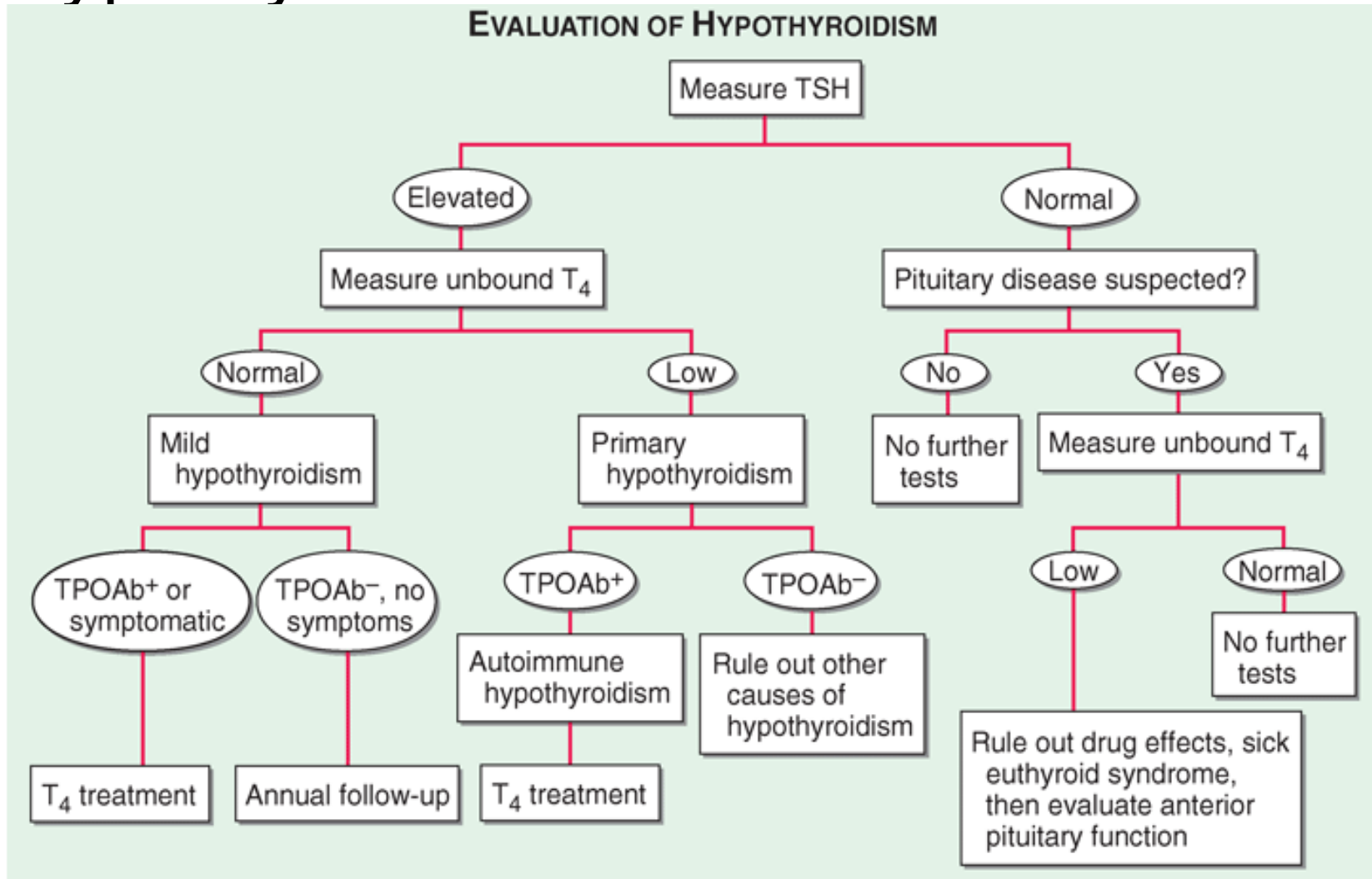
Signs

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands, and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

Facial appearance in hypothyroidism



Laboratory evaluation of Hypothyroidism



Treatment: Hypothyroidism

- The goals of pharmacotherapy are to reduce morbidity and to prevent complications.
- If there is no residual thyroid function, the daily replacement dose of levothyroxine is **usually 1.6 µg/kg body weight** (typically **100–150 µg**).
- In patients who develop hypothyroidism after the treatment of Graves' disease, there is often underlying autonomous function, necessitating lower replacement doses (**typically 75–125 µg/d**).
- Adult patients under 60 without evidence of heart disease may be started on **50–100 µg** levothyroxine (T₄) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH

Myxedema coma

- Myxedema coma is a complicated state of hypothyroidism having a high mortality rate, despite intensive treatment.
- Myxedema coma occurs rarely, appearing in 0.1% of all cases of hypothyroidism.
- **Clinical manifestations include reduced level of consciousness, seizures, as well as the other features of hypothyroidism .**

Hypothermia can reach 23°C (74°F).

Causes/precipitating factors

- History of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed.
- **Myxedema coma almost always occurs in the elderly.**
- Factors that impair respiration, such as drugs (especially sedatives, anesthetics, antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, cerebrovascular accidents, sepsis, exposure to cold .
- Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis;
- hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma.

Treatment of Myxedema coma

- **Levothyroxine** administered as a single IV **bolus of 500 µg**, as a loading dose.
- It is usually continued at a dose of **50–100 µg/d**.
- If suitable IV preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube.
- An alternative is to give **liothyronine (T₃)** intravenously or via nasogastric tube, in doses ranging from **10 to 25 µg every 8–12 h**.
- Another option is to combine levothyroxine (**200 µg**) and liothyronine (**25 µg**) as a single, initial IV bolus followed by daily treatment with levothyroxine (**50–100 µg/d**) and liothyronine (**10 µg every 8 h**).
- Supportive therapy should be provided to correct any associated metabolic disturbances.
- **External warming** is indicated only if the temperature is <30 °C.
- Parenteral **hydrocortisone** (50 mg every 6 h) should be administered
- Any precipitating factors should be treated

Thyrotoxicosis

- *Thyrotoxicosis* is defined as the state of thyroid hormone excess of any cause.
- It is the hypermetabolic condition associated with elevated levels of free thyroxine (FT₄) and/or free triiodothyronine (FT₃).
- *Hyperthyroidism* is the result of excessive thyroid function
- **The major etiologies of thyrotoxicosis are hyperthyroidism caused by Graves' disease, toxic MNG, and toxic adenomas**

Causes of Thyrotoxicosis

Primary hyperthyroidism

Graves' disease

Toxic multinodular goiter

Toxic adenoma

Functioning thyroid carcinoma metastases

Activating mutation of the TSH receptor

Activating mutation of G_s (McCune-Albright syndrome)

Struma ovarii

Drugs: iodine excess (Jod-Basedow phenomenon)

Thyrotoxicosis without hyperthyroidism

Subacute thyroiditis

Silent thyroiditis

Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma

Ingestion of excess thyroid hormone (thyrotoxicosis factitia)

Secondary hyperthyroidism

TSH-secreting pituitary adenoma

Thyroid hormone resistance syndrome

Chorionic gonadotropin-secreting tumors^a

Gestational thyrotoxicosis^a

Pathophysiology and pathogenesis

- The **hypermetabolic** effect of thyrotoxicosis affects every organ system
- Thyroid hormone is necessary for normal growth and development, and it regulates cellular metabolism.
- Excess thyroid hormone causes **an increase in the metabolic rate** that is associated with increased total body heat production and cardiovascular activity (increased heart contractility, heart rate, vasodilatation).

Pathogenesis (cont...)

- Thyroid hormone excess causes left ventricular thickening, which is associated with an increased risk of CHF. Thyrotoxicosis has **been associated with dilated cardiomyopathy**, right heart failure with pulmonary hypertension, and diastolic dysfunction
- An increase in the rate of bone resorption
- The pathogenesis of Graves opthalmopathy lies in the deposition of glycosaminoglycans (GAG) in the extra ocular muscles and adipose and connective tissue of the retro-orbit, leading to T-cell activation.
- Graves disease affects the skin by deposition of glycosaminoglycans in the dermis of the lower leg

Clinical Manifestations

-Younger patients tend to exhibit symptoms of more sympathetic activation, such as anxiety, hyperactivity, and tremor, while older patients have more cardiovascular symptoms, including dyspnea and atrial fibrillation with unexplained weight loss.

-The clinical manifestations of thyrotoxicosis do not always correlate with the extent of the biochemical abnormality.

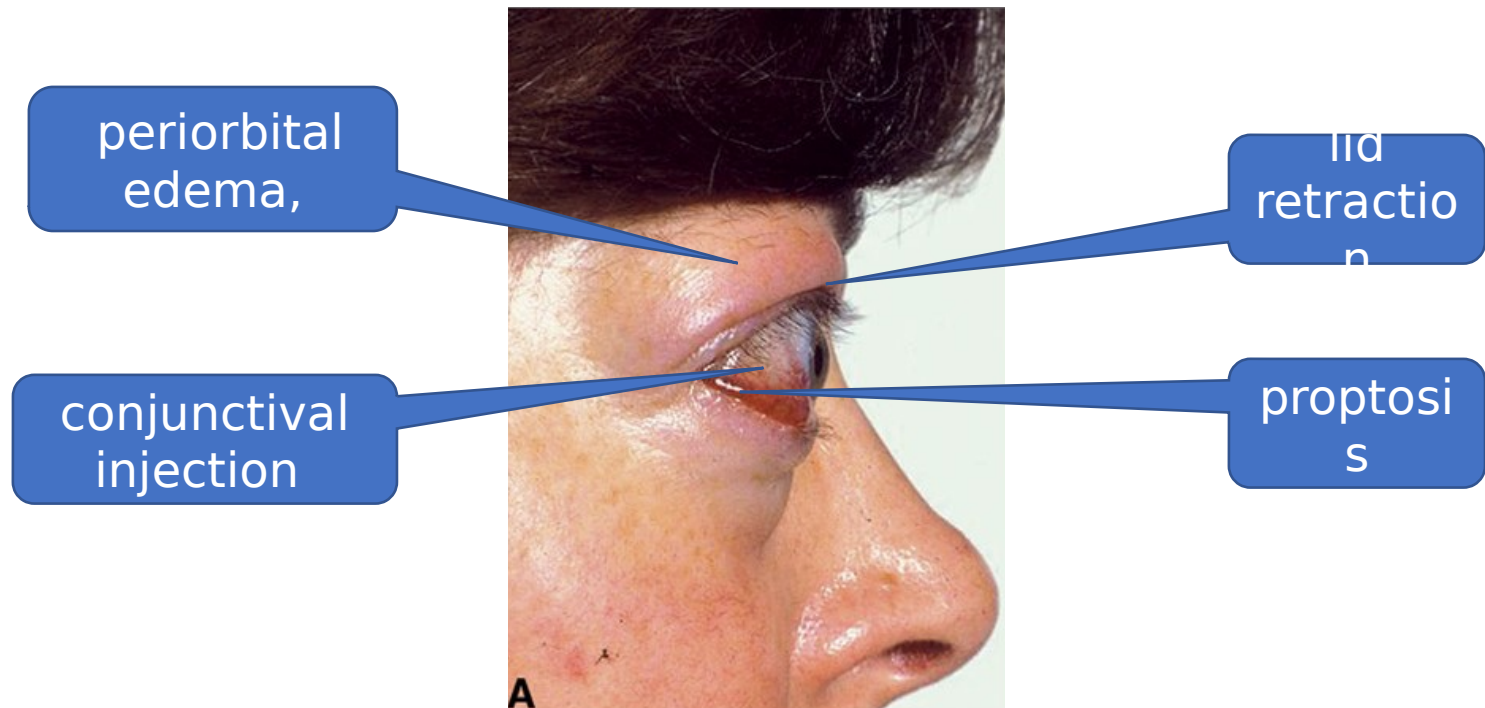
Symptoms

- Hyperactivity, irritability, dysphoria
- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight loss with increased appetite
- Diarrhea
- Polyuria
- Oligomenorrhea, loss of libido

Signs

- Tachycardia; atrial fibrillation in the elderly
- Tremor
- Goiter
- Warm, moist skin
- Muscle weakness, proximal myopathy
- Lid retraction or lag
- Gynecomastia

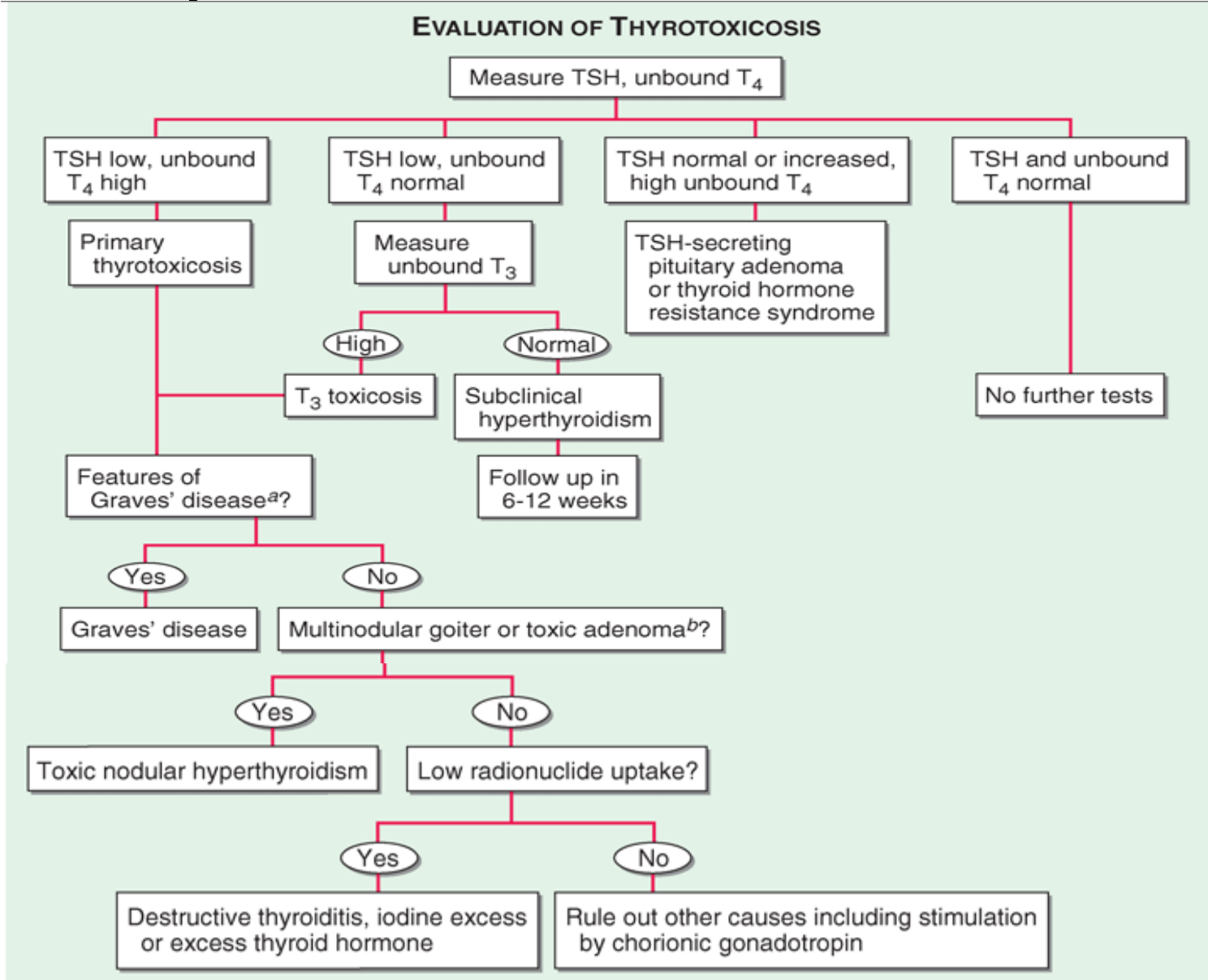
Patient with Graves disease





Thyroid
dermatopathy

Laboratory Evaluation



Treatment: thyrotoxicosis

The treatment of hyperthyroidism includes symptom relief, as well as therapy with antithyroid medications, therapy with radioactive iodine¹³¹ I, or thyroidectomy.

- **Symptom Relief**

- Many of the neurologic and cardiovascular symptoms of thyrotoxicosis are relieved by beta-blocker therapy

- **Reducing thyroid hormone synthesis** with antithyroid drugs

- *carbimazole or methimazole 10–20 mg every 8 or 12 h, but once-daily dosing is possible after euthyroidism is restored. Propylthiouracil is given at a dose of 100–200 mg every 6–8 h,*
- *Propranolol (20–40 mg every 6 h) or longer-acting beta blockers such as atenolol, may be helpful to control adrenergic symptoms*

- **Reducing the amount of thyroid tissue** with

- radioiodine (¹³¹I) treatment or
- thyroidectomy

Thyroid storm

- **Thyroid storm** is a rare and potentially fatal complication of hyperthyroidism.
- It occurs in patients with untreated or partially treated thyrotoxicosis.
- Thyroid storm is a rare disorder. Approximately 1-2% of patients with hyperthyroidism progress to thyroid storm.
- Thyroid storm must be recognized and treated on clinical grounds alone.
- Thyroid storm triggering events
 - Infection
 - Surgery
 - Cardiovascular events
 - Toxemia of pregnancy
 - Diabetic ketoacidosis, hyperosmolar coma, and insulin-induced hypoglycemia
 - Thyroidectomy
 - Discontinuation of antithyroid medication
 - Radioactive iodine
 - Vigorous palpation of the thyroid gland in hyperthyroid patients

Thyroid storm(cont...)

- Adult mortality rate from thyroid storm is approximately 10-20%, but it has been reported to be as high as 75% in hospitalized populations
- Patients typically appear markedly hypermetabolic with high fevers, tachycardia, nausea and vomiting, tremulousness, agitation, and psychosis.
- Late in the progression of disease, patients may become stuporous or comatose with hypotension.
- Thyroid function studies do not distinguish thyrotoxicosis from thyroid storm;
- laboratory abnormalities encountered in thyroid storm.
 - Hyperglycemia
 - Hypercalcemia
 - Hepatic function abnormalities
 - Low serum cortisol
 - Leukocytosis
 - Hypokalemia_ (in thyrotoxic periodic paralysis)

Treatment of thyroid storm

- Do not delay treatment once thyroid storm is suspected.
- Patients with severe thyrotoxicosis must be placed on a cardiac monitor. The patient should be intubated if profoundly altered
- Fevers are treated with cooling measures and antipyretics
- Aggressive hydration of up to 3-5 L/d of crystalloid compensates for potentially profound GI and insensible losses.
- Appropriate electrolyte replacement should be directed by laboratory values.
- Intravenous glucocorticoids are indicated if adrenal insufficiency is suspected.
- Antithyroid medications such as propylthiouracil (PTU) and methimazole (MMI)
- Beta-adrenergic blocking agents are the mainstays of symptomatic therapy