

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

HYPERTHYROIDISM

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Signs and Symptoms

- ▶ *Not all patients with hyperthyroidism have all signs and symptoms of hyperthyroidism.*
- ▶ *Many hyperthyroid patients have few signs and symptoms, especially those with mild hyperthyroidism and elderly patients.*
- ▶ *On the other hand, many signs and symptoms of hyperthyroidism are nonspecific and are seen in other disorders, so that, clinically suspected diagnosis of hyperthyroidism should be confirmed by thyroid function tests (TFTs).*

- ▶ ***Clinical manifestations of hyperthyroidism are largely independent of its cause, however, Graves' disease, the most common cause of hyperthyroidism at any age, causes unique manifestations that are NOT related to high serum thyroid hormone levels, including Graves' orbitopathy and infiltrative dermopathy (localized or pretibial myxedema).***

*SPECIFIC
ORGAN
SYSTEMS*

Skin, Hair, and Nails

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- ▶ *Skin is warm, moist, and rarely erythematous due to increased blood flow (palmar erythema).*
- ▶ *Skin is smooth because of decrease in keratin layer.*
- ▶ *Excessive sweating due to increased calorogenesis (thermogenesis); this is often associated with heat intolerance.*
- ▶ *Onycholysis (separation of distal part of nails from nail bed, Plummer's nails).*





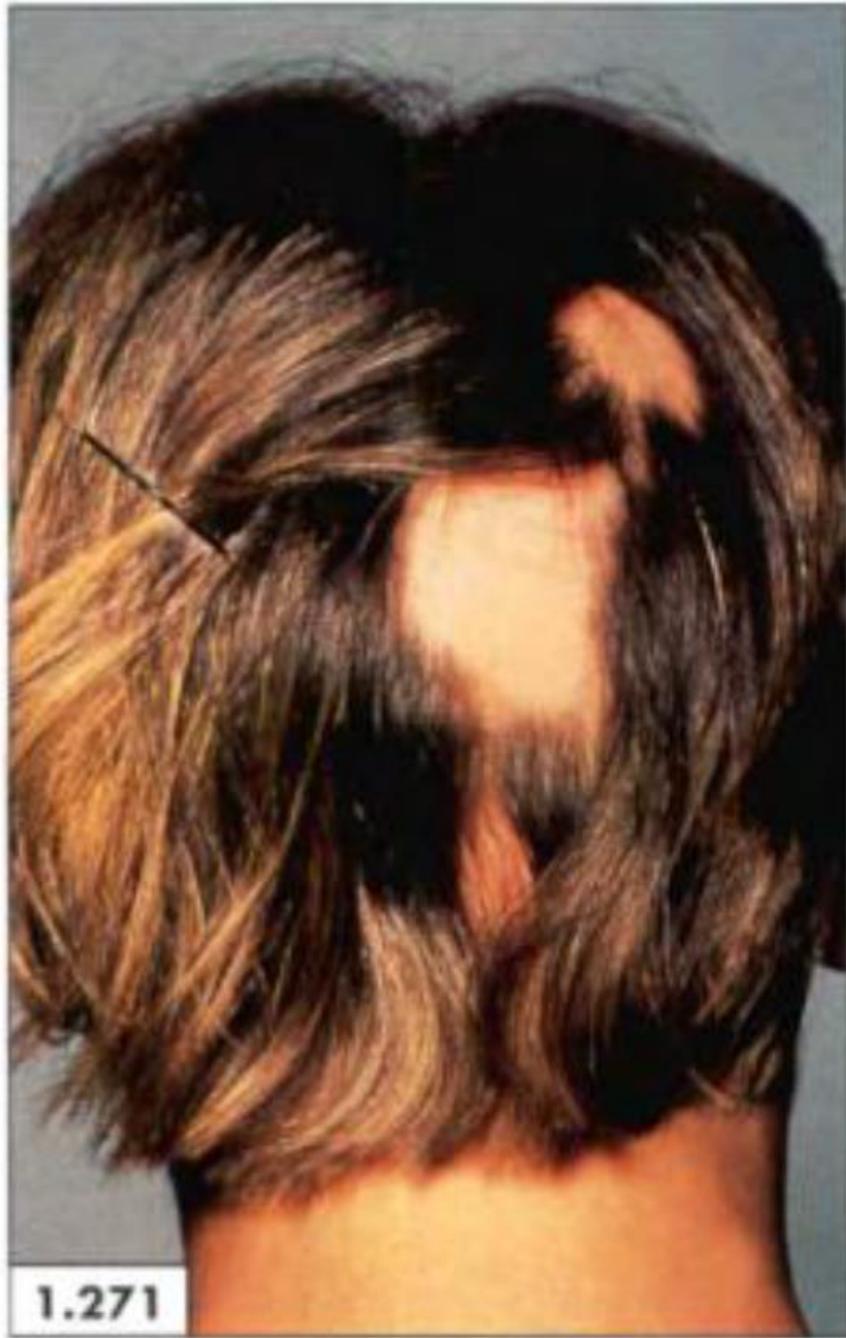


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Distal onycholysis

- ▶ Softening of nails.
- ▶ Hyperpigmentation, which can occur in severe cases; it appears to be mediated by accelerated cortisol metabolism, leading to increased ACTH secretion.
- ▶ Vitiligo and alopecia areata, as simultaneous autoimmune disorders with Graves' disease.
- ▶ Fine and friable hair
- ▶ Hair loss.





Alopecia areata

D12.
Alopecia
Areata
Sharply
demarcated
circular patch
of scalp
completely
devoid of hair.



- ▶ *Infiltrative dermopathy occurs only in patients with Graves' disease.*
- ▶ *The most common site is the skin overlying the shins (pretibial myxedema), where it presents as raised, hyperpigmented, orange-peel-textured papules.*





Fig. 18.2 Pretibial myxoedema



Eye Manifestations

- ▶ **Some retraction of upper or lower eyelids, evident as presence of a rim of sclera between either lid and limbus, may be seen in all forms of hyperthyroidism regardless of underlying cause and is responsible for typical eye stare of patient.**

- ▶ **Also common is either lid lag, a phenomenon in which upper lid lags behind globe when patient is asked to shift gaze slowly downward, or globe/global lag, which becomes evident when eye lags behind upper lid when patient looks up.**
- ▶ **These ocular manifestations appear to be result of increased adrenergic tone (hyperadrenergism).**



7 Normally, the upper lid is located 1–1.5 mm below the superior limbus, and the lower lid is located at the inferior limbus. This figure demonstrates upper lid retraction (Dalrymple sign) with temporal flare and scleral show in Graves' ophthalmopathy. (Courtesy of Dr. Richard Dallow.)

- ▶ **Only patients with Graves' disease have infiltrative orbitopathy that is characterized by inflammation of extraocular muscles and orbital fat and connective tissue, which results in proptosis (exophthalmos), extraocular muscle dysfunction (ophthalmoplegia and diplopia), and periorbital and conjunctival edema and conjunctivitis.**
- ▶ **Risk factors for developing Graves' orbitopathy include cigarette smoking, advancing age, and male sex.**



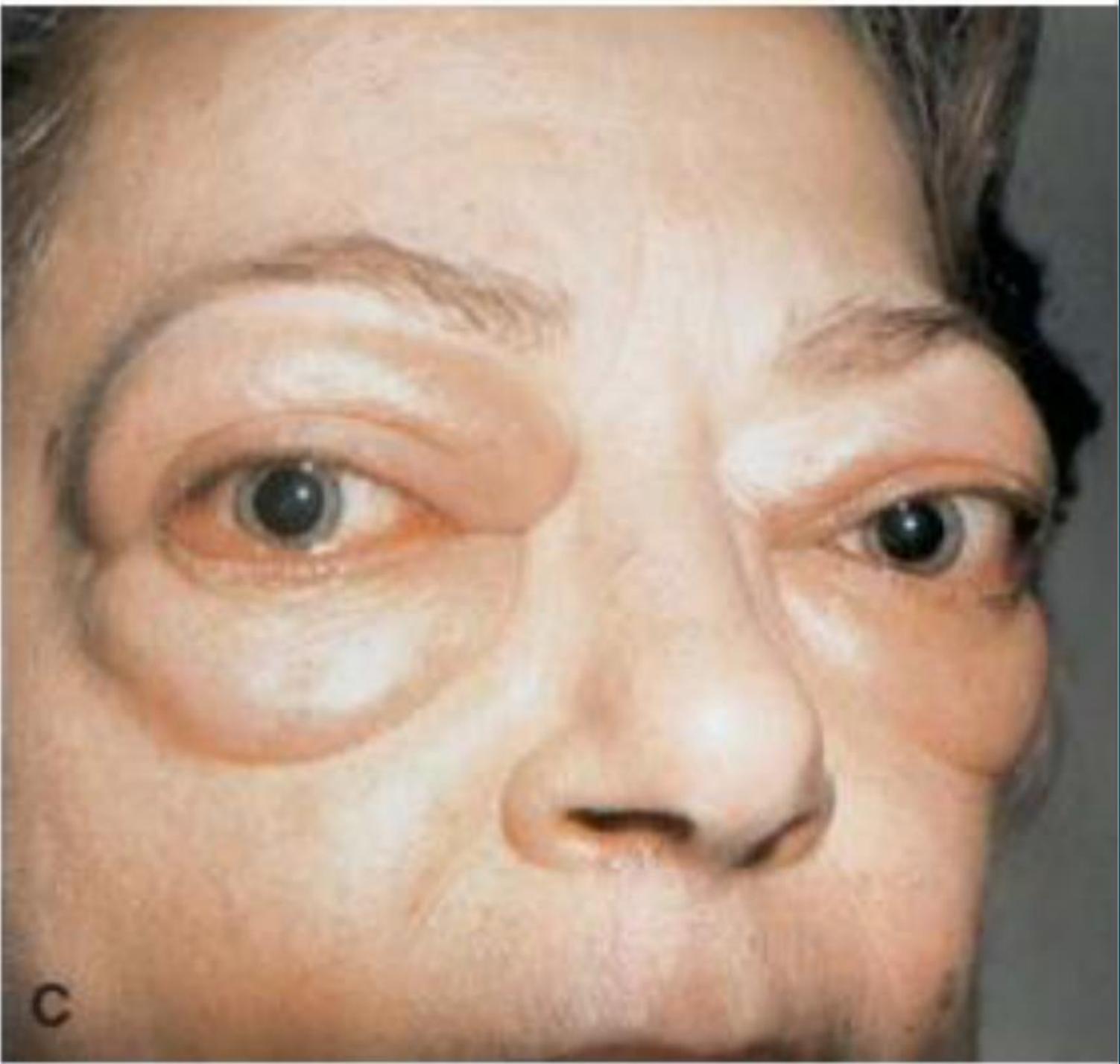


Fig. 19.3 A Patient with TAO. Note upper lid retraction, proptosis, chemosis and hypervascularisation





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- ▶ *Patients with orbitopathy may have gritty feeling or pain in their eyes, and they may have diplopia due to extraocular muscle dysfunction.*
- ▶ *Corneal ulceration can occur as a result of proptosis and lid retraction (lagophthalmos), and severe proptosis can cause optic neuropathy and even blindness.*



Lagophthalmos

Fig. 19.11 TAO:
Difficulty in
closing the
eyelids

Cardiovascular System

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- ▶ **Patients with hyperthyroidism have an increase in cardiac output, due to increased peripheral oxygen demands (secondary to hypermetabolism), increased heart rate, and increased cardiac contractility (increased stroke volume).**
- ▶ **Heart rate is increased (sinus tachycardia is the most common rhythm disorder).**
- ▶ **Tachycardia, arrhythmias, and forceful cardiac contractions result in palpitation.**

- ▶ Pulse pressure is increased due to decreased DBP (secondary to decrease in peripheral vascular resistance) and increased SBP (secondary to increased cardiac output).
- ▶ Left ventricular ejection fraction does not increase appropriately during exercise (exercise intolerance), suggesting presence of true thyrotoxic cardiomyopathy.
- ▶ Congestive heart failure (CHF) can occur in patients with severe hyperthyroidism, and it worsens in patients with preexisting CHF.

- ▶ **Atrial fibrillation (AF) occurs in 10-20% of patients with hyperthyroidism, and it is more common in older patients.**
- ▶ **Even subclinical hyperthyroidism is associated with an increased rate of atrial ectopy (PACs) and a three-fold increased risk of AF.**
- ▶ **In 60% of patients with AF, it converts spontaneously to sinus rhythm when hyperthyroidism is treated (most within 4 months).**
- ▶ **Anticoagulation should be considered in hyperthyroid patients with AF.**

Skeletal System

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- ▶ **Thyroid hormones directly stimulate bone resorption, resulting in decreased BMD of cortical bone and reduced volume of trabecular bone (osteopenia and osteoporosis).**
- ▶ **Loss in cortical bone density is greater than that of trabecular bone.**
- ▶ **Serum alkaline phosphatase and osteocalcin levels are high, indicative of increased bone turnover.**

- ▶ *Increase in bone resorption may lead to an increase in serum calcium levels, thereby inhibiting PTH secretion and subsequent conversion of calcidiol (25-hydroxyvitamin D) to calcitriol (1,25-dihydroxyvitamin D).*
- ▶ *In addition, metabolic clearance rate of calcitriol is increased.*
- ▶ *Renal calcium reabsorption may be impaired leading to increased urinary calcium excretion.*
- ▶ *Net effect is osteoporosis and increased osteoporotic fracture risk in patients with chronic untreated hyperthyroidism.*

- ▶ **Graves' disease may also be associated with thyroid acropachy, with clubbing and periosteal new bone formation in metacarpal bones or phalanges.**
- ▶ **Patients with thyroid acropachy commonly present with asymptomatic clubbing, severe ophthalmopathy, and dermopathy.**
- ▶ **A high percentage of patients with thyroid acropachy are cigarette smokers.**



Fig. 18.3 Thyroid-associated acropachy



Serum Lipids

- ▶ *Patients with hyperthyroidism tend to have low total and HDL cholesterol.*
- ▶ *Serum triglyceride levels are usually slightly decreased.*
- ▶ *These values normalize after treatment of hyperthyroidism.*

Protein Metabolism

- ▶ ***Despite an increased food intake, a state of chronic caloric and nutritional inadequacy often ensues, depending on the degree of increased metabolism.***
- ▶ ***Both synthesis and degradation rates of proteins are increased, the latter to a greater extent than the former, with the result that in severe hyperthyroidism there is a net decrease in tissue protein as evidenced by weight loss, muscle wasting, proximal muscle weakness, and even mild hypoalbuminemia.***

Hyperglycemia

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- ❑ *Hyperthyroidism is associated with both increased insulin secretion, and antagonism to peripheral action of insulin.*
- ▶ *Antagonism to peripheral action of insulin usually predominates, and may cause **glucose intolerance and hyperglycemia** in untreated hyperthyroid patients.*
- ▶ *Preexisting diabetes may be aggravated.*

Nervous System

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- ▶ *Alterations in function of nervous system are manifested by nervousness, emotional lability, and hyperkinesia.*
- ▶ *Fatigue may be due both to muscle weakness and to insomnia that is commonly present.*
- ▶ *Manic depressive or paranoia may be seen.*

- ▶ *Hyperkinesia* of is characteristic and may manifest to such a point that patient is almost levitating.
- ▶ During interview, patient shifts positions frequently and movements are quick, exaggerated, and purposeless.
- ▶ There may be a fine tremor of hands, tongue, or lightly closed eyelids.

Muscular System

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- ▶ **Muscle weakness and fatigability are common and generalized muscle wasting is associated with weight loss.**
- ▶ **Muscle weakness is most prominent in proximal muscles of limbs, causing difficulty in climbing stairs or fatigue from minimal exertion (exercise intolerance).**

- ▶ ***Proximal muscle wasting may be inappropriate to overall weight loss (often referred to as *thyrotoxic myopathy*).***
- ▶ ***Muscular strength returns to normal when a *normal metabolic state (euthyroidism)* is restored, but muscle mass takes longer to recover.***

Respiratory System

- ▶ Resting dyspnea and dyspnea on exertion (DOE) may occur.
- ▶ Respiratory muscle weakness is an important cause of dyspnea, and reduced exercise capacity (exercise intolerance) is largely due to respiratory muscle weakness.

- ▶ *There may be tracheal obstruction from a large goiter.*
- ▶ *Hyperthyroidism may exacerbate underlying asthma.*
- ▶ *Pulmonary arterial SBP may be increased (pulmonary HTN).*

Gastrointestinal System

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- ▶ **Weight loss is due primarily to hypermetabolism and secondarily to hyperdefecation and malabsorption (due to gut hypermotility).**
- ▶ **Rare patients have steatorrhea.**
- ▶ **Celiac disease (an autoimmune disease) is also more prevalent in patients with Graves' disease.**

- ▶ *Most patients have hyperphagia, but occasional patients with mild hyperthyroidism may have sufficient appetite stimulation that results in weight gain (more commonly in younger patients).*
- ▶ *Anorexia may be prominent in older apathetic hyperthyroid patients.*

- ▶ *Dysphagia due to large goiter may occur.*
- ▶ *Abnormalities in liver function tests, particularly high alkaline phosphatase and, rarely, cholestasis may occur.*
- ▶ *Serum ALT may be elevated.*

Hematologic System

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- ▶ RBC mass is increased, but plasma volume is increased more, that may result in normochromic, normocytic anemia.
- ▶ Serum ferritin levels may be high.
- ▶ Graves' disease may be associated with autoimmune hematologic disorders such as immune thrombocytopenia (ITP) and pernicious anemia, and some patients have antineutrophil antibodies.

- ▶ **About 10% of patients with Graves' disease have neutropenia.**
- ▶ **Hyperthyroidism may also be prothrombotic state, and may be associated with a rise in prothrombotic factors, including factors VIII, IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1 (PAI-1).**

Genitourinary System

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- ▶ *Urinary frequency and nocturia are relatively common in hyperthyroidism, possible causes include primary polydipsia and hypercalciuria.*
- ▶ *Enuresis is common in children.*

- ▶ *Amenorrhea can occur in women with severe hyperthyroidism.*
- ▶ *In women, high SHBG (serum sex hormone-binding globulin) result in high total estradiol and low-normal free estradiol, high serum LH, reduced mid-cycle LH surge, oligomenorrhea, and anovulatory infertility.*

- ▶ *In men, high SHBG results in high total testosterone, but free testosterone is normal or low.*
- ▶ *Extragonadal conversion of testosterone to estradiol is increased, so that serum high estradiol may cause gynecomastia, reduced libido, and erectile dysfunction.*
- ▶ *Spermatogenesis is often decreased or abnormal, (more spermatozoa are abnormal or nonmotile).*

Neuropsychiatric System

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- ▶ **Patients with thyrotoxicosis may experience behavioral and personality changes, such as psychosis, agitation, and depression.**
- ▶ **Manifestations that are more common in less severe hyperthyroidism include anxiety, restlessness, irritability, and emotional lability.**

- ▶ Insomnia is relatively common.
- ▶ Symptoms often worsen in patients with preexisting psychiatric disorders.
- ▶ Behavioral manifestations may include impaired concentration, confusion, poor orientation and impaired immediate memory.

GERIATRIC HYPERTHYROIDISM

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- ▶ *Hyperthyroidism in older patients may be apathetic (masked or apathetic hyperthyroidism), rather than having hyperactivity, tremor, and other symptoms of sympathetic overactivity.*
- ▶ *Older patients may have higher prevalence of CHF and arrhythmia and weight loss without increased appetite.*

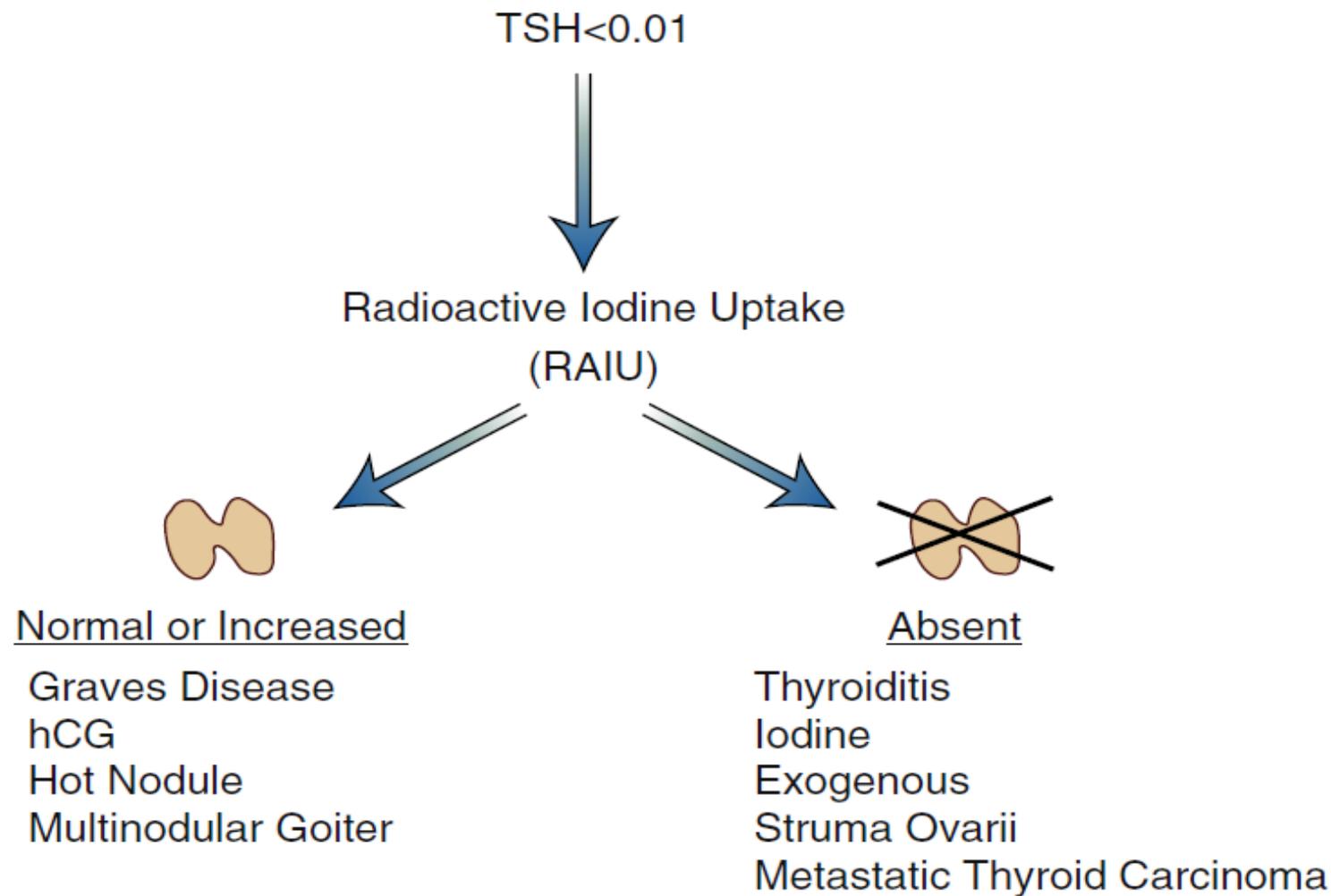
- ▶ *Older patients may also have higher rate of AF and ophthalmopathy.*
- ▶ *Toxic multinodular goiter is more common in older patients, although the majority of hyperthyroid patients at any age have Graves' disease.*

- ▶ *Older patients often have persistent constipation.*
- ▶ *Anorexia may be prominent in older apathetic hyperthyroid patients.*

DIAGNOSIS

- ▶ *Diagnosis of hyperthyroidism is based upon TFTs.*
- ▶ *In patients in whom there is clinical suspicion of hyperthyroidism, the best screening test is measurement of serum TSH.*

- ▶ **Measurement of TSH alone is NOT sufficient for determining severity of hyperthyroidism (subclinical vs overt hyperthyroidism) as well as decision making about treatment.**
- ▶ **Accordingly, it is better to measure at least serum TSH and free T4 simultaneously.**



• **Fig. 12.1** Determination of the cause of hyperthyroidism based on the ^{123}I uptake in the gland. In the setting of a suppressed thyroid-stimulating hormone (TSH) a normal or increased uptake is indicative of something else driving uptake rather than endogenous TSH. In the absence of uptake the gland has either been damaged or an external factor such as exogenous hormone or iodine is playing a role. Rarely, ectopic thyroid hormone production may occur. *hCG*, human chorionic gonadotropin.

DIFFERENTIAL DIAGNOSIS

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- ▶ **Once diagnosis of hyperthyroidism has been established, cause of hyperthyroidism should be determined.**
- ▶ **Diagnosis may be obvious at presentation; for example, a patient with ophthalmopathy, diffuse goiter, and hyperthyroidism has Graves' disease.**

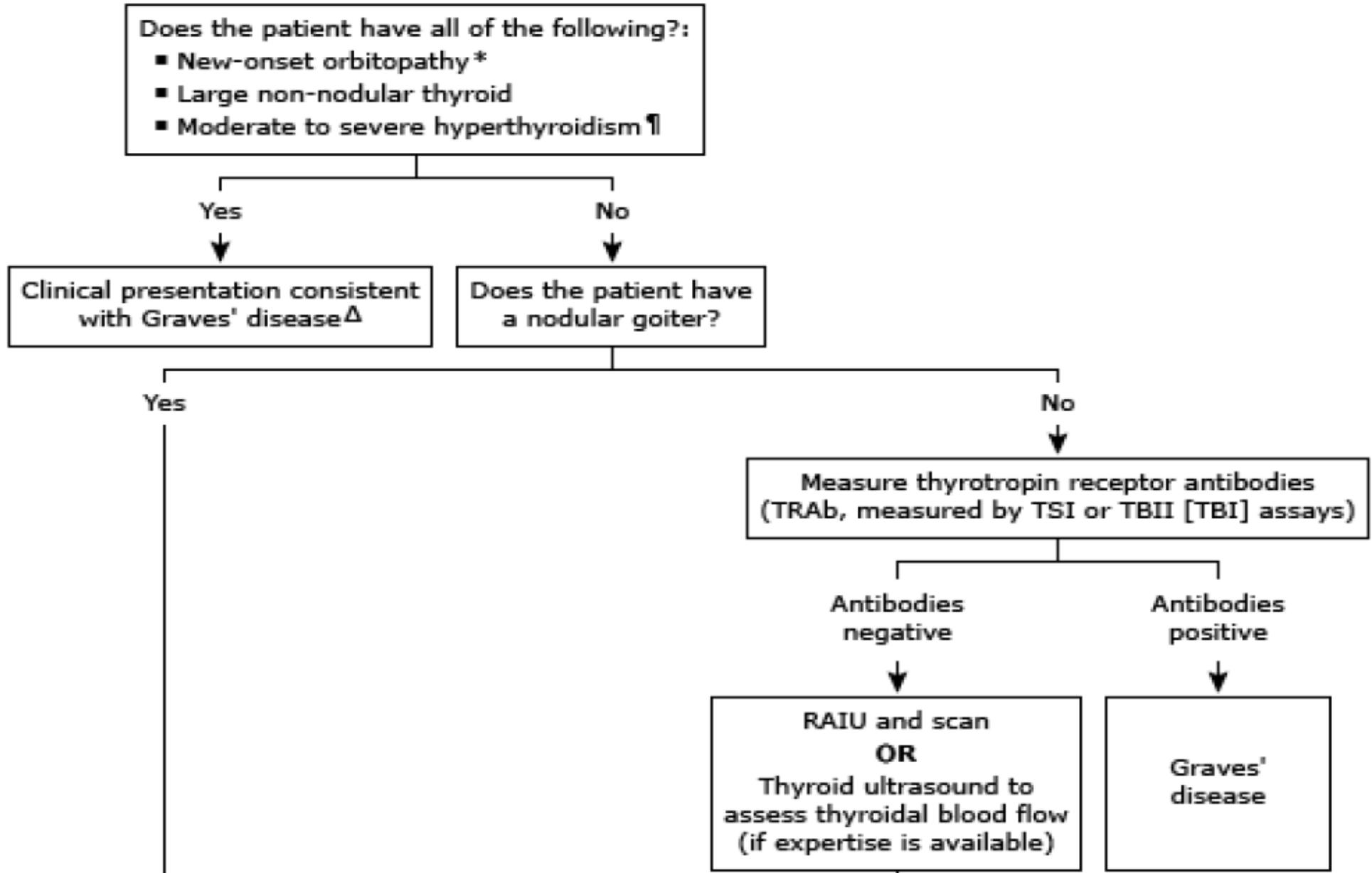
▶ *If diagnosis is not apparent based on clinical presentation, other diagnostic testing is indicated and can include the following, depending on available expertise and resources:*

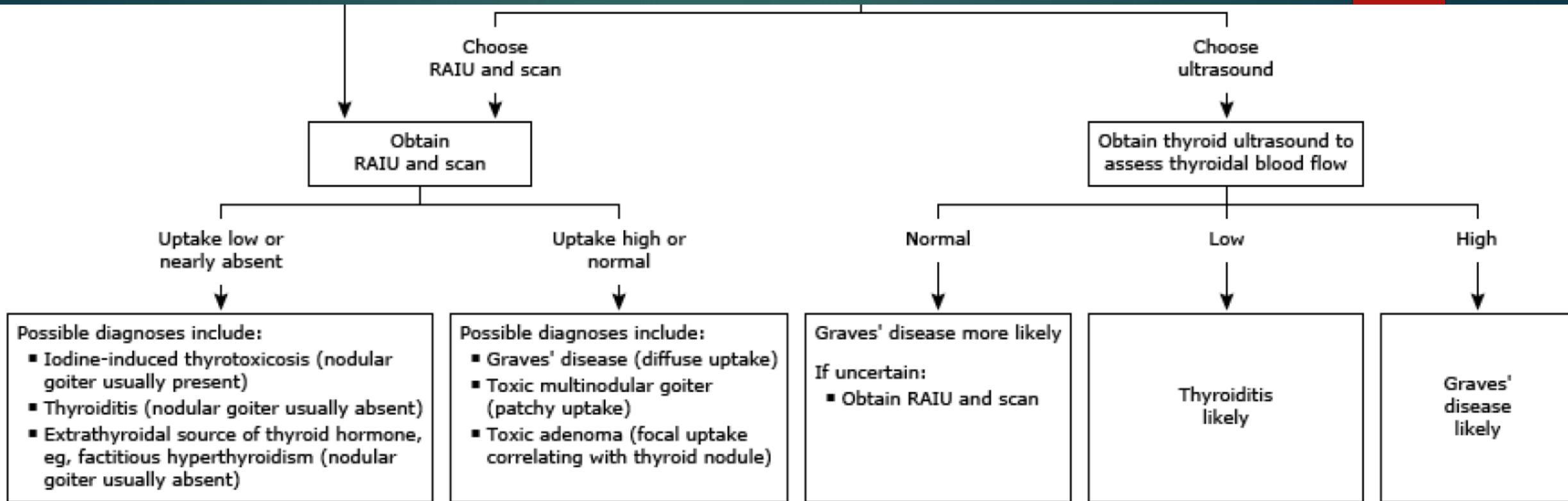
1) Measurement of TSH receptor antibodies (TRAb)

2) Determination of 24-h thyroid radioactive iodine uptake (RAIU)

3) Measurement of thyroidal blood flow on ultrasonography (based on 2018 European Thyroid Association guidelines).

Determining the etiology of overt hyperthyroidism in nonpregnant, non-breastfeeding adults





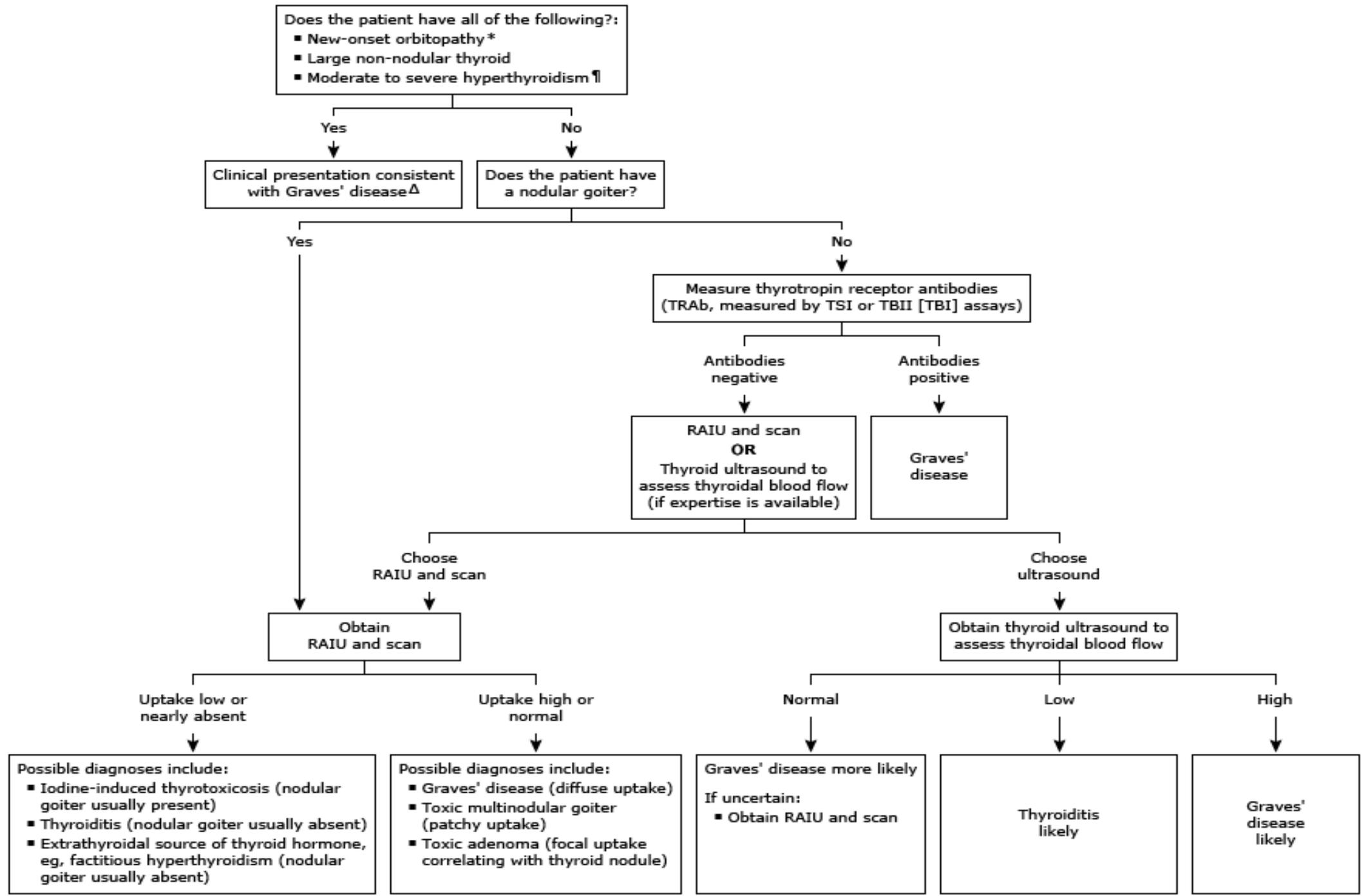
Overt hyperthyroidism in nonpregnant, non-breastfeeding adults is defined by a low serum TSH with high free T4 and/or T3 (free or total T3) concentrations.

TRAb: thyrotropin receptor antibodies; TSI: thyroid-stimulating immunoglobulins; TBI/TBII: thyrotropin receptor-binding inhibitory immunoglobulin; RAIU: radioactive iodine uptake; TSH: thyrotropin; T4: thyroxine; T3: triiodothyronine.

* The presence of orbitopathy (ophthalmopathy) alone may be sufficient to diagnose Graves' disease.

∧ There is no formal definition of moderate to severe hyperthyroidism. A total T3 >300 ng/dL and/or free T4 >3 ng/dL suggests moderate to severe disease.

∩ We obtain a baseline TSI after diagnosis of Graves' disease to guide therapy with thionamides.



- ▶ *For patients without obvious clinical manifestations of Graves' disease, measurement of serum TRAb, determination of RAIU, or ultrasonographic assessment of thyroidal blood flow are acceptable options to distinguish Graves' disease from other causes of hyperthyroidism (algorithm 1).*
- ▶ *In this setting, TRAb is typically measured first.*

- ▶ If TRAb is positive, it confirms the diagnosis of Graves' disease.
- ▶ If TRAb is negative, it does NOT distinguish among etiologies of hyperthyroidism.
- ▶ In this setting, the next step is to measure RAIU.
- ▶ An alternative is to assess thyroidal blood flow on ultrasound in those centers where expertise is available.

RAIU

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► From pathogenetic viewpoint, thyroid hormone excess results from two different mechanisms that can be distinguished by findings on 24-hour RAIU:

1) increased thyroid hormone synthesis and secretion from cervical thyroid gland (so-called **HYPERTHYROIDISM**), and

2) excess thyroid hormones from sources other than cervical thyroid gland (so-called **THYROTOXICOSIS**).

- ▶ **Because of hyperfunctioning cervical thyroid gland, thyroid RAIU increases in hyperthyroid states (usually $>25/30\%$, NL: 5-25/30%), examples include Graves' disease, toxic thyroid adenoma, toxic multinodular goiter, hCG-induced hyperthyroidism, and pituitary TSH-secreting tumors.**
- ▶ **In contrast, in thyrotoxic states, cervical gland function is suppressed and thyroid RAIU is low (usually $<1\%$).**

I. Excessive TSH-Receptor Stimulation

Graves disease (TRAb)
Pregnancy-associated transient hyperthyroidism (hCG)
Trophoblastic disease (hCG)
Familial gestational hyperthyroidism (mutant TSH receptor)
TSH-producing pituitary adenoma

II. Autonomous Thyroid Hormone Secretion

Multinodular toxic goiter (somatic mutations)
Solitary toxic thyroid adenoma (somatic mutation)
Congenital activating TSH-receptor mutation (genomic mutation)

III. Destruction of Follicles With Release of Hormone

Subacute de Quervain thyroiditis (virus infection)
Painless thyroiditis/postpartum thyroiditis (hashitoxicosis—autoimmune)
Acute thyroiditis (bacterial infection)
Drug-induced thyroiditis (amiodarone, interferon- γ)

IV. Extrathyroidal Sources of Thyroid Hormone

Iatrogenic overreplacement with thyroid hormone
Excessive self-administered thyroid medication
Food and supplements containing excessive thyroid hormone
Functional thyroid cancer metastases
Struma ovarii

hCG, Human chorionic gonadotropin; *TRAb*, thyrotropin receptor antibodies; *TSH*, thyroid-stimulating hormone (thyrotropin).

- ▶ **For hyperthyroid patients with physical examination suggesting nodular thyroid disease, RAIU is the initial test to determine the etiology of hyperthyroidism (thyroid gland contains several large hot and cold nodules).**

- ▶ **Pregnancy and breastfeeding are absolute contraindications to use radioiodine.**
- ▶ **In unusual instance where RAIU measurement is felt to be essential for definitive diagnosis in a lactating women, breast milk can be pumped and discarded for 5 days after ingestion of iodine-123 (^{123}I), then breastfeeding may be resumed; breastfeeding should NOT be resumed if iodine-131 (^{131}I) isotope is used for determining RAIU.**

▶ **Hyperthyroidism with a low (nearly absent, <1%) RAIU indicates:**

1) inflammation and destruction of thyroid tissue with release of preformed hormone into the blood, or

2) an extrathyroidal source of thyroid hormone, such as factitious/iatrogenic thyrotoxicosis and struma ovarii, where hyperfunctioning thyroid tissue is in pelvis rather than neck, in which, patient has low RAIU, low serum TSH, and no goiter.

Other Tests

- ▶ *Other measurements that help differentiate Graves' hyperthyroidism from thyrotoxicosis when RAIU is contraindicated include serum total T3/T4 ratio >20 (in standard units ng/mcg) and serum free T3/free T4 ratio >0.3 (SI units).*

***Thank you for your attention
and have a nice day***

