
IN THE NAME OF GOD
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Diagnosis of Hyperthyroidism

INTRODUCTION

A: Thyrotoxicosis is a condition having:

1- multiple etiologies

2- manifestations

3- and potential therapies

B: The term *"thyrotoxicosis"* refers to a clinical state that results from inappropriately high thyroid hormone action in tissues

C: The term *"hyperthyroidism,"* is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone by the thyroid.

D: Appropriate treatment of thyrotoxicosis requires an accurate diagnosis.

Causes of thyrotoxicosis

In general, thyrotoxicosis can occur if:

1- the thyroid is excessively stimulated by trophic factors;

2- constitutive activation of thyroid hormone synthesis and secretion occurs, leading to autonomous release of excess thyroid hormone;

3- thyroid stores of preformed hormone are passively released in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult; or

4- there is exposure to extrathyroidal sources of thyroid hormone, which may be either endogenous:

- struma ovarii,

- metastatic differentiated thyroid cancer

- or exogenous (factitious thyrotoxicosis).

Causes of Thyrotoxicosis

Thyrotoxicosis associated with a normal or elevated RAI uptake over the neck

- GD
- TA or TMNG
- Trophoblastic disease
- TSH-producing pituitary adenomas
- Resistance to thyroid hormone (T3 receptor β mutation, THRB)

Thyrotoxicosis associated with a near-absent RAI uptake over the neck

- Painless (silent) thyroiditis
- Amiodarone-induced thyroiditis
- Subacute (granulomatous, de Quervain's) thyroiditis
- Palpation thyroiditis
- Iatrogenic thyrotoxicosis
- Factitious ingestion of thyroid hormone
- Struma ovarii
- Acute thyroiditis
- Extensive metastases from follicular thyroid cancer

CAUSESOF THYROTOXICOSIS

Thyrotoxicosis Associated with an Elevated Thyroid RAIU (Hyperthyroidism)	
Type	**Etiology**
Circulating Thyroid Stimulators	
Graves'disease	Circulating TSH receptor antibody
Inappropriate TSH hypersecretion	TSH secreting pituitary tumor (t a-subunit) Pituitary resistance to thyroid hormone
Trophoblastic tumor Choriocarcinoma Hyperemesis gravida rum	Circulating HCG
Familial gestational hyperthyroidism	Mutant TSHR hypersensitive to HCG
Autonomous Thyroid Function	
Solitary hyperfunctioning adenoma Multinodular goiter	Autonomous function. Some due to constitutive activation of TSH receptor
Non-autoimmune autosomal dominant hyperthyroidism	Constitutive activation of TSH receptor

CAUSESOF THYROTOXICOSIS

Thyrotoxicosis Associated with a Low Thyroid RAIU	
Type	**Etiology**
Inflammation	
Postpartum and sporadic silent thyroiditis Silent thyroiditis can be associated with lithium, IFN-α and amiodarone (Type 2) Painful subacute thyroiditis (deQuervain's, granulomatous) Rarely acute (infectious) thyroiditis (bacterial, fungal, etc.) High-dose X-ray therapy	Release of stored hormone
Miscellaneous	
Surgical manipulation	Release of stored hormone
Infarction of thyroid adenoma	Release of stored hormone
Excess exogenous thyroid hormone	Exogenous thyroid hormone
Metastatic thyroid cancer	Foci of functional malignant thyroid tissue
Iodine-induced hyperthyroidism	Iodine excess plus goiter
Struma ovarii	Ovarian teratoma

Unusual Causes of Thyrotoxicosis

Disorder	Diagnosis	Primary management
TSH-producing adenoma	Pituitary MRI, α-subunit to TSH ratio	Surgical removal
Struma ovarii	RAI uptake over pelvis	Surgical removal
Choriocarcinoma	hCG elevation in the absence of pregnancy	Surgical removal
Thyrotoxicosis factitia (surreptitious LT_4 or LT_3)	Absence of goiter; suppressed thyroglobulin	Psychosocial evaluation
Functional thyroid cancer metastases	Whole-body RAI scanning	RAI ablation, embolization and/or surgical removal

Causes of Drug-Associated Thyrotoxicosis

Drug	Mechanism(s)	Timing of onset following initiation of the drug	Therapy
Amiodarone	Iodine induced (type 1)	Months to years	Supportive care ATDs; perchlorate Surgery
	Thyroiditis (type 2)	Often >1 year	Supportive care Corticosteroids Surgery
Lithium	Painless thyroiditis GD	Often >1 year	Supportive care ATDs and/or RAI (GD only)
Interferon α	Painless thyroiditis; GD	Months	Supportive care ATDs and/or RAI (GD only)
Interleukin-2	Painless thyroiditis GD	Months	Supportive care ATDs and/or RAI (GD only)
Iodinated contrast	Underlying thyroid autonomy	Weeks to months	ATDs and/or RAI (GD only) Antithyroid drugs
Tyrosine kinase inhibitors	Destruction	3 –12 months	Supportive care
Radioactive iodine, early	Destruction	1 – 4 weeks	Observation; if severe, administer corticosteroids
Radioactive iodine for TMNG, late	GD	3–6 months	Antithyroid drugs Repeat RAI Surgery

Clinical consequences of thyrotoxicosis

Hyperthyroidism is generally considered overt or subclinical, depending on the biochemical severity of the hyperthyroidism

Only moderate correlation exists between the degree of thyroid hormone elevation and clinical signs and symptoms.

Clinical consequences of thyrotoxicosis

Thyroid hormone influences almost every tissue and organ system.

1- It increases tissue thermogenesis and basal metabolic rate

2- Reduces serum cholesterol levels and systemic vascular resistance.

3- It causes:

- ***weight loss,***
- ***osteoporosis,***
- ***atrial fibrillation,***
- ***embolic events,***
- ***muscle weakness,***
- ***tremor,***
- ***neuropsychiatric symptoms,***
- ***rarely cardiovascular collapse***

COMMON CLINICAL MANIFESTATIONS OF THYROTOXICOSIS

Symptoms

- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity
- Palpitations
- Appetite change (usually increase)
- Weight change (usually weight loss)
- Menstrual disturbances

Signs

- Hyperactivity
- Tachycardia or atrial arrhythmia
- Systolic hypertension
- Warm, moist, smooth skin
- Stare and eyelid retraction
- Tremor
- Hyperreflexia
- Muscle weakness

SOME CLINICAL MANIFESTATIONS OF SPECIFIC CAUSES OF THYROTOXICOSIS

Clinical finding	Cause
Diffuse goiter	Graves' disease, silent thyroiditis
Uninodular goiter	Thyroid autonomy
Multinodular goiter	Thyroid autonomy
Nonpalpable thyroid gland	Exogenous thyroid hormone
Thyroid pain and tenderness	Subacute thyroiditis
Ophthalmopathy	Graves‘ disease
Localized dermopathy	Graves‘ disease
Thyroid acropachy	Graves' disease

Biochemical evaluation

Clinical Utility of Thyroid-Related Laboratory Tests

NAME OF TEST	ABBREVIATION	CLINICAL UTILITY
Tests for Evaluation of Thyroid Status		
Thyrotropin (by asensitive IA)	sTSH	Best general test;
(by conventional RIA)	TSH	should be phased out
Free thyroxine (by appropriate method)	FT_4	Second-best general test
Free (3,5,3′) triiodothyronine	FT_3	Adjunct test, diagnosis of T_3 toxicosis, rare forms of hyperthyroidism
Total (3, 5, 3′ -) triiodothyronine	T_3	Used in lieu of FT_3
Total thyroxine	T_4	Inadequate as general test
Thyroglobulin	Tg	Valuable in follow-up of thyroid cancer
TSH response to TRH	TRH	Largely superseded by sTSH
Reverse (3,3′5′ -) triiodothyronine	rT_3	Not used routinely
Free T_4 index:	FT_4I/FTI	
$T_4 \times T_3$-BR		Should be replaced by FT_4
$T_4 \times T_4$-BR		Need further evaluation
T_4/TBG ratio	T_4/TBG	Should be replaced by FT_4
Free T_3 index ($T_3 \times$ THBR)	FT_3I	Obsolete

Thyroid-Stimulating Hormone (TSH)

tests that assess the state of the hypothalamic-pituitary-thyroid axis play a critical role in the diagnosis of thyroid disease.

TSH in Patients with Thyroid Dysfunction

Patients with hyperthyroidism or thyrotoxicosis always have a subnormal TSH. The values fall into two general categories:

1) those between the lower limit of normal and 0.1 mU/L, (subclinical hyperthyroidism), and

2) those less than 0.1 mU/L. (symptomatic thyrotoxicosis)

TSH in Patients with Thyroid Dysfunction

An elevation in both serum TSH and free T_4 is unusual and indicates either autonomous TSH production, as with a TSH secreting pituitary tumor (TSH-oma) or resistance to thyroid hormone (RTH)

Clinical Utility and Limitations of TSH Immunometric Assays *Limitations.*

A subnormal sTSH is not entirely specific for, or diagnostic of, hyperthyroidism. A misleading, subnormal sTSH may be recorded in

(1) hypopituitary or hypothalamic disease,

(2) in the first trimester of pregnancy,

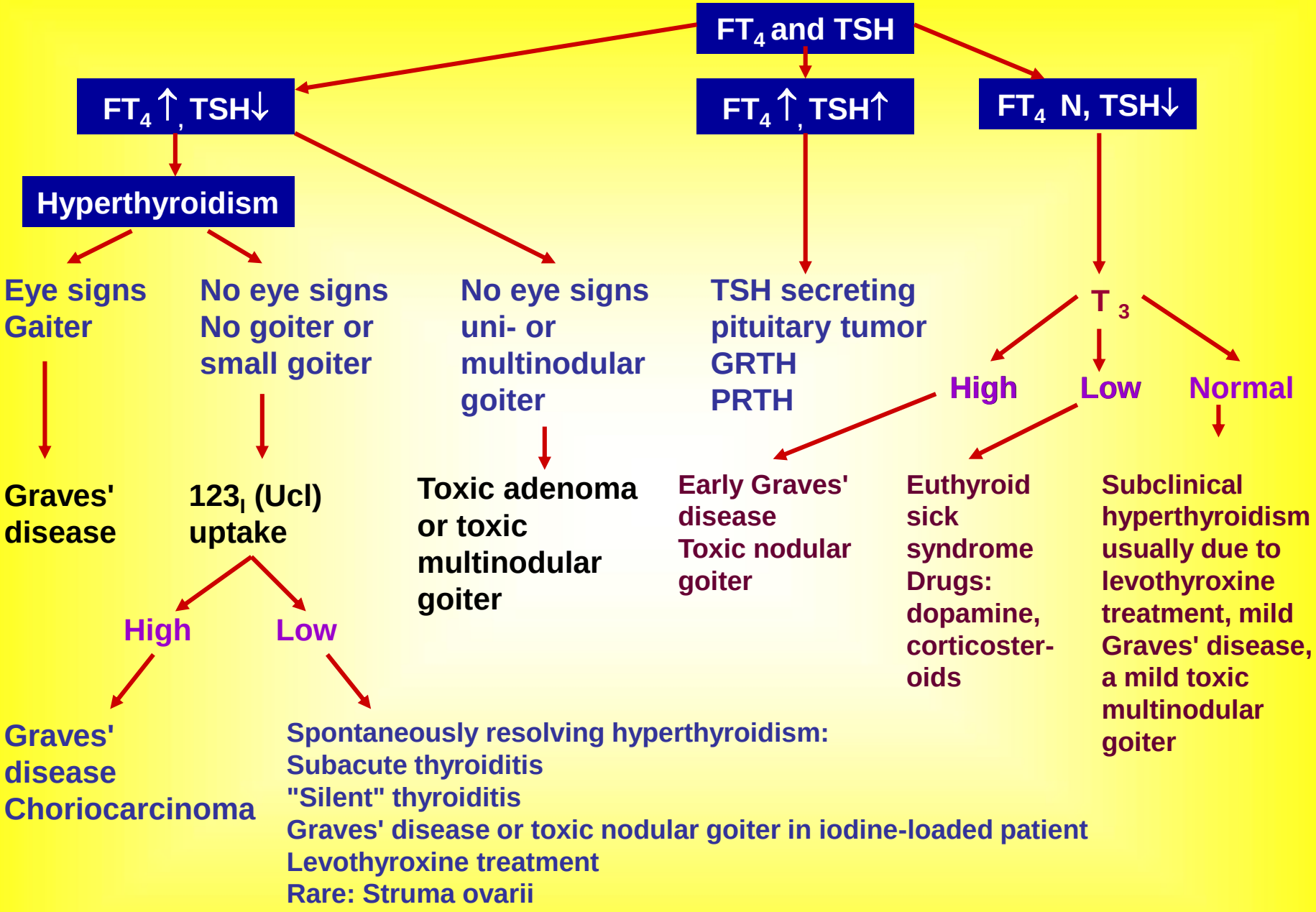
(3) in patients with NTI and/or under treatment with dopamine, glucocorticoids, and certain other drugs, and

(4) in acute psychiatric illness.

Elevated sTSH levels are not always a sign of hypothyroidism.

Causes of a low or undetectable TSH level

Lowered TSH	Free thyroid hormone levels
Overt thyrotoxicosis	↑
Subclinical thyrotoxicosis	N
Recently treated hyperthyroidism	N
Thyroid-associated ophthalmopathy without Graves' disease	N
Excessive thyroxine treatment	N or↑
Nonthyroid illness (sick euthyroid syndrome)	↓ or N
First trimester of pregnancy	N or↑
Pituitary or hypothalamic disease	N or↓
Anorexia nervosa	N or↓
Dopamine, somatostatin (acute effect)	N
Glucocorticoids	N



Laboratory tests useful in the differential diagnosis of hyperthyroidism (see text for details)

Determination of etiology

The etiology of thyrotoxicosis should be determined. If the diagnosis is not apparent based on the clinical presentation and initial biochemical evaluation, diagnostic testing is indicated and can include:

1- measurement of TRAb,

2- determination of the radioactive iodine uptake (RAIU)

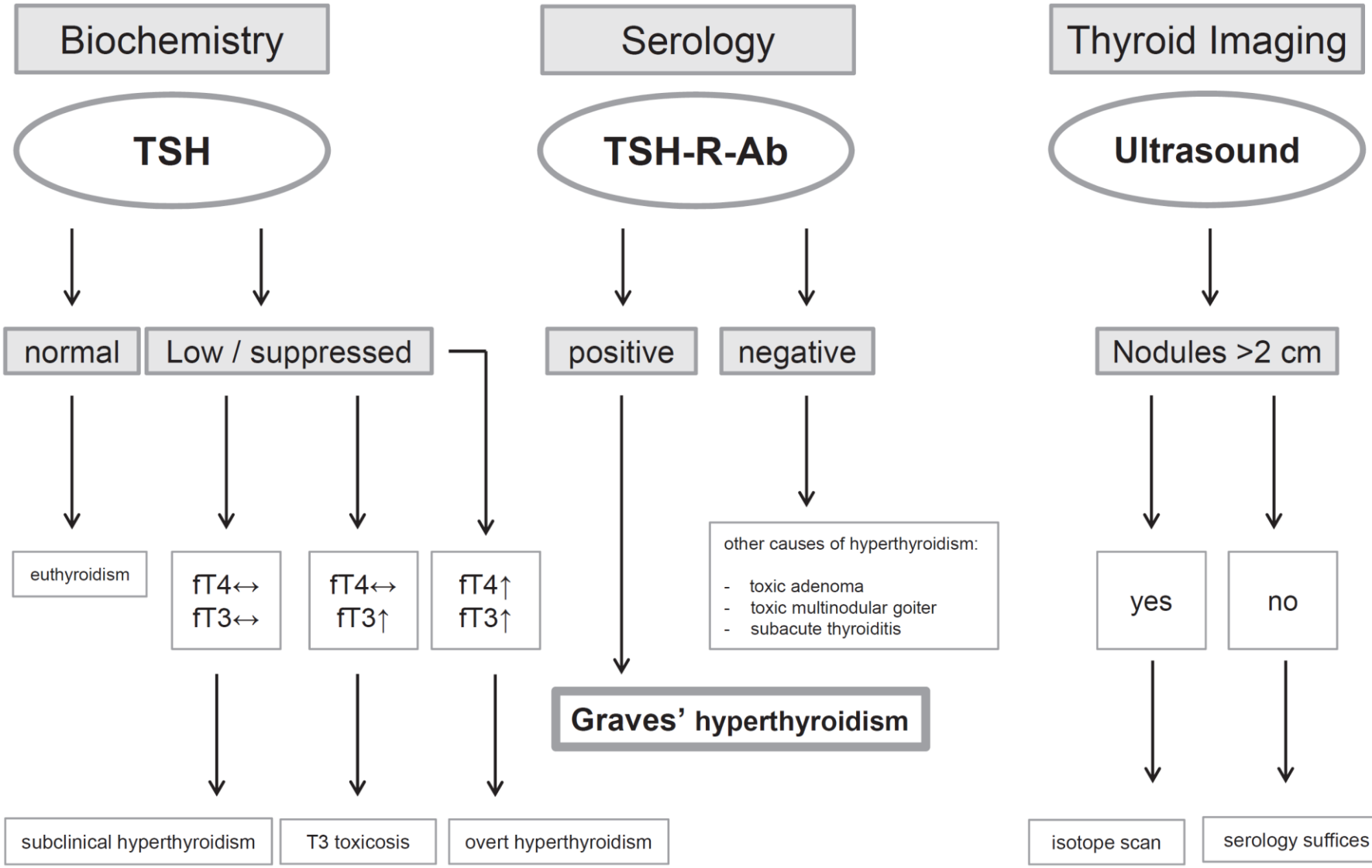
3- measurement of thyroidal blood flow on ultrasonography

4- A ^{123}I or 99mTc pertechnetate scan should be obtained when the clinical presentation suggests a TA or TMNG.

Recommendations

1- The measurement of TSH-R-Ab is a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism.

2- When technically available, determination of TSH-RAb is helpful and predictive in Graves' patients during pregnancy/postpartum, as well as for extrathyroidal manifestations.



Algorithm for investigating a patient with suspected Graves' hyperthyroidism.


Thank you
for your
attention