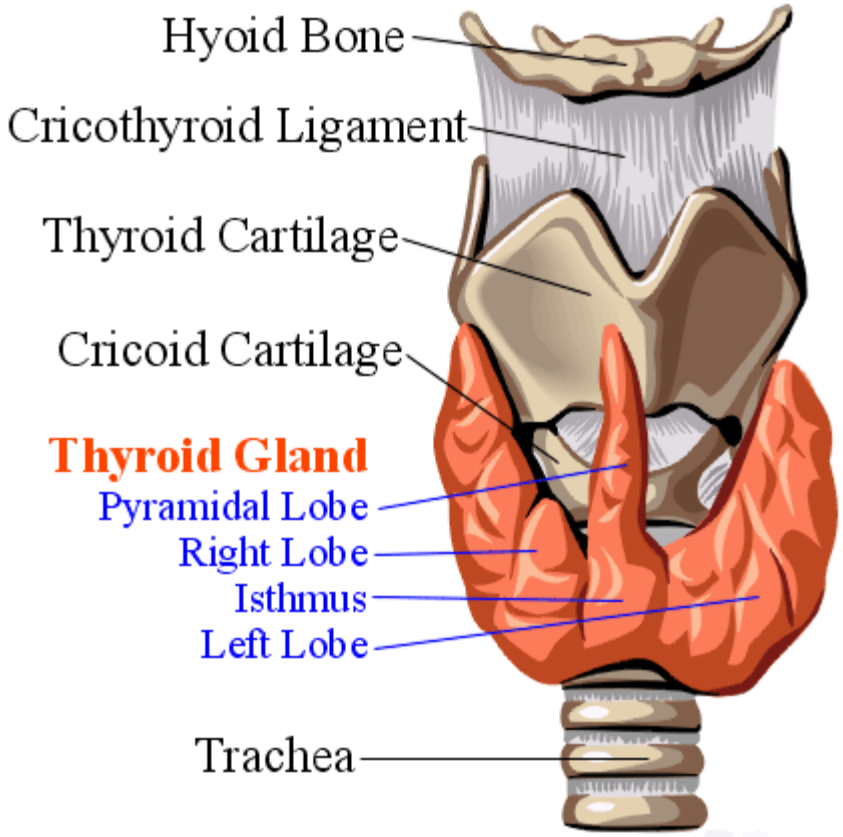


Adapted from Corel Draw 9

Francesco Lombardo

IPERTIROIDISMO

Tireotossicosi ed ipertiroidismo

La tireotossicosi indica il quadro clinico che consegue all'esposizione dei tessuti ad alti livelli di ormoni tiroidei circolanti. Nella maggior parte dei casi è causata da aumentata produzione ormonale da parte della tiroide e, questa condizione, si definisce ipertiroidismo.

CLASSIFICAZIONE DELLE TIREOTOSSICOSI	
Iperfunzione tiroidea	
Gozzo diffuso tossico o Morbo di Basedow	Molto frequente
Adenoma tossico o Morbo di Plummer	Frequente
Gozzo multinodulare tossico	Frequente
Da eccesso di iodio (es. terapia con amiodarone)	Poco frequente
Fase di ipertiroidismo della tiroide di Hashimoto (Hashitossicosi)	Poco frequente
Da eccessiva produzione di TSH (adenoma ipofisario TSH secernente o resistenza ipofisaria agli ormoni tiroidei)	Rara
Dimissione di ormoni preformati	
Tiroidite sub-acuta	Frequente
Tiroidite silente	Poco frequente
Tiroidite da amiodarone	Poco frequente
Assunzione eccessiva di ormoni tiroidei	
Tireotossicosi *factitia*	Rara
Produzione ectopica di ormoni tiroidei	
Struma ovarico	Molto rara
Carcinoma metastatico della tiroide	Molto rara

In general, hyperthyroidism/thyrotoxicosis can occur if

(i) the thyroid is excessively stimulated by trophic factors;

(ii) constitutive activation of thyroid hormone synthesis and secretion occurs, leading to autonomous release of excess thyroid hormone;

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

(iv) there is exposure to extrathyroidal sources of thyroid hormone, which may be either endogenous (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis).

Hyperthyroidism

Thyrotoxicosis

GRAVES DISEASE

Autoimmune disease that destroys the thyroid gland

Women to men ratio is 8:1

1st described by Robert Graves in 1835

Affects 6 per 1000 persons in the US

Causes 50–80% cases of hyperthyroidism in the US

Fatigue is present in 70% of the patients

Palpitations and weight loss are seen in 50% of the patients

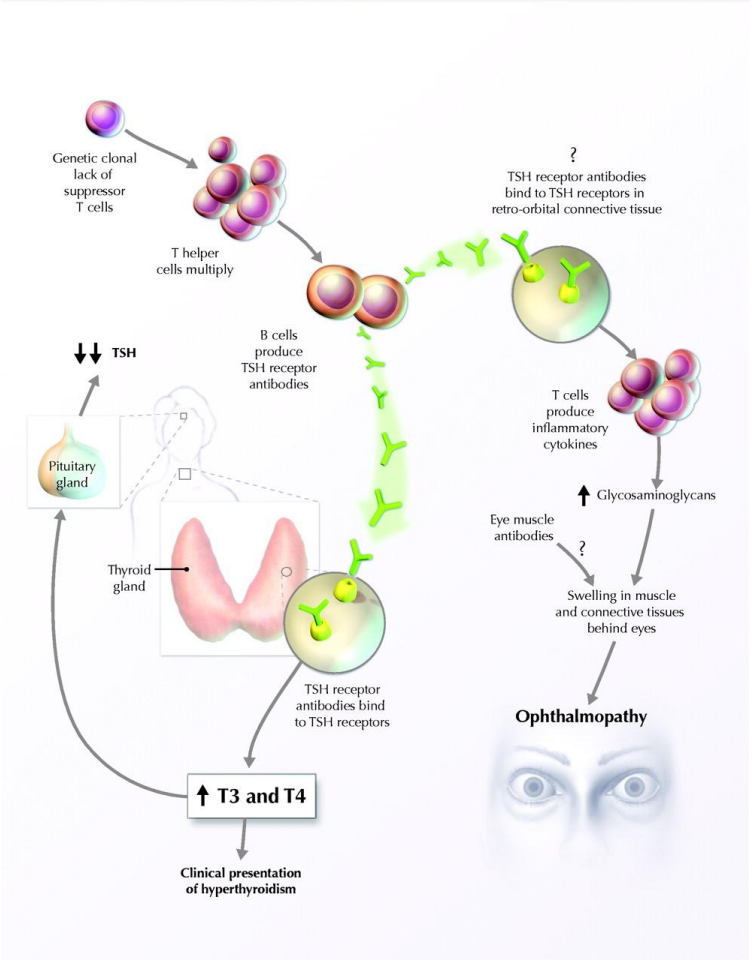
Other symptoms include heat intolerance, hair loss & hand tremor

Diagnosed by blood tests & radiography of thyroid gland

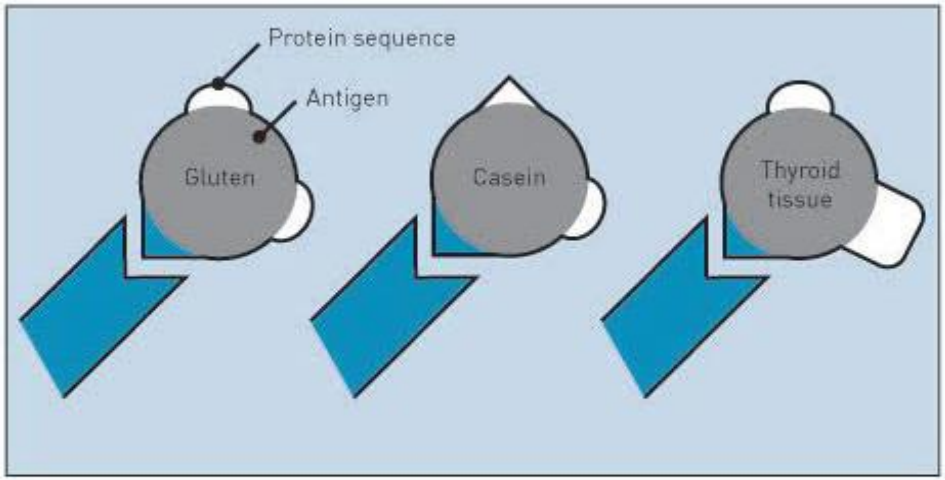
Treatment includes radioiodine therapy, medications & thyroid surgery

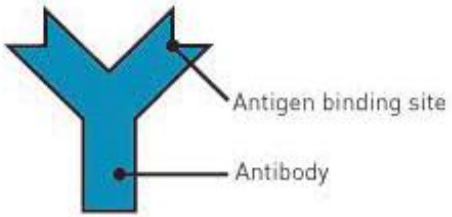
XpertDox
Clinical, Education, Research

- Graves' disease (GD) is an autoimmune disorder characterized in its typical presentation by the unique association of hyperthyroidism, goiter and ophthalmopathy.
- GD is caused by circulating antibodies that mimic the action of the TSH, namely binding to and activating its receptor (TSHR), resulting in increased synthesis and release of TH and hypertrophy of thyroid follicular cells (goiter).
- Ophthalmopathy is clinically present in about 50% of patients, and, although its pathogenesis remains to be completely elucidated, it is believed to be due to an autoimmune reaction against antigens shared by the thyroid and orbital tissues, among which the TSHR is the most reasonable candidate.



Molecular Mimicry

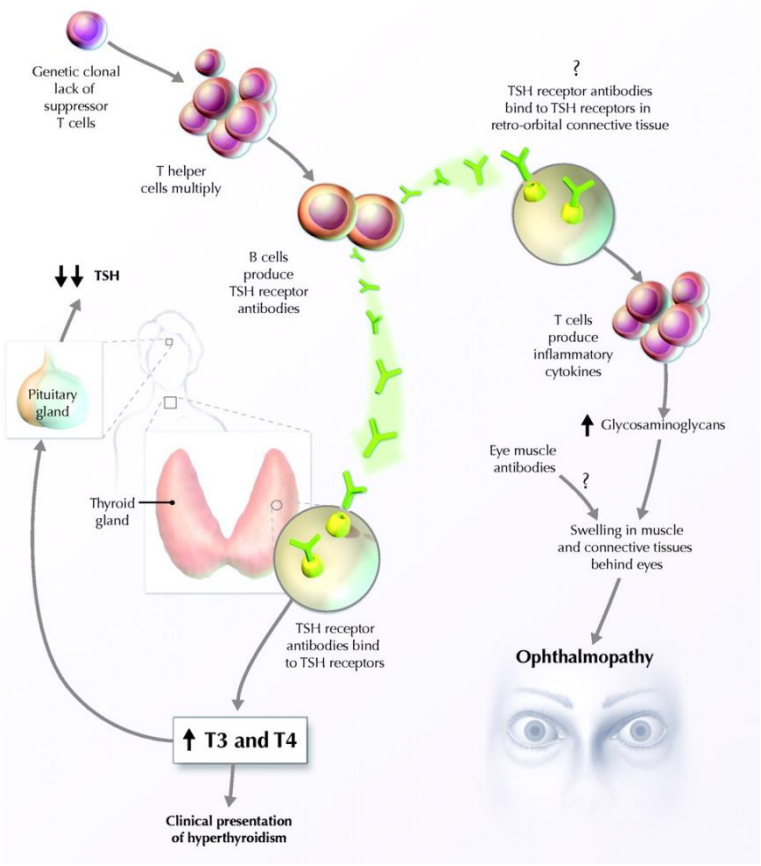




Antibodies bind to the specific protein sequences of antigens. While gluten, casein, and your own tissues may all be different, they share some of the same protein sequences. A cross reaction occurs when your immune system cannot distinguish between these molecules.

Molecular mimicry implies structural similarity between some infectious or other exogenous agent and human cell protein, such as Abs formed in response to the exogenous agent react with one or more of the thyroid proteins.

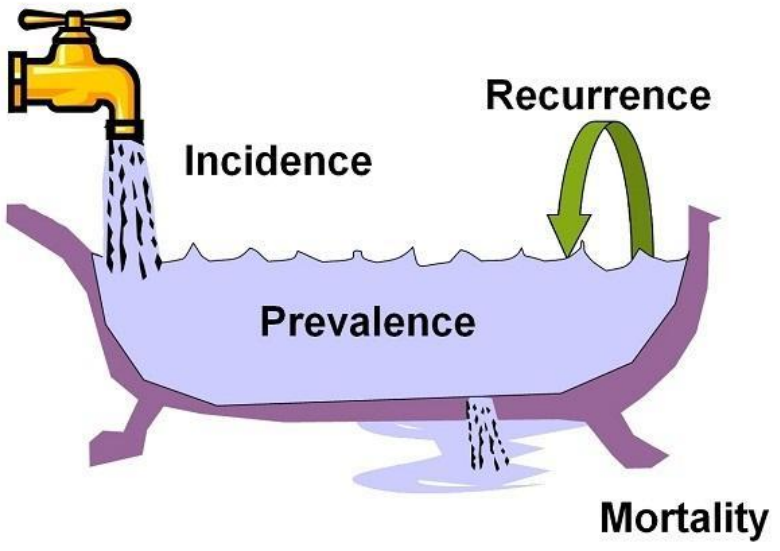
- GD is a multifactorial disease caused by a complex interaction between genetic and environmental factors that lead to the loss of immune tolerance to thyroid Ags, and therefore to the initiation of an immune reaction against the thyroid.
- Several GD susceptibility genes have been identified, which can be classified into immune regulatory genes (HLA-DR, CTLA4, CD40, PTPN22) and thyroid specific genes (Tg, TSHR).
- The penetrance of the genetic determinants is likely quite low, as also suggested by the fact that GD is not a hereditary disease, although it often recurs, along with autoimmune thyroiditis, within the same families.
- Among the nongenetic factors involved in the etiology of GD, infections, iodine intake, smoking and psychic stress have all been postulated to play a role, although no firm evidence is available.



Epidemiology

- ✓ GD is one of the most frequent diseases among autoimmune disorders, with an annual incidence of approximately 14 per 100,000. In iodine sufficient areas, it accounts for 70-80% of all cases of thyrotoxicosis .
- ✓ As in most autoimmune diseases, GD is more frequent in women than in men, with a ratio of approximately 5/1.
- ✓ Can be observed at any age, including childhood, although its incidence peaks between the fifth and sixth decades.
- ✓ Ethnical differences in the incidence of GD have not been investigated consistently, although there seems to be a higher prevalence of the disease in Caucasians and Asians than in Africans.

Prevalence	Measures **existing** cases of disease and is expressed as a proportion
Incidence	Measures **new** cases of disease and is expressed in person-time units



Clinical manifestations

- GD is usually classified as an organ-specific autoimmune disease, although organs other than the thyroid can be involved, including the eyes, the skin and the joints.
- Furthermore, TH affect the function of most organs leading to a wide range of symptoms when they are in excess.
- Thus, GD clinical features can be divided into those due to the excess of circulating TH and those specific to the disease.

Table 1
Symptoms of hyperthyroidism.

Symptoms	Frequency (%)
Nervousness	80–95
Palpitations	65–99
Sweating	50–90
Heat intolerance	40–90
Weight loss	50–85
Fatigability	45–85
Dyspnea	65–80
Fatigue	50–80
Oligomenorrhea	45–80
Increased appetite	10–65
Diarrhea	10–30

Clinical manifestations

- ✓ The onset of hyperthyroid symptoms is generally gradual and most patients refer to the doctor for nervousness, difficulty in sleeping, fatigue, weight loss (despite increased appetite), tremor and palpitations. Other symptoms like dyspnea, fatigability, heat intolerance, sweating, and increased bowel movements may also be present.
- ✓ Women frequently experience irregular menses, whereas decreased libido, erectile dysfunction and ginecomastia may affect men.
- ✓ In the elderly, the symptoms mentioned above may not be present or may be less pronounced; apathy and lethargy can be the main features, which is referred to as "apathetic thyrotoxicosis". More frequent cardiovascular involvement with atrial fibrillation and, less often, congestive heart failure .

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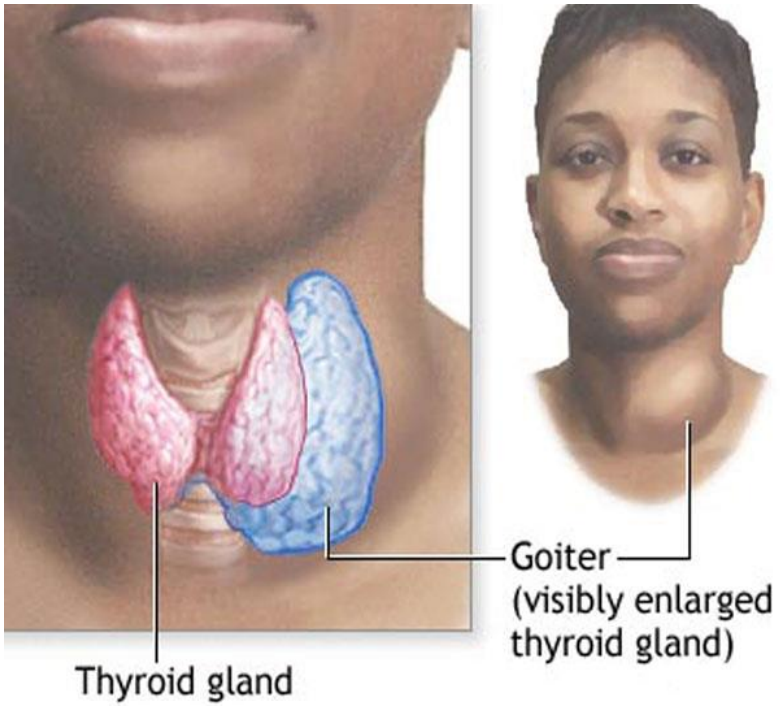
Increased appetite	10–65
Diarrhea	10–30

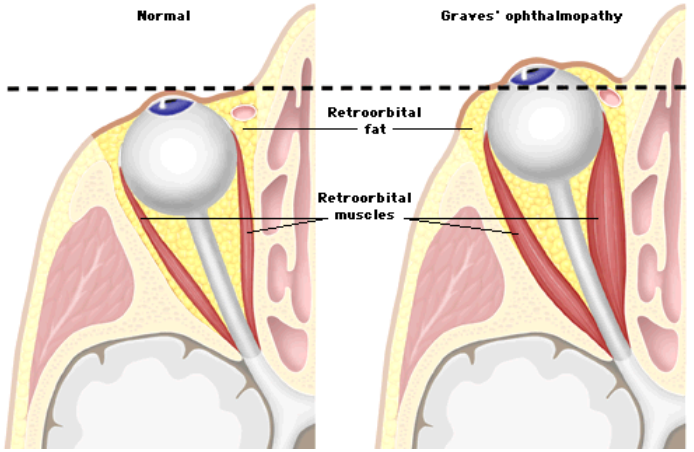
Goiter

- ✓ **A diffuse enlargement of the thyroid gland, which can vary from large, more common in the past, to minimally enlarged. In some cases the thyroid size can be normal.**
- ✓ **In iodine deficient areas, a pre-existing nodular goiter can be present.**
- ✓ **Because of the increased blood flood to the thyroid, thrills and bruits can be heard, especially in larger goiters.**



Ophthalmopathy

- ✓ Characterized by enlargement and inflammation of orbital tissues, especially retro-orbital fat.
- ✓ The increase in the orbital content results in exophthalmos (proptosis) and swelling of soft tissues because of venous engorgement.
- ✓ Ocular muscles are often **hypertrophic**, which results in their impaired function leading to diplopia of various degrees (intermittent, present in peripheral or primary gaze).



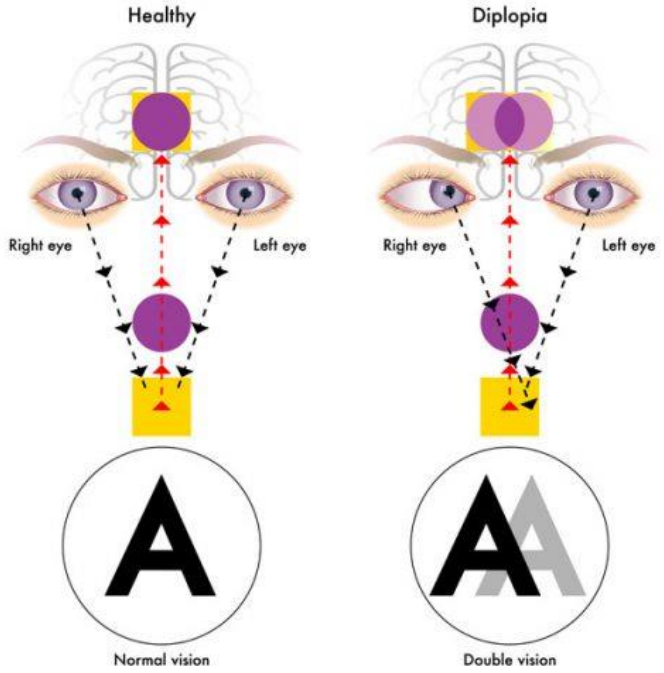


TABLE 15. RISK FACTORS FOR GRAVES' ORBITOPATHY

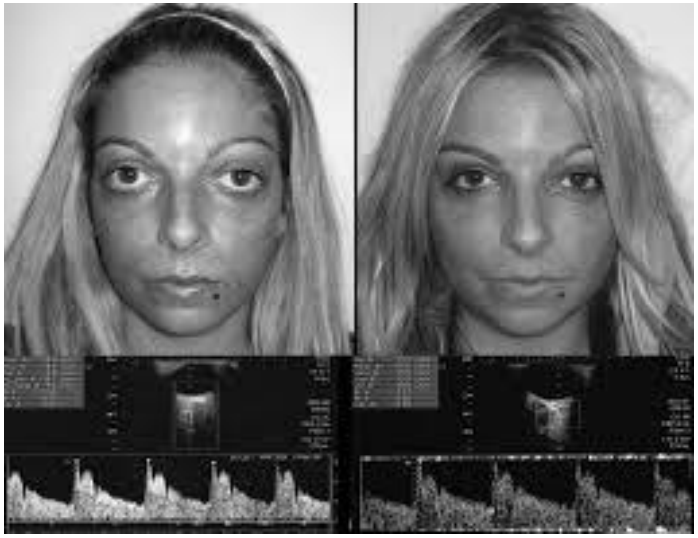
Risk factor	*Amenable to intervention*	*Comments*
Age	No	Advanced age, risk for more severe GO.
Sex	No	GO is more frequent in women (as GD is); more severe in men.
Genetics/ancestry	No	Highest prevalence of GO in Caucasians, lowest in Asians. Immunomodulatory genes likely involved.
Mechanical factors	No	Noted wider lateral wall orbital angle in GO.
TSH receptor antibody	No[a]	Predicts GO risk and GO therapy response.
Smoking	Yes	Increases GO progression and decreases therapy efficacy. Smoking-cessation clinics favored for intervention.
Thyroid dysfunction	Yes	Need for expeditious control of hyperthyroidism then prevention of hypothyroidism post GD therapy.
RAI therapy	Yes	Risk is additive to smoking; increased with preexistent and active GO; preventable by glucocorticoids 6–12 weeks post RAI.

[a]Decreased TRAb noted with methimazole therapy yet available data are unable to separate that change from the natural history of GO with improving TRAb.

Clinicians should use smoking cessation programs based on effective and evidence-based approaches to aid in smoking cessation and avoidance of secondhand smoke.

Ophthalmopathy

- ✓ Overall, ophthalmopathy is the most invalidating and psychologically disturbing feature of GD and it can affect to a quite large extent the QoL of patients, both because of its functional consequences and because of the change in their physical appearance.
- ✓ The majority of GD patients have only a mild-to-moderate eye involvement, whereas a minority has a severe ophthalmopathy, which, in its worst presentations, can be complicated by compression of the optic nerves (optic neuropathy), resulting in the decrease and, eventually, the loss of visual acuity.



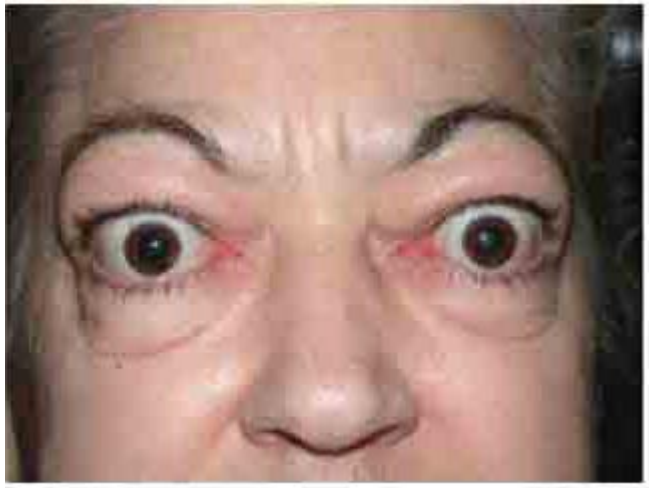


Fig 2 : Kocher's sign - Staring look

TABLE 12. ASSESSMENT OF GRAVES' ORBITOPATHY: CLINICAL ACTIVITY SCORE ELEMENTS[a]

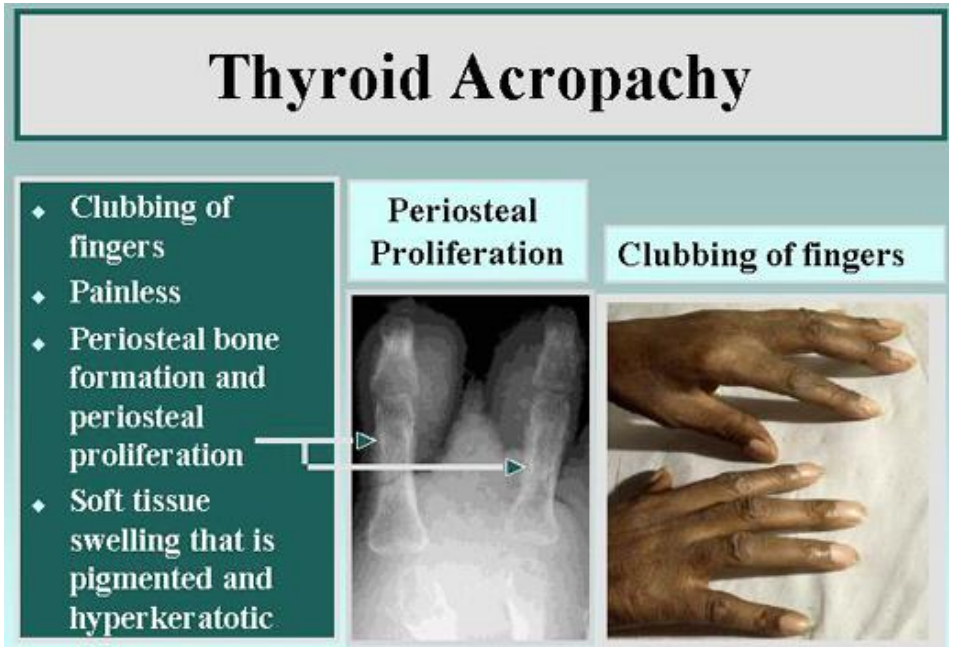
Elements[b]	*Each visit*	*Comparison with previous visit*	*Score*
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of eye)	X		1
Increase in proptosis ≥2 mm		X	1
Decreased eye movements ≥5° any direction		X	1
Decreased visual acuity ≥1 line on Snellen chart		X	1

[a]Sources: Adapted from Mourits *et al.* (523,524).
[b]A 7-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a clinical activity score (CAS) ≥3.

Some of the eye changes seen in hyperthyroidism, like lid retraction or stare, result from the increased sympathetic state, and when present without associated eye changes, they are not considered to reflect GO.

Acropachy

- ✓ It is characterized by clubbing and soft tissue swelling of the last phalanx of the fingers and toes.
- ✓ It is an extremely rare manifestation of GD and is found in patients with severe and long lasting GD with ophthalmopathy and pretibial myxedema.



Laboratory findings

- ✓ The laboratory hallmark of GD is the finding of elevated levels of serum fT4 and fT3, associated with undetectable serum TSH.
- ✓ TSH is the initial screening test in the evaluation of a suspected thyrotoxicosis, but it is strongly recommended to add measurement of fT4 to improve diagnostic accuracy.
- ✓ The relationship between fT4 and TSH when the pituitary–thyroid axis is intact is an inverse log-linear relationship; therefore, small changes in fT4 result in large changes in serum TSH concentrations.
- ✓ Serum TSH levels are considerably more sensitive than direct thyroid hormone measurements for assessing thyroid hormone excess.

Table 2. Diagnostic and Monitoring Laboratory Tests for Graves' Disease

Hormone	Normal	Abnormal
TSH	0.4-4.0 mIU/L	<0.4 mIU/L
	0.5-3.0 mIU/L[a]	<0.5 mIU/L
Free T_4	0.8-2.7 ng/dL	>2.7 ng/dL
Total T_4	4.5-11.2 mcg/dL[b]	>11.2 mcg/dL
Total T_3[c]	100-200 ng/dL	>200 ng/dL

[a] Values for treating a patient with a thyroid disorder.
[b] Values vary slightly by laboratory.
[c] T_3 is usually disproportionately higher than T_4.
TSH: thyroid-stimulating hormone; T_3: triiodothyronine; T_4: thyroxine.
Source: References 1, 7.

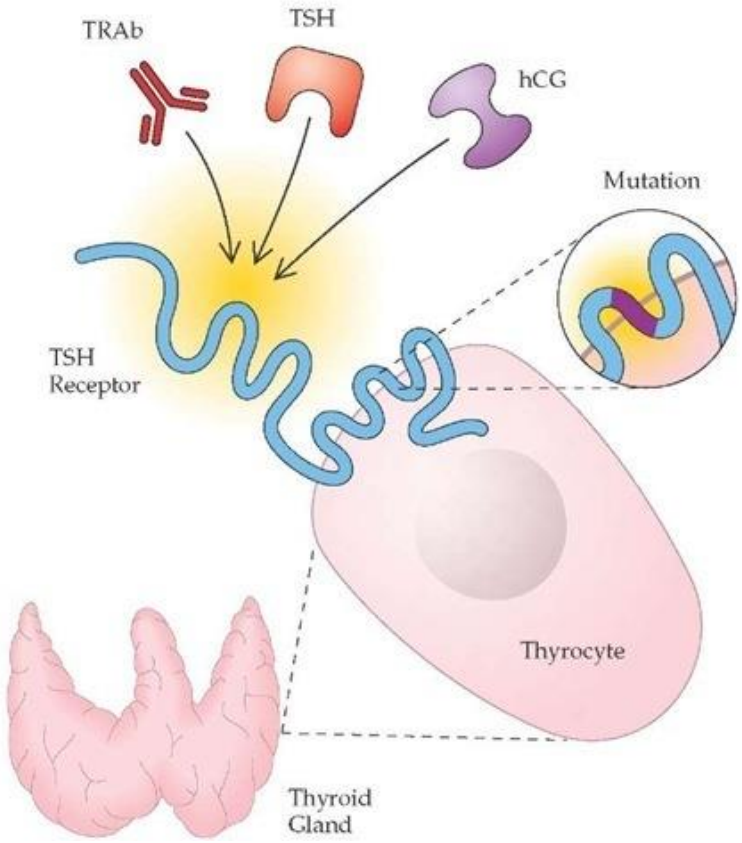
Because a hyperactive gland produces more T3 than T4, T3 will be elevated above the upper limit of normal more than T4 in thyrotoxicosis caused by hyperthyroidism, whereas T4 is elevated more than T3 in thyrotoxicosis caused by thyroiditis.

Laboratory findings

- **Biotin, also known as vitamin B7 or vitamin H, is a water-soluble B-complex vitamin that serves as a covalently-bound coenzyme of carboxylases. It is now well documented that biotin has actions other than participating in classical enzyme catalysis reactions.**
- **Several lines of evidence have demonstrated that pharmacological concentrations of biotin affect glucose and lipid metabolism, hypertension, reproduction, development, and immunity. The effect of biotin on these functions is related to its actions at the transcriptional, translational, and post-translational levels.**
- **The best supported mechanism involved in the genetic effects of biotin is the soluble guanylate cyclase/protein kinase G (PKG) signaling cascade.**
- **Patients taking high doses of biotin or supplements containing biotin, who have elevated fT4 and suppressed TSH, should stop taking biotin and have repeat measurements at least 2 days later.**

Laboratory findings

- ✓ **Antibodies against the TSH receptor (TRAbs) are pathognomonic for GD.**
- ✓ **They are detectable in the serum of about 98% of untreated GD patients using a II generation assay and in an even higher proportion of patients using a III generation assay .**



Laboratory findings

Table 3
Thyrotoxicosis: essential features for differential diagnosis.

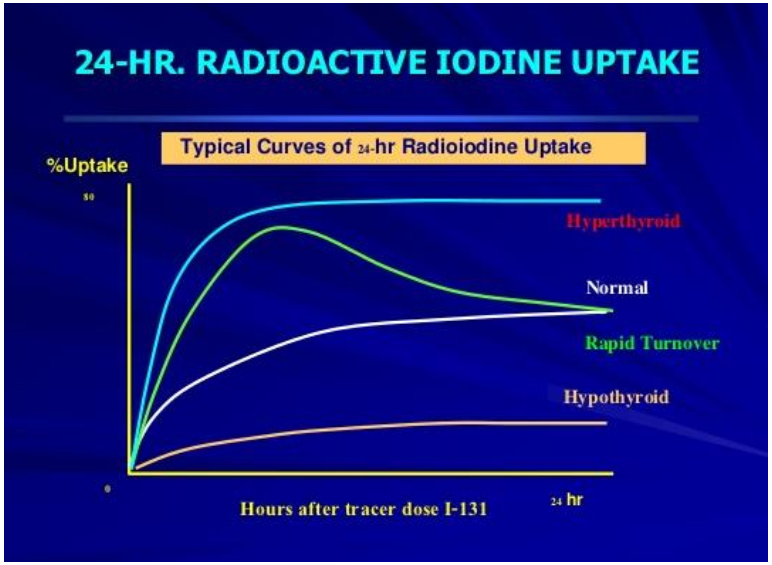
Cause of thyrotoxicosis	TRAbs	Thyroid US	CFD	RAIU/scan	Other features
Graves' disease	Present	Hypoechoic pattern	Increased	Increased	Ophthalmopathy, dermopathy, acropachy
Toxic nodular goiter	ND	Multiple nodules	–	"Hot" nodules at thyroid scan	–
Toxic adenoma	ND	Single nodule	–	"Hot" nodule	–
Subacute thyroiditis	ND	Heterogeneous hypoechoic areas	Reduced/absent flow	Low	Neck pain-fever and elevated inflammatory index
Painless thyroiditis	ND	Hypoechoic pattern	Reduced/absent flow	Low	–
Amiodarone induced thyroiditis-Type 1	ND	Diffuse or nodular goiter	Reduced/normal/increased	Low, but higher than in Type 2	High urinary iodine
Amiodarone induced thyroiditis-Type 2	ND	Normal	Absent	Low/absent	High urinary iodine
Central hyperthyroidism	ND	Diffuse or nodular goiter	Normal/increased	Increased	Inappropriately normal or high TSH
Trophoblastic disease	ND	Diffuse or nodular goiter	Normal/increased	Increased	
Factitious thyrotoxicosis	ND	Variable	Reduced/absent flow	Low	Low serum thyroglobulin
Struma ovarii	ND	Variable	Reduced/absent flow	Low	Abdominal RAIU

US: ultrasound; CFD: color flow Doppler; RAIU: radioactive iodine uptake; ND: not detectable.

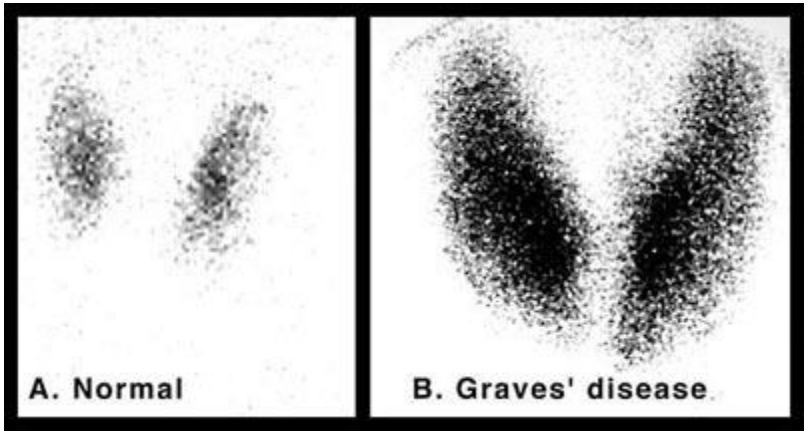
- ✓ **TRAb measurement is a very valuable tool in the differential diagnosis between GD and thyrotoxicosis due to other causes, and the detection of TRAbs rules out other causes of thyrotoxicosis .**
- ✓ **Measurement of serum anti-thyroid peroxidase (TPO) and antithyroglobulin (Tg) antibodies, although detectable on the majority of GD patients, is generally not useful for GD diagnosis.**

Imaging studies

Thyroid radioiodine uptake (RAIU)



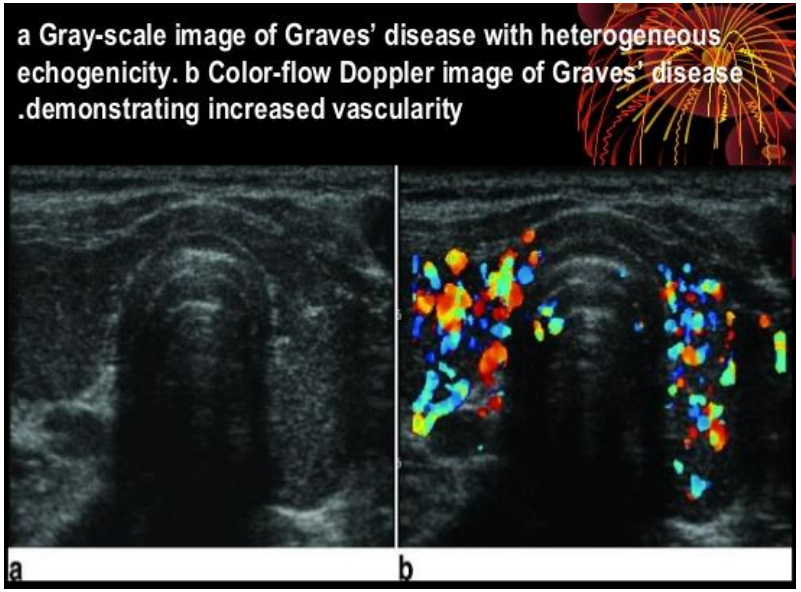
- ✓ RAIU is generally increased in GD because of the action of stimulating TRAbs. Normal values for RAIU 24 h after the administration of a tracer dose of radioiodine are ~20% in iodine sufficient and ~40% in iodine deficient areas.
- ✓ Before the availability of accurate TRAb assays, it was considered the first test for the differential diagnosis between hyperthyroidism and other forms of thyrotoxicosis, where the RAIU is low or absent.

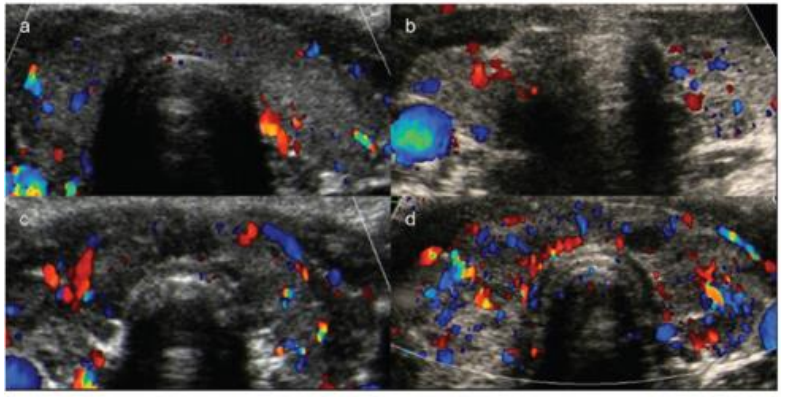


Imaging studies

- ✓ Thyroid ultrasound (TU) is a very sensitive and reliable diagnostic tool that, although not necessary for GD diagnosis, may give useful information. Typically, the thyroid pattern in GD is hypoechoic, because of lymphocytic infiltration, reduction of the colloid content, and increase in vascularity.
- ✓ Furthermore, TU gives an accurate estimation of the thyroid size, and allows the detection of thyroid nodules that may not be palpable at physical examination.

Thyroid ultrasound and Color Flow Doppler (CFD)

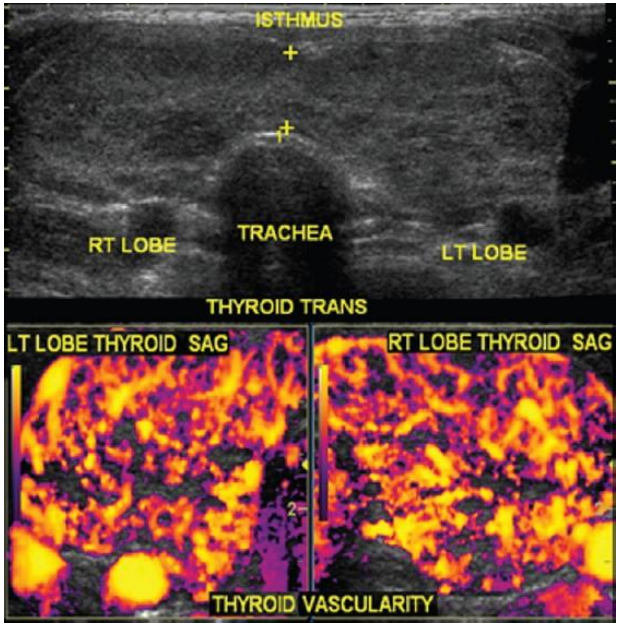




ɾ patterns. a. Pattern 0 (normal thyroid vascularity); b. color Doppler Pattern I (mini
ɔpler Pattern II (increased blood flow with a diffuse homogenous distribution); and d.

Imaging studies

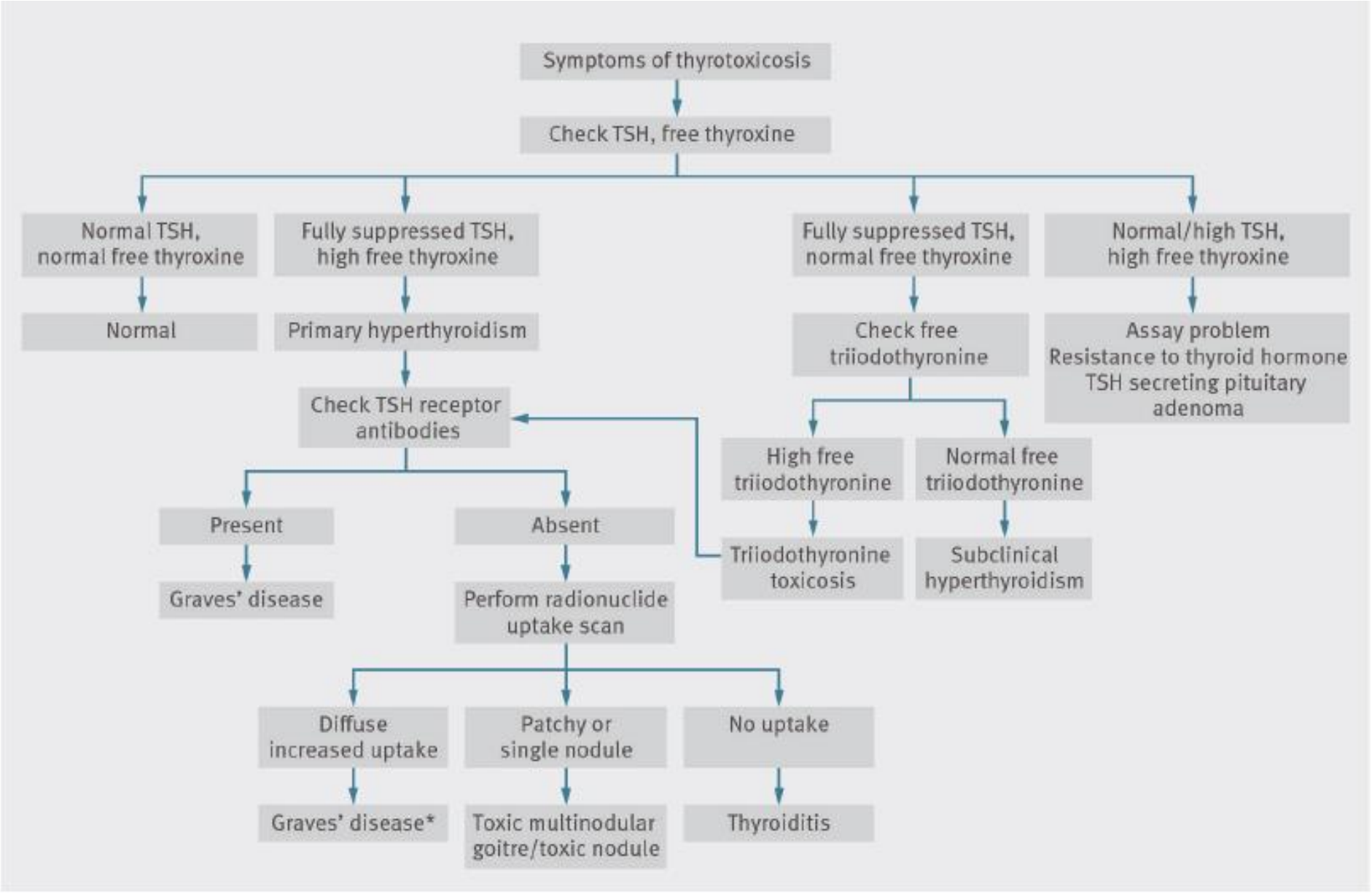
- ✓ Color flow Doppler (CFD) estimates the blood flow which, in hyperthyroid GD patients is typically increased within the thyroid gland.
- ✓ CFD can be useful in the differential diagnosis between GD and other causes of thyrotoxicosis characterized by a low blood flow to the thyroid, such as factitious thyrotoxicosis, painless and subacute thyroiditis, and type II amiodarone-induced thyrotoxicosis, in a manner quite similar to that of RAIU, but with a lower sensitivity and specificity.
- ✓ When RAIU is not available or contraindicated (for example during pregnancy or lactation), CFD can be valuable substitute.



Diagnostic criteria

Table 4
Diagnostic criteria for GD: clinical and/or biochemical evidence of thyrotoxicosis plus 1 or more of the following features confirm GD diagnosis.

GD features
Serum TRAbs
Ophthalmopathy and/or dermopathy
Diffuse elevated RAIU


Symptoms of thyrotoxicosis
Check TSH, free thyroxine
Normal TSH, normal free thyroxine
Fully suppressed TSH, high free thyroxine
Fully suppressed TSH, normal free thyroxine
Normal/high TSH, high free thyroxine
Normal
Primary hyperthyroidism
Check free triiodothyronine
Assay problem
Resistance to thyroid hormone
TSH secreting pituitary adenoma
Check TSH receptor antibodies
High free triiodothyronine
Normal free triiodothyronine
Present
Absent
Triiodothyronine toxicosis
Subclinical hyperthyroidism
Graves' disease
Perform radionuclide uptake scan
Diffuse increased uptake
Patchy or single nodule
No uptake
Graves' disease*
Toxic multinodular goitre/toxic nodule
Thyroiditis

Therapy

1. An initial medical treatment with anti-thyroid drugs (thionamides) is generally recommended in all patients to restore euthyroidism. Once euthyroidism is achieved, the long-term strategy comprises several options, including relatively long-term (usually 12 to 24 months) course of anti-thyroid drugs, RAIU or surgery.
2. Beta-blockers, if not contraindicated (asthma), can be used prior to restoring euthyroidism to alleviate symptoms of thyrotoxicosis.
3. Anticoagulation is also warranted in most patients who have atrial fibrillation.

Table 3. Antithyroid Medications (Thionamides)

Drugs	Comments
Imidazoles Methimazole	Drug of choice for the treatment of hyperthyroidism; higher efficacy at once-daily dosing (usually given 30 mg daily); higher patient compliance; serum half-life of 6-8 h
Carbimazole	Available only in Europe
Thiouracils Propylthiouracil	Not effective at once-daily dosing (usually given 100 mg 3 times a day); lower patient compliance; drug of choice for hyperthyroidism in pregnancy; serum half-life of 1-2 h

Source: References 7, 14.

TABLE 4. BETA-ADRENERGIC RECEPTOR BLOCKADE IN THE TREATMENT OF THYROTOXICOSIS

Drug[a]	*Dosage*	*Frequency*	*Considerations*
Propanolol[b]	10–40 mg	3–4 times per day	Nonselective β-adrenergic receptor blockade Longest experience May block T_4 to T_3 conversion at high doses Preferred agent for nursing and pregnant mothers
Atenolol	25–100 mg	1–2 times per day	Relative β-1 selectivity Increased compliance Avoid during pregnancy
Metoprolol[b]	25–50 mg	2–3 times per day	Relative β-1 selectivity
Nadolol	40–160 mg	1 time per day	Nonselective β-adrenergic receptor blockade Once daily Least experience to date May block T_4 to T_3 conversion at high doses
Esmolol	IV pump 50–100 μg/kg/min		In intensive care unit setting of severe thyrotoxicosis or storm

Propanolol: Inderal 40 mg

Atenolol: Seles beta 100 mg, Tenormin 100 mg

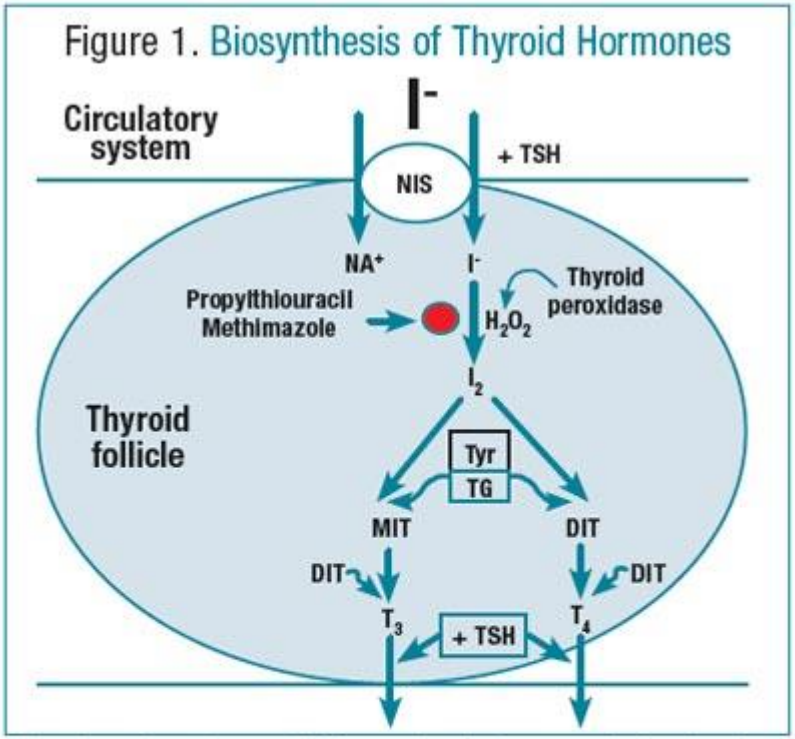
Metoprolol: Seloken 100 mg, Lopresor 100 mg

Nadolol: Corgard (out of production in Italy)

Esmolol: Brevibloc

Therapy

- ✓ **Thionamides** (methimazole, propylthiouracil), **block TH synthesis by inhibition of iodine organification and coupling of iodotyrosines.** Treatment with thionamides is generally well tolerated. Side effects include skin rash and, very rarely, hepatitis, agranulocytosis and vasculitis.
- ✓ **Methimazole** is now preferred to **PTU**, because of the evidence of a lower prevalence of severe side-effects, especially hepatitis, with the exception of the **first trimester of pregnancy**, when PTU is preferred due to the increased rate of congenital malformations, especially **aplasia cutis**, which has been reported with the use of methimazole.

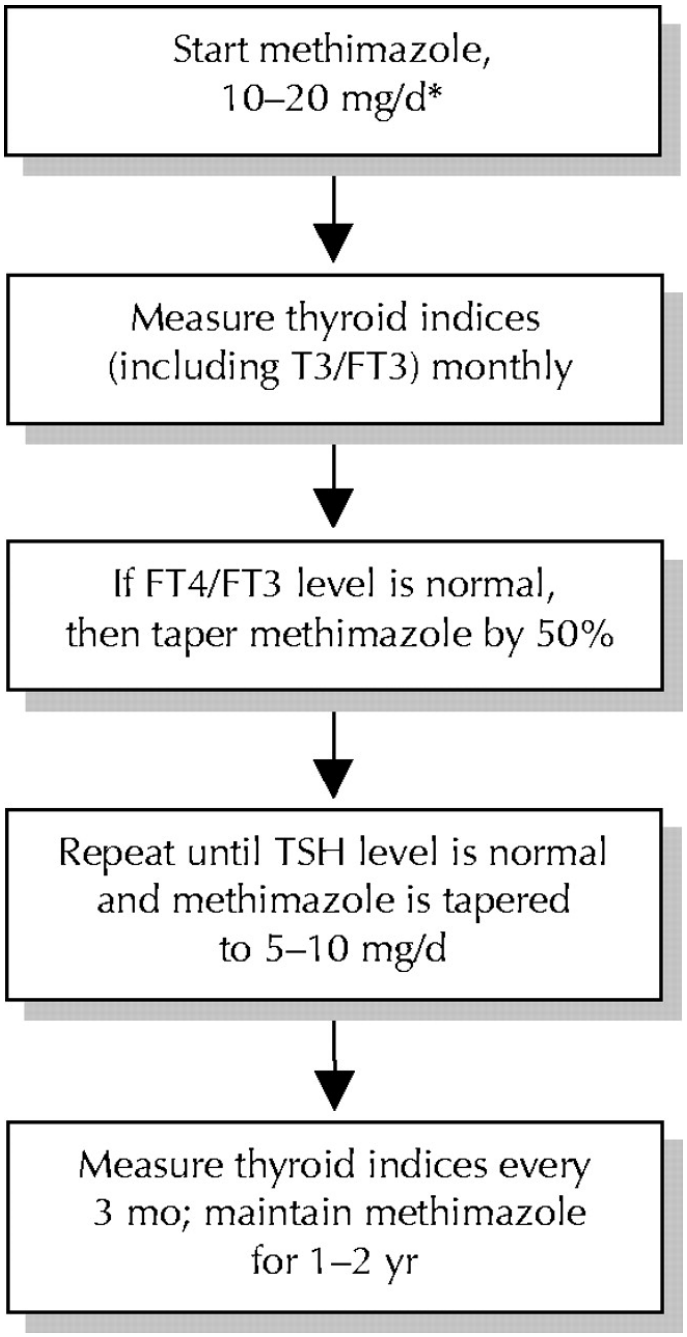


Thyroid-stimulating hormone (TSH) stimulates the absorption of iodine from the circulatory system into the thyroid follicle via the sodium-iodide symporter (NIS). Iodine is then oxidized to iodide by hydrogen peroxide (H_2O_2) containing thyroid peroxidase. Antithyroid medications such as propylthiouracil and methimazole block the synthesis of thyroid hormone at this step. Iodination of tyrosine (Tyr) containing thyroglobulin (TG) molecule results in monoiodotyrosyl (MIT) and diiodotyrosyl (DIT) residues. Coupling of one MIT and one DIT residue results in the synthesis of 3,5,3'-triiodothyronine (T_3); whereas two DIT residues combine to form thyroxine (T_4). Consequently, TSH stimulates secretion of T_3 and T_4 into the circulatory system.

Therapy

A rough guide to initial MMI daily dosing

- ✓ **5–10 mg if free T4 is 1–1.5 times the upper limit of normal;**
- ✓ **10–20 mg for free T4 1.5–2 times the upper limit of normal; and**
- ✓ **30–40 mg for free T4 2–3 times the upper limit of normal.**



Therapy

After euthyroidism is achieved, two different regimens can be employed.
In the first regimen, termed "block-replace" the dose of thionamide is kept constant (for example, carbimazole 40 mg daily), thus blocking thyroid hormone production, and levothyroxine is then added in a suitable dose to maintain euthyroidism (for example, 50 µg daily for women, 100 µg daily for men).
In the second regimen, termed "titrated" the thionamide dose is progressively lowered at regular intervals to allow endogenous synthesis of thyroid hormone to continue in a regulated fashion.

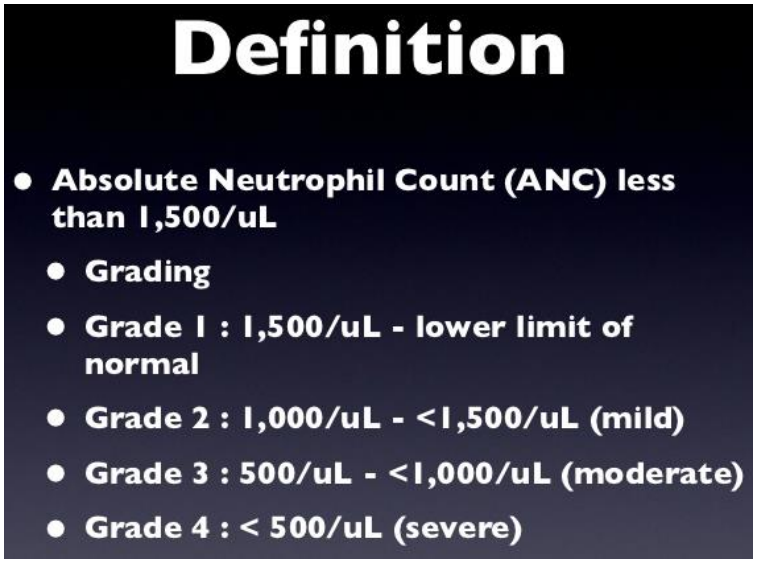
Table 2| **Considerations in administering the block-replace versus titrated regimens of antithyroid drugs**

Factors	Block-replace	Titrated dose
Stability	Easier to maintain stable euthyroidism	Prone to fluctuating hypothyroidism and hyperthyroidism
Monitoring	Fewer thyroid function tests and clinic visits	More thyroid function tests and clinic visits
Side effects	High risk	Low risk
Optimal remission*	Ranges from 6-12 months	Ranges from 12-18 months
Ease of use	More complex regimen with less likelihood of compliance and more prone to drug errors	Simpler regimen with better compliance and less prone to drug errors
Prediction of remission	Not possible to predict remission by dose changes	Prediction of early remission by successful dose reduction
Cost of drugs	High	Low

*No significant difference in early or late remission rates between either regimen.

Therapy

A pruritic rash, which is often transient, is seen in about 5% of patients taking antithyroid drugs. The much rarer but occasionally lethal problem of thionamide induced agranulocytosis occurs in about 1 in 300 people. It usually presents with sore throat, mouth ulcers, and high fever. All patients embarking on antithyroid drug treatment should receive clear verbal and written information about this adverse effect with advice to stop the drug and have a blood test for full blood count if they develop these warning symptoms. Agranulocytosis occurs most commonly in the first three months of treatment (median 30 days) and is rare after six months.



No predictive risk factors for the development of agranulocytosis could be identified!

Therapy

Hepatotoxicity is another major adverse effect of ATD therapy. MMI hepatotoxicity has been described as typically cholestatic, but hepatocellular disease may be seen.

In contrast, **PTU** can cause fulminant hepatic necrosis that **may be fatal**; liver transplantation has been necessary in some patients taking PTU.

It is for this reason that the Food and Drug Administration (FDA) issued a safety alert in 2010 regarding the use of PTU, and an analysis of FDA Medwatch data concluded that **children are more susceptible to hepatotoxic reactions from PTU than are adults**.

Minor side-effects (2–5% of patients)
- pruritus
- urticarial or maculopapular rash
- arthralgia
- fever
- gastrointestinal upset
- altered taste

Major side-effects (less than 0.2% of patients)
- agranulocytosis
- aplastic anaemia
- thrombocytopenia
- hepatitis (propylthiouracil)
- cholestatic jaundice (carbimazole)
- SLE-like syndrome

A baseline absolute neutrophil count < 1000/mm^3 or liver transaminase enzyme levels elevated more than 5-fold above the upper limit of normal should prompt serious reconsideration of initiating ATD therapy.

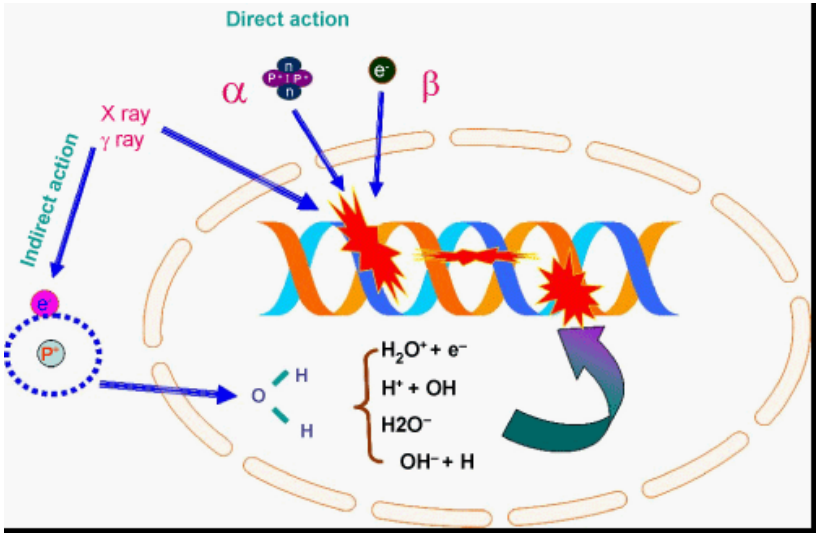
Therapy

Whether using titrated or block-replace regimens, trials have shown that prolonged treatment beyond 18 months has no advantage in remission rates, and the drugs should generally be stopped at this stage, with testing of thyroid function at 4-6 weeks to detect early relapse. The ideal patients to treat with antithyroid drugs for Graves' disease are those with a high chance of remission after treatment.

Thus women, age over 40 years, small thyroid size, no extrathyroidal manifestations, mild hyperthyroxinaemia, or triiodothyronine thyrotoxicosis at presentation and a low titre of TSH receptor antibodies are most likely to have a successful outcome from drug treatment. After relapse, a long term, small dose of thionamide is an acceptable option where definitive treatment with radioiodine or surgery is not feasible.

Therapy

- ✓ Radioiodine (iodine-131) is a β and γ radiation emitter, which is rapidly concentrated by the thyroid after oral ingestion.
- ✓ The β radiation has a 2 mm radius of activity and induces DNA damage leading to death of thyroid cells.
- ✓ Six weeks to six months after RAI treatment most patients with Graves' disease are rendered sequentially euthyroid and then hypothyroid.



Therapy

- ✓ RAI therapy **should not be used** in patients with **large goiter** because of the low success rate, unless repeated treatments are planned. Acute side effects of radioiodine are mild, well tolerated and generally self-limiting. **Radiation thyroiditis** can rarely cause a transient pain and swelling of the neck and it rarely requires treatment with oral glucocorticoids.
- ✓ Preformed thyroid hormones are released during the destructive process and may **transiently exacerbate symptoms of thyrotoxicosis**.
- ✓ A transient exacerbation or, more rarely, the new appearance of ophthalmopathy may occur after RAI treatment.
- ✓ In patients with active and moderate-to-severe or sight threatening GO we **recommend against** RAI therapy.

Therapy

- There is no evidence of an increased risk of thyroid cancer and other solid tumors as well as of leukemia after radioiodine therapy in adults with GD.
- No large studies are available in children. Therefore, RAI treatment is not recommended before the age of 18–20 years.
- No effects on the reproductive system in male and female have been described, with the exception of a transitory decrease in T levels in men. Hence, considering the minor and infrequent acute effects and the long term safety, RAI represents an excellent treatment option in GD patients.

Table 5
Possible radioiodine adverse effects.

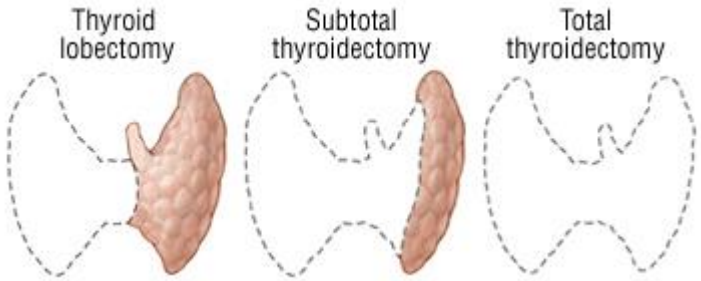
Acute
Radiation induced acute thyroiditis
Recurrence of thyrotoxicosis
Exacerbation of preexisting ophthalmopathy (preventable with glucocorticoids)
Long term
None

Therapy

Life After Thyroidectomy

Thyroidectomy is indicated in patients with a large goiter.

The rate of post-operative complications (e.g. surgical hypoparathyroidism, laryngeal nerve paralysis) is not increased compared with that observed using other less aggressive surgical procedures.



Therapy

- Treatment of ophthalmopathy depends upon the severity and activity of the disease. The administration of intravenous glucocorticoids is the first-line treatment in patients with moderately severe ophthalmopathy.
- In patients with sight treating ophthalmopathy, if intravenous glucocorticoids fail, orbital decompression should be performed.
- Rehabilitative surgery, such as orbital decompression, muscle or eyelid surgery should be considered when the eye disease is inactive.
- The majority of patients have a mild ophthalmopathy for which no major treatments are required, and patients are given local measurement (e.g. eye lubricants, sun glasses).

Activity of Graves' ophthalmopathy is measured by the clinical activity score: the final score (maximum 7) is the sum of all the symptoms listed below that are present.

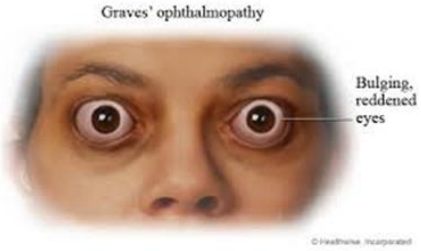
Spontaneous retrobulbar pain
Pain on attempted up gaze, side gaze or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Inflammation of the caruncle and/or plica
Conjunctival edema

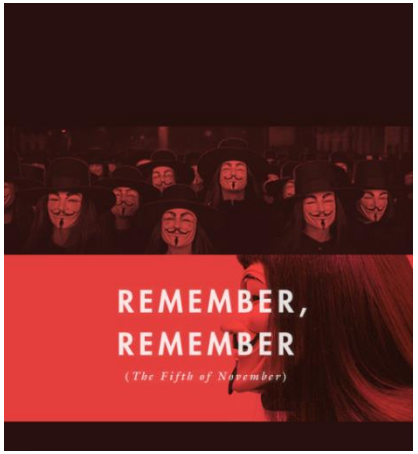
Severity of Graves' ophthalmopathy is assessed with the mnemonic NOSPECS: these features and measurements can be used to classify disease severity (classes 1–6).[a]

No signs or symptoms
Only signs, no symptoms (class 1): lid aperture (in mm)
Soft tissue involvement (class 2): swelling, redness
Proptosis (class 3): exophthalmos (in mm)
Extraocular muscle involvement (class 4): diplopia score;[b] ductions (in degrees)
Corneal involvement (class 5): punctate keratopathy, ulcer
Sight loss (optic nerve involvement; class 6): best corrected visual acuity; color vision; visual fields; optic disk

[a]Mild Graves' ophthalmopathy comprises moderate soft-tissue involvement, slight proptosis (up to 23–24 mm), and intermittent diplopia. Everything between mild and very severe Graves' ophthalmopathy (class 6; dysthyroid optic neuropathy) is classified as moderately severe. [b]Subjective diplopia score: 0, no diplopia; 1, intermittent, (diplopia in primary position of gaze when tired or when first awakening); 2, inconstant (i.e. diplopia at extremes of gaze); 3, constant (i.e. diplopia always present).

Therapy





- **RAIU should be avoided in active Graves' ophthalmopathy.**
- **Antithyroid drugs in a block-replace regimen is probably the optimal treatment until the ophthalmopathy becomes inactive.**
- **If this cannot be tolerated then total thyroidectomy is a good option.**

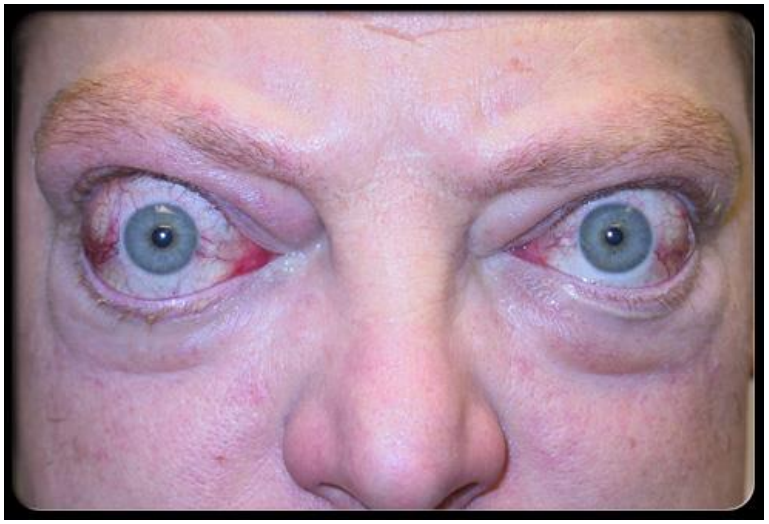


TABLE 5. CLINICAL SITUATIONS THAT FAVOR A PARTICULAR MODALITY AS TREATMENT FOR GRAVES' HYPERTHYROIDISM

Clinical situations	*RAI*	*ATD*	*Surgery*
Pregnancy[a]	x	√√ / !	√ / !
Comorbidities with increased surgical risk and/or limited life expectancy	√√	√	x
Inactive GO	√	√	√
Active GO	[b]	√√	√√
Liver disease	√√	!	√
Major adverse reactions to ATDs	√√	x	√
Patients with previously operated or externally irradiated necks	√√	√	!
Lack of access to a high-volume thyroid surgeon	√√	√	!
Patients with high likelihood of remission (especially women, with mild disease, small goiters, and negative or low-titer TRAb)	√	√√	√
Patients with periodic paralysis	√√	√	√√
Patients with right pulmonary hypertension, or congestive heart failure	√√	√	!
Elderly with comorbidities	√	√	!
Thyroid malignancy confirmed or suspected	x	-	√√
One of more large thyroid nodules	-	√	√√
Coexisting primary hyperparathyroidism requiring surgery	-	-	√√

√√ = preferred therapy; √ = acceptable therapy; ! = cautious use; - = not first-line therapy but may be acceptable depending on the clinical circumstances; X = contraindication.

Drug induced thyrotoxicosis

- **Amiodarone induced thyrotoxicosis may result from autoimmunity (type 1) or a destructive thyroiditis with release of preformed thyroid hormones (type 2).**
- **The most common form is type 2 amiodarone induced thyroiditis, and the most effective treatment for this was prednisolone.**
- **Type 1 amiodarone induced thyrotoxicosis is treated with antithyroid drugs.**

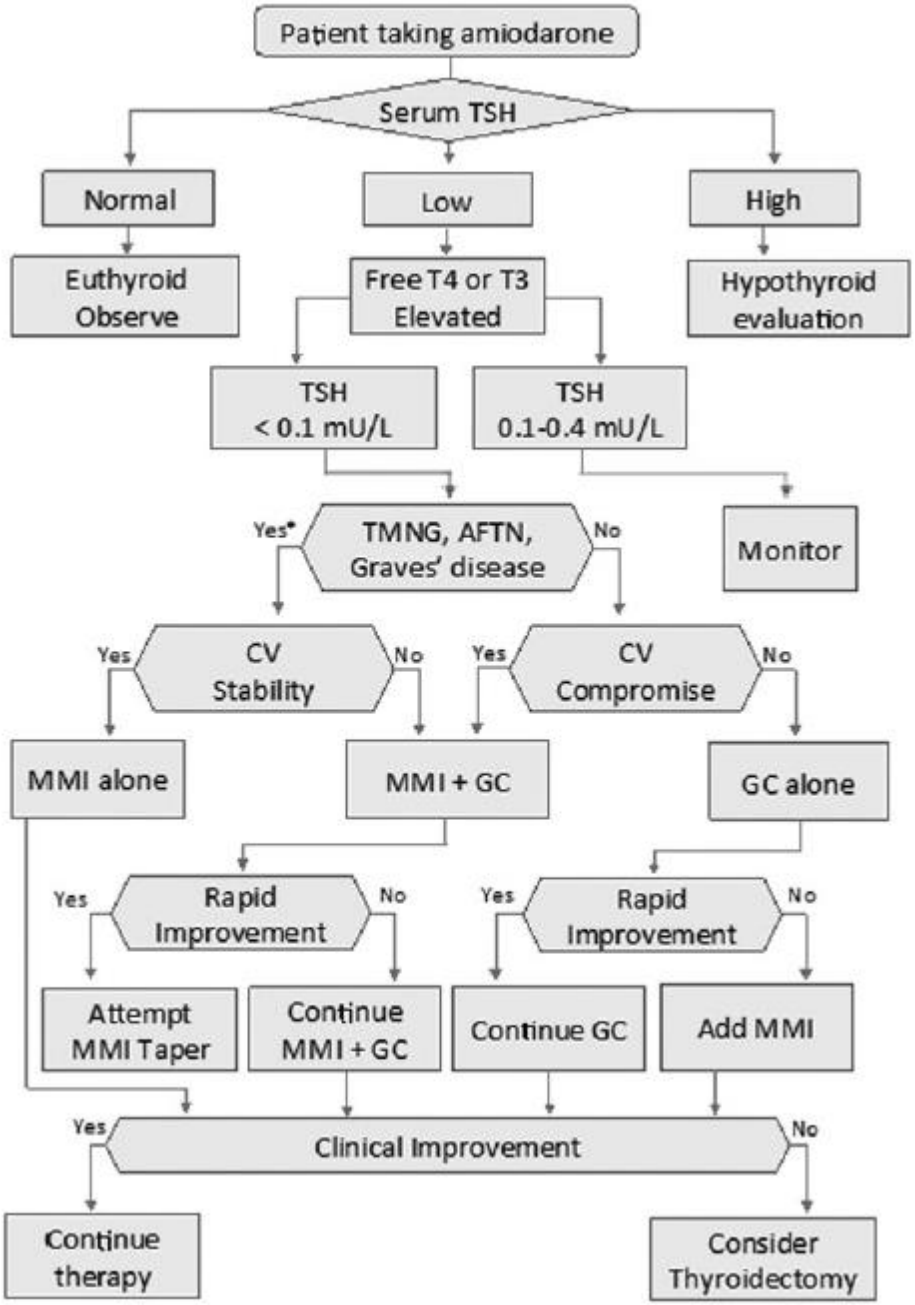
Table 2 - Comparison of AIT type 1 and 2

Factor	Type 1	Type 2
Goiter	Often present	Usually absent
Duration of amiodarone therapy	Shorter (1-2 years)	Longer (>2 years)
RAIU	Low, normal or high	Low/suppressed
Interleukin -6	Slightly increased	Markedly increased
Thyroid ultrasound	Increased parenchymal blood flow	Normal or decreased blood flow
Therapy	Thionamides, perchlorate, lithium	Prednisone, lithium
Subsequent hypothyroidism	No	Possible

Adapted from refs 2, 3.

TMNG = toxic multinodular goiter

AFTN = autonomously functioning thyroid nodule



Pregnancy and lactation

GD is the commonest cause of hyperthyroidism presenting in pregnancy; however, it needs to be distinguished from gestational hyperthyroidism mediated by βHCG.

The latter is characterised by the absence of ophthalmopathy or a large goitre, absent Trab, and spontaneous resolution of hyperthyroidism by 20 weeks of gestation.

Back to basics

Thyroid disease and pregnancy

Sandra Lowe
MBBS FRACP MD

Thyroid disease may affect all aspects of obstetrics and gynaecology, from fertility to fetal outcome. The recognition of these conditions and their practical impact on obstetrics is discussed in the following brief review.

Normal pregnancy

Normal pregnancy is associated with a 50 per cent increase in thyroid hormone production which is required to maintain normal free T3 and T4 levels in the presence of an increase in thyroid binding globulin. The fetal thyroid does not become functional until around 12 weeks gestation and does not produce significant amounts of hormone until 18 to 20 weeks gestation. Prior to that time, the fetus is completely dependant upon transplacental transfer of maternal thyroid hormone. Later in pregnancy, maternal thyroid hormone contributes approximately 20 to 30 per cent of fetal thyroid hormone levels, but even this small contribution appears to be critical for fetal development.

Normal pregnancy is associated with potential iodide deficiency secondary to increased renal excretion of iodide. If iodide deficiency occurs, as had been demonstrated in a number of studies in Australia, there may be both maternal and fetal consequences. These include goitre, subclinical or clinical hypothyroidism and even fetal cretinism. Recommended iodide intake for pregnant women or women planning pregnancy is 150 to 250 µg daily. A number of standard pregnancy vitamin supplements now include iodide and these should be recommended, especially when the intake of iodised salt is low.

Even in iodide replete women, the thyroid gland may be palpable due to increased vascularity. The investigation of goitre in pregnancy should be limited to thyroid function tests (specifically requesting at least TSH and free T4) and ultrasound of solitary nodules or multinodular goitre if not previously investigated. In some cases, fine needle biopsy of the dominant nodule may be indicated if any of the nodules are > 10 mm in diameter, especially solid compared with cystic nodules. Nuclear thyroid scanning is contraindicated at all stages of pregnancy. Thyroid cancer is uncommon and the prognosis does not appear to be adversely affected by pregnancy.

A significant number of women (around ten per cent) will have circulating antithyroid antibodies, particularly to thyroid peroxidase, which even in the absence of clinical or biochemical thyroid dysfunction have been associated with adverse outcomes in pregnancy. Negro et al demonstrated an association between positive antithyroid antibodies and both miscarriage and preterm delivery, even in euthyroid women. These events were reduced by the administration of thyroxine.

Hypothyroidism

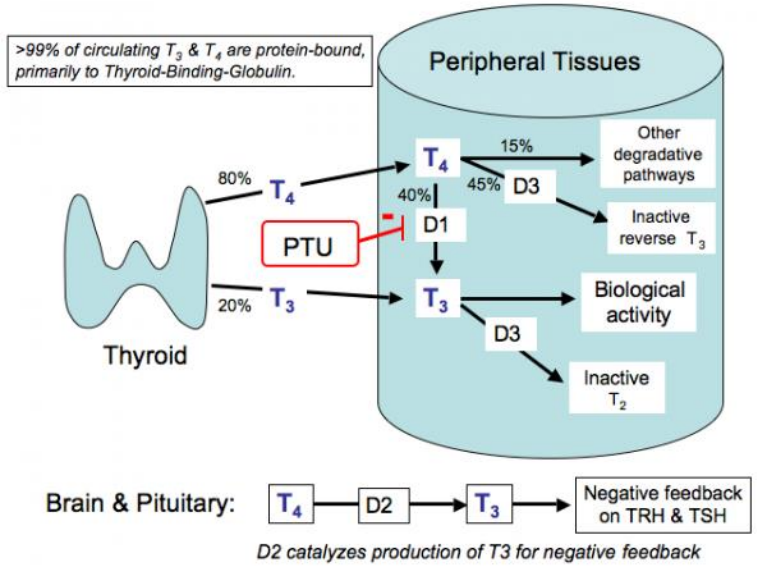
Inadequate circulating thyroid hormone may lead to amenorrhoea, reduced libido and subsequent sub- or infertility. If pregnancy does occur, there is an increased incidence of miscarriage, hypertension and placental abruption. Fetal complications include: fetal distress, preterm delivery, low birth weight, and fetal/perinatal death. Treatment with thyroid hormone replacement has been demonstrated to reduce these risks, including miscarriage. The risk of these complications is greatest in women with overt hypothyroidism compared with subclinical hypothyroidism. Of most concern is the increasing data supporting an association between maternal thyroid deficiency during pregnancy and problems with neuropsychological development of the offspring. Such problems can occur even with milder degrees of thyroid deficiency. Although theoretically adequate thyroid replacement therapy should reduce these risks, currently there is little evidence to support this.

'Normal pregnancy is associated with a 50 per cent increase in thyroid hormone production'

Despite these findings, screening of asymptomatic pregnant women is not recommended, although a TSH measurement would appear to be a sensible precaution prior to conception if feasible. In women with overt or subclinical hypothyroidism, serum TSH should be measured as soon as possible after a positive pregnancy test. Dose adjustments or initiation of therapy is made with increments of 50 to 100 µg/day of thyroxine based on maintaining the free T4 in the upper half of the normal range and the TSH within the lower end of the normal range. This should be rechecked six weeks after any change in dose or at least once each trimester. Another approach recommended by one group is to increase the dose by about 30 per cent as soon as pregnancy is confirmed, with further dose changes as above. In women with previous thyroid cancer, the dose should be adjusted to maintain TSH levels below 0.5 µU/mL. The dose can be reduced to pre-pregnancy levels after delivery but serum

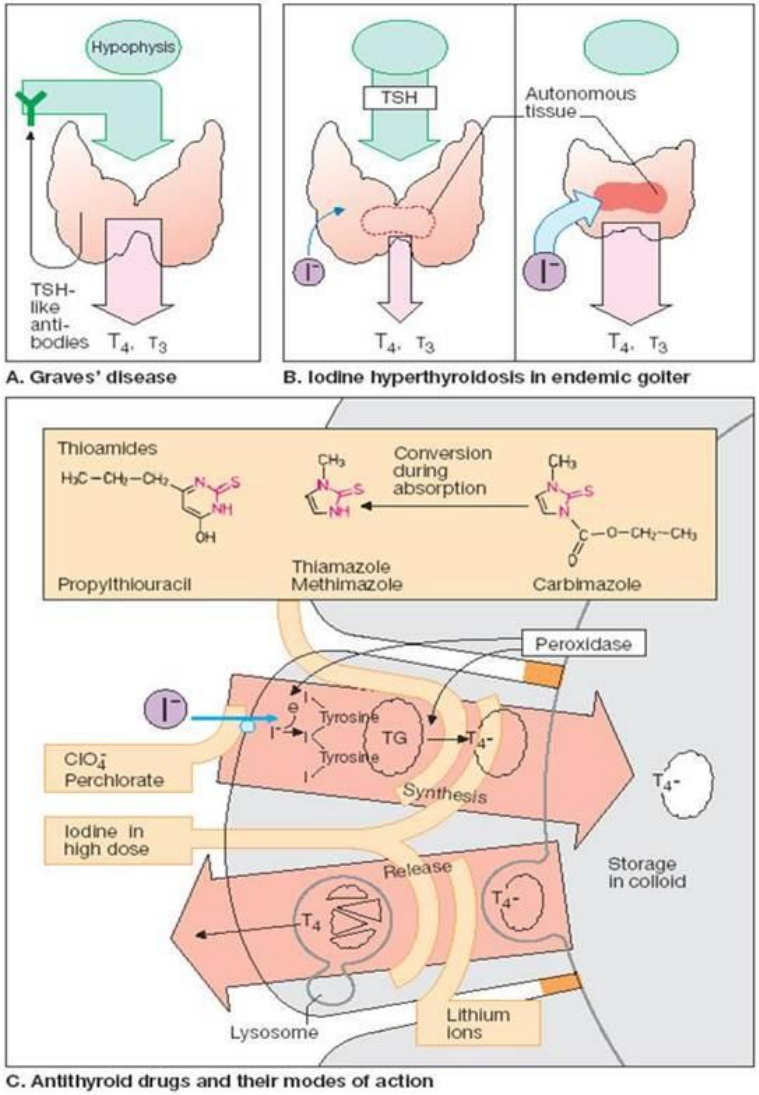
Pregnancy and lactation

- **Antithyroid drugs are the mainstay of treatment for hyperthyroid GD in pregnancy, and a titrated dose regimen is mandatory as block-replace regimens are associated with a risk of fetal hypothyroidism and goitre.**
- **There is evidence for a small risk of embryopathy with all antithyroid drugs.**
- **Current guidelines recommend that PTU is preferred during the first trimester of pregnancy.**
- **If women of childbearing age present with hyperthyroid GD and express the wish for future pregnancy, the advantages of early definitive treatment with radioiodine or surgery should be discussed.**



Pregnancy and lactation

Breast feeding is safe with all antithyroid drugs (daily doses of up to 20 mg methimazole or carbimazole or 300 mg PTU); however, because of the small risk of severe liver toxicity associated with PTU, the current guidelines recommend methimazole or carbimazole as the preferred antithyroid drugs for lactating women.



Subclinical hyperthyroidism
SHy

SHy refers to a state of low or suppressed serum TSH levels with normal circulating fT4 and fT3 levels. It occurs in 2-3% of patients over the age of 80 years, with around 0.7% having the more important abnormality of suppression of serum TSH levels to <0.1 mIU/L.

More than 50% of patients with SHy, and particularly those with a low but not suppressed TSH level (range 0.1-0.4 mIU/L), have a transient abnormality.

A low or suppressed TSH level may also be caused by several drugs, including opiates, levodopa, anti-inflammatory doses of glucocorticoid, metformin, and levothyroxine. In addition, persistently low or suppressed serum TSH levels can presage more major systemic illness, such as chronic infection or covert cancer.

Table 1. **Classification of Thyroid Dysfunction**

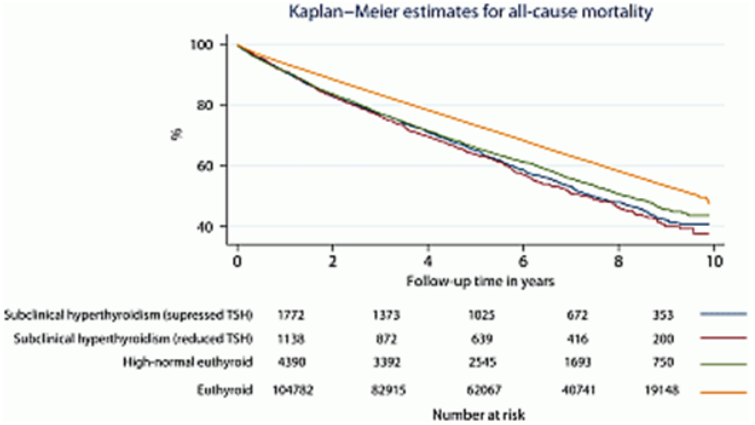
Type	Biochemical Criteria	
	TSH Level	Thyroid Hormone Level
Overt hyperthyroidism	Low or undetectable	Elevated FT_4 or FT_3
Subclinical hyperthyroidism	Low or undetectable	Normal FT_4 and FT_3
Overt hypothyroidism	>5 mU/L	Low FT_4
Subclinical hypothyroidism	>5 mU/L*	Normal FT_4

* Others use different cutoffs. FT_4 = serum free thyroxine; FT_3 = serum free triiodothyronine; TSH = thyroid-stimulating hormone.

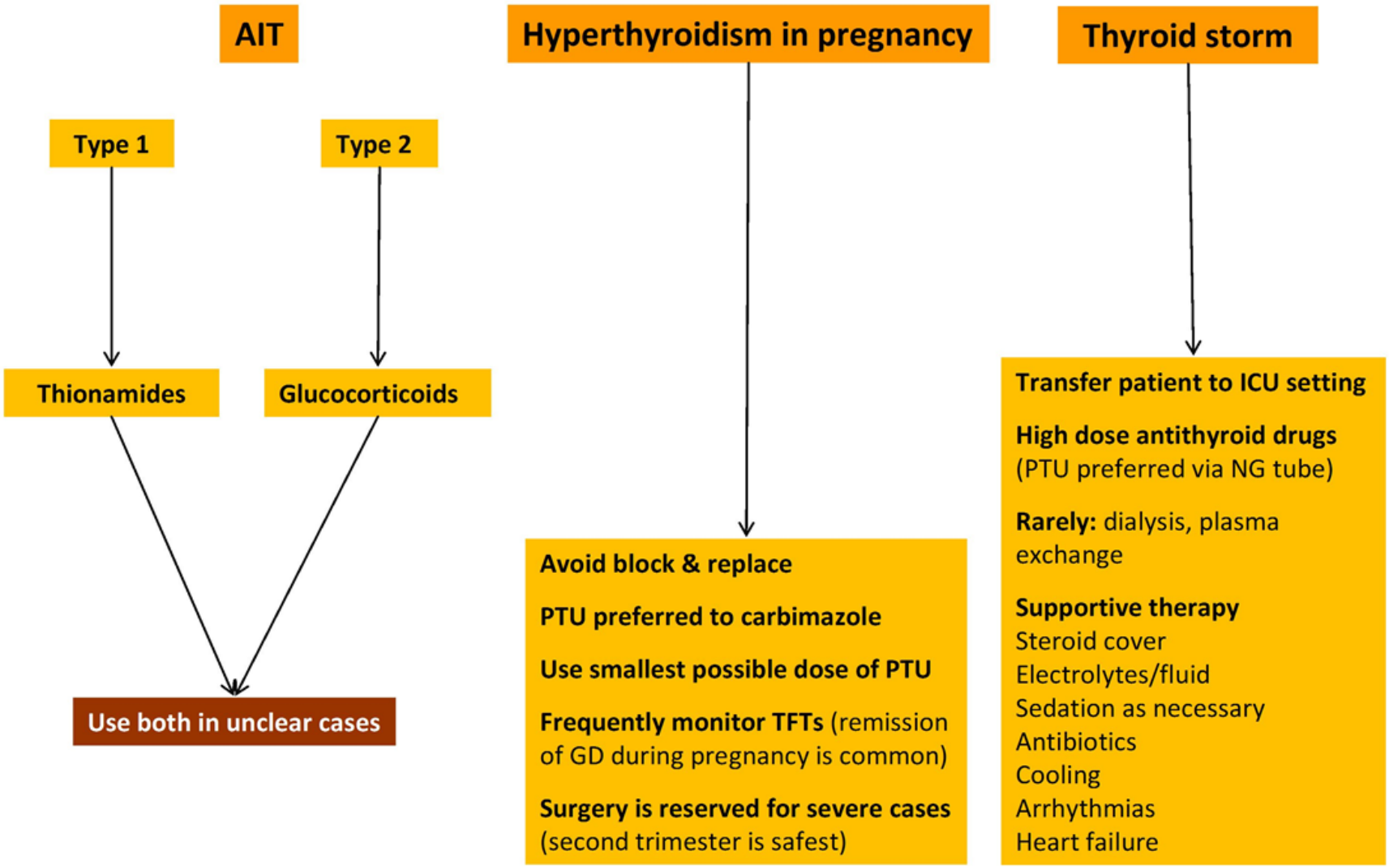
Subclinical hyperthyroidism

Although epidemiological studies show that a low serum TSH level is associated with an increased risk of atrial fibrillation, and in some studies excess vascular mortality, only a few patients have evidence of intrinsic thyroid disease.

Current opinion favours consideration of antithyroid treatment in patients aged more than 65 years with a persistently suppressed TSH level (<0.1 mIU/L), particularly in the presence of atrial fibrillation or other cardiac problems. In people with untreated subclinical hyperthyroidism, thyroid function tests should be carried out annually to detect progression to overt thyrotoxicosis.



Management of special cases of hyperthyroidism



ICU: Intensive Care Unit