
بسم الله الرحمن الرحیم

Management of Hyperthyroidism

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مرکز تحقیقات دیابت

Agenda

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- Diagnosis
- Cause of the hyperthyroidism
- Indications for treatment
- Therapeutic approach
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- Pretreatment evaluation
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- Evaluation prior to stopping therapy
- Monitoring for recurrence
- Predictors of remission

Clinical manifestations

- Overt hyperthyroidism : Most patients with overt hyperthyroidism have a dramatic constellation of symptoms
- These symptoms characteristically include:

- Anxiety
- Weakness
- Tremor
- Palpitations
- Heat intolerance
- Increased perspiration
- Weight loss (Despite a normal or increased appetite)

Hyperthyroid symptoms :

May be present in patients with subclinical disease and

Absent in those with overt disease, especially older adults

Clinical manifestations

- Hyperdefecation (not diarrhea)
- Urinary frequency
- Oligomenorrhea or amenorrhea in women
- Gynecomastia and erectile dysfunction in men
- Osteoporosis
- Hypercalcemia
- Heart failure
- Shortness of breath
- Deterioration in glycemic control in patients with previously diagnosed diabetes

Older patients

Cardiopulmonary symptoms may predominate such as:

- Tachycardia (or AF)
- Dyspnea on exertion
- Edema

Physical examination

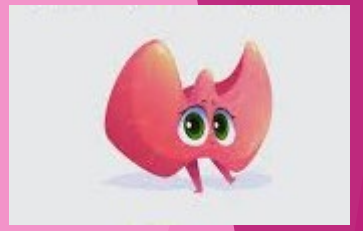
- Hyperactivity and rapid Speech
- Stare (lid retraction) and lid lag (representing sympathetic hyperactivity)
- Warm and moist skin
- Thin and fine hair
- Tachycardia (the pulse is irregularly irregular in patients with AF)

- Systolic HTN
- Hyper dynamic precordium
- Tremor
- proximal muscle weakness
- Hyperreflexia

Only in greaves

- Exophthalmos
- periorbital and conjunctival edema
- limitation of eye movement
- Infiltrative dermopathy (pretibial myxedema)

DIAGNOSIS



All patients with primary hyperthyroidism have :

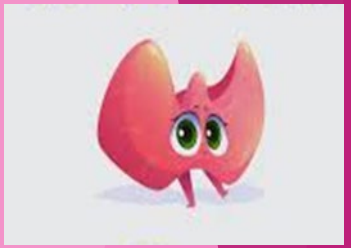
- **low TSH** (The serum TSH concentration alone cannot determine the degree of biochemical hyperthyroidism)
- In patients with subclinical hyperthyroidism, TSH is below normal (but more frequently >0.05 mU/L)

Nonspecific laboratory findings:

- low serum LDL،HDL (increase after treatment)
- Increased RBC mass but plasma volume is increased more

(resulting in a normochromic, normocytic anemia)

- High Serum AIP and osteocalcin (indicative of increased bone turnover)



- **Overt hyperthyroidism** :Except for laboratory error or assay interference due to biotin ingestion, all patients with low serum TSH and high free T4 and/or T3 concentrations have primary hyperthyroidism

- **T3-toxicosis** :Most patients with overt hyperthyroidism caused by Graves' disease or nodular goiter have greater increases in serum T3 than in serum T4

(An occasional patient will have normal serum T3 and free T4 levels but an elevated serum **free T3**)

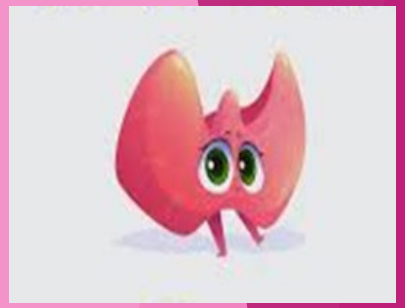
- **T4-toxicosis** : The pattern of low TSH, high serum free T4, and normal T3

Subclinical hyperthyroidism

- Most of these patients have **no clinical** manifestations of hyperthyroidism
- Those symptoms that are present are **mild and nonspecific**

- **Diagnosis :**
- low serum TSH concentrations (<0.4 mU/L)
- Normal serum free T4, T3, and free T3 concentrations

Subclinical Hyperthyroidism Differential Diagnosis



- Central hypothyroidism : low serum TSH and normal (but usually low-normal) free T4 and T3 concentrations

- Nonthyroidal illness : Euthyroid patients with nonthyroidal illness, especially those receiving high-dose glucocorticoids or dopamine, may have low serum TSH , low or low-normal free T4 and very low serum T3

- Recovery from hyperthyroidism : Serum TSH may remain low for up to several months after normalization of serum T4 and T3 in patients treated for hyperthyroidism

- The "physiologic" lowering of serum TSH in pregnancy

- An altered set point of the hypothalamic-pituitary-thyroid axis in some otherwise healthy older persons

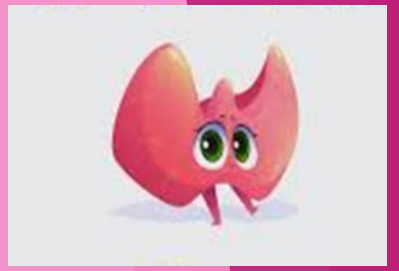
Cause of the hyperthyroidism

- Once the diagnosis of **hyperthyroidism** has been established, the cause of the hyperthyroidism should be determined

- If the diagnosis is not apparent based on the clinical presentation, diagnostic testing is indicated and can include :

- Measurement of thyrotropin receptor antibodies (TRAb)
- Determination of the radioactive iodine uptake
- Measurement of thyroidal blood flow on ultrasonography

Cause of the hyperthyroidism



Hyperthyroid patient :
without a nodular thyroid and
without obvious clinical manifestations of Graves' disease
(eg, without ophthalmopathy)

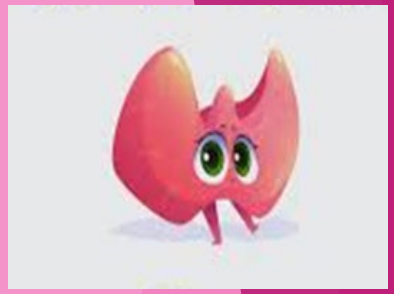
- Measurement of TRAb
- Determination of radioactive iodine uptake
- Assessment of thyroidal blood flow on ultrasonography
- Are acceptable options to distinguish Graves' disease from other causes of hyperthyroidism

TRAb

- If positive, it confirms the diagnosis of Graves' disease.
- If negative, it does not distinguish among the etiologies, as TRAb may not be elevated in patients with mild Graves' disease

In this setting:
1. Radioactive iodine uptake
2. Assess thyroidal blood flow on ultrasound

Cause of the hyperthyroidism

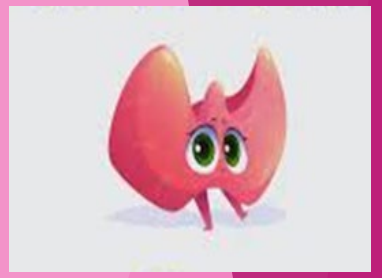


Hyperthyroid patients with physical examination findings consistent with or suspicious for **nodular thyroid** disease:

- Obtain a radioactive iodine uptake and
- Isotope scan as initial test to distinguish :

- Toxic MNG
- Toxic adenoma
- Graves' disease

Toxic adenoma and TOXIC MNG



- A radioactive iodine uptake scan is an **initial test** to:

1. Distinguish toxic MNG and toxic adenoma from Graves' disease, or
2. Assess the functionality of nodules, which may coexist with Graves' disease

There are two clinical situations in which establishing the diagnosis of a toxic adenoma or toxic MNG is more difficult

- **First:** The autonomously functioning tissue may be sufficiently diffuse that it is difficult to differentiate an MNG from Graves' disease by **thyroid scintigraphy alone**

When it is important to distinguish these disorders:

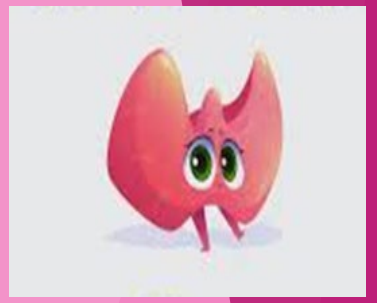
A high serum concentration of TRAb usually indicates Graves' disease

A low titer TRAb may not exclude the diagnosis in patients with very mild hyperthyroidism

- **Second:** In iodine-induced hyperthyroidism, the exogenous iodine load can dilute the radioiodine tracer and result in both a low radioiodine uptake

Repeat scanning weeks or months later may be necessary

INDICATIONS FOR TREATMENT



- **overt hyperthyroidism** All patients require treatment
- Normal thyroid function Patients with large goiters and symptoms of obstruction require treatment even if thyroid function is normal
- **subclinical hyperthyroidism** The decision to treat is based upon the risk for developing complications such as(skeletal, cardiovascular) and the degree of TSH suppression

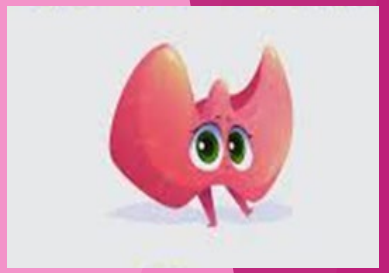
Therapeutic approach to graves' hyperthyroidism

- **Symptom control** :A **beta blocker** should be started in most patients as soon as the diagnosis of hyperthyroidism is made

(even before confirming that the cause of hyperthyroidism is Graves' disease)

- Beta blockers ameliorate the symptoms of hyperthyroidism that are caused by increased beta-adrenergic tone (palpitations, tachycardia, anxiety, heat intolerance)

Treatment options



- There are three treatment options for Graves' disease:
- Antithyroid drugs (thionamides)
- Radioiodine
- Surgery

- **Choice of therapy**
- For patients with Significant **symptoms** of hyperthyroidism, or
- patients with a significant **risk** of hyperthyroid complications (eg, older age, cardiovascular disease)

Suggest starting a thionamide (in addition to beta blockers)

to achieve euthyroidism quickly

Thionamides

- The goal of thionamide therapy in Graves' hyperthyroidism is to

  Attain a euthyroid state within **three to eight weeks**

- This can be followed by:
- Ablative therapy with radioiodine
- Ablative therapy with surgery
- Continuation of the drug for one to two years or for long-term therapy

Remission: the percentage of patients who remain Euthyroid one year after the drug is withdrawn

- Antithyroid drugs will control hyperthyroidism in **most patients**
- But remission rates average **under 40 %** after one to two years of treatment

- Remission is more likely in patients with:
- Mild hyperthyroidism
- Patients with small goiters
- With goiters that shrink during thionamide therapy

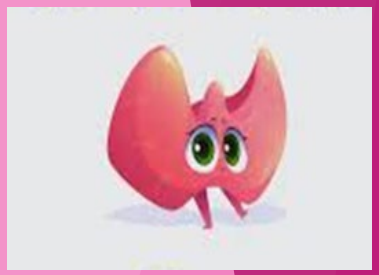
Pretreatment evaluation

- Prior to initiating thionamides, obtain baseline blood tests, including:
- **CBC** (white count with differential) and
- **liver profile** (bilirubin and transaminases)

- Do not use thionamides in patients with a baseline absolute neutrophil count <1000 cells/microl
- or
- Elevated liver transaminases (more than fivefold the upper limit of normal)

- Thionamide drugs are contraindicated in patients with a previous major adverse reaction (eg, agranulocytosis, hepatotoxicity, pancreatitis)

Choice of thionamide



- **Methimazole** is the primary drug used to treat Graves' hyperthyroidism because :

- longer duration of action(allowing for once-daily dosing)
- Rapid efficacy
- lower incidence of side effects

There are three clinical settings in which ptu is preferred:

- In patients during the first trimester of pregnancy
- For the initial management of life-threatening thyrotoxicosis or thyroid storm
- In patients with **minor reactions** to methimazole who do not want definitive treatment with radioiodine or surgery

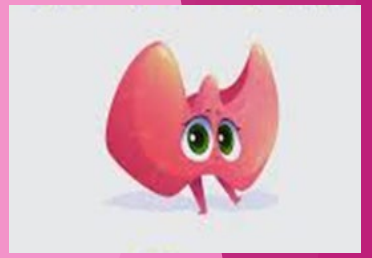
Dosing

- The starting dose of methimazole varies according to the severity of the hyperthyroidism

- Patients with small goiters and **mild hyperthyroidism , FT4 levels 1 to 1.5** times the upper limit of normal, can be started on **5 to 10 mg once daily**

- Patients with **FT4 levels ,1.5 to 2 times** the upper limit of normal can be started on **10 to 20 mg daily**

- Patients with larger goiters and more **severe hyperthyroidism ,FT4 levels approximately 2 to 3** times the upper limit of normal should be started on **20 to 40 mg daily**



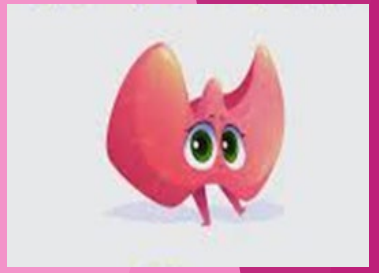
- For patients taking ≥20 mg daily, administer initial therapy in divided doses for **a week or two:**
- To normalize thyroid function more quickly and
- To minimize gastrointestinal (GI) side effects
  and then change to single daily dosing (unless GI side effects persist and are minimized by divided dosing)

- If long-term medical therapy is chosen, the dose of methimazole is then tapered to a maintenance dose
  (Typical maintenance doses average **5 to 10** mg **once daily**)
  with the goal of maintaining a euthyroid state

Surgery is indicated

- Severe hyperthyroidism and a large goiter
- Allergic to thionamides and are unable to or do not want to receive radioiodine
- Obstructive goiter or a very large goiter
- Moderate to severe, active orbitopathy who desire definitive therapy for their hyperthyroidism
- In pregnant women who are allergic to antithyroid drugs
- Allergies or poor compliance on antithyroid drugs but refuse radioiodine
- coexisting suspicious or malignant thyroid nodule
- coexisting primary hyperparathyroidism

Monitoring after treatment



- **Initial monitoring:** should consist of
- Periodic clinical assessment and
- Measurements of serum free T4 and often total T3 levels

- Serum TSH concentrations should be interpreted with caution since they may remain low for several weeks after the patient becomes euthyroid

- In comparison with the importance of serum T3 and T4 values, serum TSH values may be misleading during the initial period of treatment

- Pituitary TSH production is suppressed by hyperthyroidism, an effect that can persist for several months after serum T4 and T3 concentrations become normal

- As a result, serum TSH concentrations are often low despite normal or even low serum T4 and T3 concentrations during the first several months of treatment

- Patients should have their thyroid function assessed
- At four- to six-week intervals until stabilized on maintenance thionamide
- Then at three- to six-month intervals

- Patients with persistently low serum TSH concentrations after more than six months of therapy with a thionamide are unlikely to have a remission when the drug is stopped

- Patients with persistently high levels of TRAb after one or more years of treatment are also unlikely to remain euthyroid if thionamides are discontinued

Adverse effects

- Complications, are rare but serious
- Agranulocytosis
- Hepatotoxicity
- Pancreatitis

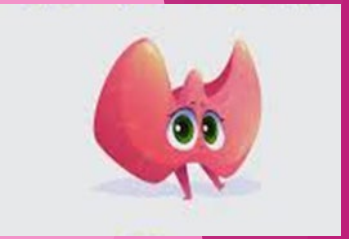
- It is preferable that information about serious adverse events be given to the patient in writing and discussed at each follow-up visit

Adverse effects

- Controversy exists as to the value of monitoring white blood cell counts

- We do not routinely monitor white blood cell count (for the development of agranulocytosis) or liver function tests (for the development of hepatotoxicity) in patients taking thionamides

- A CBC (white count with differential) should be obtained during any febrile illness and at the onset of pharyngitis



- Liver function should be assessed in patients with signs or symptoms of hepatitis (eg, jaundice, light-colored stool or dark urine, pruritic rash)

- Amylase and lipase should be measured in patients with nausea, vomiting, and abdominal pain

- Patients should be instructed to discontinue thionamides and contact the clinician when there are such symptoms

Approach to stopping therapy
&
Duration of therapy

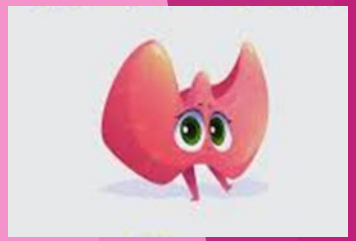
Methimazole as primary therapy

- For patients taking methimazole as primary therapy, it should initially be continued for 12 to 18 months

- If remission is not obtained after a 12- to 18-month ,long-term treatment with methimazole for 10 years or more has been shown to be effective and safe

- Remission rates are lower if patients are treated for less than 18 months

Evaluation prior to stopping therapy



- 1. In patients with normal TFT , measure serum TRAbs, initially **after 12 to 18** months of thionamide therapy :

- Thionamides can be discontinued if TRAbs and TSH are normal

- Patients with normal levels TRAbs have a greater chance for remission (up to 80 %)

Evaluation prior to stopping therapy

- 2. Persistently **high levels of TRAbs** are associated with very high relapse rates

  Such patients should either:

- Continue methimazole or
- proceed with definitive therapy (radioiodine or surgery)

- 3. In some patients with **borderline elevated TRAbs**:
- Methimazole can be discontinued
- They should be monitored frequently and plan on definitive therapy as soon as recurrent hyperthyroidism is documented

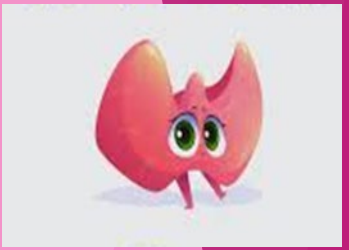
Monitoring for recurrence

- For patients with normal TRAbs and TSH (12 to 18 months) &discontinuation of thionamides , TFT measured initially at two- to three-month intervals
- Beginning two to three months after stopping treatment
- Earlier measured if the patient notes recurrent hyperthyroid symptoms

- If TFT remain normal for six months, monitoring should occur at four- to six-month intervals for the next six months and then every 6 to 12 months

- For patients who remain euthyroid for a year, TSH can be performed annually

Time of relapse



- Recurrent hyperthyroidism is initially manifested by a low serum TSH concentration
- The time to relapse is related to the presence or absence of TRAbs
- In TRAbs-positive patients, relapse can occur as soon as 10 days after drug cessation
- In TRAbs-negative patients, it can take many months or even years for recurrence to develop
- Recurrences are particularly common in the postpartum period in women who were previously in remission after thionamide treatment

Treatment of recurrence

For patients with recurrent hyperthyroidism after a course of methimazole:

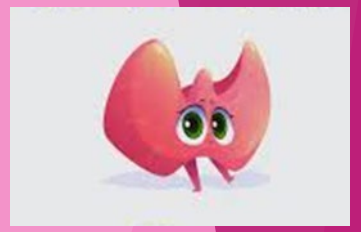
1. Radioiodine
2. Surgery
3. A longer course of methimazole are all reasonable options

If long-term methimazole is chosen:

TRAb levels can be monitored every **1-2 years**

Mechanism of remission

There are three mechanisms whereby patients with graves' disease can achieve a spontaneous remission:



1. A fall or disappearance of TRAbs

2. Destruction of functioning thyroid tissue by extensive lymphocytic infiltration, may prevent the gland from responding to TRAbs and can eventually result in spontaneous hypothyroidism

3. Serum TPO concentrations correlate with the degree of lymphocytic infiltration, and patients with higher concentrations have a higher rate of spontaneous "remission" of Graves' disease

- Rarely, remission can be associated with the appearance of **thyrotropin receptor-blocking antibodies** (also called thyroid-blocking immunoglobulins), which occupy the thyrotropin receptor and block the stimulatory action of TSH or TRAbs

These patients can spontaneously develop hypothyroidism and occasionally fluctuate between hyperthyroidism and hypothyroidism states depending upon the relative titers of stimulating and blocking antibodies

Predictors of remission

- Patients who are initially TRAb negative (77 versus 36 %)
- Disappearance of TRAbs during thionamide therapy
(70 to 80 % chance of remission)
- Women
- patients with mild hyperthyroidism
- patients over age 40 years
- patients with a small goiter or a goiter that shrinks during thionamide therapy
- Those with high serum TPO concentrations
- Cessation of cigarette smoking
- Longer duration of therapy improves remission rates
(>84 % after 5 to 10 years of treatment)

Toxic adenoma and Toxic multinodular goiter (MNG)

Therapeutic approach

- Treatment of hyperthyroidism due to toxic adenoma or toxic MNG consists of both:

1. Symptomatic relief with beta blockers and

2. Decreasing the production of thyroid hormone with radioiodine ablation or surgery

3. prolonged (probably lifelong) thionamide therapy is an increasingly popular option for patients who would like to avoid both radioiodine and surgery

Choice of therapy

- Surgery is prefer for patients with :
- Very large goiters (>80 g)
- Symptoms or signs of compression/obstruction
- Need for rapid return to euthyroidism
- Coexisting thyroid cancer
- Coexisting primary hyperparathyroidism

- In the absence of one of these indications for surgery, radioiodine, antithyroid drugs, or surgery are all options

- Radiation safety regulations in some countries advise mothers receiving radioiodine to severely limit the time spent with their infants for up to **five days**

- If suitable childcare is unavailable, patients may opt to take thionamides for several years prior to receiving radioiodine, or may choose surgery over radioiodine

- The patient's fears regarding radiation exposure, general anesthesia, or surgical complications :

- For them, prolonged thionamide therapy is acceptable as long as it is **tolerated** and the hyperthyroidism is **controlled**

- Percutaneous ethanol injection
- RFA or
- laser therapy

are alternatives to prolonged thionamide therapy

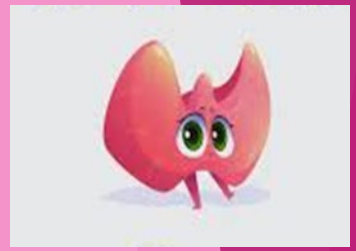
Subclinical hyperthyroidism

In patients at high risk for skeletal or cardiac complications (older patients **≥65 years**, patients with or at risk for **CVD**, or postmenopausal women with or at risk for **osteoporosis**), use the following approach

- If the serum TSH value is **<0.1** mU/L, **treat** the underlying cause

- If the serum TSH is **0.1 to 0.5** mU/L, **treatment suggested**, especially if there is :
- Underlying cardiovascular disease
- low bone density
- patient has hyperthyroid symptoms

Subclinical hyperthyroidism



Patients at low risk for complications (individuals <65 years, premenopausal women),use the following approach

- If the serum TSH value is **persistently <0.1** mU/L, suggest **treating** the underlying cause of subclinical hyperthyroidism, especially if the patient has :
- symptoms suggestive of hyperthyroidism and
- patient's thyroid radioiodine scan shows one or more focal areas of increased uptake

- If the TSH is between **0.1 to 0.5** mU/L, **observation** alone is appropriate.
- Measure TSH, free T4, and T3 every six months

Treatment options

- Subclinical hyperthyroidism treatment options are the same as those for overt hyperthyroidism and depend upon the underlying etiology

- Beta-adrenergic antagonist are useful to control symptoms of adrenergic over activity (eg, palpitations, tremor)