Thyrotoxicosis

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Thyrotoxicosis & Hyperthyroidism

Thyrotoxicosis:

A clinical state that results from inappropriately high thyroid hormone action in tissues generally due to inappropriately high tissue thyroid hormone.

Hyperthyroidism:

Is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone by the thyroid gland.

Causes of Hyperthyroidism

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 (hashitoxicosisÃ¢â‚¬â„¢autoimmune)
- Acute thyroiditis (bacterial infection)
- Drug-induced thyroiditis (amiodarone, interferon-ÃŽÂ³)

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

Causes of Thyrotoxicosis

Thyrotoxicosis with hyperthyroidism (primary)

- Grave,s disease
- Toxic adenoma
- Toxic multinodular goiter
- Activation mutation of TSH receptor
- Stroma ovary
- Functioning metastatic thyroid cancer
- Iodine : Jod-Basedow phenomenon

Causes of Thyrotoxicosis

Thyrotoxicosis without hyperthyroidism

- Subacute thyroiditis
- Silent thyroiditis
- Thyroid destruction: Amiodarone, Radiation
- Thyrotoxicosis Factitia

Causes of Thyrotoxicosis

Secondary hyperthyroidism

- TSH-secreting pituitary adenoma
- Thyroid hormone resistance syndrome
- Chorionic gonadotropin secreting tumors

Thyrotoxicosis

Symptoms

Nervousness
Fatigue
Heat intolerance
Weight loss
Palpitation
Hyperphagia
Hyperdefecation
Proximal muscle weakness
Tremor
Irregular menses
Restlessness
Irritability
Anxeity

Signs

Warm & moist skin
Hyperhydrosis
Alopecia
Onycholysis
Vitiligo
Pretibial myxedema
Acropachy
Tachycardia
Increased pulse pressure
Scratch murmur
Fine tremor
Hepatomegaly
Muscle atrophy
Gynecomastia
Orbitopathy

Grave's Disease

The most common form of thyrotoxicosis,

accounts for 60–80% of thyrotoxicosis

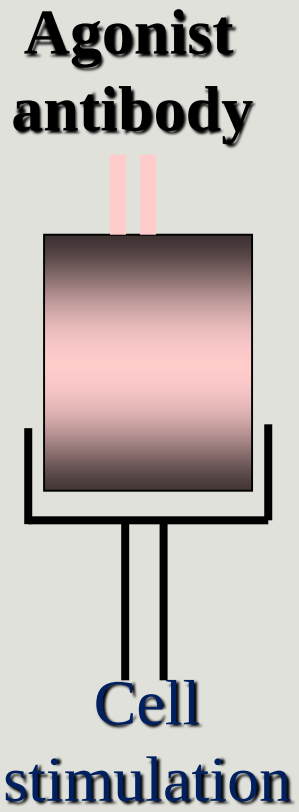
More common in female than male (5:1)

Is an autoimmune disorder: thyroid receptor stimulating antibody (TSI)

HLA-B8, HLA-DR3, HLA-BW35, HLA-BW40, 46

Occurs in up to 2% of women(20-50 y.)

Thyroid receptor stimulating antibody (TSI)

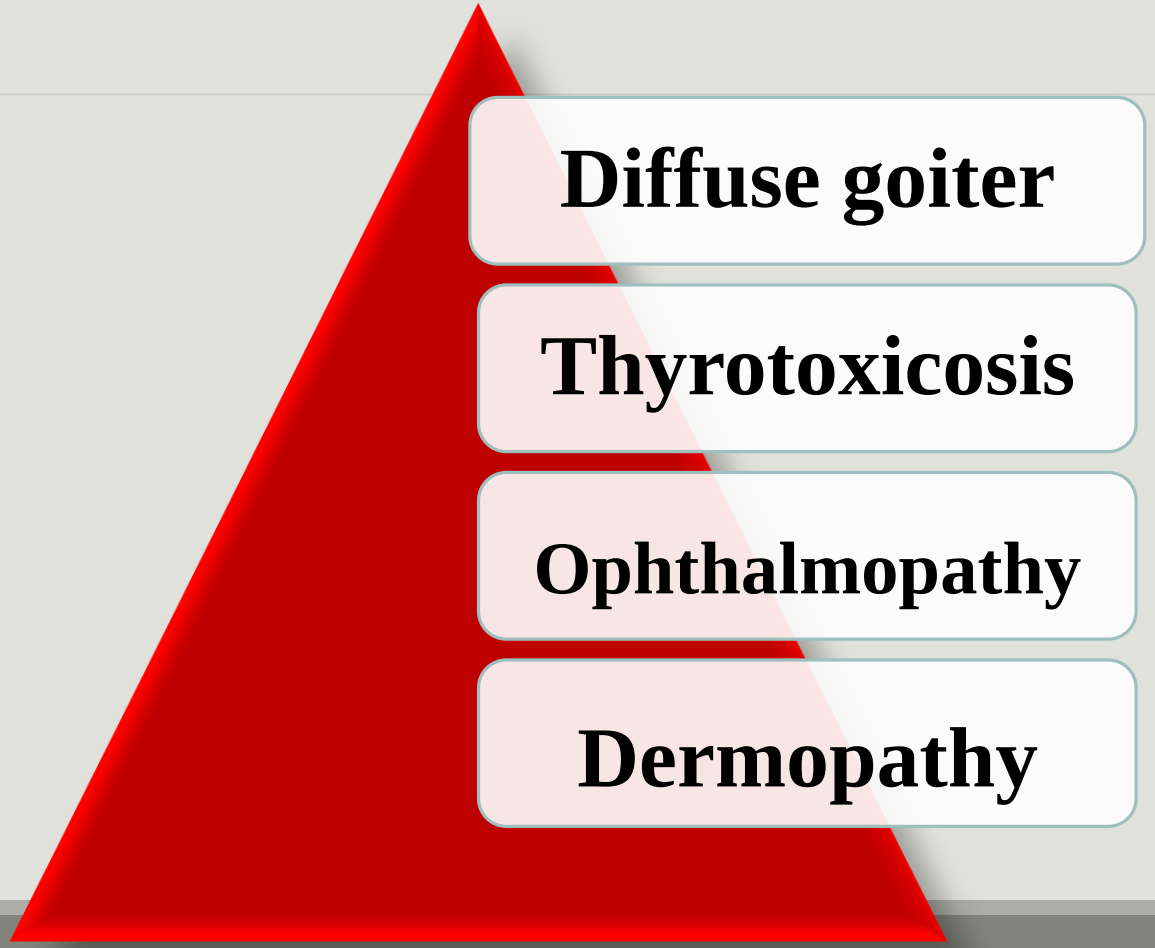


Pathogenesis

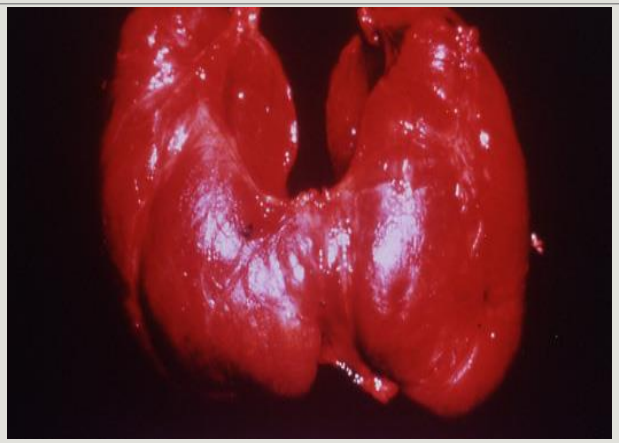
Grave's Disease

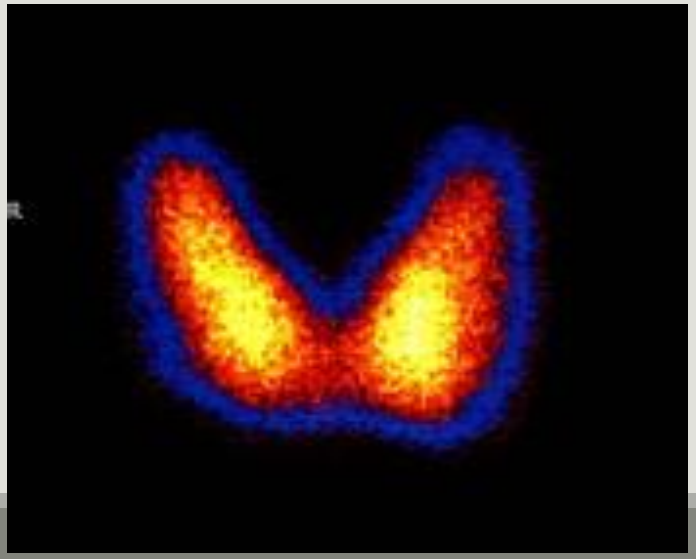
- The concordance for graves' disease in monozygotic twins is 20–30%, compared to <5% in dizygotic twins.
- Combination of environmental and genetic factors, including polymorphisms in HLA-DR
- Stress and smoking are important environmental factors.
- Sudden increases in iodine intake.
- Postpartum period.

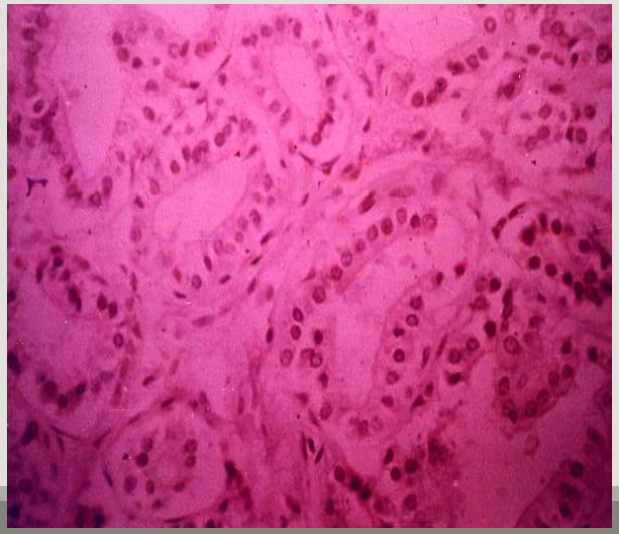
Clinical Manifestation **Grav,s**:



Grave,s Dis. : Diffuse goiter







Graves : Ophtalmopathy

It is an autoimmune process.

Incidence:

- female 16/ 100,000
- male 3/ 100,000

Clinically observed = 30%

Imaging > 70%

Sever (male > female) = 5%

Usually bilateral

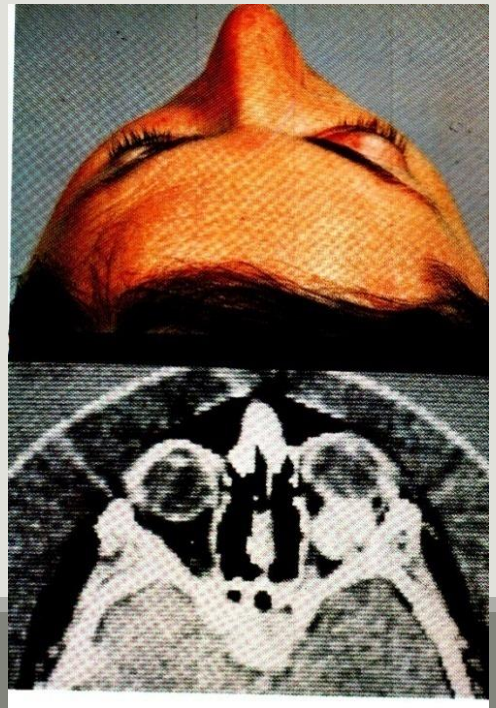
Coincident with thyrotoxicosis (most cases)

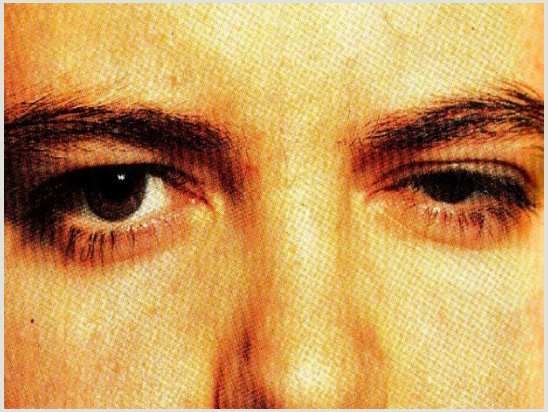
Euthyroid ophthalmopathy (10 - 15 %)

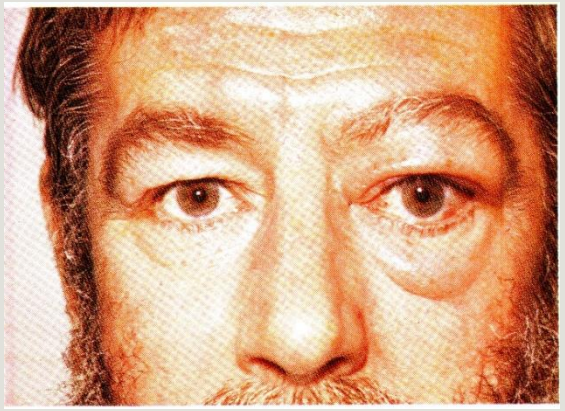
Grav,s : Ophtalmopathy

- Lacrimation
- Photophobia - Sandy sensation
- Fish eye - Proptosis
- Blurred vision - Diplopia
- Periorbital edema
- Pain (intermittant - sustain)
- Ophthalmoplegia
- Sight loss

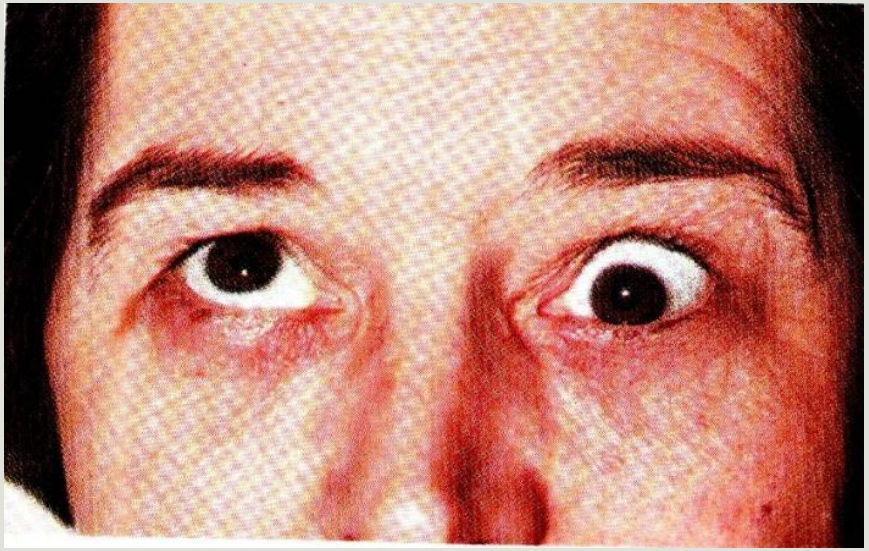
GRAVE,S : Eye Signs







GRAVE,S : Eye Signs



OPHTALMOPLASIA

Graves : Thyroid Dermopathy

- Occurs in <5% of patients with Graves' disease.

Although most frequent over the anterior and lateral aspects of the lower leg (*pretibial myxedema*), skin changes can occur at other sites.

The typical lesion is a noninflamed, indurated plaque with a deep pink or purple color and an "orange skin" appearance.

- Nodular involvement can occur, and the condition can rarely extend over the whole lower leg and foot, mimicking elephantiasis.

Grave's : Dermopathy

Pretibial and shoulder myxedema

Grave's : Acropachy

Clubbing

Onycholysis

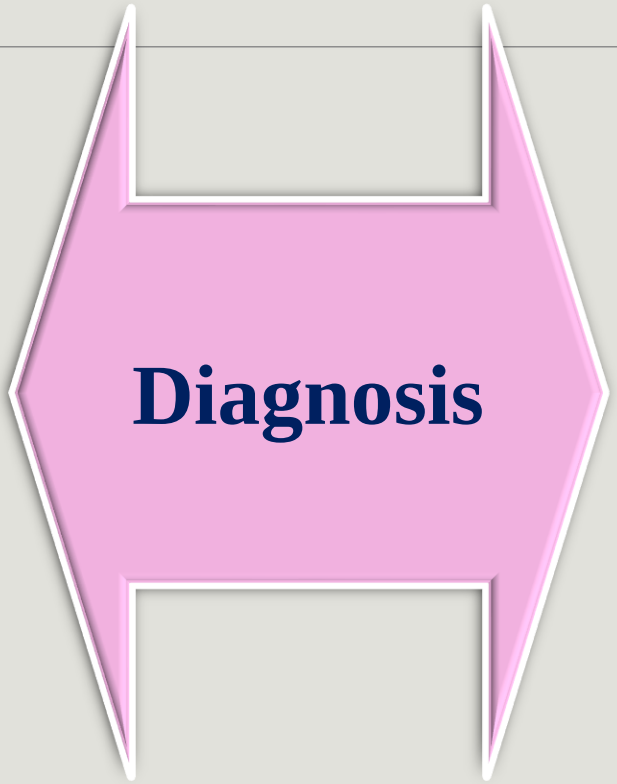
Palmar erythema

Confirmation of thyrotoxicosis

↑ Free T3

↑ Free T4

↓ TSH



Definition of etiology

TRAb

TPO-Ab

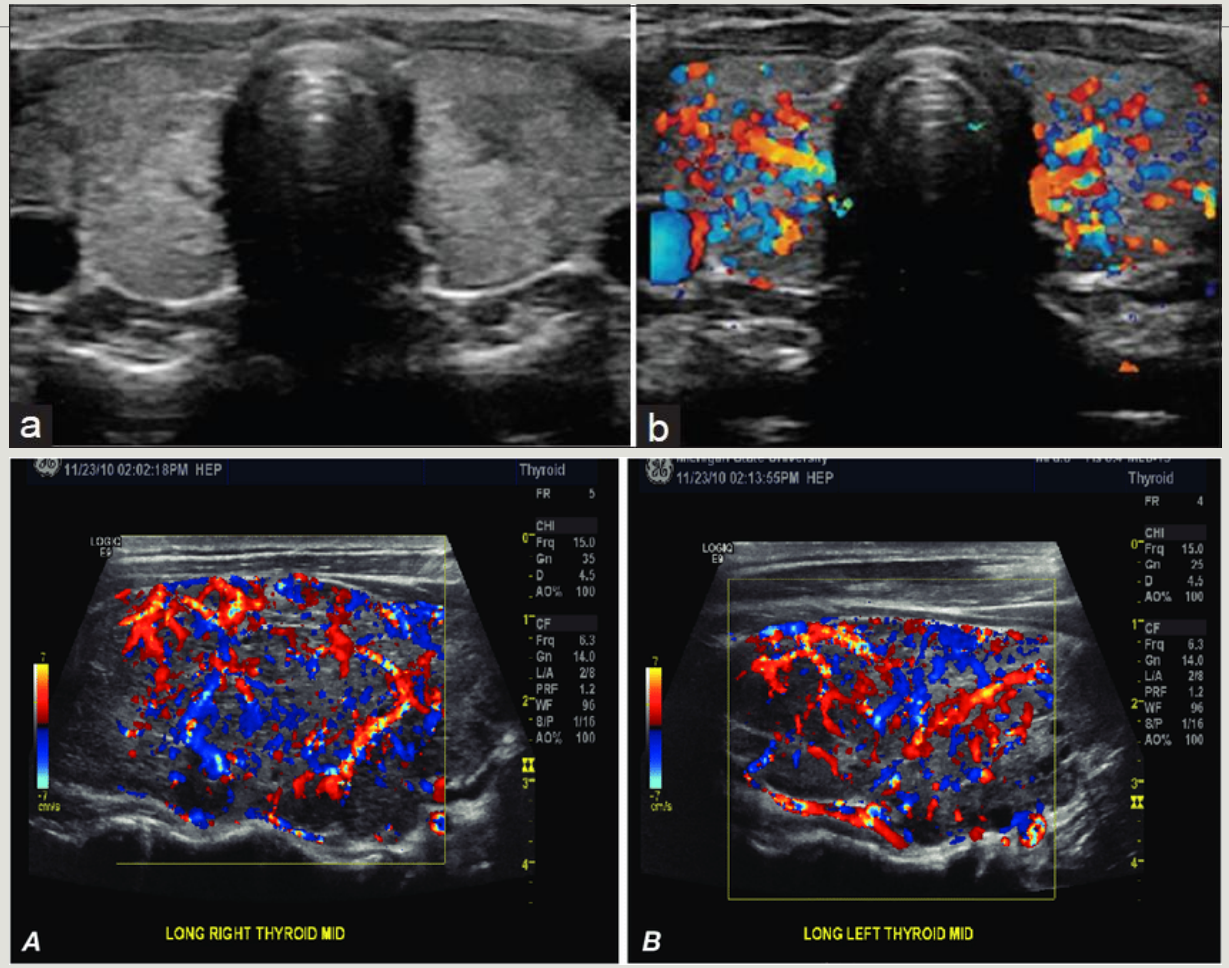
Tg- Ab

Thyroid US

Thyroid scan

RAIU

Graves' Disease: Color Doppler Ultrasound



Sub classification

Painful graves disease

Atrophic

Apathetic

Myopathic

Isolated graves ophtalmopathy

Hashitoxicose

Intermitant hypo & hyper

Treatment

- Anti-thyroid medications
- Radioactive Iodine (I_{131})
- Surgery (Thyroidectomy)

Clinical situations that favor a particular modality as treatment for Graves'

ATDs:

- Patients with high likelihood of remission (women, with mild disease, small goiters, and negative or low-titer TRAb).
- Pregnancy.
- The elderly or others with comorbidities increasing surgical risk or with limited life expectancy.
- Patients with previously operated or irradiated necks.
- Patients with lack of access to a high-volume thyroid surgeon.
- Patients with moderate to severe active GO.
- Patients who need more rapid biochemical disease control.

Clinical situations that favor a particular modality as treatment for Graves'

RAI therapy:

Women planning a pregnancy in the future.

Individuals with comorbidities increasing surgical risk.

Patients with previously operated or externally irradiated necks.

Lack of access to a high-volume thyroid surgeon.

Patients with contraindications to ATD use **or** failure to achieve euthyroidism during treatment with ATDs.

Patients with periodic hypokalemic paralysis, right heart failure, pulmonary hypertension, or congestive heart failure.

High TRAb, High ATD requirement.

Clinical situations that favor a particular modality as treatment for Graves'

Surgery:

Women planning a pregnancy in <6 months.

Symptomatic compression or large goiters (≥80 g).

Relatively low uptake of RAI.

When thyroid malignancy is documented or suspected.

Large thyroid nodules especially if greater than 4 cm or if nonfunctioning, or hypofunctioning.

Coexisting hyperparathyroidism requiring surgery.

If TRAb levels are particularly high.

Patients with moderate to severe active GO.

ATDs: Thionamides:

1

Inhibition of:

Oxidation

Organic binding - coupling

Peripheral conversion (PTU > 600mg/D)

2

Immunosuppressive action

3

Inhibition of follicular cell growth

Thyonamides

MMI and **PTU**, in some countries, **Carbimazole**.

(10 mg of carbimazole is metabolized to 6 mg of MMI).

MMI: initial dose is10–30 mg daily, can then be titrated down to a maintenance level (generally 5–10 mg daily)

Rough guide to initial MMI daily dosing:

- 5–10 mg for free T_4 1–1.5 times the upper limit of normal;
- 10–20 mg for free T_4 1.5–2 times the upper limit of normal;
- 30–40 mg for free T_4 2–3 times the upper limit of normal.

MMI has the benefit of once-a-day administration and a reduced risk of major side effects compared to PTU.

PTU has a shorter duration of action and is usually administered two or three times daily, starting with 50–150 mg three times daily.

Duration of ATD therapy for GD

Measure **TRAb** levels prior to stopping ATD therapy.

MMI should be continued for approximately 12–18 months, then discontinued if the **TSH** and **TRAb** levels are normal.

Hyperthyroid after completing a course of MMI:

- Treatment with **RAI** or **Thyroidectomy.**
- Continued low-dose **MMI** treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach.

Long Term Remission In Graves Disease

1- T3 toxicosis.

2- Small thyroid gland.

3- Decrease thyroid size.

4- Return of the TSH to normal.

5- Negative test for TRAb.

7- Long term treatment.

ATDs : Side Effects

Common, minor allergic side effects

Rash - Urticaria – fever

(MMI=6% , PTU=3%)

Arthralgia

Rare serious allergic/toxic events

Agranulocytosis (0.2 – 0.7%)

Aplastic anemia

Thrombocytopenia

Hepatitis (PTU=2.7%, MMI=0.4%)

Cholestatic hepatitis

Vasculitis (PTU>MMI)

Lupus like syndrome

Preparation of Patients with GD for RAI therapy

β-adrenergic blockade and MMI, prior to RAI therapy, MMI should be discontinued 2–3 days prior to RAI.

In patients who are at increased risk for complications due to worsening of hyperthyroidism (elderly patients or in those with underlying cardiovascular disease), resuming MMI 3–7 days after RAI administration should be considered.

Administration of RAI in the treatment of GD

A pregnancy test should be obtained within 48 hours prior to treatment in any woman with childbearing potential.

Typically a mean dose of 10–15 mCi render the patient with GD hypothyroid.

Success rate is 81% with 15 mCi.

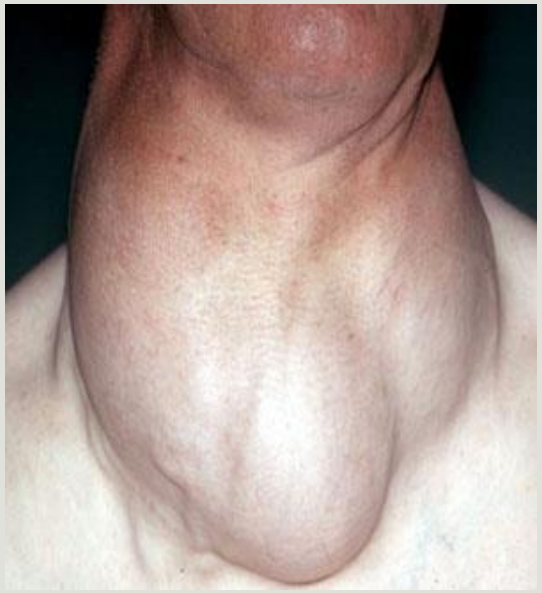
Failure rate 8%.

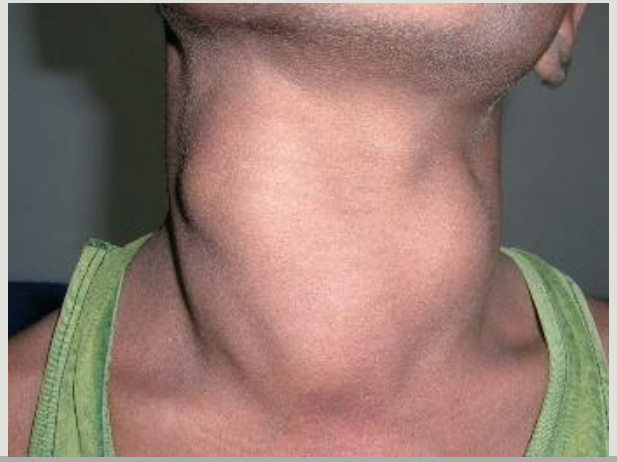
Biochemical monitoring 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement.

Conception should be delayed 4-6 months in women.

Conception should be delayed 3–4 months in men.

Multinodular goiter





Multinodular goiter

- The molecular basis for autonomy in toxic MNG remains unknown.

- The patient is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss

MNG : Treatment

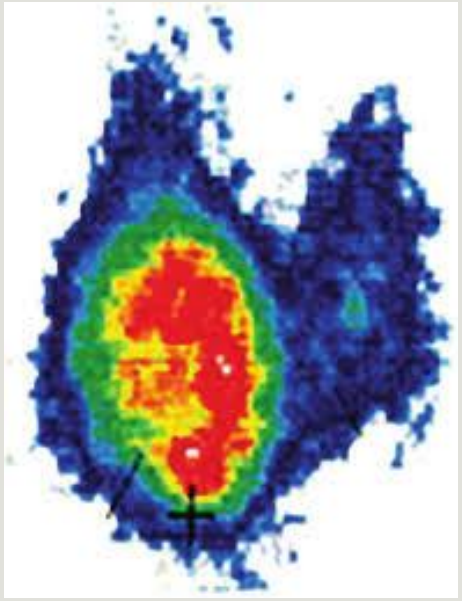
Anti-thyroid drugs normalize thyroid function and are particularly useful in the elderly or ill patients with limited lifespan.

In contrast to Graves' disease, spontaneous remission does not occur.

Radioiodine is generally the treatment of choice.

Surgery is indicated for huge goiter

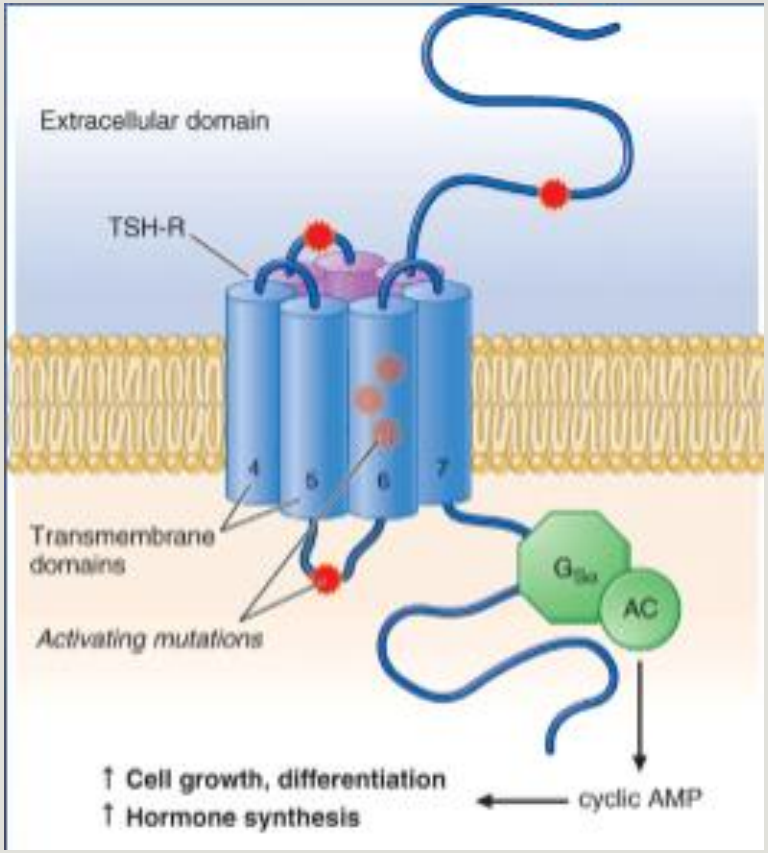
Autonomous solitary functioning nodule



Autonomous solitary functioning nodule

- Activating mutations in the TSH-R or the $G_{s\alpha}$ subunit that stimulate the TSH-R signaling pathway.

- Leading to enhanced thyroid follicular cell proliferation and function (THYROTOXICOSIS).



Sub clinical hyperthyroidism

FACTORS	TSH < 0.1	TSH = 0.1 – 0.4
> 65Y	yes	consider treating
< 65Y + comorbidity	yes	consider treating
Heart disease	yes	consider treating
osteoporosis	yes	consider treating
Menopausal No estrogen no Bis	yes	consider treating
symptomatic	yes	consider treating
< 65 y , symptomatic	consider treating	observe

biotin