Review Article ISSN 2767-5416

Journal of Medical Clinical Case Reports

Hyperthyroidism and Thyrotoxicosis

Andre Manov MD,FACP,MSHM

Transitional Year Residency Program Director
Core Faculty of Internal Medicine Residency Program,
Mountain View Hospital, Sunrise Health GME Consortium
Professor of Internal Medicine, University Of Las Vegas,
Nevada Medical School, Las Vegas, Nevada
Professor in the Department of Internal Medicine, TCU
Burnett Medical School, Fort Worth, Tx.

***Corresponding Authors**

Andre Manov MD,FACP,MSHM,
Transitional Year Residency Program Director
Core Faculty of Internal Medicine Residency Program,
Mountain View Hospital, Sunrise Health GME Consortium
Professor of Internal Medicine, University Of Las Vegas,
Nevada Medical School, Las Vegas, Nevada
Professor in the Department of Internal Medicine, TCU
Burnett Medical School, Fort Worth, Tx.

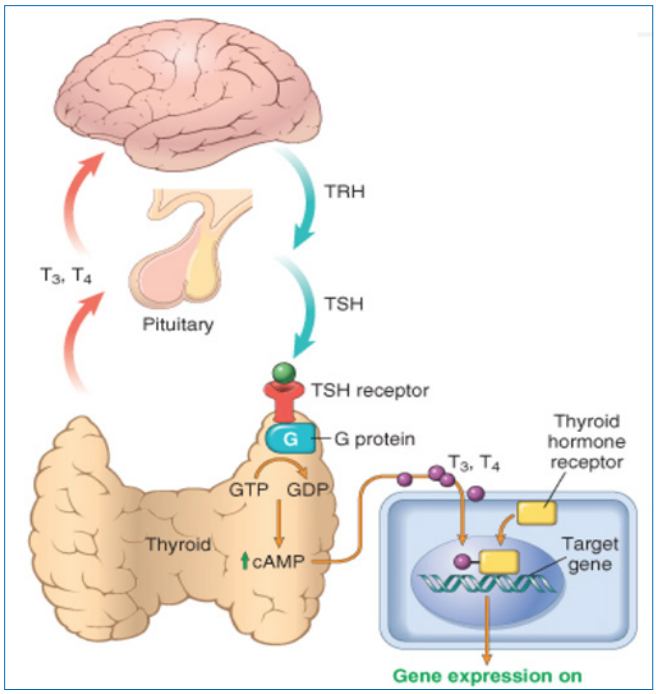
Submitted : 14 Aug 2025 ; Published : 30 Aug 2025

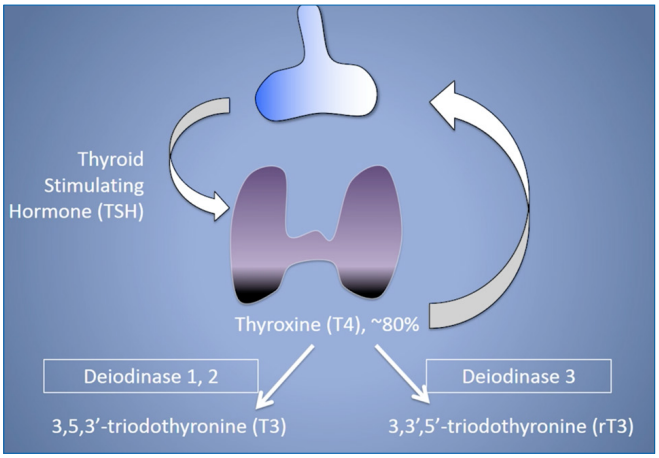
Citation: A. Manov (2025). Hyperthyroidism and Thyrotoxicosis. *J Medical Case Repo* Special Issue :1-9.
DOI : https://doi.org/10.47485/2767-5416.1124

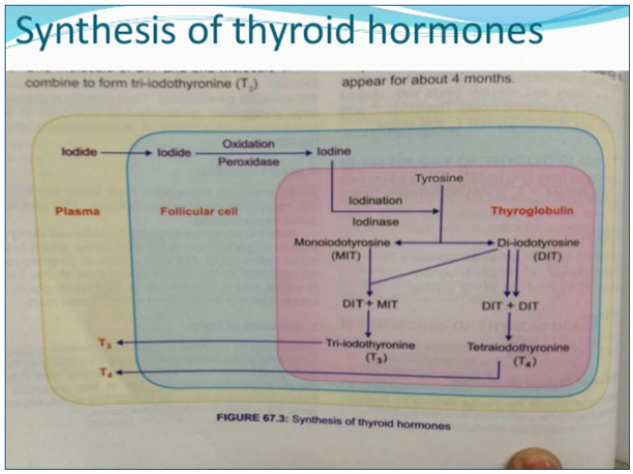
Objectives

1. Description of Thyroid Physiology
2. Differentiate between Hyperthyroidism and Thyrotoxicosis
3. Clinical picture of thyrotoxicosis
4. Diagnosing different forms of thyrotoxicosis
5. Diagnosis of the major disease states associated with Graves disease and their diagnosis and treatment
6. Descriptions of the drugs affecting interpretation of Thyroid tests or causing thyrotoxicosis
7. Treatment of different forms of thyrotoxicosis
8. Questions

Hypothalamic - pituitary-thyroid axis







Hyperthyroidism vs Thyrotoxicosis[1,2]

Hyperthyroidism: overproduction of thyroid hormones due to overactivity of the thyroid glands.

Thyrotoxicosis: biochemical manifestation of excess thyroid hormones from any source

Thyrotoxicosis can be caused by

- Hyperthyroidism
- Inflammation of the thyroid gland causing release of thyroid hormones
- Exogenous ingestion of thyroid hormone or HP–TSH secreting adenomas. Thyroid storm is a complication of thyrotoxicosis
- Way to remember - all hyperthyroid patients have thyrotoxicosis, but not all patients with thyrotoxicosis have hyperthyroidism

Epidemiology

- More common in **women** (5:1) and in smokers
- Graves' disease: Most common form of hyperthyroidism in the US (60-80% of thyrotoxicosis)
  - Peak occurrence in 20-40 year olds
  - More common in younger women
- **Toxic multinodular goiter** (15-20% of thyrotoxicosis)
  - More common in regions of iodine deficiency
  - More common in older women
- **Toxic adenoma** (3-5% of thyrotoxicosis)

Hyperthyroidism[1,2]

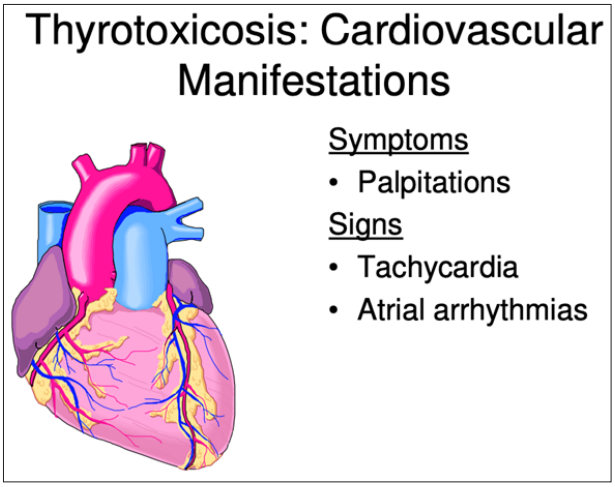
- **Graves' disease (most common)-90% TSI/TBII(TRAB)**
- **Toxic multinodular goiter (Plummer's disease)**
- **Toxic adenoma**
- **Iodine-induced – Jod-Basedow phenomenon**
- **Struma ovarii**
- **Functioning thyroid carcinoma metastasis, well-differentiated follicular cancer, is rare.** When there are large tumor masses, T3 elevation is common.
- **Activating mutations of the TSH receptor** - familial, autosomal dominant, no autoimmune signs of Graves' disease, and no TSI/TRAB. Dx is supported by genetic testing in the families- there is a gain-of-function of the TSH-Receptor.

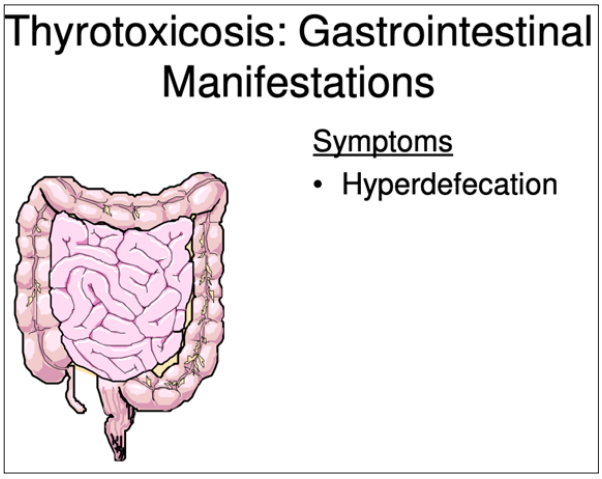
Secondary hyperthyroidism

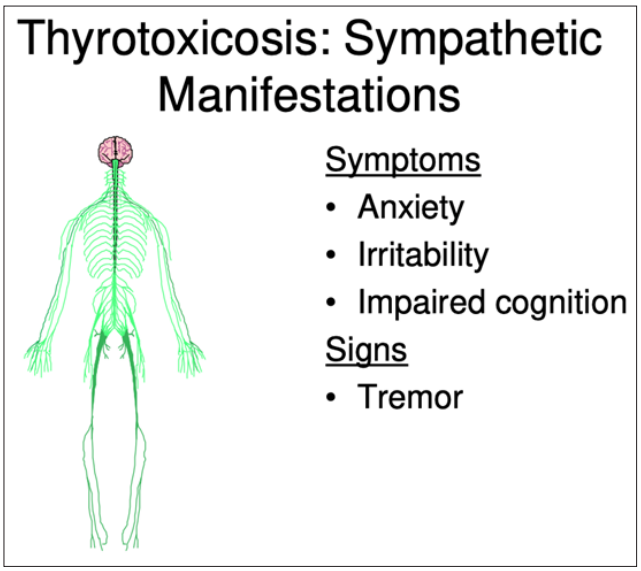
- **TSH-secreting pituitary adenoma**
- **Thyroid hormone resistance syndrome:** occasional patients have symptoms of thyrotoxicosis
- **Gestational Thyrotoxicosis -** due to Human chorion gonadotropin (hCG) increment during 1st trimester of pregnancy, usually in patients with hyperemesis gravidarum and or molar pregnancy. hCG shares a similar alpha subunit with TSH and stimulates the thyroid gland (although milder stimulation). TSH is therefore decreased because of this during the 1st trimester of pregnancy – FT4 increases
- **Chorion Gonadotropin-secreting testicular tumors** - TSH levels are low in this type of tumors - testicular cancers usually with hCG level above 50k mIU/ml

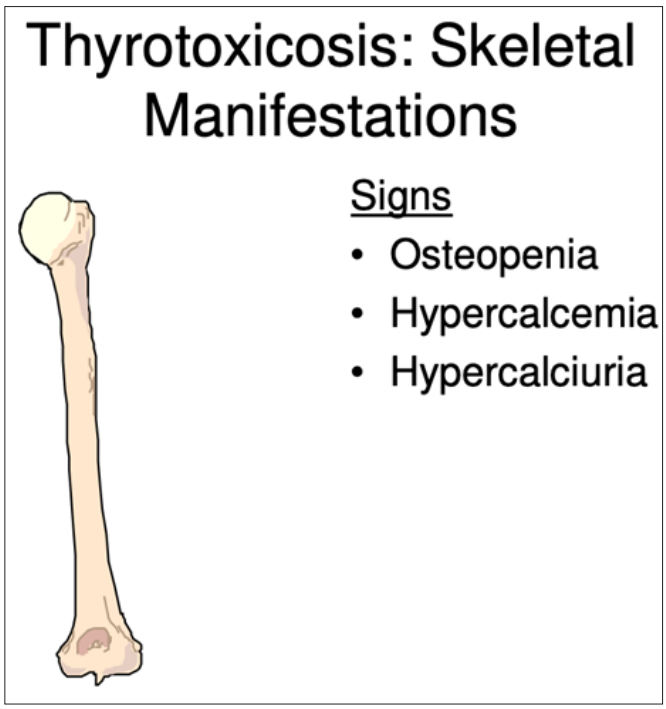
Thyrotoxicosis [3,4,5]

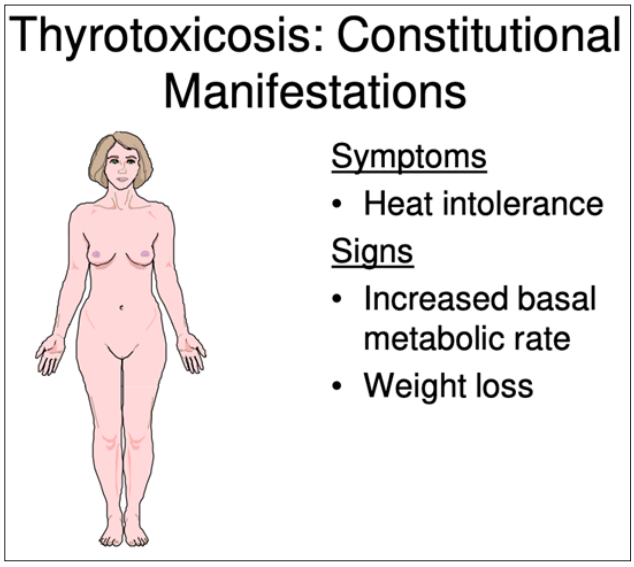
- Exogenous intake of thyroid hormone
- Autoimmune Thyroiditis-Hashimoto thyroiditis – hyperthyroid phase, Silent/postpartum thyroiditis
- Subacute thyroiditis – hyperthyroid phase
- Destruction of the thyroid gland
- Radiation thyroiditis
- Amiodarone and other drugs











Testing of Thyroid Function

- **TSH:** the single best screening test if your hypophyseal-thyroid axis is normal
- **Radioactive iodine uptake (RAI) and scan**
- **Total T4 and T3:** Can be altered by changes in the levels of binding proteins (see table on next slide)
- **Free T4/Free T3:** Preferred screening test for thyroid hormone levels. Free T3 – less reliable test. Equilibrium dialysis FT4 – most accurate test.
- **Doppler** ultrasound of the thyroid – increased vascularization in Graves' disease.
- Thyroid-stimulating Immunoglobulin(TSI) and thyroid receptor antibodies (TRAB), Thyroid peroxidase(TPO), and thyroglobulin (TG AB).

Drugs that alter TBG and protein binding or Thyroid Function

Drugs that may increase TBG

Estrogen, SERMS, heroin, methadone, mitotane,5-FU-False elevation of total T3 and T4 ; free T3 and Free T4 may be more accurate reflection of the hormonal levels

Drugs that may decrease TBG

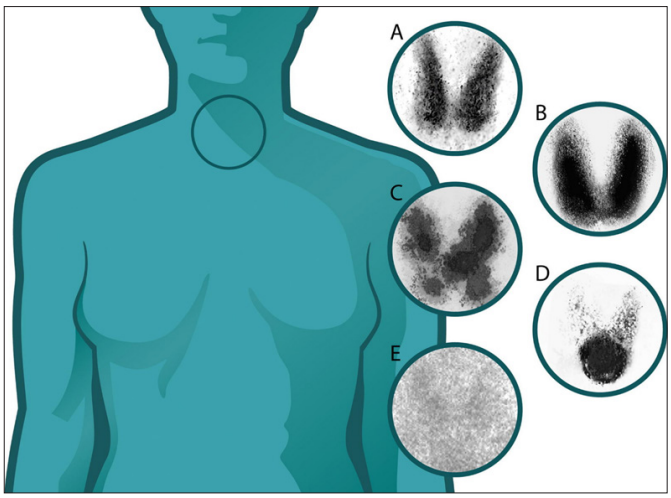
Anabolic steroids, niacin, danazol, glucocorticoids- False lowering of the total T4 and total T3; while using these drugs use Free T4 and Free T3 – they more accurately reflect the hormonal levels

Common drugs that cause protein-binding replacement

- Furosemide
- Heparin
- Hydantoins
- NSAIDS
- Salicylates

Drugs That Affect Thyroid Function

- **Decrease absorption of thyroid hormones**
  Calcium, PPI, Iron, Sucralfate
- Increased metabolism of levothyroxine
- Phenytoin, Carbamazepine, Rifampin, Phenobarbital, Sertraline
- Thyroiditis
- Amiodarone, Lithium, Alfa-Interferon, Interleukin-2, Tyrosine kinase inhibitors (the TKI can cause consumptive hypothyroidism or thyroiditis), CTLA-4 and PDA-1 inhibitors (cause Thyroiditis or Hypophysitis with thyrotoxicosis, followed by hypothyroidism or central, usually permanent hypothyroidism).
- De novo development of antithyroid antibodies Interferon alfa-Patients might develop Hashimoto thyroiditis, Graves disease or painless thyroiditis.
- Inhibition of TSH synthesis or release Dopamine, Dobutamine, Octreotide, Glucocorticoids, Dopamine agonists- Cabergoline, Ipilimumab, and Bexarotene cause secondary hypothyroidism
- False TSH Elevation or Decrement Heterophile or Human anti-animal antibodies can cause false elevation of TSH or false decrement of TSH, Macro-TSH – elevated TSH with normal FT4, FT3
- Biotin above 5 mg per day can cause falsely low TSH with an increase in FT3 and FT4 mimicking Thyrotoxicosis. Stop it and recheck TFT in 7 days- Normalization of thyroid tests.

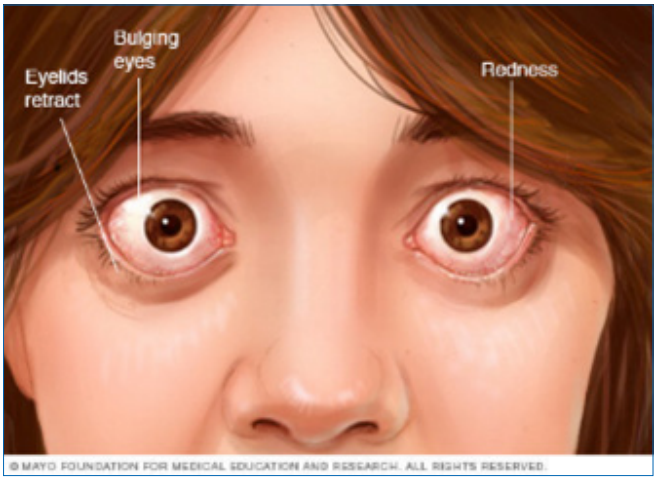


5 different scintograms taken from thyroids with different syndromes: A) normal thyroid, B) Graves disease, diffuse increased uptake in both thyroid lobes, C) Plummers disease (TMNG, toxic multinodular goiter), D) Toxic adenoma, E) Thyroiditis. Marker 99Tc

Thyrotoxicosis with Low Radioactive Iodine Uptake In The Thyroid

1. Silent thyroiditis
2. Subacute thyroiditis
3. Postpartum thyroiditis
4. Struma ovarii
5. Functioning thyroid cancer metastasis
6. Amiodarone-induced Thyrotoxicosis
7. Iodine-induced thyrotoxicosis

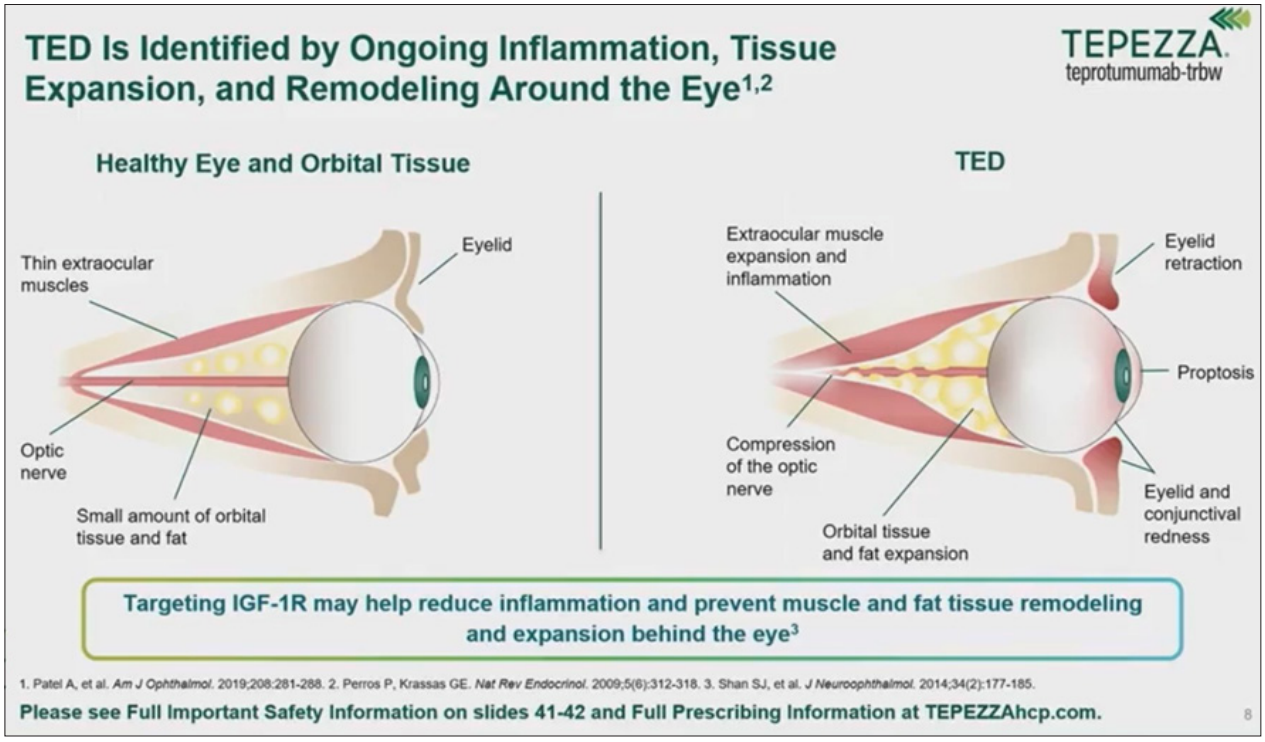
Graves' Exophthalmopathy



- Antibody-mediated reaction against the TSH-receptor with orbital fibroblast, modulation of activated T cell, which infiltrate orbital contents and stimulate fibroblasts as well as activation of the IGF1- Receptor on the orbital fibroblasts.
- Enlargement of extraocular muscles due to fibroblast production of glycosaminoglycans and collagen, which cause the muscles to swell as well as fat expansion retro-orbitally

Proliferation of orbital fat and connective tissue

- Initial sensation of grittiness, excess tearing. Proptosis. Can be measured using exophthalmometer. Proptosis can cause corneal exposure, ulcers. Also periorbital edema, conjunctival injection, edema, conjunctivitis, muscle swelling with diplopia, compression of the optic nerve at the apex orbit and papilledema, peripheral field defects and permanent vision loss



Grading Orbitopathy Clinical Activity Score

Pain behind globe	1 pt
Pain w/ eye movement	1pt
Conjunctival redness	1 pt
Eyelid redness	1 pt
Chemosis	1 pt
Swelling of caruncle	1 pt
Lid edema	1 pt
	7 pts

Mourits et al. Thyroid 1992; 2: 235-236

Additional points if the patient was evaluated in the last 3 months, if worsening vision-decreased acuity equivalent to 1 Snellen line, decreased ocular excursion in any direction more than >8 degrees, or increased > 2 mm of the proptosis-10 points.

GO is considered active if >3 out of 7 on the first examination or >4 out of 10/ if previously evaluated / points are positive.

Dysthyroid optic neuropathy /DON/ happens in 5% of patients and can lead to LOV.

Go Severity Assessement

Degree of Severity	Lid Retraction	Soft Tissue Involvement	Proptosis[a]	Diplopia	Corneal Exposure	Optic Nerve Status
Mild (≥1 of following)	<2 mm	Mild	<3 mm	Transient[b] or absent	Absent	Normal
Moderate to severe (≥1 of following)	≥2 mm	Moderate or severe	≥3 mm	Inconstant[b] or constant	Mild	Normal
Sight threatening (1 of last 2 categories)	Not contributory	Not contributory	Not contributory	Not contributory	Ulceration	Compromised

[a]proptosis refers to the variation compared with the norm for each race or to the patient's baseline if available.

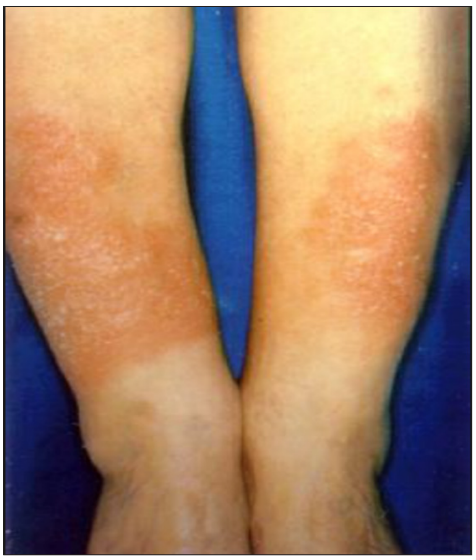
[b]Intermittent diplopia: present when the patient is fatigued; inconstant diplopia: present at extremes of gaze; constant diplopia: present in primary gaze.

Management of Graves ophthalmopathy

- Tobacco abstinence, achievement of euthyroidism, sleep with elevation of the head, artificial tears, gels, dark sunglasses, cool compresses for mild active disease, and referral to an eye specialist. Recent trials with antioxidants were positive- Allopurinol 300 mg a day, Nicotinamide 300 mg a day or Selenium 100 mkg twice a day
- Usually self-limited
- In moderate to severe active disease, IV GC improves proptosis, soft tissue abnormalities, diplopia, or visual acuity over 12 weeks. This improvement is observed in 70% of patients, with 4.5 g of Solumedrol administered IV every week for 8-9 weeks. Cyclosporine added to p.o GC is helpful, but alone is less effective than IV GC.
- Rituximab promising- one positive and one negative trial. Most likely if early used, positive results like in Italian versus Mayo trials in 4.5 months after onset of GO. Usually, patients are not very responsive to IVGC.
- IL-6 inhibitor Tocilozumab improved the activity score by 2 or more points in 93% of patients.
- Orbital radiotherapy in moderate to severe active disease helps ocular dysmotility- helps diplopia, mostly after IV steroids or with them, and proptosis , but problems-carcinogenesis, cataracts, retinopathy, and Botulinum injections in EOM help diplopia.
- The new treatment with IGF1-Receptor antibody-Teprotumumab- Game changer! Indications- age > 18, activity >4, non-pregnant, less than 9 months GO. Decreases proptosis-83%,diplopia-70%, and redness and inflammation 59%. 83 % reduction of proptosis! 8 infusions given 3 weeks apart. Side effects- increased BS, muscle spasms, and hearing loss are usually reversible. By the 6 week-43%, 4% of patients had a response. Especially important is the reduction of the proptosis.
- For sight-threatening conditions- DON, corneal ulceration, globe subluxation- immediate decompressive surgery. For DON- IVGC first followed by decompressive surgery with excellent results..
- In non-eye-threatening GO, wait until active disease is under control for 6 months and then refer if needed for orbital surgery and rehabilitation for strabismus, diplopia, etc.

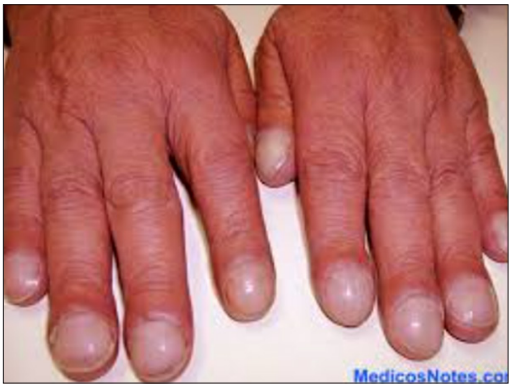
Thyroid Dermopathy

- In less than 5 % of patients with Graves' disease, almost always in those who have moderate/severe ophthalmopathy, there is a finding on the **anterior-lateral part of the legs/pretibial myxedema.**
- **Non-inflamed, indurated, pink-purple plaque with orange-skin appearance. It can occur in other sites, especially after trauma. It can be nodular and involve the whole leg and mimic elephantiasis.**
- **Treatment** - local steroid injection and compression wraps/stockings



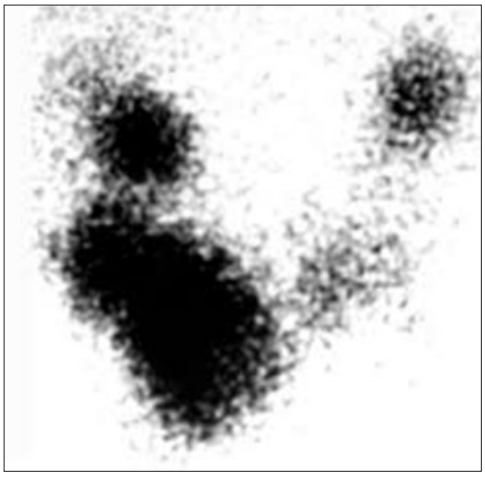
Thyroid Acropachy

In less than 1 % of patients with Graves' disease, who have dermopathy. **Form of clubbing of the fingers, swelling of the fingers and toes, and periosteal reaction.** Treatment- local steroid injection and intravenous IG



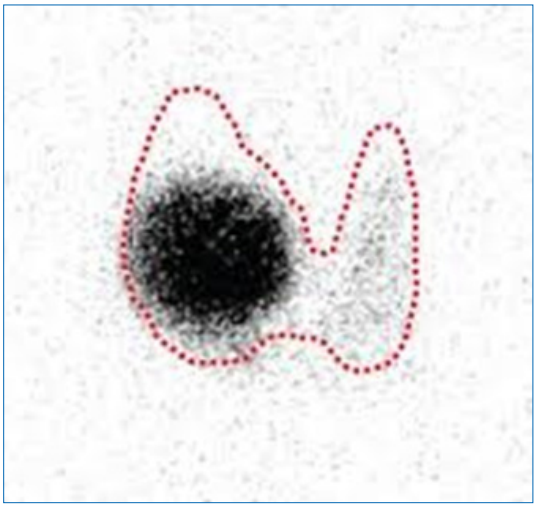
Toxic Multinodular Goiter (Plummer's Disease)

- **Autonomous hyperactivity due to somatic mutation of the TSH receptor**
- Hyperthyroidism – multiple nodules which are autonomous with hypersecretion of thyroid hormones.



Toxic Adenoma

- Genetic mutation in a single precursor cell
- Average about 3 cm, but can be up to 10 cm
- Solitary, spherical, well-demarcated
- **Because thyroid hormone autonomous overproduction is not very efficient, this thyroid nodule needs to become larger to have a clinical picture of hyperthyroidism.**



Diagnosis of Graves Disease,Toxic Adenoma and Toxic MNG[6,7]

- Graves' disease- the most common form of hyperthyroidism in younger patients, usually female who has diffuse goiter with bruit, thrill. Low/undetectable TSH, High FT4 and FT3/TT3, positive anti-TSH receptor antibodies-TSI or thyrotropin binding inhibitory immunoglobulin/TBII/, increased RIU above 25% in 24 hours, and thyroid scan with I 123 shows diffuse uptake.
- Might have complications – Graves' ophthalmopathy, pretibial myxedema, or thyroid acropachy. If so, after confirmation of hyperthyroidism with checking of TSH, FT3/TT3, and FT4, there is no need for RAI with iodine 123 uptake and scan of the thyroid unless nodules/nodules are palpated or seen on other imaging studies!
- In Toxic MNG or Toxic adenoma- less obvious hyperthyroid symptoms usually, sometimes only after iodine administration – Jod-Basedow Phenomenon. After confirmation of hyperthyroidism with TSH, FT4, and TT3/FT3, we need RAI uptake and scan to confirm the hot nodule/ nodules, usually in older patients.

Struma ovarii

- Usually, in a teratoma of the ovary, and if the thyroid tissue is more than 50 % of the overall tissue. Presents as pelvic mass, pain, ascites, and hyperthyroidism. TSH is low, FT3 and FT4 are high. RAI 123 of the thyroid is low or undetectable in the neck, but there is RAI 123 uptake in the pelvis, and Tgl is increased. Not palpable thyroid gland
- Rarely, patients with Struma ovarii have goiter, coexistence of Graves' disease with TSI stimulating thyroid tissue in the neck and in the ovary

Thyrotoxicosis Due To Hp Tsh Secreting Adenomas[8]

1. Elevated T4 and T3, and usually normal/ or increased TSH, alpha SU to TSH molar ratio more than 1.
2. MRI- macro-adenoma of the HP gland.
3. Treatment- euthyroidism with Somatostatin receptor ligands and in 4% Methimazole/PTU needed, and then removal of the HP macroadenoma by TSS, or if it can not be done/surgical contraindications - Radiation/Gamma knife/ of the pituitary and/or somatostatin receptor Ligands.

Jod-Basedow Phenomenon

- Hyperthyroidism following administration of iodine or iodide as a dietary supplement or as a contrast media
- Also, a side effect of amiodarone.
- Iodine-induced hyperthyroidism- typically in patients who have endemic goiter due to iodine deficiency/MNG with autonomous nodules or a single autonomous thyroid nodule or subclinical Graves disease who relocate from iodine-deficient areas to iodine-abundant geographic areas and ingest extra iodine.
- The Jod-Basedow Phenomenon does not occur in people with normal thyroid glands who ingest extra iodine. This condition occurs with a small increment of iodine intake in people who have thyroid abnormalities that cause the gland to function autonomously without the control of TSH from the pituitary.

Treatment Options for Hyperthyroidism/Graves Disease

- Pharmacologic – thionamides, beta blockers
- Thionamides: PTU & Methimazole block the synthesis of the thyroid hormones. Can cure Graves disease in around 33% -60% of patients after 12-18 months of treatment - they have immunomodulatory properties
- PTU also blocks the peripheral conversion of T4 to T3 by blocking type 1,2 deiodinase
- PTU vs Methimazole in pregnancy:
- Use PTU in the first trimester—Methimazole is teratogenic. Methimazole is associated with aplasia cutis in newborns, choanal and esophageal atresia, and tracheoesophageal fistula. Following the first trimester, Methimazole is preferred to avoid the risk of liver damage induced by PTU in the mother
- Patients started on PTU in the ICU for treatment of thyroid storm should be transitioned to Methimazole before discharge.
- Beta Blockers – Do not block hormone production, but block the effect of thyroid hormones and the conversion of T4 to T3
- Risk for Recurrence after medication treatment of Graves disease: GO, smoking, large goiter, higher serum FT4, male gender, age below 40 and most importantly, positive TSI and TBII

Clues to the Risk of Recurrent Hyperthyroidism if ATD's are stopped

Factor	Lower chance of recurrence	Higher chance of recurrence
Duration of MMI Therapy	More than 6 months	Less than 6 months
MMI Dose	<5-10 mg/day	>10mg/day
Serum TSH on MMI	Normal	Low
TSI/TRAb	Normal or slightly elevated	High levels

Antithyroid Drugs

	Methimazole	Propylthiouracil
Dose	10-40 mg qd	50-150 mg bid-tid
Half life	75 minutes	4-6 hours
Duration of action	20 hours	4-6 hours
Potency	15x	1x
T4→ T3 inhibition	No	Yes

Side Effects of Thionamides

1. Agranulocytosis- rare, but medications need to be stopped immediately if it develops
2. Rash
3. ANCA-positive Vasculitis - medications need to be stopped
4. LFT elevation - especially dangerous with PTU. Medications need to be stopped. Acute liver failure might ensue. This is why Methimazole is preferred (methimazole also has better immunomodulatory properties)
5. Aplasia cutis during the first trimester of pregnancy with Methimazole - use PTU in these instances
6. GI side effects, Low Platelets, etc.

Treatment Options for Hyperthyroidism/Graves Disease

- Radioiodine131 – usually contraindicated in moderate-severe Graves' ophthalmopathy, smokers, pregnancy, and within 6 months of pregnancy. It can cause mild pain in the thyroid gland due to mild radiation thyroiditis.
- Thionamides should be held for 5-7 days before the treatment. It can cause exacerbation initially of the hyperthyroidism, which is why patients should be first treated with thionamides and be euthyroid before RAI ablation. Leads to hypothyroidism usually in Graves disease in 3-6 months – f/o TFT every month.
- In smokers, cover with oral Prednisone- 0.2-0.5 mg/kg in mild GO for a month and taper over an additional 2 months, not to worsen GO. It can be considered in non-smokers with mild GO.

Radioactive Iodine Treatment

- Administered as a single oral dose
- Can't be given to women who are pregnant or breastfeeding
- Need to avoid pregnancy for 6 months after treatment
- Dose range and expected response vary depending on indication

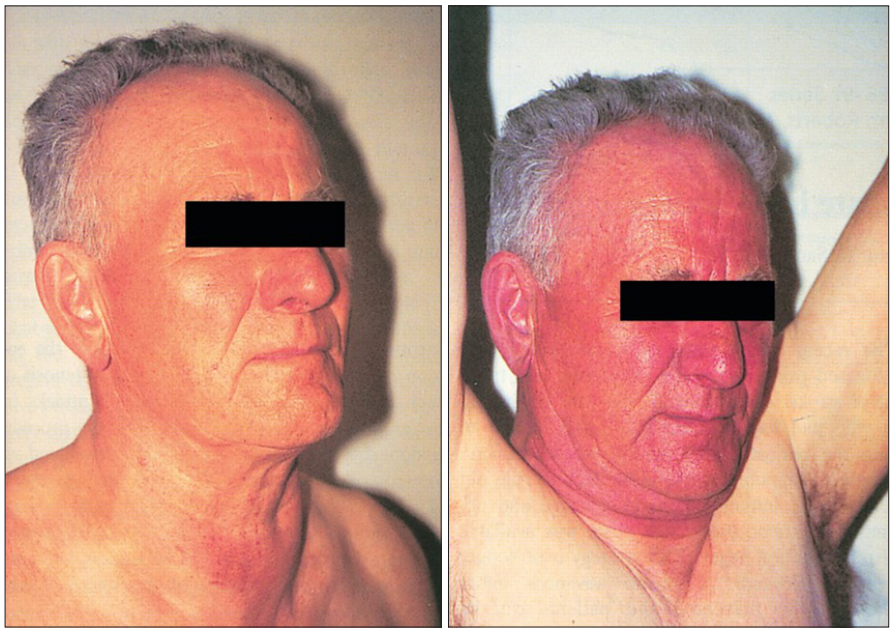
RAI 131 treatment of Graves' disease, Toxic adenoma, and Toxic multinodular Goiter TMNG[9]

1. Lower Dose in Graves' disease- usually permanent hypothyroidism
2. May cause radiation thyroiditis with transient thyrotoxicosis
3. Ablates hyperfunctioning tissue over weeks to months
4. In toxic adenoma and TMNG, permanent hypothyroidism is rarer than in Graves- around 60-%.

Thyroid Surgery

Considered in specific circumstances

- Patients with severe hyperthyroidism who have a demonstrated allergy to antithyroid drugs and are unable or unwilling to undergo radioactive iodine treatment
- Patients with cold nodules that show fine needle aspiration biopsy findings suspicious for malignancy
- Patients with dysphagia or dysphonia from substernal extension of large nodules
- Graves' disease and toxic multinodular goiter usually addressed with subtotal thyroidectomy
- Toxic adenoma many only require nodulectomy Preparation with saturated solution of potassium iodide (SSKI) to decrease vascularity and limit release of hormone during surgery
- Risks
  - Recurrent laryngeal nerve injury
  - Hypoparathyroidism



Hyperthyroidism : Key Points

- Thyrotoxicosis does not always reflect endogenous hyperthyroidism
- Graves' disease is a clinical diagnosis
- A thyroid uptake study can distinguish between hyperthyroidism and non-hyperthyroid thyrotoxicosis
- A thyroid scan can clarify the cause of hyperthyroidism
- Selection of treatment may depend on complicating factors (especially pregnancy)

References

1. Ross DS, Burch HB, Cooper DS et al.2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016 Oct;26(10):1343-1421.
2. Devereaux D, Tewelde SZ. Hyperthyroidism and thyrotoxicosis. *Emerg Med Clin North Am*. 2014 May;32(2):277-92
3. Adams R, Oh ES, Yasar S, Lyketsos CG, Mammen JS. Endogenous and Exogenous Thyrotoxicosis and Risk of Incident Cognitive Disorders in Older Adults. *JAMA Intern Med*. 2023 Dec 01;183(12):1324-1331
4. Sharma A, Stan MN. Thyrotoxicosis: Diagnosis and Management. *Mayo Clin Proc.* 2019 Jun;94(6):1048-1064.
5. Adams R, Oh ES, Yasar S, Lyketsos CG, Mammen JS. Endogenous and Exogenous Thyrotoxicosis and Risk of Incident Cognitive Disorders in Older Adults. *JAMA Intern Med*. 2023 Dec 01;183(12):1324-1331.
6. Sharma A, Stan MN. Thyrotoxicosis: Diagnosis and Management. *Mayo Clin Proc*. 2019 Jun;94(6):1048-1064
7. Kravets I. Hyperthyroidism: Diagnosis and Treatment. *Am Fam Physician*. 2016 Mar 01;93(5):363-70
8. Beck-Peccoz P, Giavoli C, Lania A. A 2019 update on TSH-secreting pituitary adenomas. *J Endocrinol Invest*. 2019 Dec;42(12):1401-1406.
9. Campennì A, Avram AM, Verburg FA, Iakovou I, Hänscheid H, de Keizer B, Petranović Ovčariček P, Giovanella L. The EANM guideline on radioiodine therapy of benign thyroid disease. *Eur J Nucl Med Mol Imaging*. 2023 Sep;50(11):3324-3348