Research Article

Management of Hyperthyroidism in Diseased States

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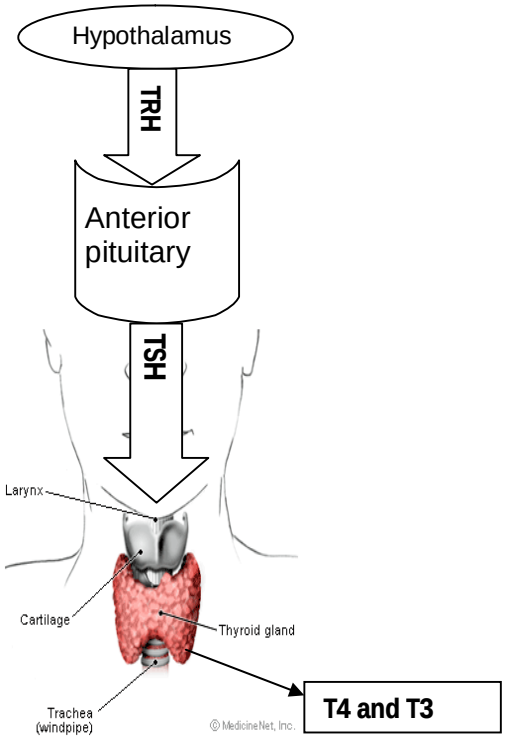
INTRODUCTION

THYROID

The thyroid is a gland. It consists of two lobes and it is situated in the lower neck. The function of thyroid gland is synthesizes, stores and releases two major metabolically active hormones like Tetra Iodothyronine (Thyroxine T4) and Tri Iodothyronine (T3).

The regulation of hormone synthesis is by secretion of the glycoprotein Thyroid Stimulating Hormone (TSH) from the anterior pituitary region.

The TSH is regulated by Hypothalamic secretion of the tri peptide Thyrotrophin releasing hormone (TRH).



Low circulating levels of thyroid hormone initiate the release of TSH and also TRH.

TSH levels rising it promote increased iodide trapping by the gland and subsequently increases the thyroid hormone synthesis. The increase in circulating hormone levels feeds back on the pituitary and hypothalamus, shutting off TRH, TSH and further hormone synthesis.

Both T4 and T3 are produced within the follicular cells in the thyroid.

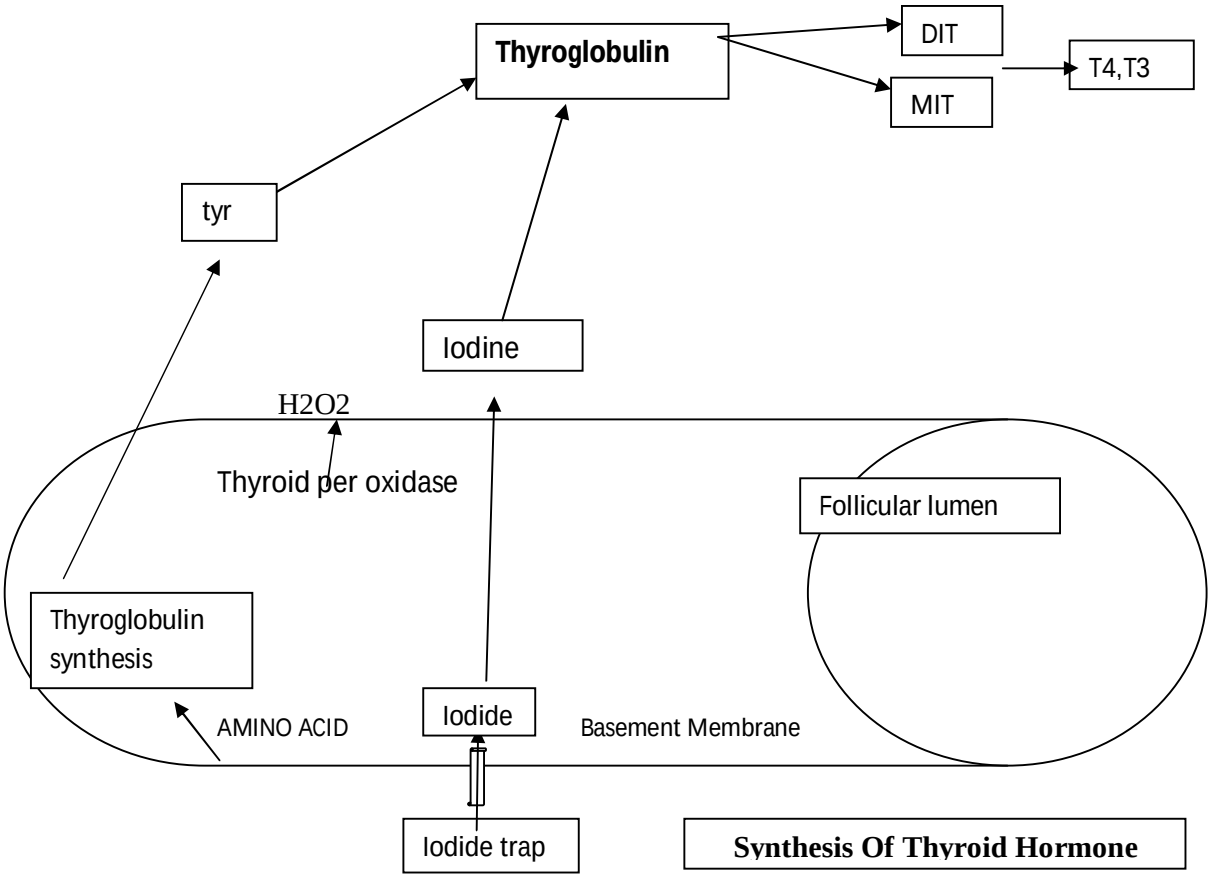
SYNTHESIS OF THYROID HORMONE

Thyroglobulin and thyroid per oxidase are synthesized by follicular cells. Hydrogen peroxide (H2O2) is synthesized at the follicular luminal membrane.

The dietary inorganic iodide is trapped from the circulation and transported to the follicular lumen then iodide is oxidized by H2O2 results iodine will form.

Iodine is then transferred on to the tyrosine residues in thyroglobulin by iodinase enzymes forming Monoidotyrosine(MIT) and Dio Iodotyrosine (DIT).

Finally T4 formation occurs due to coupling of two DIT residues and T3 formation occurs due to coupling of a DIT and MIT residue.



Synthesis Of Thyroid Hormone

The formed hormone are stored within the gland. The ratio of T4:T3 secreted by the thyroid gland is 10:1, approximately 80-100 ug of T4 and 10 ug T3 per day.

T4 is 99.98% bound, only 0.02% circulating free, T3 is 99.8% bound only 0.2% free. The hormones are metabolized by kidney, liver, heart by de iodination. Eliminated by biliary secretion. T4 half life is about 6-7 days, T3 half life 24-36 hr.

HYPERTHYROIDISM

Definition

Hyperthyroidism is defined as the production by the thyroid gland of excessive amount of thyroid hormones. Thyrotoxicosis refers to the clinical syndrome associated with prolonged exposure to elevated levels of thyroid hormone.

Epidemiology

Hyperthyroidism affects approximately 2% of women and

0.2% of men. The prevalence of hyperthyroidism in older patients varies between 0.5% and 2.3% but accounts for 10% to 15% of all thyrotoxic patients.

Aetiology of Hyperthyroidism

Hyperthyroidism is a disorder of various aetiologies.

Condition	Frequency	Clinical features	I uptake
THYROTOXICOSIS (increased hormone synthesis**)**			
Graves disease	70%	Antibody mediated (TRABs)	Increased
Multinodular goitre	20%	Benign autonomous nodules often secreted T3	Increased
Toxic single adenoma	5%		Increased
Iodine induced	<1%	Increased urine iodine	Variable
TSH dependent	rare	Pituitary tumour (thyro tropin-secreting tumour of the pituitary)	Increased
THYROID DESTRUCTION (leakage of stored thyroid hormones)			
Acute	2%	Probably viral neck pain	Absent
Silent	2%	Viral autoimmune	Absent
Drugindused: amiodarone, iodides, interleukin.	1%	Increased urine iodine	Absent

Pathophysiology

Graves disease

Graves disease is the most common cause of thyrotoxicosis. Graves disease is an autoimmune disorder caused by an abnormal thyroid receptor IgG-stimulating immunoglobulin (e.g., TRab) that binds to the TSH receptor on the thyroid follicular cell causes uncontrolled thyroid hormone production.

The maternal IgG immunoglobulin can pass through the placenta to the fetus resulting in transient neonatal thyrotoxicosis.

Nodular disease

Single or multiple nodule can produce hyperthyroidism because the nodules function independently of TSH control. In nodular disease TSH will be suppressed finally T3 level are elevated.

Thyroiditis

The thyroid is inflamed by viral or rapid autoimmune attack resulting follicular cell death will lead to release of thyroid hormones. Thyroiditis is common for the patient for patient using Thionamides.

Drugindused

amiodarone induces thyrotoxicosis by interfere with deoidinase of iodide and also reduces the conversion of T4 to T3.

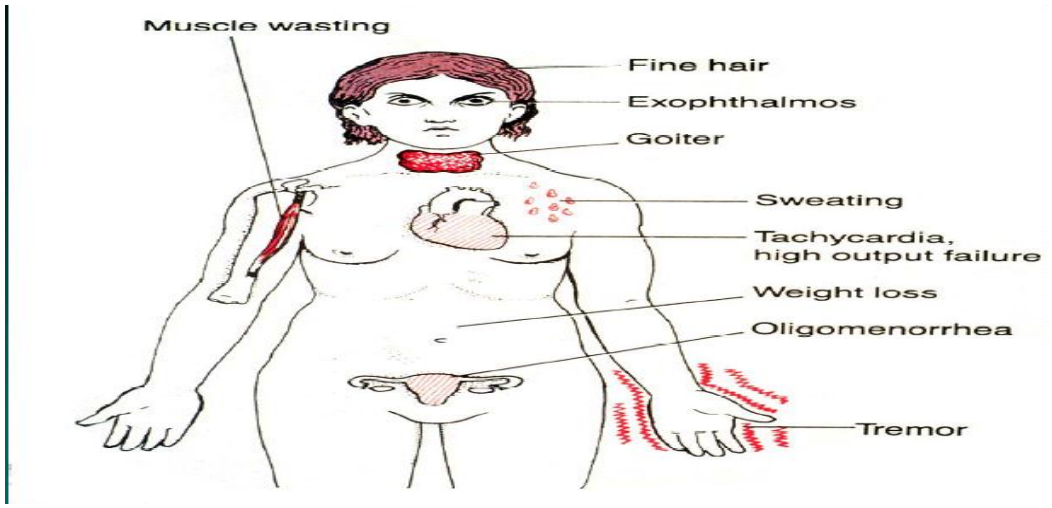
Clinical presentation

Thyrotoxicosis is characterized by increased metabolism of all body systems due to excessive quantities of thyroid hormone.

Signs and symptoms of thyrotoxicosis

Skin and appendages	Warmth, moist skin, thinning or loss of hair, increased sweating, heat intolerance.
Nervous system	Insomnia, irritability, nervousness, Lid retraction-staring eyes, symptoms of an anxiety state psychosis.
Musculoskeletal	Tremor, proximal muscle weakness , osteoporosis .
Gastrointestinal	Weight loss, Diarrhoea.
Cardiovascular	Palpitation, tachycardia, shortness of breath, atrial fibrillation, congestive cardiac failure, worsening of angina.

The major clinical manifestation of Grave's diseases



Diagnosis

- LowTSH serum concentration. Elevated free and total T3 and T4 serum concentrations, particularly in more severe disease.
- Elevated radioactive iodine uptake (RAIU) by the thyroid gland when hormone is being overproduced; suppressed RAIU in thyrotoxicosis caused by thyroid inflammation (thyroiditis).

Other Tests

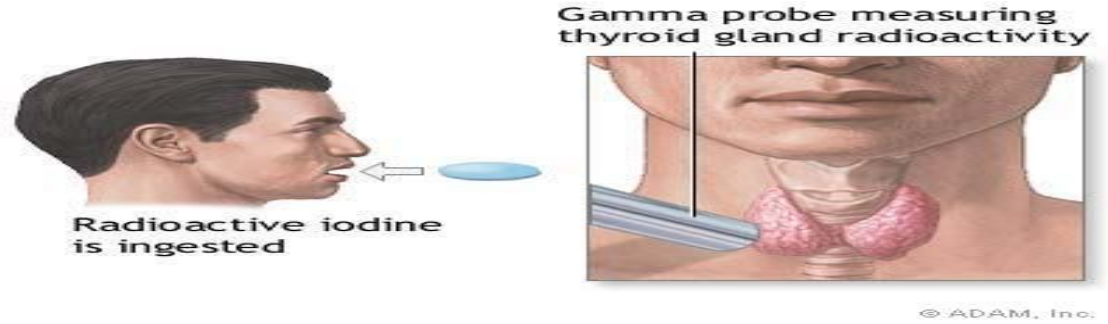
- Thyroid stimulating antibodies (TSAb)
- Thyroglobulin
- Thyrotropin receptor antibodies
- Thyroid biopsy
- Thyroperoxidase antibodies (TPO antibodies)

Thyroid function test results in different thyroid conditions

	Total T4	Free T4	Total T3	T3 resin uptake	Free thyroxine index	TSH
Normal	4.5-12.5 mcg/dl	0.8-1.5 ng/dl	80-220 ng/dl	22%-34%	1.0-4.3 units	0.25-6.7 mlu/L
Hyperthyroid	⇧⇧	⇧⇧	⇧⇧⇧	⇧	⇧⇧⇧	⇩⇩

RAIU

The elevated 24 hr radioactive iodine uptake (RAIU) indicates true hyperthyroidism the thyroid gland is over producing T4, T3 or both (normal RAIU 10% to 30%).



American Thyroid Association (ATA), have established clinical guidelines for the diagnosis of hyperthyroidism

The diagnosis of hyperthyroidism is confirmed by findings of abnormally high levels of FT_4 or TT_3 and an undetectable TSH. The presence of positive antibodies (i.e., ATgA and TPO), ophthalmopathy, or dermopathy confirm the diagnosis of Graves disease.

Positive Hyperthyroidism, goitre, and ophthalmopathy or dermopathy family history Females > males patients Elevated FT_4 or FT_4I, TT_4, TT_3 Suppressed /Undetectable TSH level Positive ATgA, TPO, TRab Unknown duration of disease
FT_4, free thyroxine level; FT_4I, free thyroxine index; TT_4, total thyroxine level; TT_3, triiodothyronine; TSH, thyroid-stimulating hormone; ATgA, antithyroglobulin antibody; TPO, thyroperoxidase antibody; TRab, thyroid receptor antibody; FT_3, free triiodothyronine.

Management of Hyperthyroidism

Three forms of therapy available

- Antithyroid drugs
- Radioactive iodine
- Surgery

Acute management of thyrotoxicosis

β Blocker in standard antihypertensive dose are effective within hour and should be given to non asthmatic with severe thyrotoxicosis.

Carbimazole (40mg o.d) or Propyl thio uracil (300mg b.d).

Graves disease

High dose of thionamide treatment to maintain thyroidism. If high TRAB or relapsed once after a course of drug treatment such patient have a discussion about either surgical or Radio Iodine thyroid ablation.

Antithyroid drug

The thionamides, propyl thiouracil (PTU), thiamazole (methimazole), and its precursor carbimazole.

PTU: These drug prevent thyroid hormone synthesis by inhibiting the oxidative binding of iodide and its coupling to tyrosine residues.

Carbimazole : inhibits the peripheral deiodination of T4 to T3.

Thionamide : immunosuppressive action.

Adverse reaction: the most common adverse effect is Rash and Arthropathy (5%) and less commonly Agranulocytosis, Hepatits, Aplastic anaemia and thrombocytopenia.

Caution:Pregnancy

Contra indication: Previous allergy

Dosage Regimen:

Drug	Initial dose	Maximum dose
Carbimazole	40-60mg daily	
Propyl thiouracil	300-600mg daily 3-4 divided dose	1200mg
Methimazole	30-60mg/day 3 divided dose	120mg

Iodides

Iodide used as a adjunctive therapy. Iodides acutely blocks thyroid hormone release, inhibit the thyroid hormone biosynthesis by interfering with intra thyroidal iodide utilization and decreases the size of the gland. E.g.: Potassium iodide SSKI (saturated solution of potassium iodide):38mg of iodide per drop. Lugols solution: 6.3mg iodide per drop. Dose: SSKI: 3-10 drop daily (120-400mg) in water.

Time of administered 7-14days pre operatively , 3-7 days after RAI. Adverse reaction: Hypersensitivity reaction, Gynecomastia, salivary gland swelling.

β blockers

β blocker used as a adjunctive therapy e.g. : propranolol , nadolol. Partially block the conversion of T4 to T3. And also required to relive the symptoms like anxiety, tremor, heat intolerance. The initial dose 20 to 40mg four times daily, for severely toxic patient require 240 to 480mg/day.

Thyroid ablative therapy

This therapy is required for patient with toxic multi nodular goitres, those who have relapsed or are likely to relapse after drug therapy for graves disease and those allergic to thionamides. Thyroid ablative can be achieved by radio iodine or surgery.

Radio active iodine (RAI)

e.g. I^{131}(sodium iodide) : RAI is administered as a colourless and tasteless liquid, I^{131} is a β and γ emitter with a tissue penetration of 2 mm and half life of 8 days. RAI initially disrupt hormone synthesis by incorporate into thyroid hormone and thyro globulin. Contraindicated: Pregnancy

Dose : single dose of RAI 4000 to 8000 rad. After six month second dose should be given. β blocker are the primary adjunctive therapy to RAI. Hence, β blocker may given any time. If iodides are administered they should be given 3 to 7 days after RAI to prevent interference with the uptake of RAI in the thyroid gland.

Surgery

Surgery is required for those patient with very large goitre, lack of remission on anti thyroid drug treatment and patient with contraindication to thionamide and RAI. Complication of surgery include persistent or recurrent hyperthyroidism (0.6-18%), hypothyroidism (up to 49%), hypo parathyroidism (up to 4%).

The American Association of Clinical Endocrinologists, and others have published clinical guidelines for treatment of hyperthyroidism

Method	Drug	Dose	Mechanism of Action	Toxicity	Comments
Thioamides	Propylthiouracil (PTU) 50-mg tablets; can be formulated for rectal administration	300–400 mg/day given q 6–8 hours initially, maintenance of 50–150 mg daily	Blocks organification of hormone synthesis, also inhibits peripheral conversion of T_4 to T_3; immunosuppres	Skin rash, bitter taste, agranulocytosis, gastrointestinal symptoms, hepatocellular hepatitis	Remission rate of 20%–30%; onset of action approximately 2–4 weeks; used in pregnancy and during

			sive		lactation
	Methimazole(Tapazole) 5- and 10-mg tablets; can be formulated for rectal administration	30–40 mg once daily initially, maintenance of 5–15 mg daily	Blocks organification of hormone synthesis; immunosuppressive	See PTU; secreted in breast milk; might be teratogenic (e.g., scalp defects); obstructive jaundice	DOC for once daily dosing; remission rate of 20%–30%; onset of action approximately 2–4 weeks;
Iodides	Lugol's solution 8 mg iodide/drop: Saturated solution of potassium iodide (SSKI) 50 mg/drop	6 mg iodide/day although larger doses are given;	Block hormone release; decreases gland vascularity and increases gland firmness to facilitate surgical removal	Hypersensitivity reactions—rash, Contraindicated in pregnancy.	Provides symptomatic relief before onset of thioamides; use in thyroid storm do not use before rai.
Adrenergic antagonists	Propranolol (Inderal) Metoprolol (Lopressor) Atenolol (Tenormin) Various tablet strengths; IV propranolol 1 mg/mL; Avoid β-blocker with ISA activity	Propranolol 20–40 mg po every 6 hours or equivalent β-blocker	Blocks the peripheral action of thyroid hormone, no effect on disease state. Blocks peripheral T_4 to T_3 conversion	Bradycardia, congestive heart failure, asthma, inhibits hyperglycemic response to hypoglycemia. Avoid in pregnancy	Provides rapid symptomatic relief while awaiting activity of thioamides, RAI, or surgery
Radioactive iodine	^{131}I	80–150 µCi/g thyroid tissue; usual dose of 8–10 mCi.	Destruction of the gland	Hypothyroidism, rarely radiation thyroiditis; fear of malignancy, leukemia, and genetic damage. Contraindicated in pregnancy.	Slow onset of action approximately 2–4 weeks, full effects seen within 3–6 months.
Surgery	Iodides, thioamides orβ-blockers preoperatively to prevent storm and facilitate surgery	5–10 drops/day of iodides for 10–14 days before surgery; see β-blockers and thioamides dosing	Removal of the gland; total thyroidectomy might be surgery of choice to prevent recurrent hyperthyroidism.	Hypothyroidism, hypoparathyroidism complications of surgery and anesthesia	Incidence of hypothyroidism indirectly proportional to gland remnant left
Iodinated contrast media	Ipodate, iopanoic acid 500-mg tablets	500 mg–1 g po qd or 3 g q 3rd day po	Blocks T_4 to T_3 conversion; release of iodides. See iodides	Similar to iodides; nausea, vomiting, abdominal cramps, diarrhea, dizziness,	Rapid onset of action; adjunct to thioamides, not for chronic use because

				headache.	effects not sustained.
Ionic exchange resin	Cholestyramine 4 g oral powder packets	4 g po tid	Increases fecal excretion of T_4 by binding T_4 in the intestine	Gastrointestinal: bloating, flatulence, constipation; impairs absorption of concurrent medication	Adjunct to thioamides, useful when additional decline in hormones levels is desirable.
Monovalent anions	Potassium perchlorate 200-mg capsules	800–1,000 mg/day po in four divided doses for 2–6 weeks	Competitive inhibitor of iodide binding; discharges nonorganified iodide	Gastric irritation, nausea, vomiting, fever, rashes. Aplastic anemia, bone marrow suppression	Useful short-term adjunct to thioamides for amiodarone induced hyperthyroidism
Lithium	Lithium carbonate, various dosage forms available	800–1,200 mg/day in 2–3 divided doses.	Acts similar to iodides to block hormone release	Nausea, vomiting, diarrhea, tremor, ataxia, dizziness, confusion, coma. Maintain normal serum levels. Avoid hyponatremia or sodium depletion.	Reserved for special situations when other agents contraindicated or ineffective.

q, every; T_3, triiodothyronine; T_4, thyroxine; DOC, drug of choice; RAI, radioactive iodine; IV, intravenously; ISA, intrinsic sympathomimetic activity; po, by mouth; qd, every day; qid, four times daily; tid, three times daily; IDDM, insulin-dependent diabetes mellitus.

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