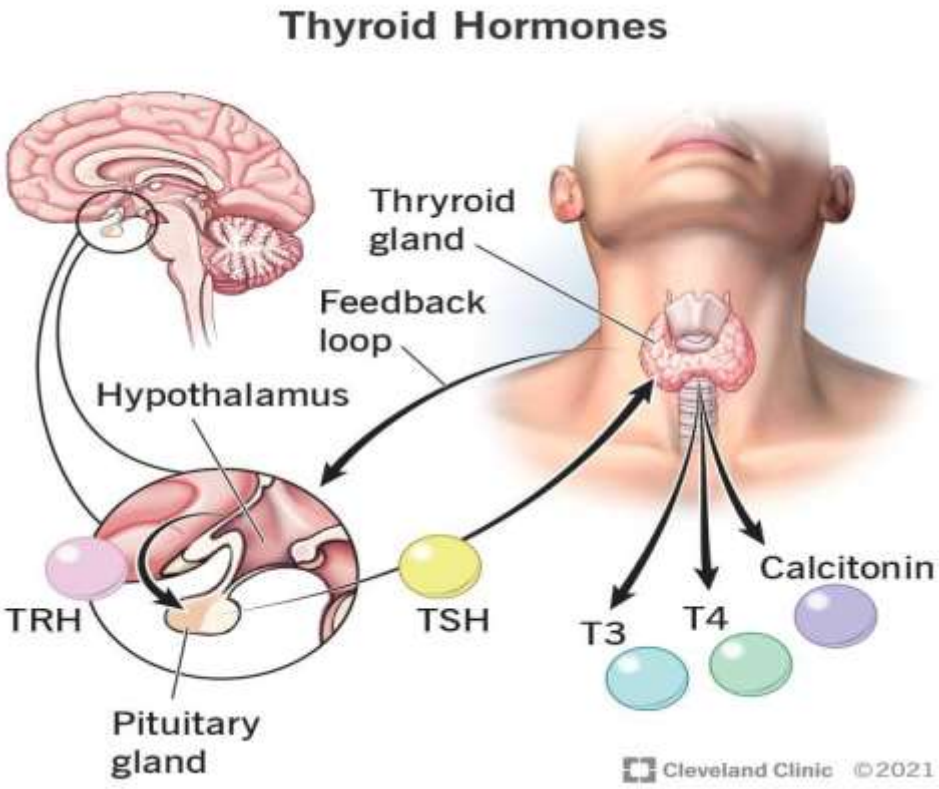
Thyroid gland is composed over a million cluster of follicles Follicles are spherical & consists of epithelial cells surrounding a central mass (colloid) Normal thyroid gland secretes thyroid hormones Natural hormone compounds having biological activity (Iodide containing): ◦ L-Thyroxine (T4 or tetraiodo-L-thyroxine) ◦ Liothyronine (T3 or triiodo-L-thyronine) ◦ Both forms are available for oral use Parafollicular (C) cells produce calcitonin



1. Normal human growth & development, esp.CNS 2. In adults,maintain metabolic homeostasis, affecting all organ systems ¬ Large preformed hormone stores in thyroid ¬ Metabolism of thyroid hormone occurs in liver and brain ¬ TSH regulates serum thyroid hormones by a negative feedback system ¬ Bind to nuclear thyroid hormone receptors, modulates gene transcription

- **Changes in** shape or size of gland } Changes in secretion } Thyroid nodules and goiter } Cretinism or congenital hypothyroidism } Thyroid hormone replacement therapyefficacious, cost effective and available } Pts. cured or controlled
- **Thyroid gland** is unique in storing large amount of preformed hormone } Thyroid follicular colloid stores thyroid hormone as amino residues of thyroglobulin }

Iodide is required for synhesis of thyroid hormone } Sea fish, eggs, milk and water - dietary sources of iodide, carried in plasma as inorganic iodide } Sources: Food, water or medication } Daily Requirement for adult: 150 µg (200 µg in pregnancy and lactation) } Total body content of Iodine 30 – 50 mg (1/5th in thyroid gland) } Iodine denotes all form of the element and Iodide denotes only the ionic form (I-) } 75 µg is utilized daily for hormone synthesis by thyroid gland

Iodide uptake or pump } Rate –limiting step in thyroid hormone synthesis which needs energy } Follicles have in their basement membrane an iodide trapping mechanism which pumps dietary I - into the cell } Normal thyroid: serum iodine is 30-40:1 ◦ Iodide uptake enhancers: □ TSH □ Iodine deficiency □ TSH receptors antibody ◦ Iodide uptake inhibitors □ Iodide ion □ Drugs □ Digoxin □ Thiocynate □ perchlorate

Iodide oxidation to iodine and Organification } Inside the cells, iodide is oxidized by membrane bound peroxidase system to more reactive iodine (Iodinium or I+), or HOI or E-OI } Iodine immediately reacts with tyrosine residue on a thyroid glycoprotein called “thyroglobulin” to form: MIT and DIT } Both processes are catalyzed by thyroid peroxidase enzy

Coupling } T1& T2 couple together to form T3 & T4 } MIT +DIT = T3 (Tri-iodothyronine) } DIT + DIT = T4 (Thyroxine) } Normally high amount of T4 is formed } Homeostasis: In case of Iodine deficiency more MIT is formed and hence more T3 – leading to more active hormone with less Iodine

MIT, DIT, T3 and T4 - all attached to thyroglobulin and stored in the colloid Thyroglobulin molecule } This process is stimulated by TSH } Taken up by follicular cells by the process of endocytosis and broken down by lisosomal proteases } T3 and T4 released and also MIT and DIT } MIT and DIT are deiodinated and reutilized } T4 & T3 enter circulation directly from follicular cells } Free (unbound) hormone is a small percentage, 0.03%T4 and 0.3%T3 of the total plasma hormone } Only unbound form has metabolic activity } Peripheral tissues – liver and kidney } T4 to T3 } 1/3rd of T4 undergoes these changes and most of T3 available are derived from liver } Equal amounts of T3 and rT3 are produced in periphery } Drugs like Propylthiourcil,

propranolol and glucocorticoids inhibit peripheral conversion 4) Storage and release 5) Peripheral conversion

Highly bound to plasma protein } Only 0.04% of T3 and 0.2% T4 are in free form } All Protein Bound Iodine (PBI) in plasma is thyroid hormone – 95% is T4 } Main Plasma proteins for T4 are – TGB, TBP and albumin } Only free form of hormone is available for action and metabolism } Metabolism occurs by deiodination and conjugation, mainly in liver and kidneys } T4 is deiodinated to T3 (active) or rT3 (inactive) by deiodination } Conjugated products are excreted in bile – enterohepatic circulation } Finally excreted in urine

T3 is 5 times more potent > T4 } Half life of T4 is 6-7 days and T3 is 1-2 days – hyper and hypothyroidism } T4 is the major circulating hormone – bound more to plasma proteins } T4 is less active and a precursor of T3 - the major mediator of physiological effects } The term thyroid hormone is used to comprise both T4 plus T3 } T4 deiodination to T3 or reverse T3 } T3 & reverse T3 deiodination to three di-iodothyronines, deiodinated to two monoiodothyronines - (inactive)

Regulation of thyroid Function: Negative feedback by Thyroid hormone is Exercised directly on pituitary and hypothalamus

Iodine essential for thyroid hormone } Excess TSH, thyroid hyperplasia, hypertrophic } Adult hypothyroidism and cretinism occurs in severe iodine deficiency } Daily adult require 1 to 2 µg / Kg / day. } Iodine used for iodine-deficiency goiter } Iodine or iodate added to table salt (iodized salt) 100 µg of iodine per gram

Age group Iodine requirement(µg) } Infants (0 -11mth) 50 } Children (12 mnth - 59 mnth) 90 } School age child (6-12 year) 120 } Adults (above 12 year) 150 } Pregnant & lactating women 200

T3 binds to high affinity receptors)} Three thyroid hormone receptor:- TR α1, TRβ1, TRβ2 TRα1, binds to DNA sequence in specific genes) T3 modulates gene transcription and protein synthesis) T4 binds with lower affinity than T3 but does not alter gene transcription)T3 causes all actions of thyroid hormones at transcriptional level

Growth and development Normal growth and development of organism DNA transcription, critical control of protein synthesis and translation of genetic code T3 –

Tadpole to frog transformation Brain development Irreversible mental retardation (cretinism) in absence of thyroid hormones during active neurogenesis (upto 6 month postpartum) Severe morphological alteration in brain Supplementation during first 2 weeks of life prevent development of brain changes

Metabolism: Lipid: Induce lipolysis (catecholamines), ↑ free plasma fatty acid and all phases of cholesterol metabolism enhanced (bile acid more) ◦ Hyperthyroidism – hypercholesterolemia Carbohydrate:Stimulation of carbohydrate metbolism, glycogenolysis, gluconeogenesis ◦ Hyperthyroidism – diabetes-like state Protein: Certain protein synthesis increased but overall catabolic action – negative nitrogen balance ◦ Hyperthyroidism – Weight loss and wasting

- 21. **Calorigenic & CVS** Effects T3 and T4 increases BMR by stimulation of cellular metabolism – maintenance of body temperature Brain, gonads and spleen unresponsive to calorigenic effects Hyperdynamic state of circulation - due to direct CVS action and ↑ peripheral demand Hyperthyroidism: tachycardia, ↑ SV, ↑ TPR } Hypothyrodism: bradycardia, ↓ cardic index, pericardial effusion , ↓ TPR, ↓ PP Others: Nervous system – mental retardation, GIT – Increased gut motility, Haematopoiesis – anaemia

  Steps of Thyroid Hormone Synthesis 1. Iodide uptake or pump 2. Iodide oxidation to iodine and Organification 3. Coupling 4. Storage and release 5. Peripheral conversion MOA - modulates gene transcription and protein synthesis Actions of Thyroid Hormones ◦ Growth and development ◦ Metabolism – lipid, carbohydrate and protein ◦ Calorigenic & CVS Effects

  As Replacement therapy in deficiency states Available as l-thyroxine sod. 100, 50, 25 mcg tablets Liothyronine is available as 5, 25 mcg tabs and Injection Mixture of T3 and T4 tablets T4 - consistent potency and prolonged duration ofaction. 50% - 80% GIT absorption. T3 for quicker onset of action as in myxedema coma or preparation of a patient for I131 therapy in thyroid cancer

  Cretinism, Adult hypothyroidism, Myxoedema, Non toxic goitre, Thyroid nodule Carcinoma of thyroid etc. Re-evaluation: Serum TSH conc. not less than 4-6 weeks Goal - achieve Serum TSH value in normal range Start with 50 µg / day of T4 – increase every 2-3 weeks upto 200 µg / day Over-replacement may ↓ TSH Non

compliant young patients – cumulative weekly dose of T4 as single dose Over 60 yrs – lower dose of T4 25 µg / day ↑ dose 25 µg every few months until TSH normalized Cardiac patients: T4 12.5 µg / day, ↑ T4 12.5 to 25 µg / day every 6 to 8 weeks

Endemic or sporadic Endemic - extreme iodine deficiency Sporadic – failure of thyroid to develop normally or defective hormone synthesis Detectable at birth, may not be recognized until 3- 5 mths of age Dwarfism ,mental retardation, short extremities, inactive, listless, puffy & expressionless face, enlarged tongue, skin yellow, dry & cool, bradycardia, low body temp., late teeth eruption, delayed closure of fontanelle Poor appetite, feeding slow, constipation, umbilical hernia Iodine replacement institution prior to pregnancy till end of 2nd trimester

- 26. } **T4 10-15** µg/kg daily T4 levels normalize within 1-2 weeks Adjust dosage at 4-6 weeks in first 6 months and then at 2 month during 6 to 18 month. Thereafter, 3 - 6 month to maintain T4 10 - 16 µg/dL and TSH normal range

  Causes: ◦ thyroiditis or thyroidectomy ◦ Drugs: I131, iodides, lithium and amiodarone ◦ May be simple goitre or idiopathic Face: expressionless, puffy, pallid Skin: cold, dry, scaly scalp Hair: coarse, brittle, sparse Fingernails: thickened, brittle ; Voice: husky, low pitched, slow speech Poor appetite, constipation Voluntary muscles weak and relaxation of deep tendon reflexes delayed Dilated heart, pericardial effusion, ascites, Hyperlipidemia, anaemia Cold intolerance (Subclinical hypothyroidism)

  Severe, long-standing hypothyroidism Serious medical emergency, mortality rate high (60%) despite early diagnosis and treatment Elderly patient during winter months Pulmonary infections, CVA, CHF precipitate coma. Sedative, narcotics, antidepressants and tranquillizers Profound hypothermia, respiratory depression, unconscious, bradycardia, delayed reflexes, dry skin Estimate Serum free thyroxine index & TSH LP – High proteins

  Ventilatory support Rewarming Correct hyponatremia } IV steroid } IV T4 (200 – 300 µg) bolus IV T4 (100 µg) after 24 hrs Oral T4 (500 µg) < 50 yrs plus inj.T3 IV 10 µg 8 hrly. till patient is conscious Do not exceed T4 > 500 µg / day or T3 > 75 µg / day

Nontoxic Goitre: ◦ May be endemic or sporadic ◦ T4 replacement with maintenance dose Thyroid nodule Papillary carcinoma of thyroid

Hyperthyroidism is the overproduction of thyroid hormones by an overactive thyroid Thyrotoxicosis is a syndrome of excess of thyroid hormones in the blood, causing a variety of symptoms that include rapid heart beat, sweating, anxiety, and tremor Causes of thyrotoxicosis:

1. Most common cause (70%) is Grave`s disease: overproduction of thyroid hormone by the entire gland (autoimune and IgG to TSH receptors)
2. Toxic nodular or multinodular goiter: lumps in the thyroid gland and overproduction (independent of TSH)
3. Thyroiditis: Temporary symptoms of hyperthyroidism (leakage)
4. Tablet intake (thyroid hormone) in excess – exogenous } Laboratory: High T3 and T4 + low TSH

Skin flushed, warm, moist Tremor Heat intolerance (Preference to cold) Exphthalmous (grave`s disease) Muscles weak Heart rate rapid, heart beat forceful, bounding arterial pulses ↑ energy expenditure & appetite, loss of weight Insomnia, anxiety, apprehension Diarrhoea Angina, arrhythmia and heart failure Muscular wasting, thyroid myopathy Untreated thyrotoxicosis – osteoporosis

Antithyroid drugs: ◦ Small diffuse goiter ◦ Do not decrease size Radioiodine: Diffuse, Nodular goiter ◦ Decrease size Surgery: Young pt. with relapsing thyrotoxiocsis, obstruction of neck vein or trachea

Inhibit Hormone synthesis (Antithyroid Drugs): Propylthiouracil, Carbimazole, Methimazole – also called Thioamides (Thiourea derivatives) Destroy Thyroid tissue: Radioctive Iodine (131, 125, 123) Inhibits Hormone Production and release: Iodine, Iodides of Na and K, Organic Iodide Ionic Inhibitors: Thiocyanates (-SCN), Perchlorates (-ClO4), Nitrates (-NO3)

Reduce formation of thyroid hormone Inhibit oxidation and oraganifiction of iodine – bind to thyroid peroxidase Inhibit coupling of iodotyrosines to form T4 and T3 Result in intrathyroidal iodine deficiency Maximum effect delayed until existing hormone stores exhausted High dosage leads to hypothyroidism

Propylthiouracil inhibits peripheral conversion of T4 to T3 at high doses used in thyroid storm

Propylthiouracil 1. Less potent

2. Highly Plasma bound

3. Less Placenta and milk entry

4. T1/2: 1-2 hrs

5. No active metabolite

6. Multiple dosing

7. Inhibits T4 to T3 Carbimazole 5 times more potent Less bound High entry 6-10 Hrs Active metabolite – methimazole Single dose No T4 to T3 inhibition

Pharmacokinetics: ◦ Orally absorbed well, widely distributed in the body and crosses placenta and enter milk ◦ Metabolized in liver and excreted in urine ◦ All are concentrated in thyroid - intrathyroid t1/2 is longer – effect does not reflect in plasma conc. } Preparation: PTU – 50 mg tabs., Methimazole – 5 & 10 mg tbs. and Carbimazole – 2.5/5 mg tabs.

Hyperthyroidism: 1. Principal therapy (definitive therapy)

 Clinical improvement - 2 to 4 wk

 Euthyroid - 4 to 6 wk

 Guide to therapy - decrease nervousness, palpitation, increase strength and weight gain and pulse rate

 Optimal treatment - decreased gland size } Adjuvant to radioiodine to control disease ◦ Initial 1 to 2 wks and followed by after 5 to 7 days ◦ Gradual withdrawal after 3 to 4 months (I131action developes) ◦ Preferred in older patients ◦ However – no remission for toxic nodular goitre – used in less responsive patients with I131 (lifelong) } To prepare patient for surgery: Carbimazole

Minor : ◦ GIT intolerance, rashes, urticaria, arthralgia, fever, anorexia, nausea, taste and smell abnormalities } Major : ◦ Agranulocytosis, Thrombocytopenia, Acute hepatic necrosis, Cholestatic hepatitis, Vasculitis, Lupus-like syndrome Monitor ADR: } Blood disorder- first two months of treatment } Routine leucocytes counts } Patient advised to stop drugs if symptoms of sore throat, fever, mouth

ulcers develop and have leucocytes count performed } If agranulocytosis develops – withdraw drug, hospitalization

Increased tissue sensitivity to catecholamine in hyerthyroidism ◦ increased no. of "β" adrenoceptors (up regulation) ◦ Increased second messenger i.e. cAMP responses Some symptoms are adrenergic – palpitation, tremor, nervousness, myopathy and sweating etc. β- blocker provides quick relief (propranolol 20- 80mg 6-8 hrly) Not used as sole therapy – awaiting Carbimazole or I131 response, preoperative treatment of subtotal thyroidectomy and Thyroid crisis Do not alter course of disease and thyroid function tests

A sudden exacerbation of symptoms of thyrotoxicosis, characterized by fever, sweating, tachycardia, extreme nervous excitability, and pulmonary edema Life-threatening emergency Large amount of hormone into circulation occurs in untreated or incompletely treated patient. Precipitated by infection, trauma, toxemia of pregnancy

Inj. Propranolol2. IV, slow, 1mg / min. to max. 10 mg followed by 40-80 mg oral every 8 Hrly, Propylthiouracil- large doses 300-400 mg 4-6 Hrly , Potassium Iodide 600 mg to 1 g orally in first 24 hr to inhibit hormone release or Ipanoic acid/ipodate (radioiodine) , Hydrocortisone 100 mg 8 Hrly IV followed by oral prednisolone , Hyperthermia – cooling and aspirin } Heart failure- conventional treatment ◦ Diltiazem: 60-120 mg BD oral

Concurrent use of L- thyroxine with thionamide "block and replace regimen" facilitates maintenance of euthyroid state and reduce frequency of follow up visits , Relapse rate is not influenced by titration or block replace regimen , Second course of thionamides do not produce long term remission if hyperthyroidism recurs

Iodide well absorbed from intestine Selective uptake and 25 times conc. by thyroid Iodide deficiency ↓ thyroid hormones - Hyperplasia, increased vascularity and goiter Related to dose and thyroid status ◦ Hyperthyroidism - moderate excess of iodine ↑ synthesis ◦ Substantial excess - inhibits hormone release, promote storage, gland firm, ↓ vascularity

- THYROID CONSTIPATION (inhibit endocytosis and proteolysis) ◦ Euthyroid cases - excess iodine causes goiter, hard nodule become hypothyroid } Sources of excess- iodine containing cough medicines, iodine containing radiocontrast media and amiodarone

Large doses for thyroid crisis – to reduce release ◦ Lugol`s Iodine (6 to 10 drops or any other compound containing iodine, Preparation for thyroidectomy ◦ To make the gland firm, less vascular and easy to operate ◦ To make euthyroid add carbimazole before iodide ◦ Also Propranolol to for rapid control of symptoms ◦ KI 60 mg orally 8 hrly produces effects in 1-2 days, maximal 10-24 days , KI for 3 days to cover I132 or I123 isotopes Prophylaxis of endemic cretinism/goitre –inj. Iodized oil IM 3-5 years Antiseptic on skin / surgical scrub, expectorant

Swallowed I131 trapped and conc. in thyroid follicles ◦ Beta radiation 90 % - penetration upto 0.5 mm ◦ Gamma radiation - deep penetration ◦ Radioactive half-life 8 day, Used in diffuse toxic goiter (Thyrotoxicosis / Grave's disease), toxic nodular goiter, thyroid carcinoma ◦ Diagnosis of thyroid disorder (I123), Beneficial effects within one month } Maximal effects –3 months Life long follow-up Review at 6 weeks } Add antithyroid drugs and beta-blocker inrelapsing thyrotoxicosis Contraindication s - pregnancy, lactation, children.