Hypothyroidism

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Objectives

- Review the regulation of thyroid hormone (TH) synthesis, release, & action
- Present the clinical signs & symptoms of hypothyroidism
- Review the primary causes of hypothyroidism & some unusual cases
- Present a systematic approach to TH testing & evaluation of suspected hypothyroidism
- Review pearls TH of replacement in hypothyroidism

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Regulation of Thyroid Function

Hypothalamic-Pituitary-Thyroid Axis

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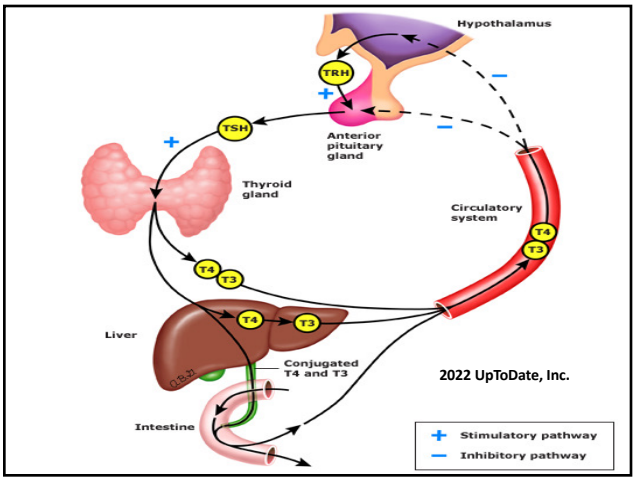

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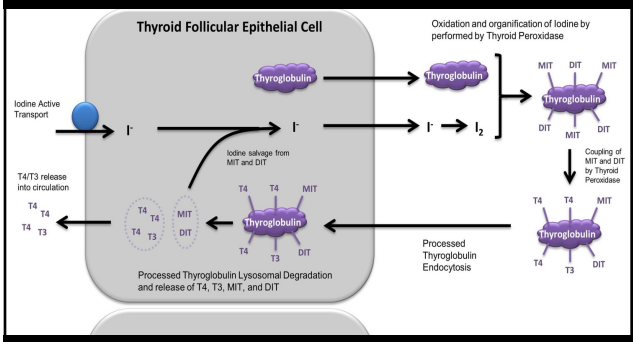
Regulation of Thyroid Hormone (TH) Synthesis & Release by Thyroid



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Thyroid Hormone Transport Proteins

- Both T_4 & T_3 are water insoluble so are transported in blood to target tissues bound to serum transport proteins (binding proteins)
- Free hormone; FT_4 (<0.1% free) & FT_3 (<0.01% free) are biologically active
- The principle TH transport protein is thyroxine-binding globulin (TBG) while transthyretin (TT), & albumin also transport TH to the tissues of the body

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Multiple medical conditions can affect transport protein concentrations which result in changes in total thyroid hormone levels (up or down) …yet free (active) hormone levels are usually unchanged

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Conditions Affecting TBG & Total TH Blood Levels

Increase TBG	Decrease TBG
• Hypothyroidism	• Hyperthyroidism
• Liver disease (hepatitis)	• Renal disease
• Estrogens/pregnancy	• Liver disease
• Acute intermittent porphyria	• Severe systemic illness
	• Cushing syndrome
	• Androgens
	• Malnutrition

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FT_3 is the biologically active form of TH & most is converted from FT_4 in target cells by deiodinase enzymes

The liver contains the most deiodinase enzymes but they are also located in most target tissues

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3 Forms of Tissue Deiodinases

Iodothyronine deiodinases control the formation T_3 from T_4 (DIO_1 is in blood & DIO_2 is in target tissues) while the degradation of T_3 by (DIO_3) into reverse T_3 (rT3) is located on target cell membranes & all 3 are critical to TH regulation

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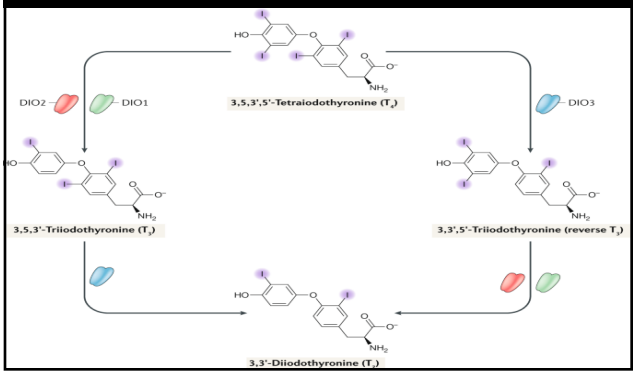
3 Functional Deiodinases; DIO_1, DIO_2, & DIO_3



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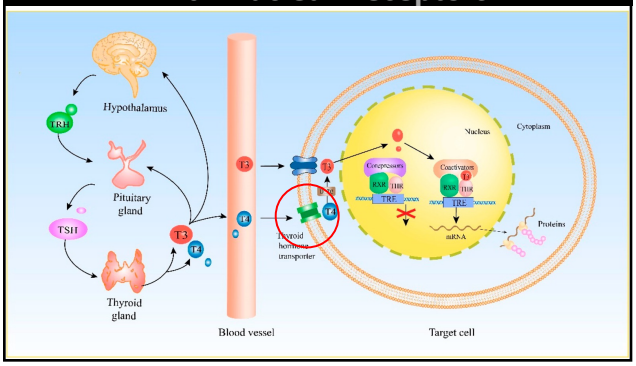
FT_4 & FT3 Enters Target Cells Via TH Transporters….. But Only FT_3 Interacts With Nuclear Receptors



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Thyroid Hormone Testing

Understanding appropriate TH testing is key to management of all thyroid conditions

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Basic TH Testing

- **Measuring FT4 & TSH are minimal tests required for initial thyroid assessment; *if they are normal…. thyroid function is usually normal***
- **A low FT4 & high TSH suggests primary hypothyroidism**
- **Low FT4 & TSH suggests secondary hypothyroidism; however a FT3 needs to be checked to rule out "T3-toxicosis"**
- **A high FT4 & suppressed TSH suggests hyperthyroidism**
- **Total T4 & T3 confuse the whole process!**

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Ancillary Thyroid Testing

- **Thyroid antibody titers; Anti-thyroid peroxidase (TPO), Anti-thyroglobulin (Tg) Antibodies are markers for Hashimoto's Thyroiditis & Graves' Disease**
- **Thyroid Stimulating Antibodies (TSI), & Thyroid Inhibiting Antibodies (TBI) are markers for Graves' Disease**
- **I-123/I-131 thyroid scans**
- **Tc-nuclear thyroid scans**
- **US's of thyroid**
- **MRI/CT scans of thyroid**

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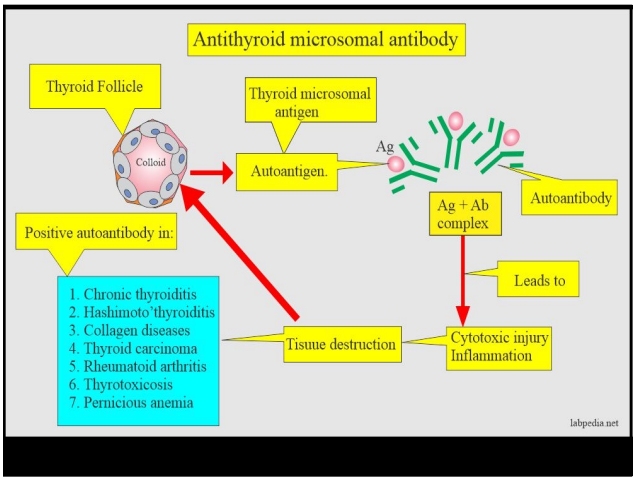

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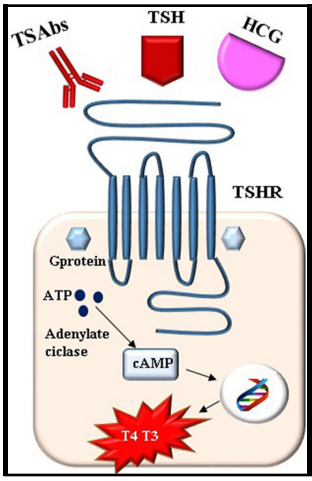

TSAbs

- TSAbs bind to TSH receptors on target cell membranes & *can either stimulate FT4/FT3 synthesis & release or block endogenous TSH binding & inhibit their release*
- TSAbs also bind to retro-orbital fibroblasts & adipocytes inducting inflammation…resulting in Ophthalmopathy

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Clinical Presentation of Hypothyroidism

Symptoms can range from none with impending hypothyroidism to coma/seizures with Myxedema

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Classic Symptoms of Hypothyroidism

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarseness
- Muscle weakness/cramps

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Physical Findings of Hypothyroidism

- Lateral thinning of eye brows/periorbital edema
- Dry skin
- +/- goiter
- Pitting/non-pitting pedal edema
- Delayed deep tendon reflexes (relaxation phase)
- Bradykinesia

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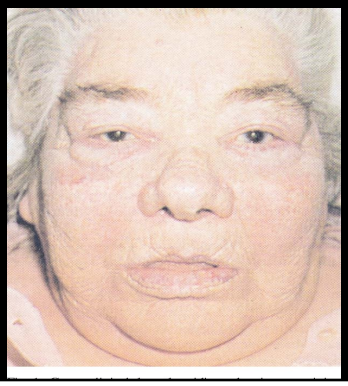
Facial Features of Hypothyroidism



Rhodus Thyroid Disorder II : hypothyroidism and thyroiditis Craig S. Miller, L. Nelson. 2006

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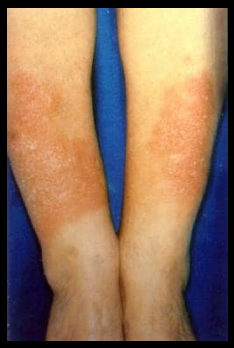
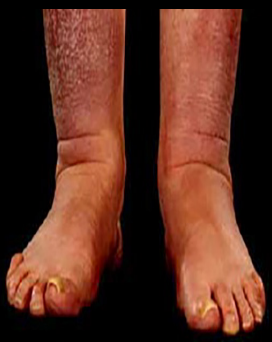
Pretibial Myxedema





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Classification of Hypothyroidism

- Primary Hypothyroidism; intrinsic loss of thyroid hormone synthesis & release by thyroid gland
  - -agenesis of thyroid
  - -iodine deficiency
  - -destruction of thyroid; autoimmune, viral mediated, I-131 ablation, external radiation
  - -surgical removal
- Secondary Hypothyroidism; loss of TSH regulation from hypothalamic/pituitary disorders

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Primary Hypothyroidism

- Hashimoto's thyroiditis
- Idiopathic hypothyroidism
- Chronic thyroiditis; silent vs painful
- Iodine deficiency(rare in US)
- Post-surgical/external radiation
- Post I-131 ablation
- Medication induced; amiodarone, lithium, different interferons
- Infiltrative diseases; sarcoidosis, hemochromatosis, amyloidosis

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Secondary Hypothyroidism

- Hypothalamic or pituitary tumors &/or their treatment from surgery or external radiation
- Hypothalamic/pituitary infiltration from sarcoidosis or Histiocytosis X
- Pituitary infarction; Sheehan syndrome
- Pituitary hemorrhage; pituitary apoplexy

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Initial Assessment of Suspected Hypothyroidism

- CBC
- CMP
- ECG
- FT4 & TSH
- Anti-thyroid peroxidase (TPO) & Anti-thyroglobulin (Tg) Antibodies
- US of the thyroid

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Hashimoto's Thyroiditis

Most common form of Hypothyroidism

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Hashimoto's Thyroiditis

- Chronic autoimmune T-cell mediated infiltration & destruction of thyroid
- Usually painless, small granular goiter, & the most common form of hypothyroidism
- Goiters can be non-palpable to very large
- Can present with T-3 Toxicosis early in the inflammatory disease process
- Lymphoma also associated with chronic inflammation (rarely)

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Pathogenesis of Hashimoto's Thyroiditis

- Virus or other environmental trigger initiates thyrocyte death & release of self-antigens
- Autoantibodies are directed against thyroid peroxidase (TPO), thyroglobulin (Tg), & TSH receptors (TSHR)
- Helper T-lymphocytes (CD4+ T-cells) activate cytotoxic T-lymphocytes (CD8+ cells) resulting in recruitment of macrophages into thyrocytes & cause further destruction
- T-cell-mediated infiltration & cytotoxicity results in thyrocyte apoptosis & eventual loss of adequate TH synthesis/secretion

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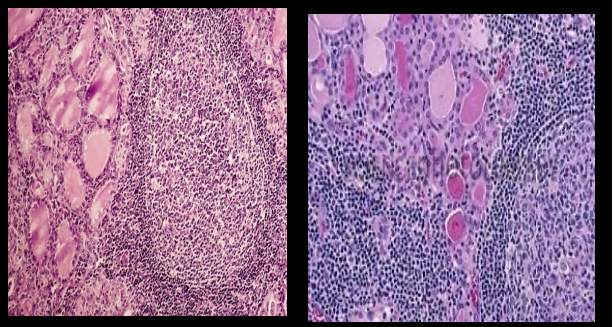
Lymphocytic Infiltration of Thyroid with Hashimoto's Thyroiditis



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Clinical Presentation of Hashimoto's Thyroiditis

- Asymptomatic goiter
- Tender goiter (subacute phase)
- Hyperthyroidism (usually mild & may be from "T-3 Toxicosis"
- "T-3 Toxicosis" can be intermittent & due to "leakage" of T3 from damaged follicles
- Progression to hypothyroidism

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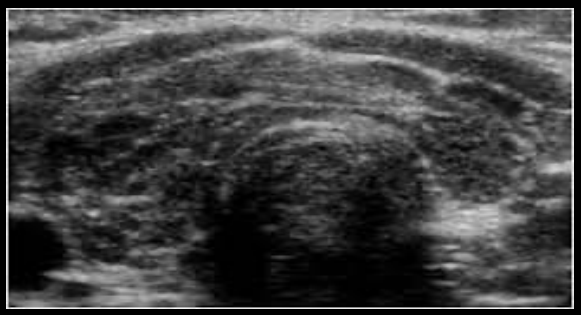
Ultrasound Characteristics of Hashimoto's Thyroiditis



Heterogeneous echo texture with fibrous stranding & "pseudonodule formation"

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Management of Hashimoto's Thyroiditis

- Thyroxine replacement if hypothyroid
- T4 suppression (TSH <0.5 but >0.1) for large goiters to prevent TSH-driven growth is controversial & not recommended
- FNA of worrisome nodules (> 1 cm)
- Remember……chronic inflammation from Hashimoto's can degenerate induce oncogenesis into a thyroid cancer or T cell lymphoma

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Idiopathic & Silent Thyroiditis

Similar pathogenesis (just no immune markers detectible)

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Riedel's Thyroiditis

A rare chronic inflammation & fibrotic condition of the thyroid gland resulting in a stone hard goiter & hypothyroidism

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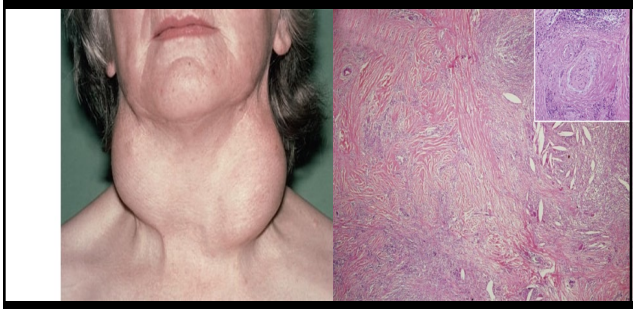
Riedel's Thyroiditis



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Riedel's Thyroiditis

- The etiology of Riedel thyroiditis (RT) is unknown, but it may be related to a relatively new group of rare disorders; IgG4-related systemic disease (IgG4-RSD)
- These are immune-mediated fibroinflammatory conditions that affecting multiple organs including; salivary glands, pancreas, orbit of the eye
- Treatment includes glucocorticoids (successful 70% with 3 mo course), tamoxifen, & surgery

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Hypothyroidism In Patients With Graves' Disease?

Yes, rarely in patients who secrete excessive concentrations of TSH Receptor Inhibiting Antibodies (TSIAb's)

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Graves' Disease

Most common form of hyperthyroidism caused by TSH Receptor Antibodies which bind to the TSH receptor (TSAbs), mimicking endogenous TSH & stimulates *both* thyroid glandular growth & excessive release of T4/T3

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Alternating Hyperthyroidism & Hypothyroidism in Graves' Disease

- There are at least 3 epitopes of TSH receptor antibodies; TSH stimulating antibodies (TSAbs), TSH blocking antibodies (TBIAbs), & TSH neutral or blocking antibodies (TIIAbs)
- Rarely patients will be seen that temporally switch between TSI & TBI antibodies resulting in alternating symptoms of hyperthyroidism & hypothyroidism
- TBIAbs antibodies can now be determined commercially & should be assayed if you suspect

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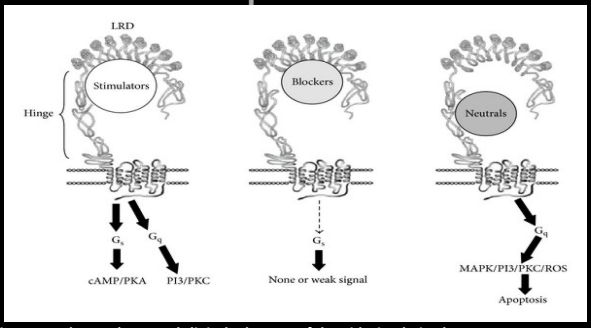
Differing Functional Classes of TSH Receptor Antibodies



Diana, T. e.al. Prevalence and clinical relevance of thyroid stimulating hormone receptor blocking antibodies in autoimmune thyroid disease Clin Exp Immunol. 2017 Sep; 189(3): 304–309

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Post-Ablative Hypothyroidism

- Post surgical
- Post I-131 ablation for functional nodules or Graves' disease
- Post-external radiation for head & neck malignancies

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Medication-Induced Hypothyroidism

- Anti-thyroidal medications (PTU & methimazole)
- Lithium; can cause hypothyroidism & goiter developmemt
- Amiodarone
- Iodides; Lugol's Solution, potassium iodide

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Effects of Lithium on TH Function

- Lithium accumulates in thyroid tissue by active transport & concentration can be 3-4X > than in plasma
- Lithium competes for iodine transport resulting in low thyroid iodine uptake
- Lithium also inhibits the coupling of iodotyrosine residues to form the iodothyronines….. thus inhibits the synthesis & release of T_4 & T_3

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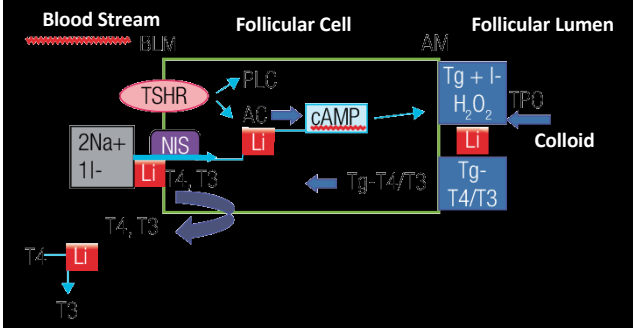
Effects of Lithium on TH Function



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Impact of Iodine Status on Thyroid Function

- Exogenous iodine has dual effects on thyroid hormone levels
- Iodine deficiency results in hypothyroidism & the development of endemic goiters
- However, medicinal iodine exposure to patients (contrast agents, amiodarone) can result in both *increased or decreased synthesis &* release of TH

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Effects of Iodine on Thyroid Function

- Acutely, iodine decreases the thyroid response of the TSH & it inhibits its own oxidation (Wolff-Chaikoff effect') & reduces its trapping thus inhibiting T4/T3 synthesis & release
- At high concentrations Iodine inhibits thyroid hormone secretion & induces hypothyroidism
- Paradoxically, in patients with endemic goiter exposure to high iodide levels long-term can result iodide-induced hyperthyroidism; *(Jod-Basedow effect)*

Chung, H.R. Iodine and thyroid function Ann Pediatr Endocrinol Metab. 2014 Mar; 19(1): 8–12.

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Effect of Amiodarone on TH Function

- Amiodarone, an iodine-rich medication *(8 iodine residues on each amiodarone molecule)* used for treatment of ventricular arrhythmias & atrial fibrillation
- Amiodarone commonly induces hypothyroidism from iodine's inhibitory effects on TH synthesis & release
- Amiodarone can also cause hyperthyroidism by 2 mechanisms; from iodine (AIT1) or from induction of a rare inflammatory thyroiditis (AIT2)

Cohen-Lehman, J. et.al. Effects of amiodarone therapy on thyroid function nature reviews endocrinology vol 6, pp. 34–41 (2010)

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Amiodarone-induced thyroiditis

AIT type 1	AIT type 2
Hyperthyroidism induced by iodine in a pathological gland (BMD or latent Graves).	Destructive thyrotoxicosis induced by Amiodarone (normal gland).
US→ Diffuse or nodular goiter.	US→ normal gland.
Doppler parenchymal hypervascularization (more specific finding to differentiate type 1 from 2).	Flow decreased or absent in Doppler US.
Treatment→ anti-thyroid drugs.	Treatment→ steroids.

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Management of Amiodarone-Induced Thyroid Dysfunction

- **Stopping the medication is helpful if clinically possible but not required**
- **Amiodarone-induced Hypothyroidism is treated with LT_4**
- **Amiodarone-induced hyperthyroidism must be treated with anti-thyroidal medications for AIT1.**
- ***Lithium can be added for resistant forms of the amiodarone-induced hyperthyroidism***
- **Surgery is often required for severe forms of AIT2**

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Unusual Causes of Hypothyroidism

Zebras in the cow pasture

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Thyroid Hormone Resistance Syndrome

Inherited condition (1 of 40,000 live births) characterized by a reduced responsiveness of target tissues to TH due to mutations of the thyroid hormone receptor

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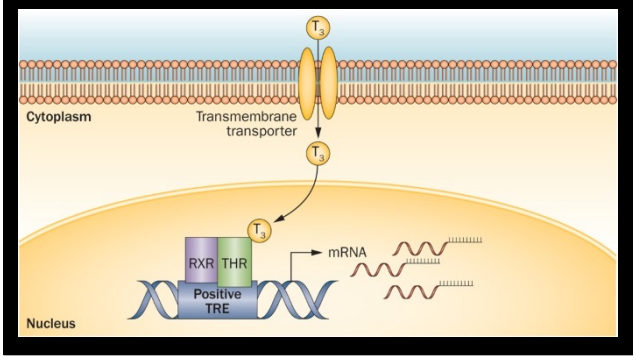
Defective Nuclear TH Receptor Causes Hormone Resistance



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Clinical Features of Thyroid Hormone Resistance Syndrome

- High FT_4 & FT_3, low rT_3, & inappropriately normal or high TSH
- Elevated CPK & goiter
- *Do not appear hyperthyroid clinically*
- Short stature, ADHD, delayed bone age, deafness, bradycardia, constipation
- Others have symptoms of macrocephaly, broad faces, skin tags, motor dyspraxia, slow speech

MORAN, C. ET. AL. LANCET; DIABETES & ENDOCRINOLOGY VOLUME 2, ISSUE 8, P619-626, AUGUST 01, 2014

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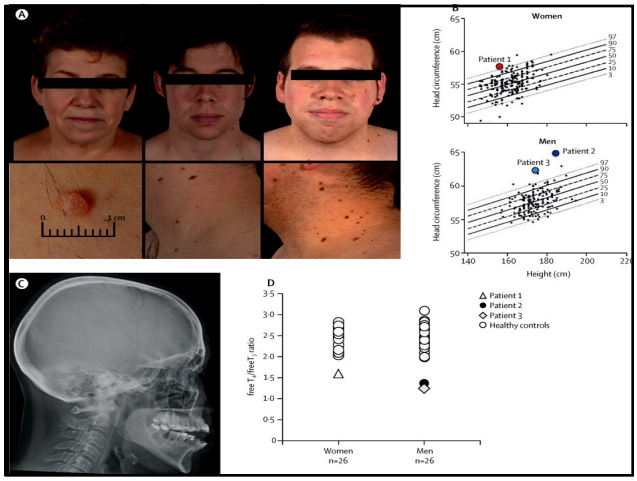

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Deiodinase Deficiencies

Iodothyronine deiodinases contribute to maintenance of the euthyroid status by regulating the formation T_3 from T_4 (DIO_1 & DIO_2) & the degradation of T_3 (DIO_3) into rT_3

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Inherited Deiodinase Deficiencies

- Patients present with mild hypothyroid symptoms, normal or slightly high FT4 with low FT3, & slightly high TSH
- However a recent paper indicated that *26% of patients with primary hypothyroidism on replacement therapy had polymorphism in the DIO_2 gene in the hypothalamus* & a decreased T_4:T_3 ratio
- Patients with hypothyroidism, decreased T_4:T_3 ratio, & clinical manifestations may benefit from combination LT_4 & LT_3 replacement

Gereben, B. et.al. Scope and limitations of iodothyronine deiodinases in hypothyroidism Nat Rev Endocrinol. 2015 Nov; 11(11): 642–652

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Environmental Chemicals Potentially Affecting TH Function

- Polychlorinated Biphenyls (PCBs), Polybrominated Diphenyl Ethers (PBDEs), Perchlorate, & Bisphenol-A identified as TH disrupting chemicals in the hypothalamus & associated with low T_4 levels
- Numerous other environment compounds have also been associated with thyroid dysfunction

Calsolaro V, et.al. Thyroid Disrupting Chemicals J Mol Sci. 2017 Dec; 18(12): 2583
Sarne D. Effects of the Environment, Chemicals and Drugs on Thyroid Function. [Updated 2016 Sep 27]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext

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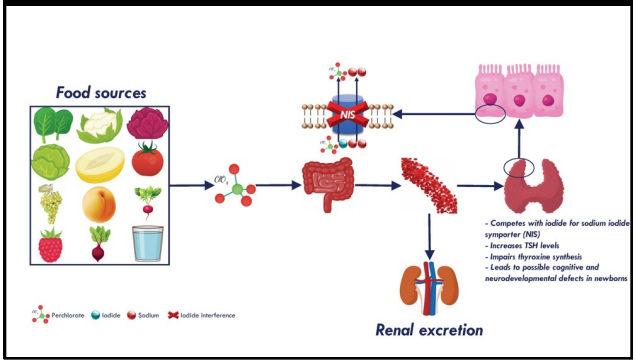
Impact of Perchlorate on Thyroid Hormone Synthesis



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Impact of Perchlorate on Thyroid Function

- Orally consumed perchlorate compounds in food & drinking water now being considered a relevant source of perchlorate
- Perchlorate-induced natrium-iodide symporter (NIS) interference is a well-recognized thyroid disrupting mechanism

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Impact of Perchlorate on Thyroid Function & Human Health

- Perchlorate exposure affects thyroid hormone synthesis in infants, adolescents & adults; particularly in the case of underlying thyroid diseases & iodine insufficiency
- Exposure to perchlorate during pregnancy leads to neurocognitive & behavioral development outcome in infants, regardless of maternal thyroid hormone levels

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Perchlorate Discharge Test

- Perchlorate used previously to diagnose thyroid Iodine trapping disorders.
- Patients would be given I-123 like a typical thyroid nuclear scan & perform the scan at 1-3 hrs. allowing time for it to be captured by the thyroid
- Then, perchlorate is administered orally which displaces non-organified iodide from the thyroid
- A perchlorate discharge test is considered positive (abnormal) if there is an abnormally rapid loss of radioactive iodine from the thyroid on the scan

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Pendred Syndrome

- Pendred syndrome is a congenital condition associated with severe sensorineural hearing loss) is evident at birth & goiter
- It is due to mutations in the *SLC26A4* gene which alters the structure or function of the protein; *pendrin*
- *Altered Pendrin* function disrupts normal ion transport of chloride, iodide, & bicarbonate into & out of cells which disrupts normal development & function of the thyroid gland & the inner ear, which leads to the characteristic features

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Clinical Approach to TH Replacement

Should be easy…….yet a common reason for endocrine referral

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Routine Thyroid Hormone Replacement

- >80% of hypothyroid patients can be treated with LT_4 without difficulty
- Individuals with variable thyroid functions on hormone replacement *you need to check for compliance, & stress need to take medication as instructed!*
- *LT_4* is taken by itself (no coffee or milk) 30 min before meals or 90 minutes after meal

Chen, X. et.al. Diagnostic Values of Free Triiodothyronine and Free Thyroxine and the Ratio of Free Triiodothyronine to Free Thyroxine in Thyrotoxicosis. J Endocrinol. 2018; 2018: 4836736

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Medications Which Interfere with TH Absorption

- Calcium carbonate
- Aluminum- containing antacids
- Sucralfate
- Iron supplements
- Cholestyramine & orlistat
- Possibly ciprofloxacin & raloxifene

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For Those Patients with Symptoms of Hypothyroidism & normal FT_4 & TSH ??

Obtain a FT_3 & check the FT_4/FT_3 ratio (cut-off value: 0.405) as they may have a Deiodinase Deficiency (DIO_2) & require duel hormone replacement

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TH Preparations Available

- Levothyroxine; LT4 available in 3 preparations Tablets: (Euthyrox, Levoxyl, Synthroid, Unithroid) Softgels: Tirosint, Liquid: Tirosint
- Liothyronine; LT3 available in tablets (Cytomel)
- Mixture of LT4 & LT3 (4:1 ratio) available in tablets: Thyrolar (Liotrix)
- Desiccated Thyroid Extract; 1 grain of desiccated thyroid extract (60 mg) should contain approximately 38 mcg T4 and 9 mcg T3 (Armour Thyroid, NP Thyroid)

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Which Patient Do You Try Combination LT_4/LT_3?

First; Exclude Co-Morbidities such as Chronic Fatigue Syndrome, Fibromyalgia, & Depression!!

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Guidelines For Patients on Combination TH Replacement

- If you add LT_3, then dose of LT_4 should be reduced
- Suggested LT_4/LT_3 ratio is 3:1 so reduce LT_4 by 30% at onset
- LT_3 has a shorter half-life than LT_4 & needs to be given twice a day
- *LT3 will usually be a dose of 5 – 20 mcg a day in a split dose*

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Monitoring Patients on Combination LT_4/LT_3

- Normal monitoring of patients of LT_4 is to obtained bloodwork fasting in AM before drug is taken
- For those on combination replacement; obtain a TSH, F_4 & FT_3 *2–4 h post-dose* as this is the expected peak of serum AM T_3 post dose
- It is important to avoid suppression of TSH due to impact on heart rhythm, bone mineral densities

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Hypothyroidism is a Common Endocrine Condition

Most can be managed by primary care providers

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