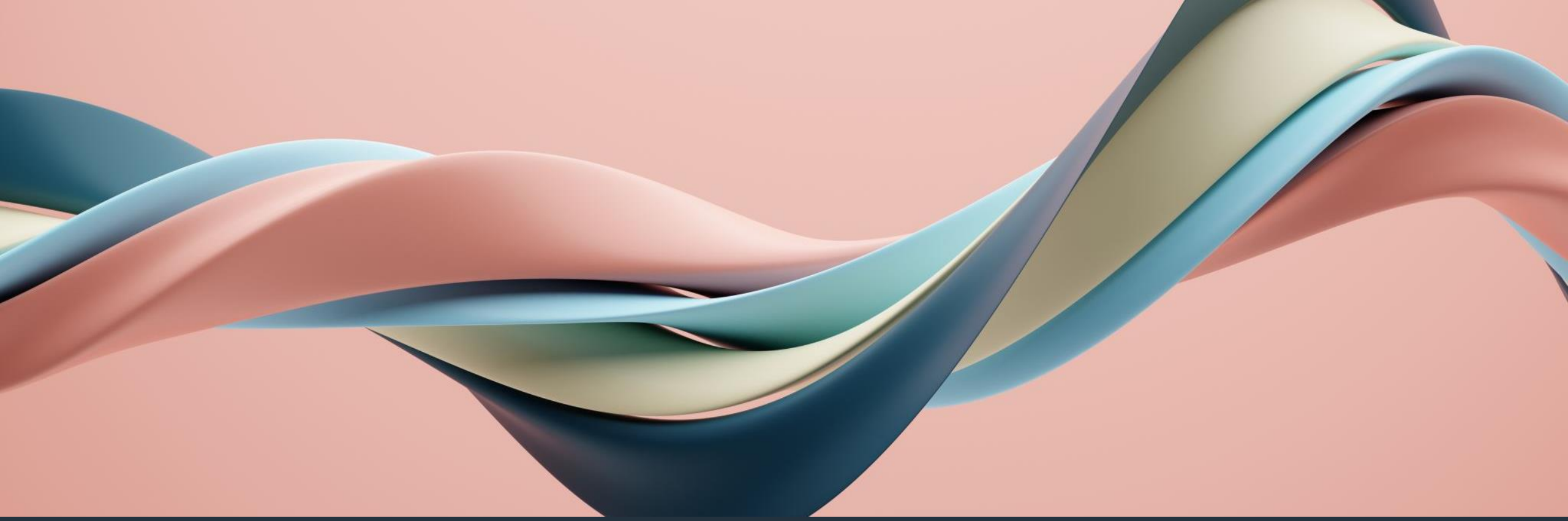
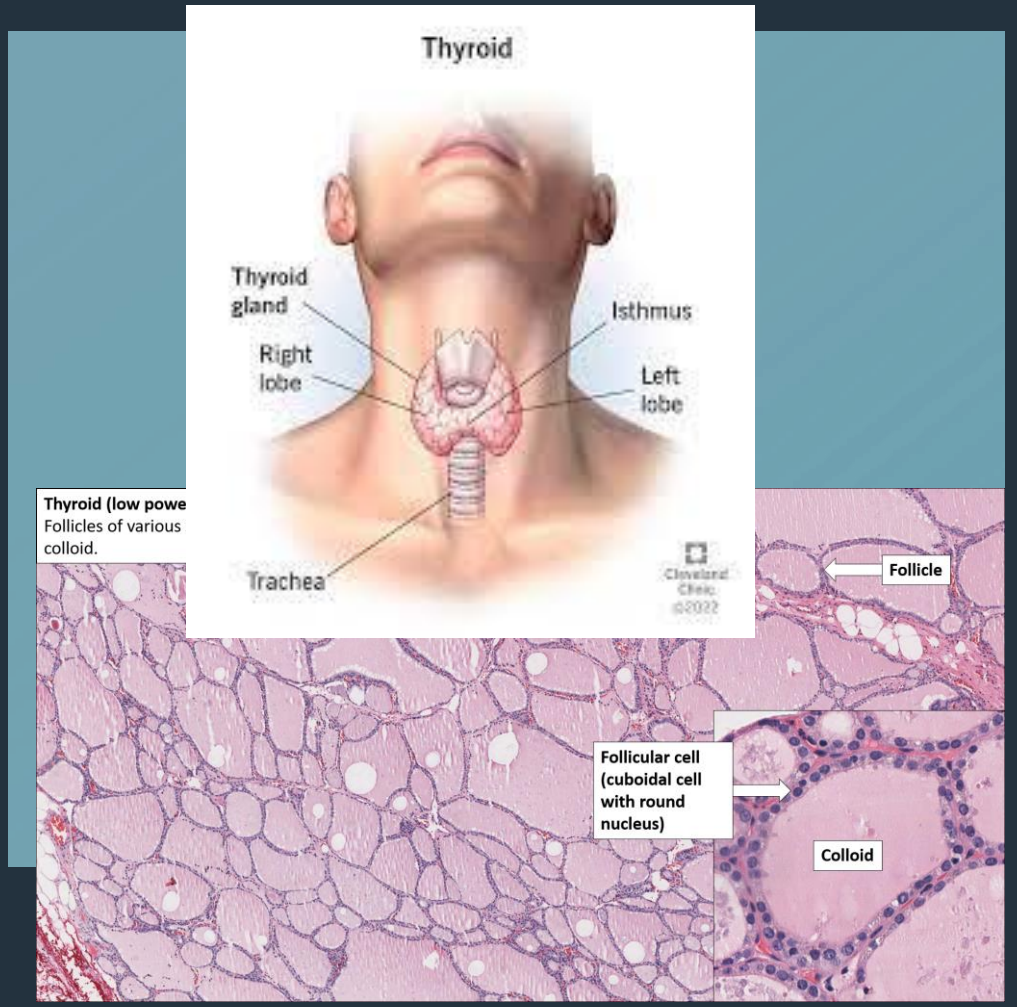


HYPOTHYROIDISM, HASHIMOTO'S AND HYPERTHYROIDISM

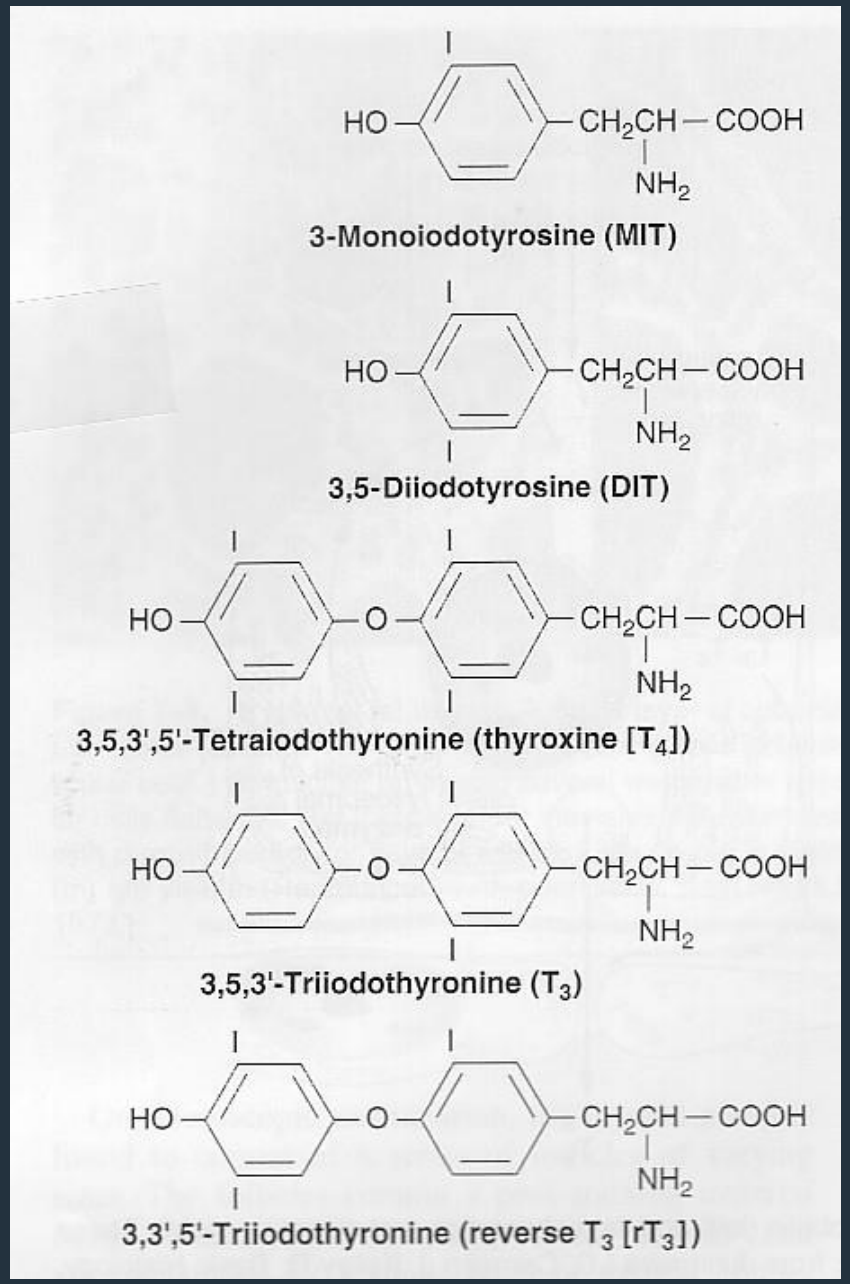
Geetanjali Kale, MD

ANATOMY AND HISTOLOGY OF THYROID GLAND

- Weighs 10-20 grams
- Produces two biologically active compounds FT3 and FT4
- Thyroid is a production as well as storage gland
- Hormones are stored in colloid along with thyroglobulin, so they are readily available as needed
- FT4 is only produced in thyroid gland
- FT3 is primarily manufactured in peripheral tissues by conversion from FT4



- Iodine is a substrate for thyroid hormone production. First step is Iodine transport (trapping) through sodium/iodide symporter (NIS).
- Next step is oxidation and incorporation into thyroglobulin (organification) is regulated by thyroid peroxidase (TPO).
- Coupling of MIT and DIT to form T3 and T4
- Less than 1% of thyroid hormone remains free in circulation
- Only the free fraction exerts biologic effect and is subject to metabolism
- Half life of FT4 is 7 days and half life of FT3 is about 24 hours



ARE IODINE SUPPLEMENTS RECOMMENDED FOR PATIENTS WITH THYROID DISEASE?

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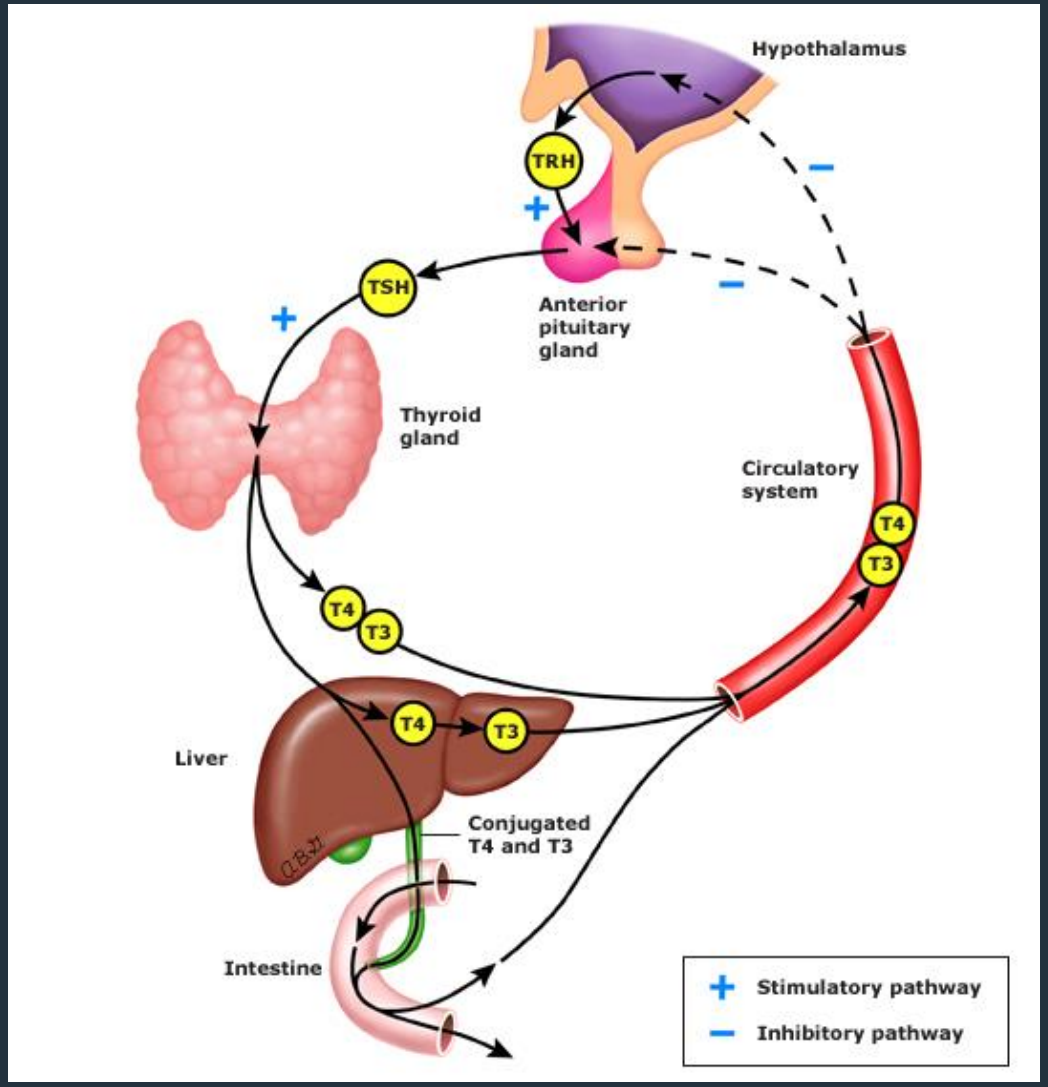
- Thyroid autoregulation allows the thyroid gland to adjust for varying levels of iodide
- **Wolff - Chaikoff Effect:** protective against iodine excess
- **Jod - Basedow Phenomenon:** protective against iodine deficiency
- In iodine sufficient areas of the world iodine supplements are not recommended

(such as products containing iodine or kelp or sea-weed)

THYROID HORMONE REGULATION

- Regulation of thyroid hormone secretion is controlled by negative feedback loops from TSH and TRH

- Peripheral regulation of thyroid hormone activity happens due to controlled conversion of FT4 to Ft3
- TSH is composed of alpha and beta sub-units; the alpha sub-unit is common to TSH, LH, FSH and HCG



DEFINITION OF HYPOTHYROIDISM

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- **Primary hypothyroidism** is characterized by a high serum thyroid-stimulating hormone (TSH) concentration and a low serum free thyroxine (T4) concentration,
- **Subclinical hypothyroidism** is defined biochemically as a normal free T4 concentration in the presence of an elevated TSH concentration.
- **Secondary (central) hypothyroidism** is characterized by a low serum T4 concentration and a serum TSH concentration that is not appropriately elevated.
- Primary thyroid disease accounts for over 95 percent of cases of hypothyroidism

DIAGNOSTIC TESTS

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- Standard of care is to order TSH, FT3 and FT4 assays, total T4 and T3 assays will indicate signs of binding protein abnormalities
- In certain patients FT4 assay with equilibrium dialysis may need to be assessed specially before ruling out central hypothyroidism
- Free T4 index, calculated using the T3 uptake (or THBI), are older methodologies to assess thyroid function while ruling out binding protein abnormalities
- Reverse T3 is measurement of inactive metabolite. It is widely measured by alternative health practitioners to justify the use of T3 therapy and supplements thought to enhance the conversion of T4 to T3. It has extremely limited utility for conventional medical practitioners for assessing rare conditions.

DIFFERENTIAL DIAGNOSIS

- Could this be lab error?
- Was the patient on Biotin or exogenous 'thyroid support' type of medications?
- Is patient recovering from nonthyroidal illness?
- Could there be resistance to TSH or thyroid hormone?
- Rarely patient could have TSH producing tumor (presenting as symptoms of hyperthyroidism)
- Consider co-existing adrenal insufficiency before initiating treatment
- If hypothyroidism is suspected…repeat thyroid hormone testing before starting treatment!

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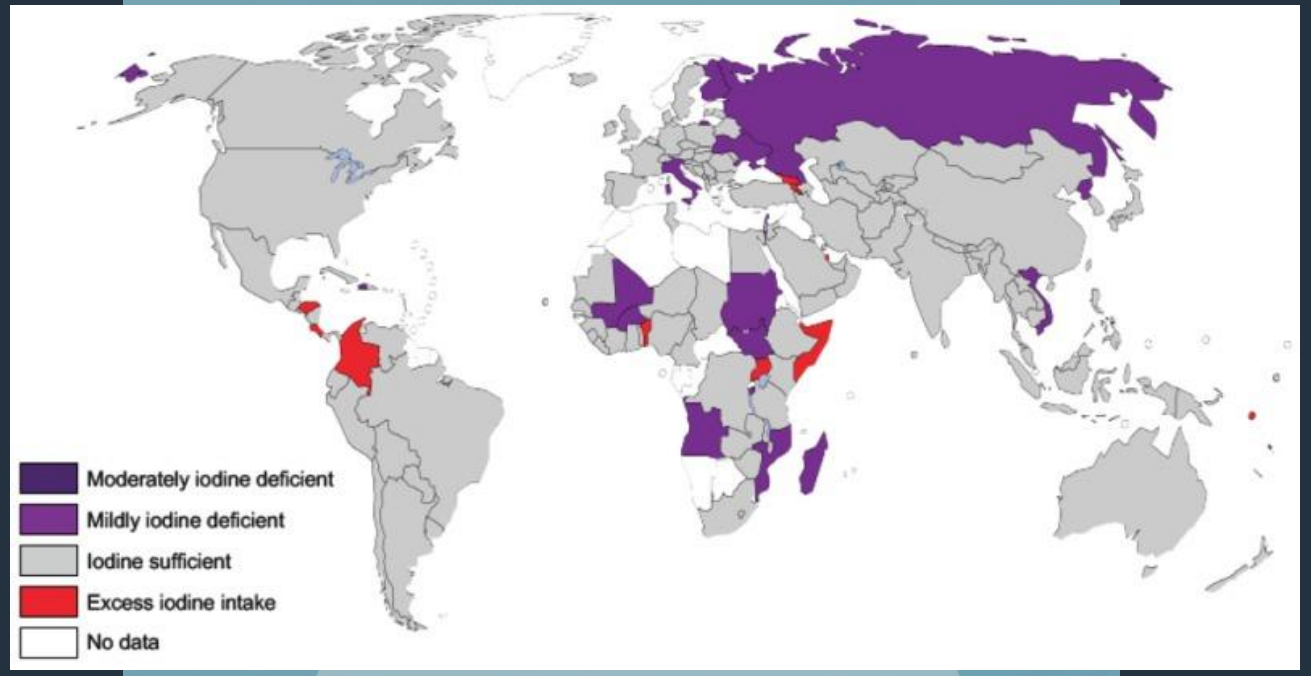
CAUSES OF HYPOTHYROIDISM

- Worldwide iodine deficiency is the most common causes of hypothyroidism but not in United States of America
- In United States of America, most common cause of hypothyroidism is chronic autoimmune disease or Hashimoto's disease
- Autoimmune mediated hypothyroidism can be goitrous or atrophic
- Only 90 percent of patients with have positive TPO antibodies
- TG antibodies are nonspecific and have limited value in diagnosis of Hashimoto's thyroiditis



WHEN TO SCREEN FOR HYPOTHYROIDISM

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Intellectual disability (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

Graphic 62676 Version 5.0

- Routine screening is not recommended
- Test when symptomatic
- Check TSH following thyroid surgery, RAI ablation or suspected thyroiditis, thyroid injury or pain
- Postpartum status
- With use of medications such as amiodarone and lithium
- Pituitary or hypothalamic disorders
- In case of dyslipidemia, hyperprolactinemia, hyponatremia, anemia etc.

TREATMENT OF HYPOTHYROIDISM: GOALS OF THERAPY

Ameliorate symptoms

Normalize thyroid-stimulating hormone (TSH) secretion

Reduce goiter size (if present)

Avoid overtreatment (iatrogenic thyrotoxicosis)

We aim to keep serum TSH within the normal reference range: approximately 0.5 to 5.0 mU/L (Individualized for patient)

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HYPOTHYROIDISM AND PREGNANCY

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Fetal thyroid is formed and 12 weeks of gestation and Pituitary-thyroid axis is established by 20 weeks of gestation

Hypothyroidism leads to adverse maternal outcomes: preterm labor, miscarriage,
Pre-eclampsia, Maternal hypertension, Post-partum hemorrhage

Fetal adverse outcomes are low birth weight, still birth, impaired offspring cognitive, psychomotor development

Trimester specific TSH normal range
1st trimester < 2.5 uIU/ml
2nd trimester < 3.0 uIU/ml
3rd trimester < 3.5 uIU/ml

Total T4 range adjusted up 1.5X usual reference range
Free T4 assays not standardized for pregnancy

TPO ANTIBODIES AND RISK OF PREGNANCY LOSS

- Prospective analysis of 984 women between 2002-2004
- TPO Ab + 11.7%
- Group A TPO+ (57) received L-T4
- Group B TPO+ (58) not treated
- Group C TPO-
- TPO+ had higher baseline TSH than TPO-

- Miscarriage rate:

Group A 3.5% $p < 0.05$

Group B 13.8%

Group C 2.4% $p < 0.01$

- Premature delivery

Group A 7% $p < 0.05$

Group B 22.4%

Group C 8.2% $p < 0.01$

Negro, et al

JCEM, 2006

DIFFERENT FORMULATIONS

- FT4 only preparations such as levothyroxine, Synthroid, Unithroid and Tirosint
- 90 percent of patients will obtain symptomatic and biochemical relief with T4 formulations alone.
- Young, healthy patient post thyroid surgery or RAI ablation can start 1.6 mcg/kg/day or full dose replacement
- In autoimmune hypothyroidism, it is recommended to start at smaller doses and titrate until biochemical as well symptomatic resolution is achieved
- FT4 plus FT3 preparations consist of NP thyroid, Nature thyroid, Armor thyroid, WP thyroid, liothyronine and brand Cytomel
- Do not use FT3 containing preparations in patients who are elderly, have cardiovascular disease or osteoporosis.
- Do not use FT3 has monotherapy or initial therapy

SICK EUTHYROID SYNDROME/NONTHYROIDAL ILLNESS

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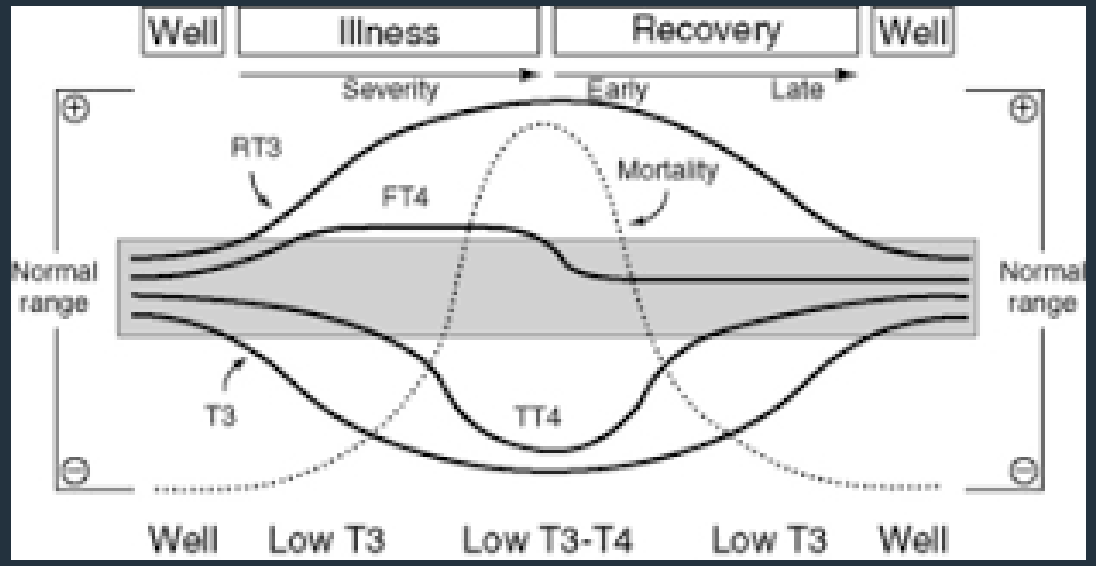
- Abnormalities in thyroid function studies related to critical illness or trauma, without underlying true thyroidal dysfunction
- Includes effects on the H-P-T axis regulation, thyroid hormone transport, metabolism and action
- Acute: slight increase in TSH and free T4, with decreased T3 (free and total)
- Chronic: loss or decrease in pulsatile secretion of TSH, reduced responsiveness of TSH to TRH stimulation, low T3
- Recovery: elevated TSH



HYPERTHYROIDISM

CAUSES OF THYROTOXICOSIS

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thyrotoxicosis can occur if

- The thyroid is excessively stimulated by trophic factors (TSH receptor antibodies)
- Constitutive activation of thyroid hormone synthesis and secretion (autonomous toxic nodule)
- Thyroid stores of preformed hormone are passively released in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult (viral, radiation, post partum, drug induced)
- Exposure to extrathyroidal sources of thyroid hormone (endogenous: struma ovarii or paraneoplastic Syndrome or exogenous intake: iatrogenic or facticious)

ENDOGENOUS HYPERTHYROIDISM

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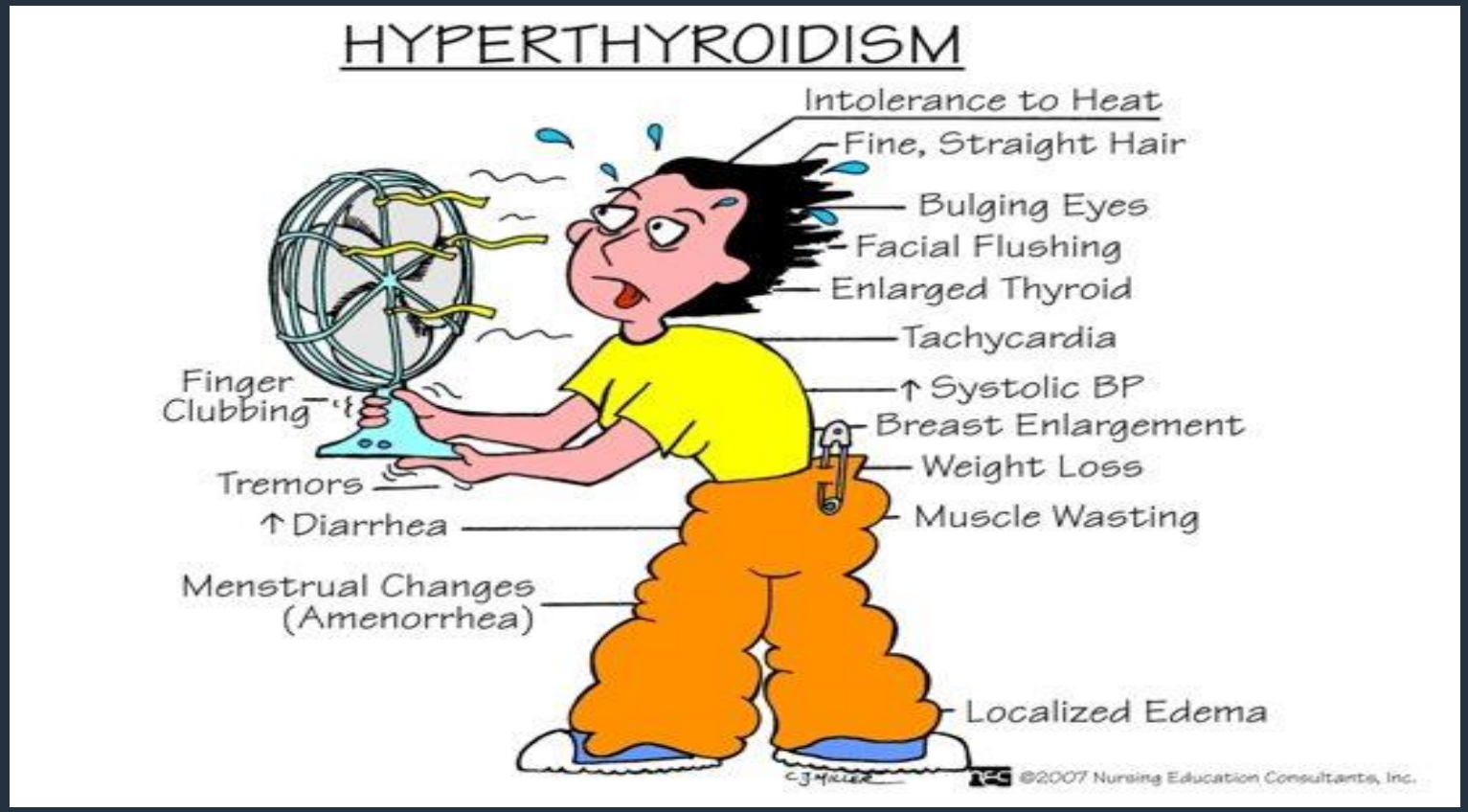
- Graves disease is most common cause of endogenous hyperthyroidism in US
- The autonomous hormone production can be caused by somatic activating mutations in these toxic thyroid nodules. Incidence of toxic nodular goiter increases with age and degree of iodine deficiency.
- Rarely germ line mutations can cause sporadic or familial non autoimmune hyperthyroidism.
- Autonomous hormone production may progress from subclinical to overt hyperthyroidism, and the administration of pharmacologic amounts of iodine to such patients may result in iodine-induced hyperthyroidism.

CLINICAL CONSEQUENCES



INITIAL ASSESSMENT OF THYROTOXICOSIS

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- Assessing degree of severity:

- No clear correlation between elevation in T4/T3 levels and severity of Symptoms
- Direct correlation with age *
- Cardiac evaluation is recommended if necessary
- Goiter size, obstructive symptoms, and the severity of Graves' orbitopathy are discordant with degree of thyrotoxicosis

*J Clin Endocrinol Metab 2010 95:2715–2726.

BIOCHEMICAL EVALUATION

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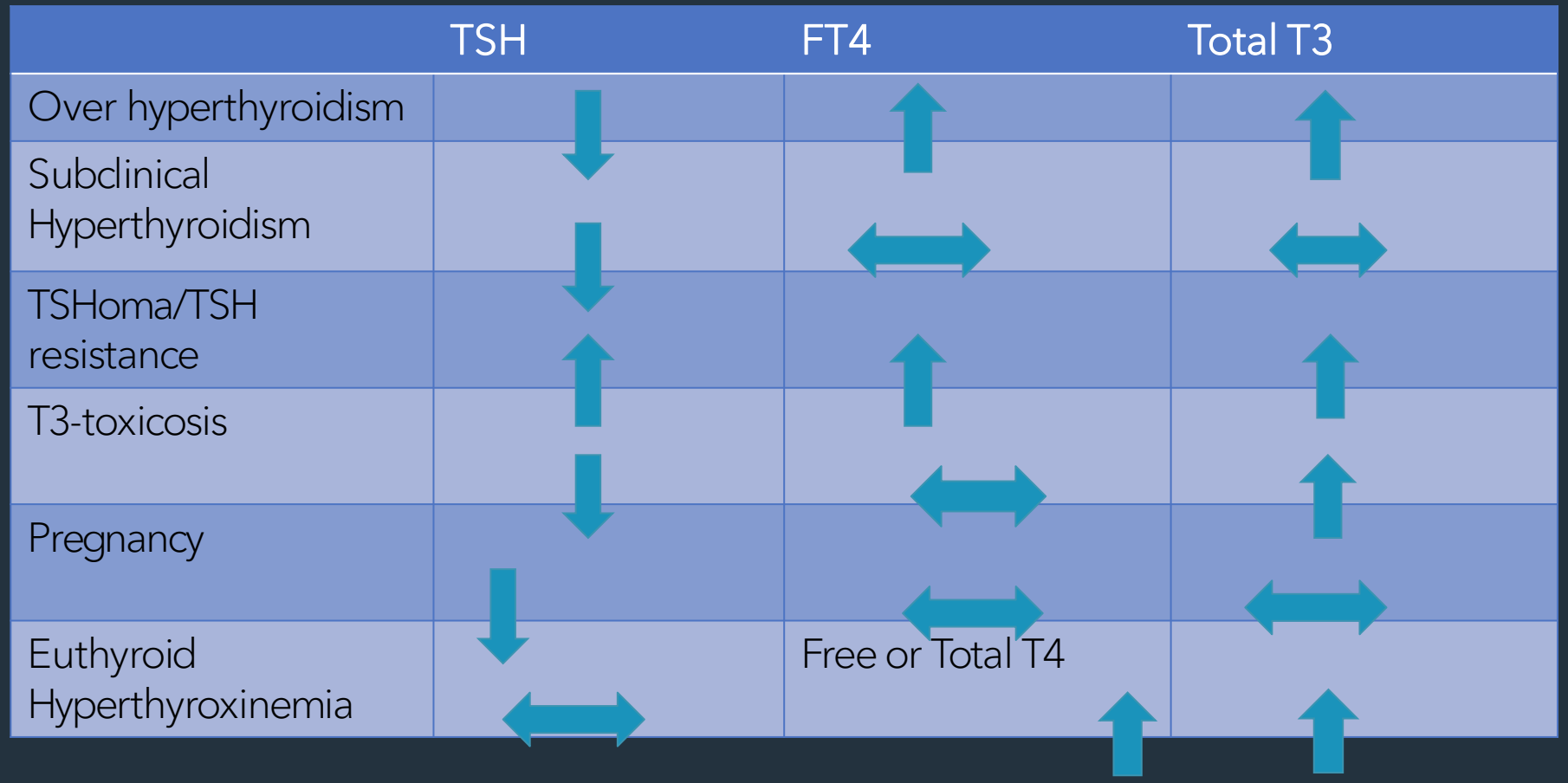

THYROID FUNCTION AND PREGNANCY

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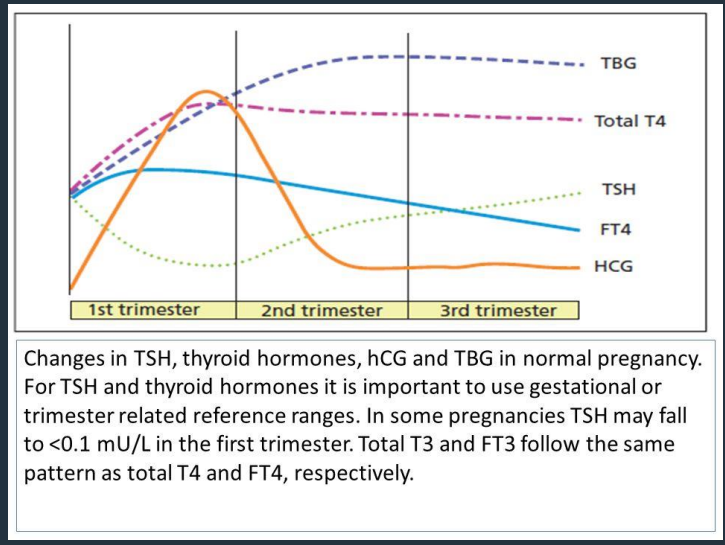
Increase in Total T4 and total T3:

Estrogen increases Thyroglobulin binding levels (TBG) leading to increase in total T4 and total T3

Low TSH:

Mild suppression is secondary to elevated circulating thyroid hormone

B HcG stimulates TSH receptors causing particularly low TSH, specifically seen in Hyperemesis Gravidarum



Changes in TSH, thyroid hormones, hCG and TBG in normal pregnancy. For TSH and thyroid hormones it is important to use gestational or trimester related reference ranges. In some pregnancies TSH may fall to <0.1 mU/L in the first trimester. Total T3 and FT3 follow the same pattern as total T4 and FT4, respectively.

DETERMINING ETIOLOGY

- **Recommendation:** A radioactive iodine uptake should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of GD; a thyroid scan should be added in the presence of thyroid nodularity.

READING THE NM UPTAKE

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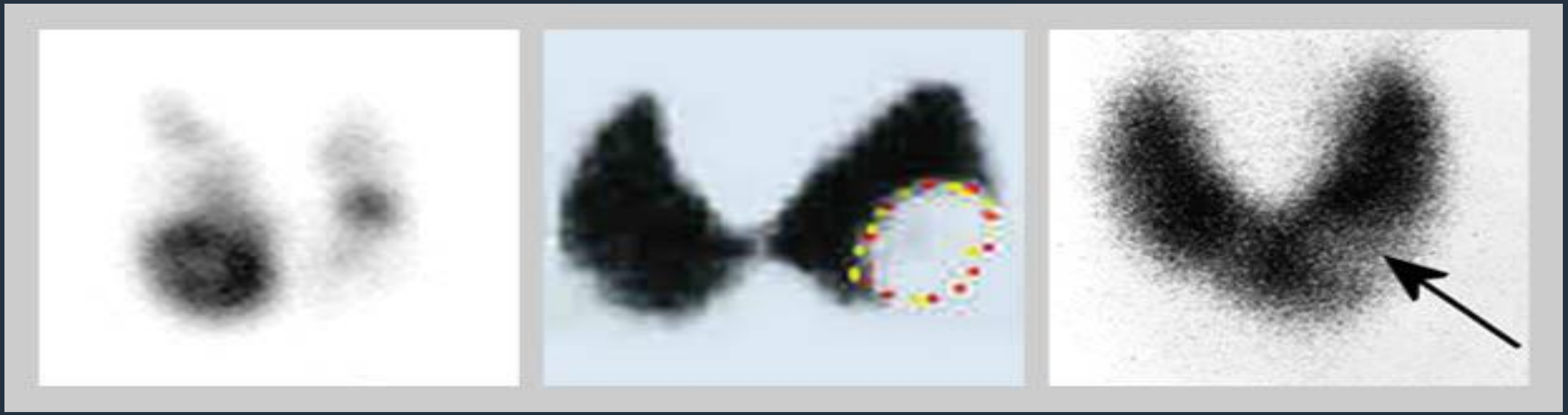
Normal or high uptake	Low uptake	Zero uptake
Graves disease	Painless thyroiditis	
Toxic nodular goiter	Subacute thyroiditis	
TSHoma	Post partum thyroiditis	
TSH hormone resistance	Struma Ovarii	
	Amiodarone/interferon induced	Amiodarone induced
	Acute infective thyroiditis	
	Iatrogenic/Factitious/excess ingestion of iodine	Iatrogenic/Factitious
	Contrast imaging within 2 months	

EXAMPLES



Toxic nodular goiter

Graves disease with cold nodule

Graves disease

AMERICAN THYROID ASSOCIATION®
FOUNDED 1923

SYMPTOMATIC MANAGEMENT

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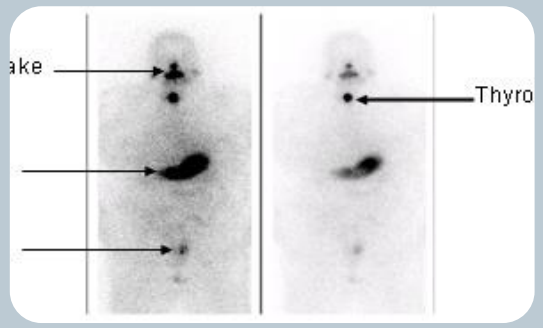
- Recommendation

  Beta-adrenergic blockade should be given to elderly patients with asymptomatic thyrotoxicosis and to other thyrotoxic patients with resting heart rates in excess of 90 bpm or coexistent cardiovascular disease.

- Recommendation

  Beta-adrenergic blockade should be considered in all patients with symptomatic thyrotoxicosis.

CHOOSING TREATMENT



RAI ablation

Antithyroid Medications

Surgery

ANTI-THYROID MEDICATIONS

- When remission is expected: Mild disease, specially females, low antibody titers in GD, when surgery or RAI is contraindicated, low life expectancy, RAIU insufficient to allow therapy in GD

- Contraindications: adverse events to antithyroid medications.

ATDs are not a preferred modality of treatment for toxic nodular goiter. However long term use of low dose methimazole has some role in special circumstances

MMI VS PTU

- Recommendation

Methimazole should be used in virtually every patient who chooses antithyroid drug therapy, except during the first trimester of pregnancy when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery.

PTU requires more frequent dosing

PTU very infrequently (ANCA)-positive small vessel vasculitis

PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU

SIDE EFFECTS OF ATDS

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- When experiencing: pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis call physician immediately due to risk of hepatitis or agranulocytosis.
- Risk of agranulocytosis is very low with PTU and low dose MMI
- Risk of side effects is dose dependent
- MMI likely causes cholestatic hepatitis and rarely hepatocellular toxicity
- MMI taken by the mother in the first trimester is also associated with a syndrome of MMI embryopathy, including choanal and esophageal atresia.
- Arthropathy and a lupus-like syndrome rarely can occur with either MMI or PTU.

MONITORING ON ATDS

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- Baseline CBC and LFTs recommended
- Free T4 and total and free T3 at 4 weeks to assess response to treatment
- TSH has a lag and not a good marker to assess response to treatment.
- Monitor TFTs every 2-3 months
- CBC if patient were to develop symptoms of febrile illness
- 3 monthly LFTs on PTU
- Minor cutaneous allergic reactions can be managed with antihistaminics

GOAL OF TREATMENT IS REMISSION

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- Goal of treatment in GD is to taper off methimazole within 12-18 months

- If a patient who responded to methimazole, becomes hyperthyroid again once MMI is taper OR if a patient is unable to come off methimazole in 18 months, alternative definitive treatment options should be explored

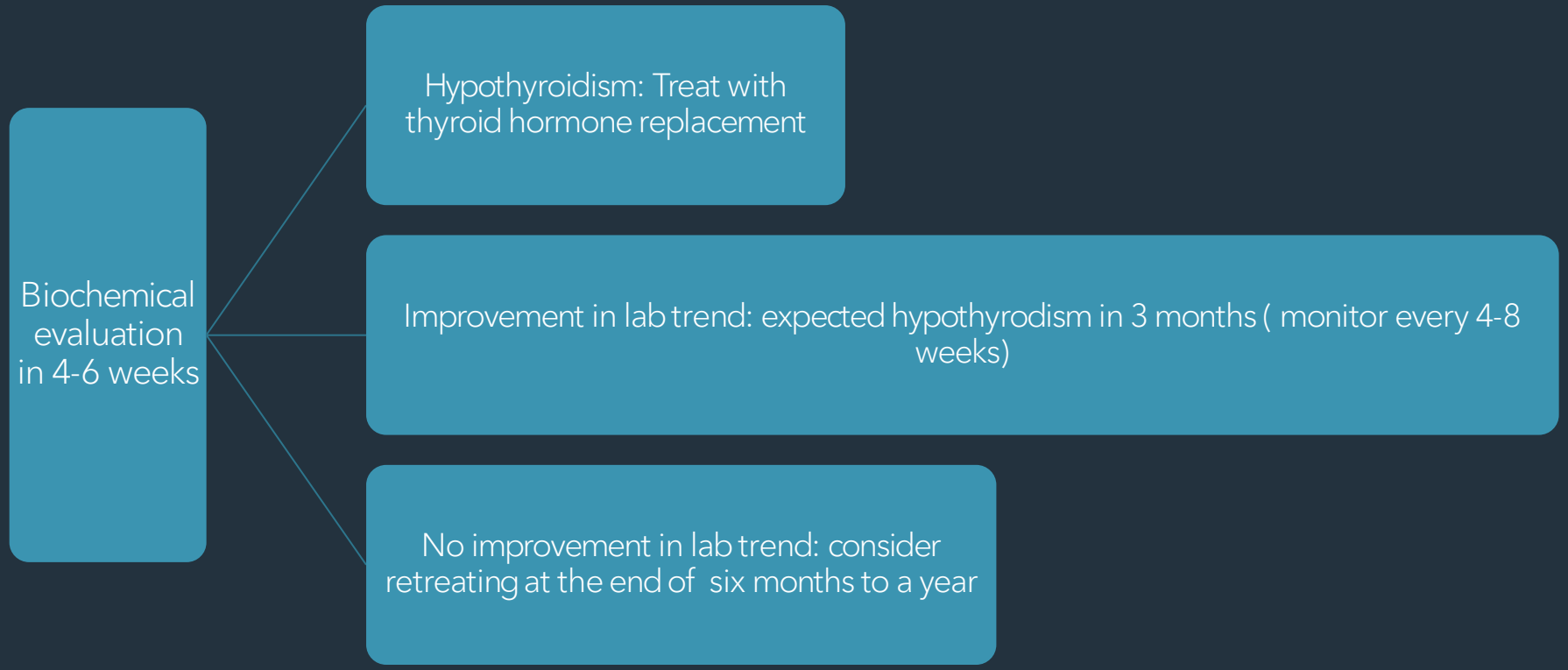
- Low titers of TSH receptor antibodies at the time of stopping MMI can be favor chance of long term remission

RAI ABLATION

- Preferred: Women planning pregnancy but willing to wait one year to concieve, higher surgical risk, previous neck irradiation, not responding to medications, lack of access to endocrine surgeon.

- Contraindicated: Pregnancy, lactation, suspicion of cancer.

FOLLOW UP AFTER RAI ABLATION



CHOOSING THYROIDECTOMY

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- Indications: avoidance of radiation exposure, intolerance or nonresponse to ATDs, special circumstances such as florid hyperthyroidism in pregnancy, large goiter size causing symptoms

- Contraindications: comorbidities, previous h/o neck radiation, pregnancy is a relative contraindication

AUTOIMMUNITY OF GRAVE'S DISEASE/ HASHIMOTO'S THYROID DISEASE

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Or opening Pandora's box?

"Autoimmunity is breakdown of self tolerance."

TSH RECEPTOR ANTIBODIES

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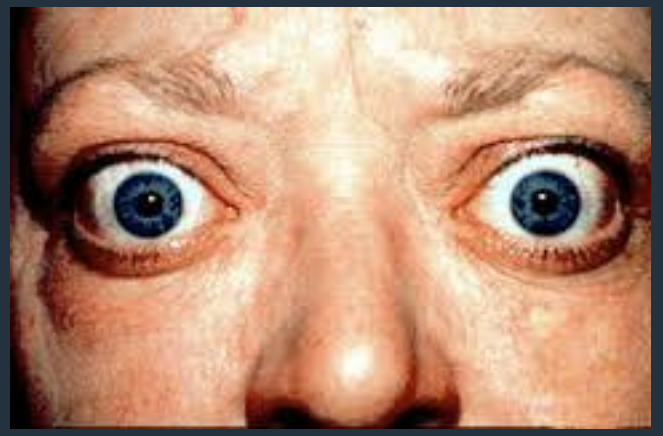
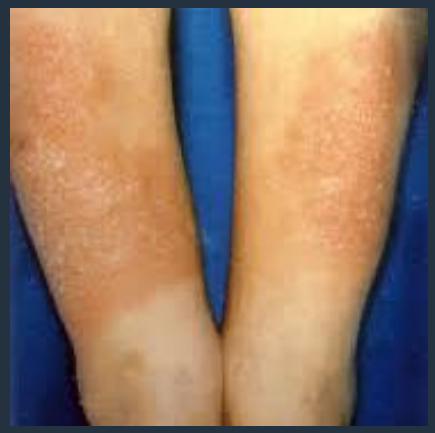
- The TSH receptor antibodies can be stimulating, blocking or neutral antibodies.
- The interaction between TSH receptor and antibodies might be modulated by other antigens on the thyroid membrane
- The antibodies are mainly IgG and can be of multiple subgroups of IgG responsible for heterogeneous polyclonal response.
- TG antibodies are NONSPECIFIC for diagnosis of Hashimoto's disease
- TPO antibodies will be elevated in only 90 percent of patients with Hashimotos disease

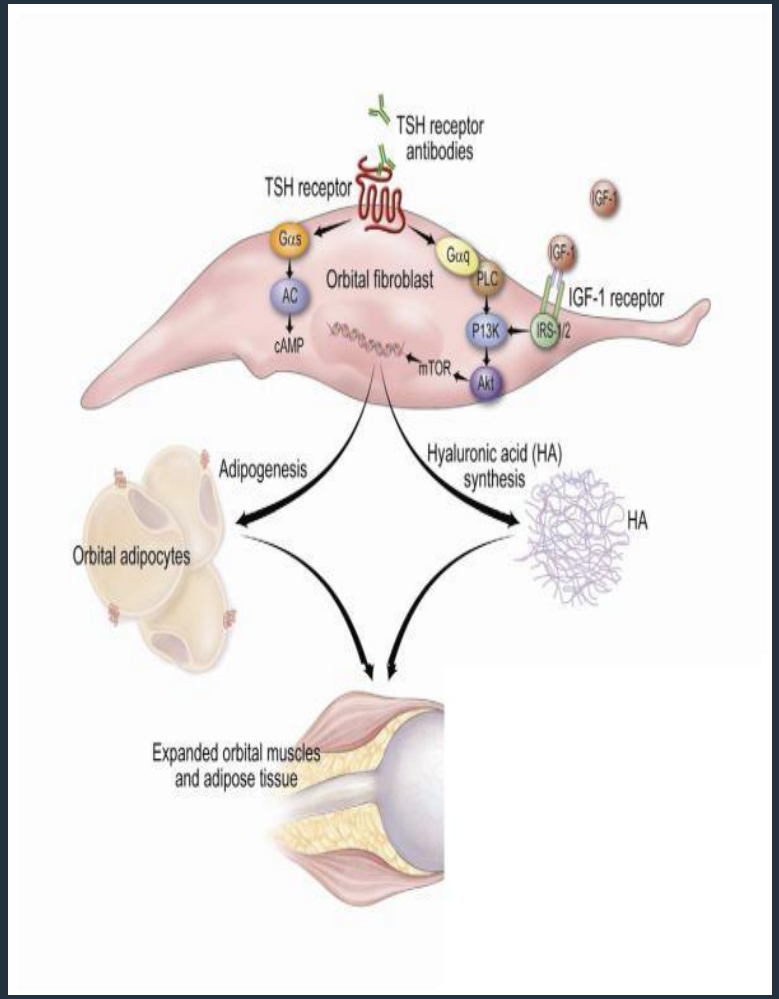




GRAVES OPHTHALMOPATHY

- Graves ophthalmopathy can worsen following RAI ablation due to surge in TSH receptor antibody titers.

- Useful in diagnosis of GO in presence of hypothyroidism or in absence of other clinical and biochemical features of Graves disease.



SUBCLINICAL HYPERTHYROIDISM

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- Low TSH, normal FT4 and T3.
- Occurs in 1% of general population and in elderly population most likely cause is toxic nodular goiter.
- Patients with SH are at higher risk of atrial fibrillation and osteoporosis
- Some correlation with increase risk of dementia, cardiac mortality and all cause mortality however the date is conflicting

THANK YOU!