Thyroid gland disorders

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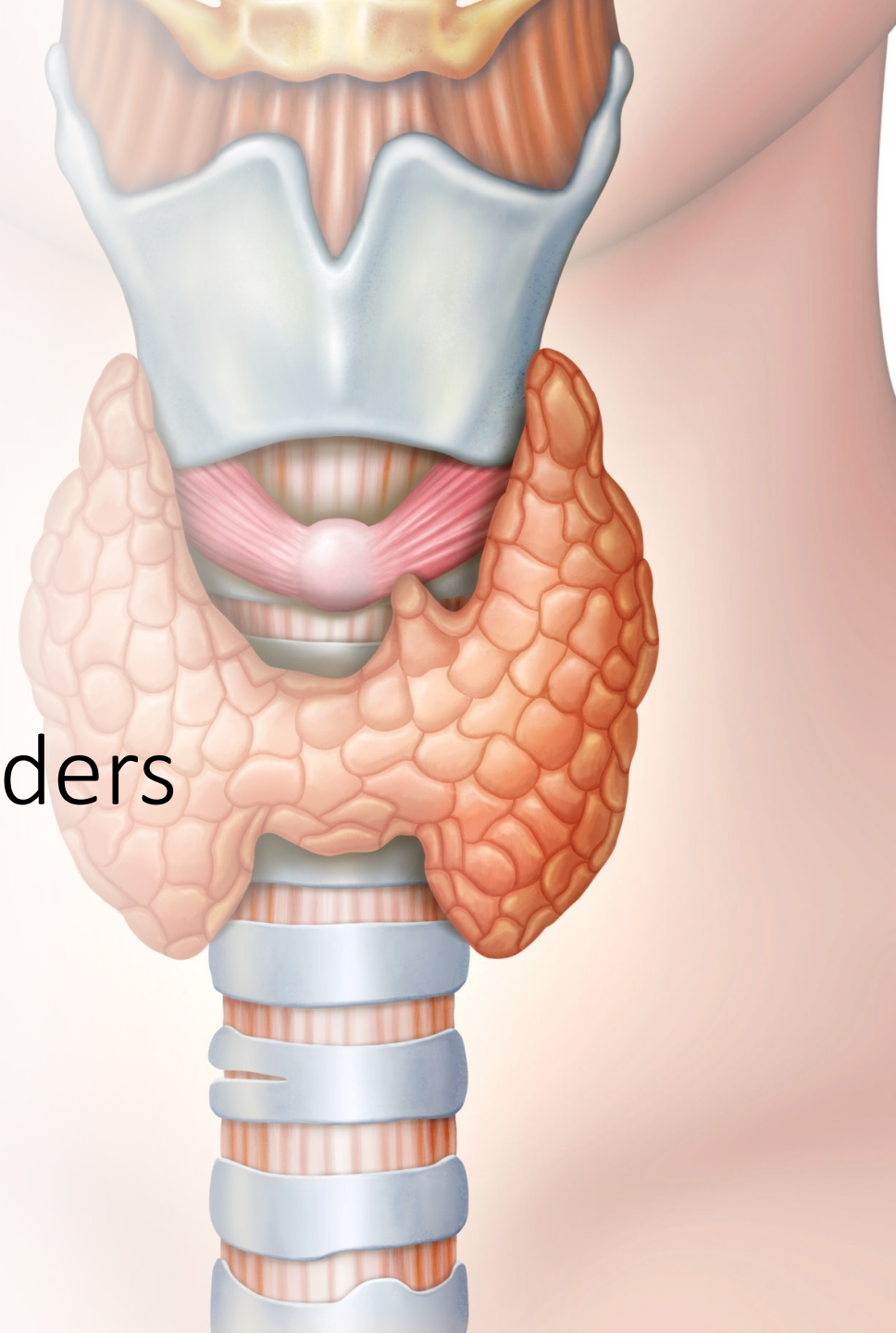

Objectives

- Review of thyroid gland anatomy and physiology
- Approach to assessment and management of hyperthyroidism
- Approach to assessment and management of hypothyroidism

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- **Review of thyroid gland anatomy and physiology**
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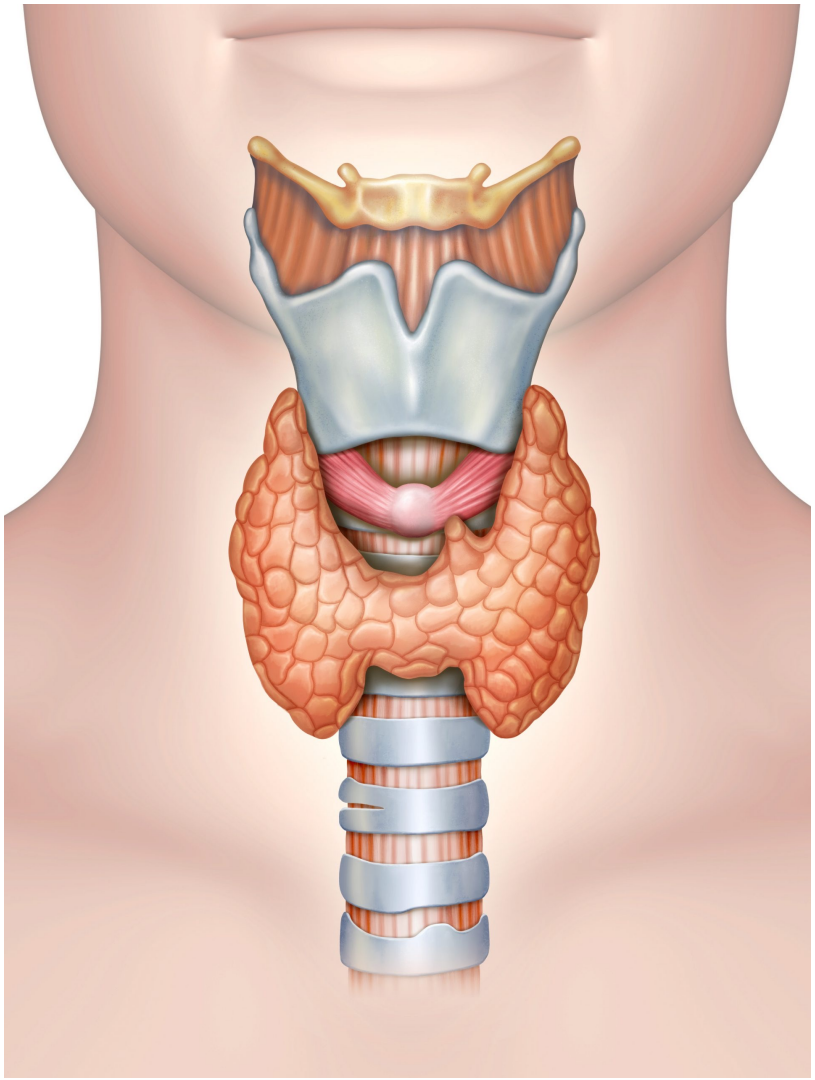
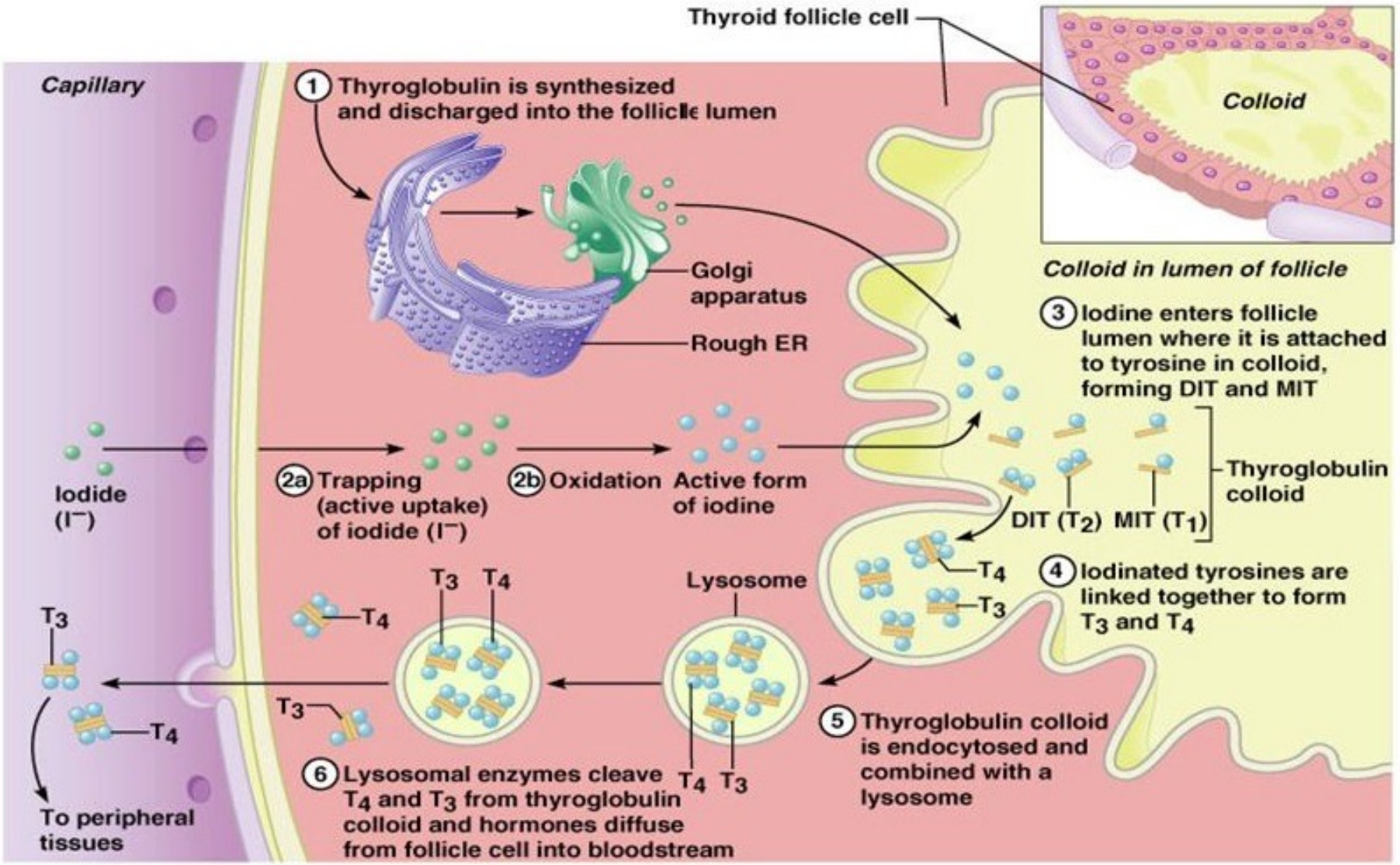
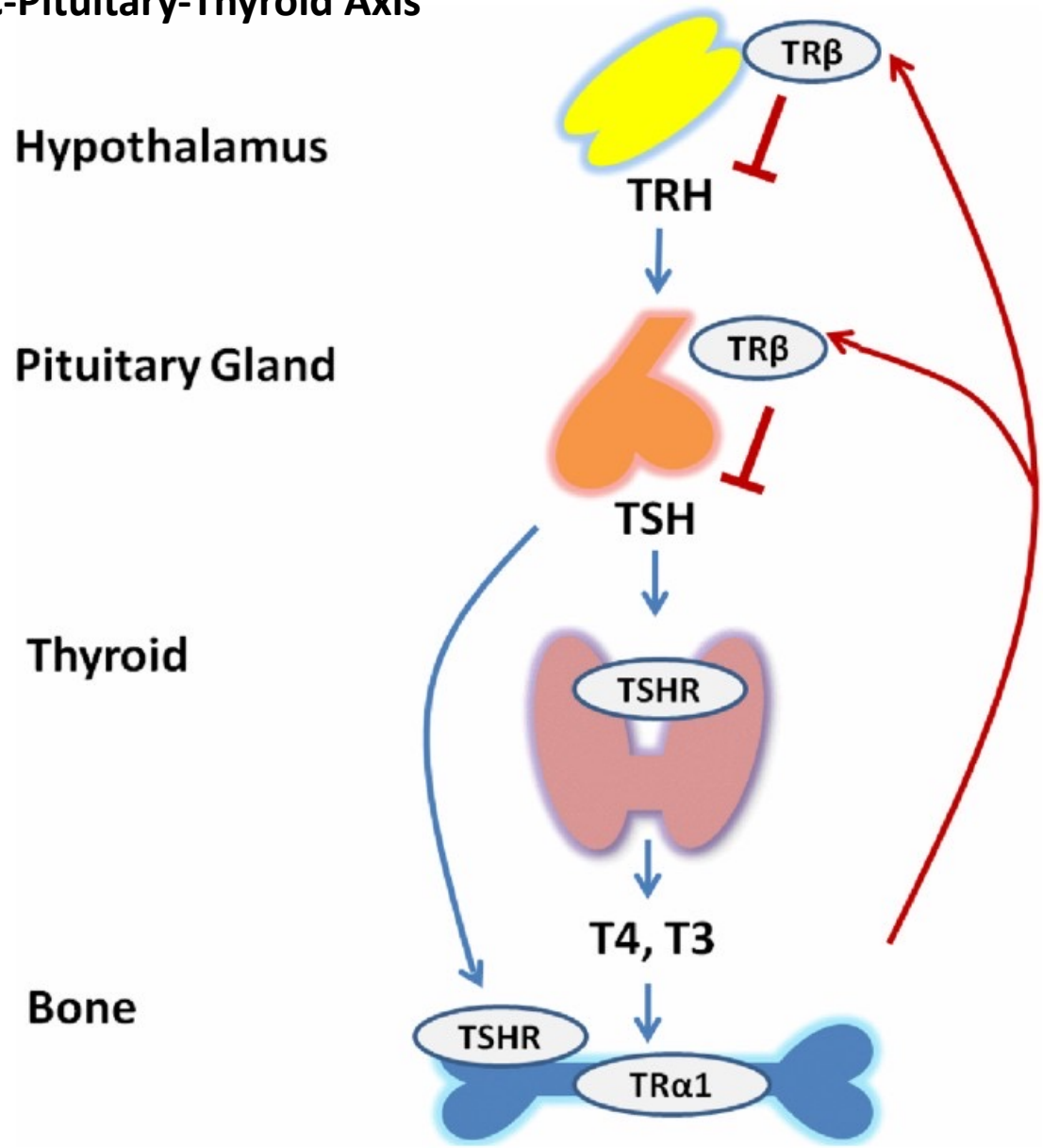
Thyroid gland: Anatomy



Thyroid hormone synthesis



Hypothalamic-Pituitary-Thyroid Axis



Thyroid hormone action

- Protein synthesis
- Carbohydrate metabolism (increase glucose)
- Lipid metabolism (decrease cholesterol)
- Increased metabolic rates
- Cardiac function (ionotropic and chronotropic)
- Increased sensitivity to catecholamines
- Stimulate GI motility
- Respiration
- Increased EPO secretion and thus RBC synthesis
- Fetal brain development
- Skeletal maturation
- Growth and development
- Thermal regulation
- Sexual function

Objectives

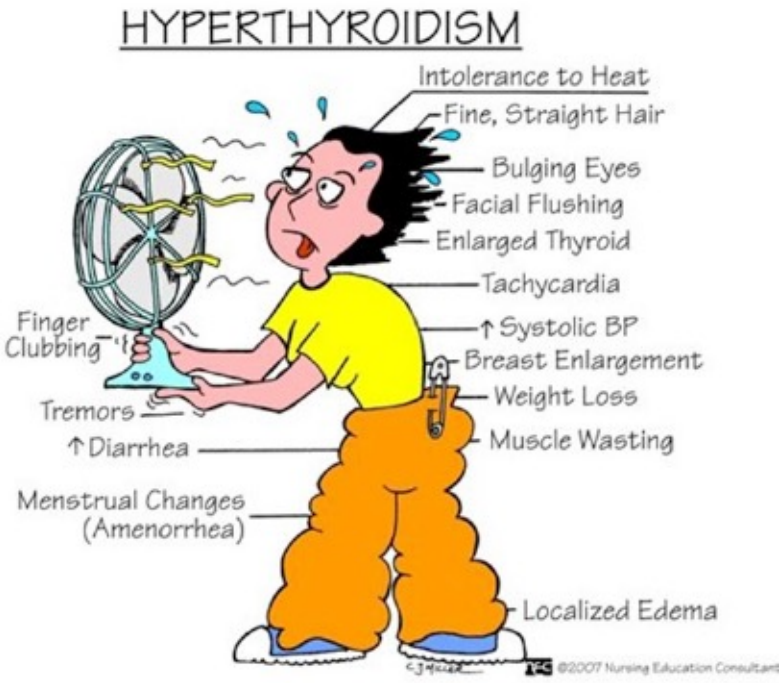
- Review of thyroid gland anatomy and physiology
- **Approach to assessment and management of hyperthyroidism**
- Approach to assessment and management of hypothyroidism

Approach to Hyperthyroidism

- Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland

- Thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source.

When to suspect?



Thyrotoxicosis symptoms:

- Heat intolerance
- Increased sweating
- Tremor
- Palpitations/Tachyarrhythmias
- Heart failure
- Insomnia
- Emotional lability/anxiety
- Unintentional weight loss despite increased appetite
- Increased bowel frequency
- Menstrual abnormalities

When to suspect?

Thyrotoxicosis signs:

- Fine tremors
- Soft, warm and sweaty skin (handshake)
- Tachycardia/atrial fibrillation
- Eyes (exophthalmos, lid lag, lid retraction)
- Increased cardiac output/wide pulse pressure
- Systolic hypertension
- Heart failure
- Hyperreflexia

Approach to differential diagnosis of thyrotoxicosis

- Increased thyroid hormone production (hyperthyroidism):
  - Grave's disease
  - Toxic nodule/toxic multinodular goiter
  - TSH-secreting pituitary tumor (rare)

- Release of preformed thyroid hormones:
  - Thyroiditis (acute, subacute, postpartum, chronic, infectious)

- Exogenous use of thyroid hormones
- Medications: amiodarone
- Laboratory interference: Biotin

- Rare: struma ovarii, metastatic functional follicular thyroid cancer

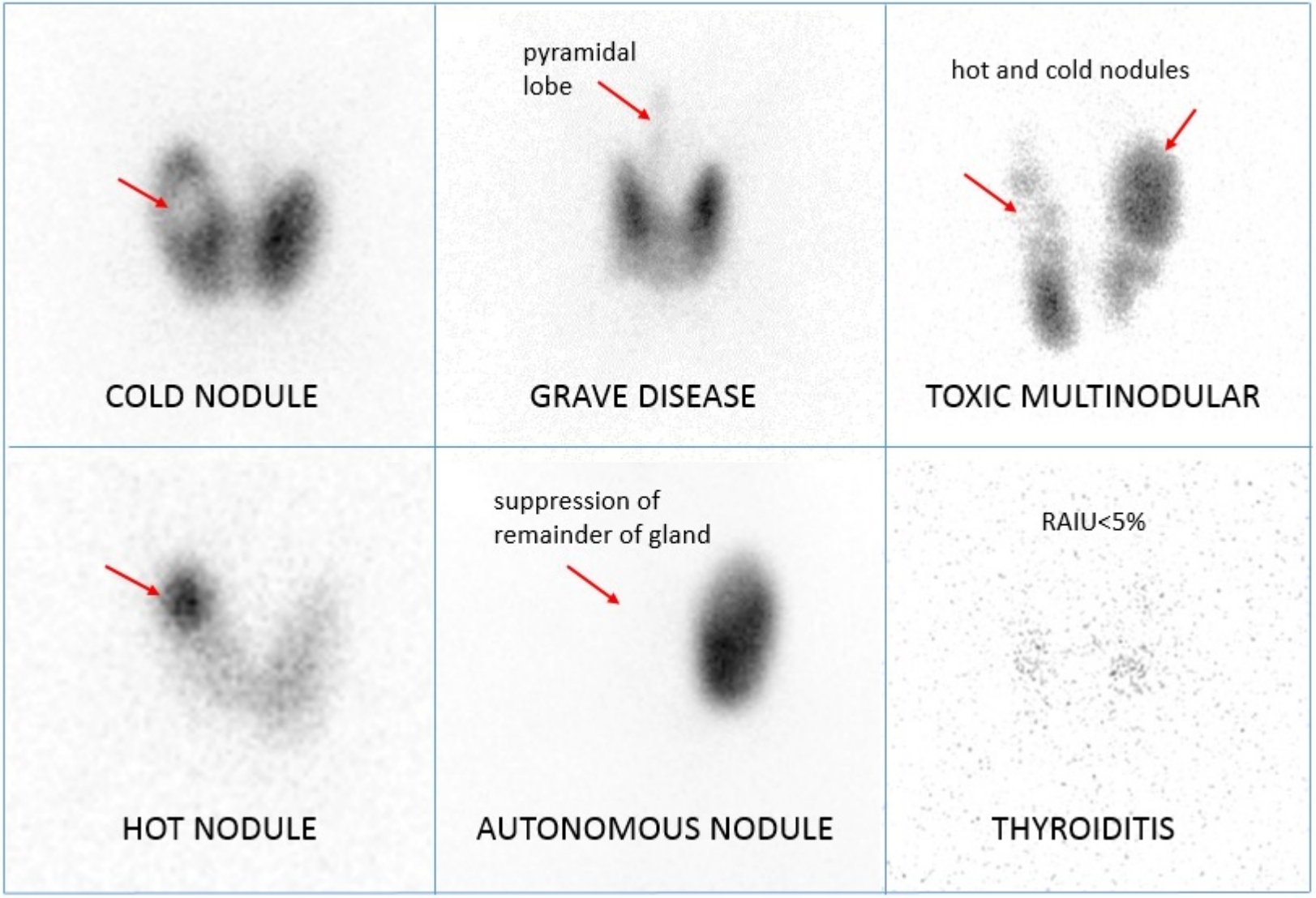
Confirmation of Thyrotoxicosis

- **Case finding: TSH**
  - Low TSH

- Confirmation:
  - Repeat ↓TSH + ↑FT4 + ↑FT3

Role of Thyroid imaging

- Thyroid radioactive iodine uptake and scan
  - Increased I-131 uptake
    - Diffuse (Graves) vs. nodule uptake (toxic nodule/TMNG)
  - Decreased I-131 uptake
    - Thyroiditis, exogenous ingestion
- Thyroid Ultrasound
  - Can show goiter/increased vascularity (Grave's) vs. decreased vascularity/atrophy (thyroiditis)
    - Not sensitive nor specific or required for the diagnosis
  - Only for palpable nodule on thyroid exam

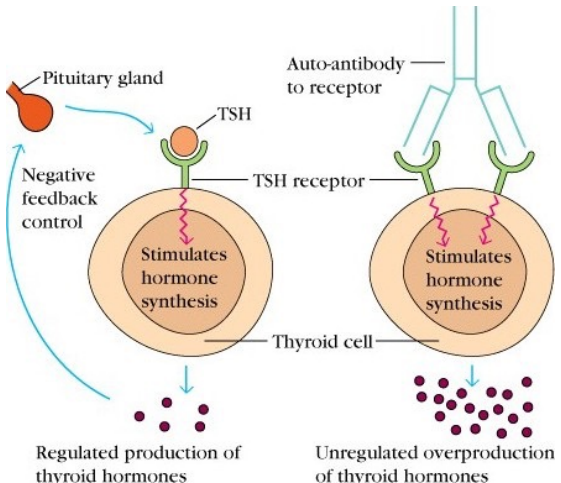

pyramidal lobe
hot and cold nodules
COLD NODULE
GRAVE DISEASE
TOXIC MULTINODULAR
HOT NODULE
suppression of remainder of gland
RAIU<5%
AUTONOMOUS NODULE
THYROIDITIS

Initial treatment

- Until the diagnosis is clear, patients with thyrotoxicosis and hyperadrenergic symptoms should be started on beta-blockers (BB)
- Propanolol reduces T4→T3 conversion
  - (only at high doses)
- Any BB will work for symptom relief
  - Improves HR, SBP, muscle weakness, tremor, irritability, and exercise intolerance

Graves Disease

- Also known as toxic diffuse goiter
- Most common cause of hyperthyroidism
- Caused by an autoantibody against the thyroid-stimulating hormone (TSH) receptor
  - TSH-receptor antibody (TRAb)
- Unlike most autoantibodies, which are inhibitory, this autoantibody is stimulatory



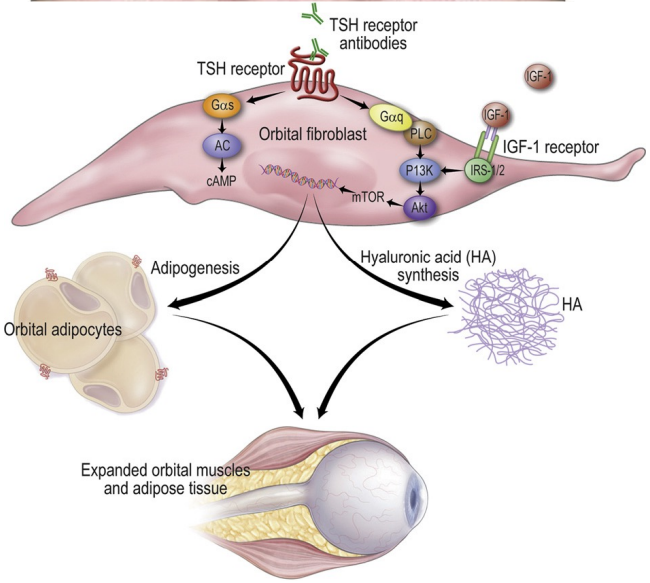
Graves Disease

- Risk factors: female, age ~ 30-50, personal or family history of autoimmune diseases, iodine load
- Symptoms: acute/subacute, thyrotoxic, goiter, bruits, Graves orbitopathy or dermopathy
- Signs: thyrotoxic, diffuse goiter, orbitopathy, dermopathy

Graves Orbitopathy

- Proptosis
- Periorbital edema
- Ophthalmoplegia/diplopia
- Chemosis
- Visual loss
  - Ocular emergency

- TRAb related



Graves Dermopathy
Pretibial myxedema

Biochemical diagnosis

- Consider pretest probability of Graves
- ↓TSH ↑fT3 ↑fT4
- fT3:fT4 ratio >0.3
- TRAb +
  - 97% sensitive, 98% specific
  - Not covered by OHIP

Graves Disease: Treatment

- Antithyroid medications (Thionamides): methimazole (MMZ) and propylthiouracil (PTU)
- First line: Methimazole OD or BID
  - fT4 1-1.5x ULN: 5-10 mg
  - fT4 1.5-2x ULN: 10-20 mg
  - fT4 2-3x ULN: 20-40 mg
- Second line: PTU
  - Higher rate of hepatotoxicity
  - Preferred 1st T pregnancy due to fewer birth defects

Graves Disease: Treatment

- Antithyroid Drugs (ATD)
  - Thyroid function is assessed every 6 - 8 weeks
  - The dose is reduced as thyroid hormone levels normalize (follow fT3 and fT4, TSH takes longer to recover)
  - 50-70% will go into **remission.** Predictors are:
    - females, non-smokers
    - mild disease, small goiter
    - low-titer or negative TRAb
  - Recurrences may occur in up to 30%
  - Lifelong or second-line therapy is needed in some

Side effects of Thionamides

- Common
  - Rash, pruritis, metallic taste, nausea, dyspepsia
- Hematologic
  - Agranulocytosis 0.1-0.5% risk
  - More likely in first 3 months
  - Controversy about CBC monitoring, not about case finding
- Hepatotoxicity
  - PTU –very rarely Hepatic Failure and death
  - MMI –cholestatic; lower risk of liver failure
- Vasculitis
  - ANCA + Vasculitis -Rare PTU +/-methimazole; Blood test may be positive with no clinical vasculitis
- Pancreatitis
  - Methimazole 6 case reports

- Baseline CBC/differential, LFTs, and q 4-6 weeks in the first 3 months and as needed if symptoms
  - Counsel the patient when to seek medical attention

Radioactive Iodine treatment

- Safe and cost-effective
- Single oral dose, outpatient procedure
- Success rate 75-90%
- Goal is Euthyroidism, gland shrinkage
  - 60-70% develop hypothyroidism
- Check labs q4-6 wks
  - Levothyroxine replacement therapy is started when low fT4/high TSH

Radioactive Iodine treatment

- Indications:
  - Contraindication or intolerance of ATD
  - No remission on ATD
  - Previous neck surgery/radiation
  - Patient preference

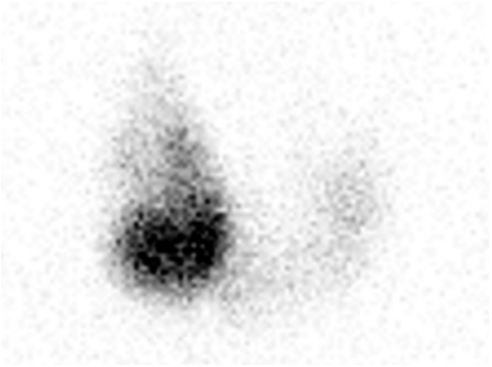
- Contraindications:
  - Planning pregnancy in <6-12 months
  - Pregnancy and breast feeding
  - Moderate to severe active Graves orbitopathy
  - Cannot follow radiation safety guidelines
  - Thyroid storm
  - Thyroid cancer or suspicion for thyroid cancer.

Surgery: Total Thyroidectomy

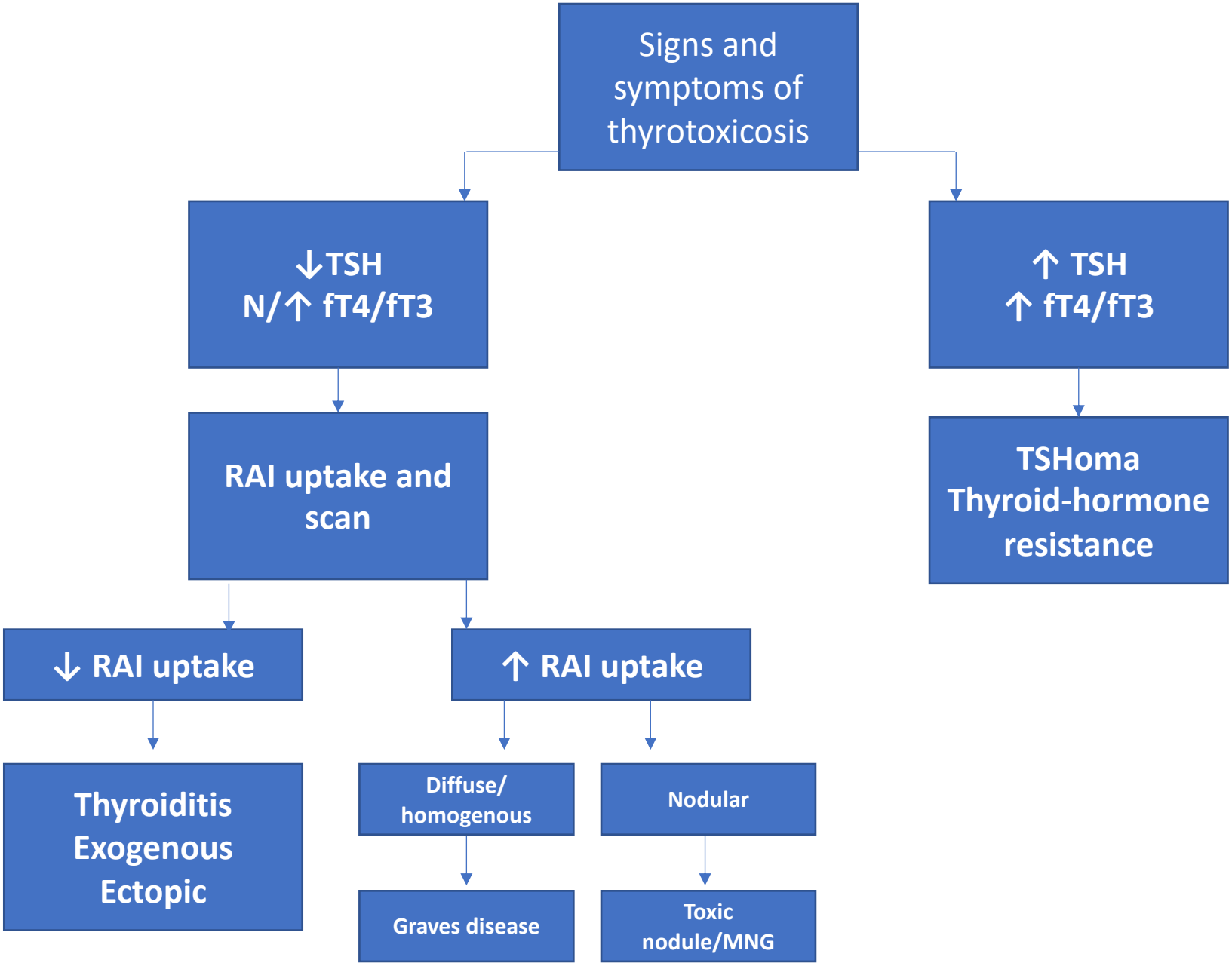
- Pre-treat with ATDs
- Consider potassium iodide pre-op to reduce blood flow
- Risks: Hypoparathyroid, RLN, bleeding
- Surgery recommended
  - Symptomatic or very large goiters
  - Suspected thyroid cancer/ worrisome nodules
  - Moderate to severe active Graves' orbitopathy and desire for definitive therapy
- Surgery discouraged
  - High risk for surgery
  - Pregnancy
    - If responsive to ATDs, if necessary, surgery in 2nd trimester is best time.

Other causes of thyrotoxicosis

- Toxic nodule or toxic MNG
  - RAI treatment, ATD or surgery

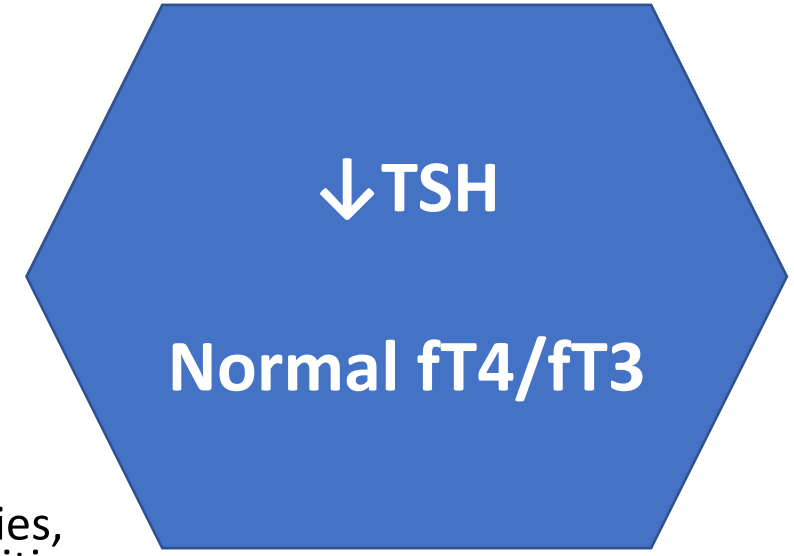


- Thyroiditis
  - Monitor
  - Treat if permanent hypothyroidism


Signs and symptoms of thyrotoxicosis
↓TSH N/↑ fT4/fT3
↑ TSH ↑ fT4/fT3
RAI uptake and scan
TSHoma Thyroid-hormone resistance
↓ RAI uptake
↑ RAI uptake
Thyroiditis Exogenous Ectopic
Diffuse/ homogenous
Nodular
Graves disease
Toxic nodule/MNG

Isolated low TSH?

- Subclinical hyperthyroidism
  - Graves disease, toxic nodule/TMNG, thyroiditis
- Recent treatment for hyperthyroidism (ATDs, RAI)
- Drugs (steroids)
- Non-thyroidal illness
- Laboratory errors
  - Assay interference (heterophile antibodies, rheumatoid factor, macroTSH), false positive
- Overtreatment with Synthroid
- hCG mediated (gestational, hyperemesis gravidarum, trophoblastic germ cell tumors)



Progression to over hyperthyroidism

- Conflicting data
  - Rates all over the place
- More likely TSH <0.1
- Spontaneous recovery
  - Sometimes happen

- Increased bone resorption and fracture risk, increased risk of CAD/CHF/arrythmias and mortality (elderly)

SC Hyperthyroidism: Treatment

- Treat if TSH <0.1 and any of the following
  - CVD or high cardiac risk
  - Osteoporosis or high fracture risk
  - Age >65 years
- Don’t treat if >0.1, no risk factors for complications and age <65 years
- Otherwise, unclear
  - Favor treatment
    - Symptoms, autonomous nodule, or CVD, osteoporosis and TSH >0.1
  - Favor observation if age > 65 years and TSH >0.1 and none of the above

Objectives

- Review of thyroid gland anatomy and physiology
- Approach to assessment and management of hyperthyroidism
- **Approach to assessment and management of hypothyroidism**

Hypothyroidism

- Poor Thyroid production

- Differential diagnosis:
  - Iodine deficiency
  - Autoimmune / Hashimoto's
  - Thyroidectomy or iodine ablation
  - Post Thyroiditis
  - Drugs (eg. lithium, amiodarone, TKI)
  - Congenital absence of gland

When to suspect? Hypothyroidism symptoms

- Fatigue
- Dry skin
- Hair loss
- Cold intolerance
- Weight gain despite decreased appetite
- Constipation
- Menorrhagia
- Memory impairment
- Poor concentrating
- Muscle ache

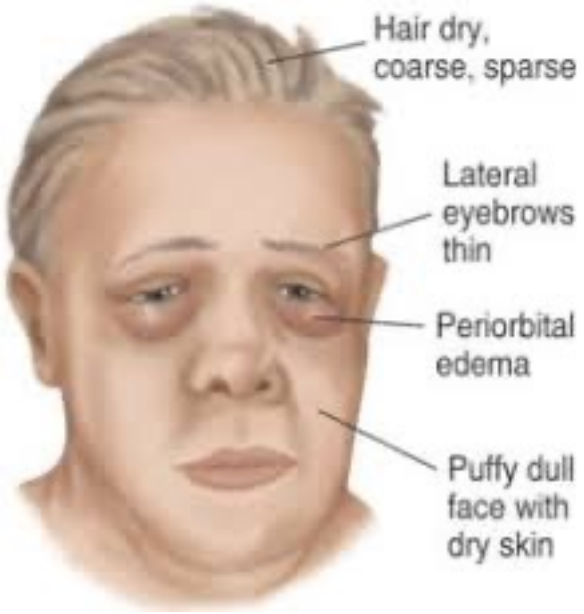
Elderly Patients:

Fewer symptoms, subtle and vague

- Confusion, memory change
- Anorexia
- weight loss
- Falling, decreased mobility
- Incontinence
- Arthralgias
- Constipation
- Heart failure
- Bradyarrhythmia

When to suspect? Hypothyroidism signs

- Puffy face
- Nonpitting edema (myxedema)
- Dry, coarse skin, hair
- Hair loss
- Hoarse voice
- Carotinemia
- macroglossia
- Bradycardia
- Diastolic hypertension
- Delayed reflex relaxation phase
- Carpal tunnel syndrome
- Pleural and pericardial effusions



Confirmation of hypothyroidism

- **Case finding: ↑TSH**
- ↑TSH + ↓fT4
- Do not order fT3
- Anti-TPO and Anti-thyroglobulin
  - Available
  - Sensitive for autoimmune hypothyroidism but less specific
  - Almost (never?) influence clinical decisions in overt hypothyroidism
  - US thyroid or radioactive iodine
    - Characteristic features in Autoimmune but not sensitive nor specific or required for the diagnosis
    - Only if palpable thyroid nodule on physical exam

Hypothyroidism: Treatment

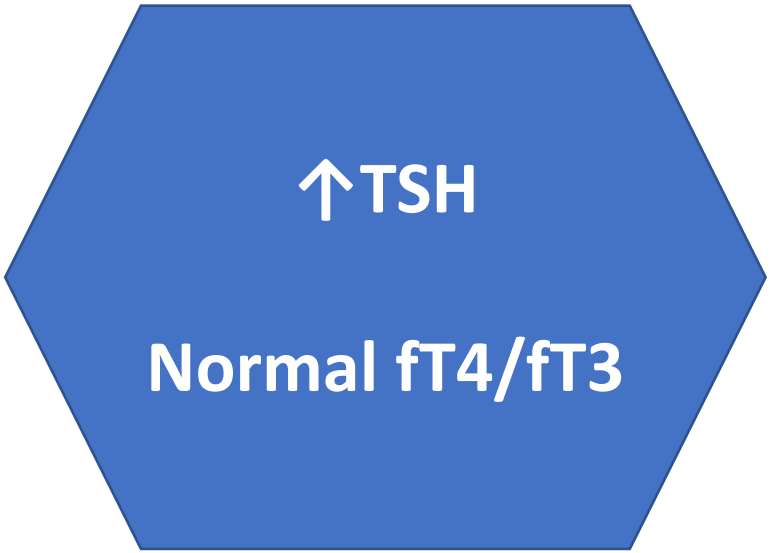
- Thyroid hormone: levothyroxine (L-T4)
  - Brand names: Synthroid, Eltroxin
- Converted to T3 peripherally by deiodinase enzymes
- Half-life of 7 days
- Given 30-60 min before breakfast with water
- Alternate: At bedtime 3 hours after last meal
- Full replacement dose ~1.6 µg/kg of IBW
  - Start low in subclinical hypothyroidism and elderly
- Wait 6-8 weeks after a change in the dosage to see the effect in the TSH
- Target normalization of TSH level
- When target TSH obtained, monitor TSH every 6-12 m

Hypothyroidism: Treatment

- Use of a consistent preparation to minimize variability
- Absorption impaired:
  - Iron, calcium, aluminum, soy, sucralfate, cholestyramine
    - Take these 4 hrs before or after the levothyroxine
    - Ask about multivitamins
  - Malabsorptive states, eg. Celiac disease (IgA, anti-TTg antibodies)
- Increased metabolism:
  - Eg. Phenytoin, carbamazepine

Isolated high TSH

- Subclinical hypothyroidism
  - Autoimmune/Hashimoto's
- Poor adherence to LT4
- Malabsorption of LT4
- Drugs (amiodarone, lithium)
- Non-thyroidal illness recovery
- Laboratory errors
  - Assay interference (heterophile antibodies, rheumatoid factor, macroTSH), false positive
- TSH resistance



SC Hypothyroidism: Treatment

- TSH >10 mIU/L
- Therapeutic trial for possible hypothyroidism symptoms
- Age <40-65
- ?Infertility, Ovulatory dysfunction
- ?DLP, CKD, CVD

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SPECIAL ARTICLE

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,[1,*] Elizabeth N. Pearce,[2,*] Gregory A. Brent,[3] Rosalind S. Brown,[4] Herbert Chen,[5] Chrysoula Dosiou,[6] William A. Grobman,[7] Peter Laurberg,[8,†] John H. Lazarus,[9] Susan J. Mandel,[10] Robin P. Peeters,[11] and Scott Sullivan[12]

Pregnancy specific reference ranges

TABLE 4. REFERENCE RANGES FOR THYROTROPIN AND FREE THYROXINE DURING EARLY PREGNANCY WORLDWIDE

Author, country (reference) (analyzing method)	N	Gestation (week)	TSH, mU/L Median	TSH, mU/L 2.5th–97.5th	FT4, pmol/L (ng/dL) Median	FT4, pmol/L (ng/dL) 2.5th–97.5th	FT4, pmol/L (ng/dL) (Median, 2.5th–97.5th)	Population characteristics: Iodine insufficiency	Population characteristics: Mean BMI	Population characteristics: Ethnicities
Bestwick *et al.*, Italy (24) (AutoDELFIA)	5505	<16	1.07	0.04–3.19	9.3	7.4–12.2	(0.73, 0.58–0.95)	Moderate-mild	[a]	NR
Bestwick *et al.*, UK (24) (Advia Centaur)	16,334	<16	1.11	0.06–3.50	13.9	10.9–17.9	(1.08, 0.85–1.40)	Moderate-mild	[a]	NR
Bocos-Terraz *et al.*, Spain (264) (Architect)	481	<14	0.94	0.41–2.63	13.9	10.8–17.8	(1.08, 0.84–1.38)	Mild	NR	Caucasian (93%)
Gilbert *et al.*, Australia (271)[b] (Architect)	1817	9–13	0.74	0.02–2.15	13.5	10.4–17.8	(1.05, 0.81–1.39)	Borderline	NR	Australian
Lamb (In										
La'ul										
Li *et* (C										
Männ (A										
Medi (Vitros ECI)								sufficient		Surinamese/Antillean (12%), Turkish (8%), Moroccan (6%)
Pearce *et al.*, USA (142) (Advia Centaur)	585	<14	1.1	0.04–3.60	2.1[h]	1.5–2.9[g]	—	Borderline	NR	White (77%) and African American (10%)
Quinn *et al.*, Russia (272) (Abbott AxSYM)	380 549	T1 T2	1.66 2.00	0.09–4.67 0.20–4.68	— —	— —	— —	Moderate	NR	Russian (presumed)
Springer *et al.*, Czech Republic (268)[h] (ADVIA Centaur)	4337	9–11	1.21	0.06–3.67	—	—	—	Mild	NR	Caucasian (99%)
Stricker *et al.*, Switzerland (262) (Architect i2000SR)	575 528	6–12 T2	0.95 1.02	0.07–2.82 0.20–2.79	13.9 12.2	10.5–18.5 9.5–15.7	(1.08, 0.82–1.44) (0.95, 0.74–1.22)	Sufficient	NR	Swiss (presumed)
Vaidya *et al.*, UK (Modular E 170) (274)	1089	<12	1.08	0.14–3.19	14.6	10.7–19.4	(1.12, 0.83–1.59)	Mild-moderate	NR	Caucasian (91) and South Asian (4)

Shift the lower limit of normal down by 0.4 (TSH ~ 0.1)
Shift the upper limit of normal down by 0.5 (TSH ~ 3.5-4)

Screen and Treat SC Hypo/Anti-TPO

- Does it decrease pregnancy loss and complications?
  - Negro et al. 2006 RCT LT4 vs placebo in euthyroid, anti-TPO positive JCEM
    - Small study. Reduced pregnancy loss. LT4 started late.
  - Negro et al. 2010 Universal screening vs case finding. JCEM
  - Larger study. No difference between groups.

Screen and Treat SC Hypo/Anti-TPO

- Does it improve neurocognitive outcomes in offspring?
  - Observational studies show association between thyroid abnormalities and poorer cognitive outcomes in pregnancy
  - Lazarus et al. 2012. Antenatal screening and child cognitive fx. NEJM (CATS trial)
    - RCT; No benefit.
  - Casey BM et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. NEJM 2017
    - RCT; No Benefit.

SC Hypothyroidism is pregnancy

ATA Recommendations

- Universal screen with TSH in early pregnancy– Insufficient Evidence
- Preconception screening with TSH –Insufficient evidence
  - Exceptions –Seeking assisted reproduction or known anti-TPO +
- Screen with FT4 –Not recommended

SC Hypothyroidism is pregnancy

Case Finding – ATA Recommended

- History of or signs/symptoms of thyroid dysfunctions
- Positive TPO+ antibody known
- Goitre
- Head and neck radiation or thyroid surgery
- Age > 30
- Type 1 diabetes or other autoimmune disorder
- Family history of thyroid dysfunction
- BMI>40
- Amiodarone, lithium or recent radiocontrast
- Iodine deficient area

SCH Pregnancy: Treatment

- Strong evidence to start treatment is TSH >10
- I would treat if TSH 4-10
- Consider treatment if TSH 2.5-4.0
  - Check anti-TPO?
  - Previous miscarriage?
  - Other risk factors for pregnancy loss?
  - Assisted reproductive technology?
  - Risk vs. benefits?
    - Very low on both sides

Objectives

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Thank you
Questions?