Thyroid Disease

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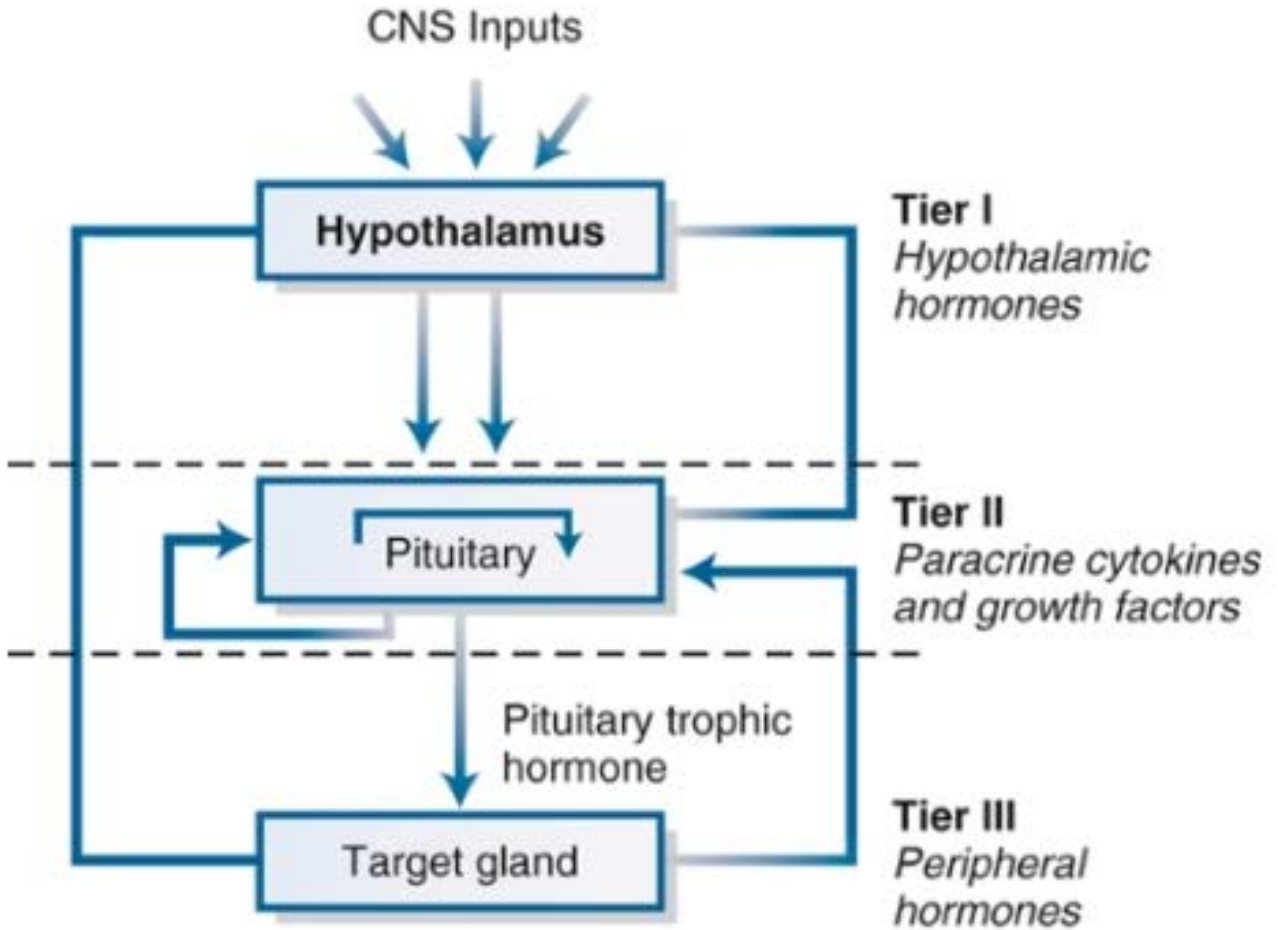
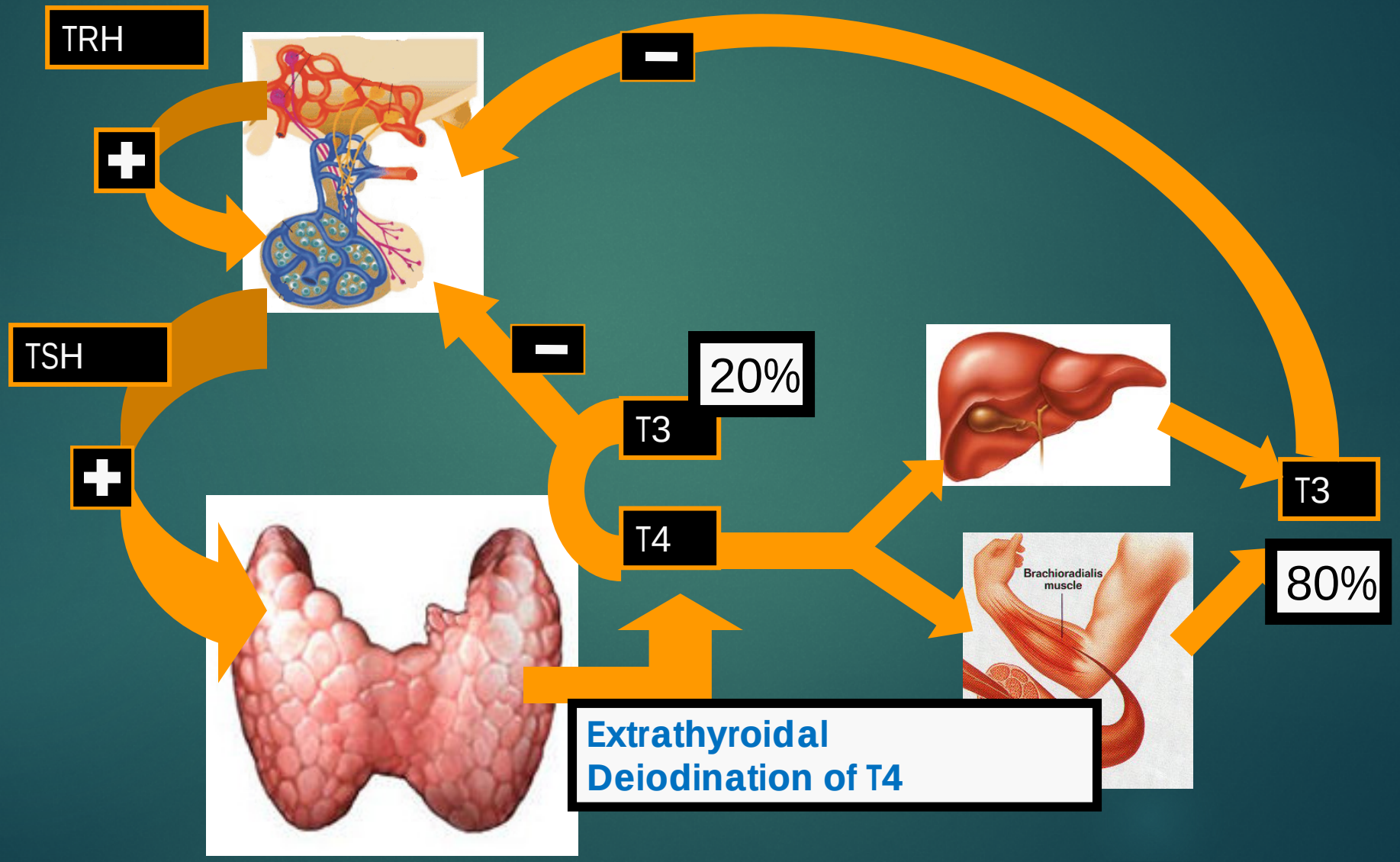
Objectives

- Review normal physiology of hypothalamus-pituitary-thyroid-target tissue axis
- Review thyroid lab testing
- Understand how to interpret thyroid function tests
- Discuss thyroid physiology in pregnancy



- Figure 8-3. Williams Textbook of Endocrinology.

Thyroid Hormone Physiology



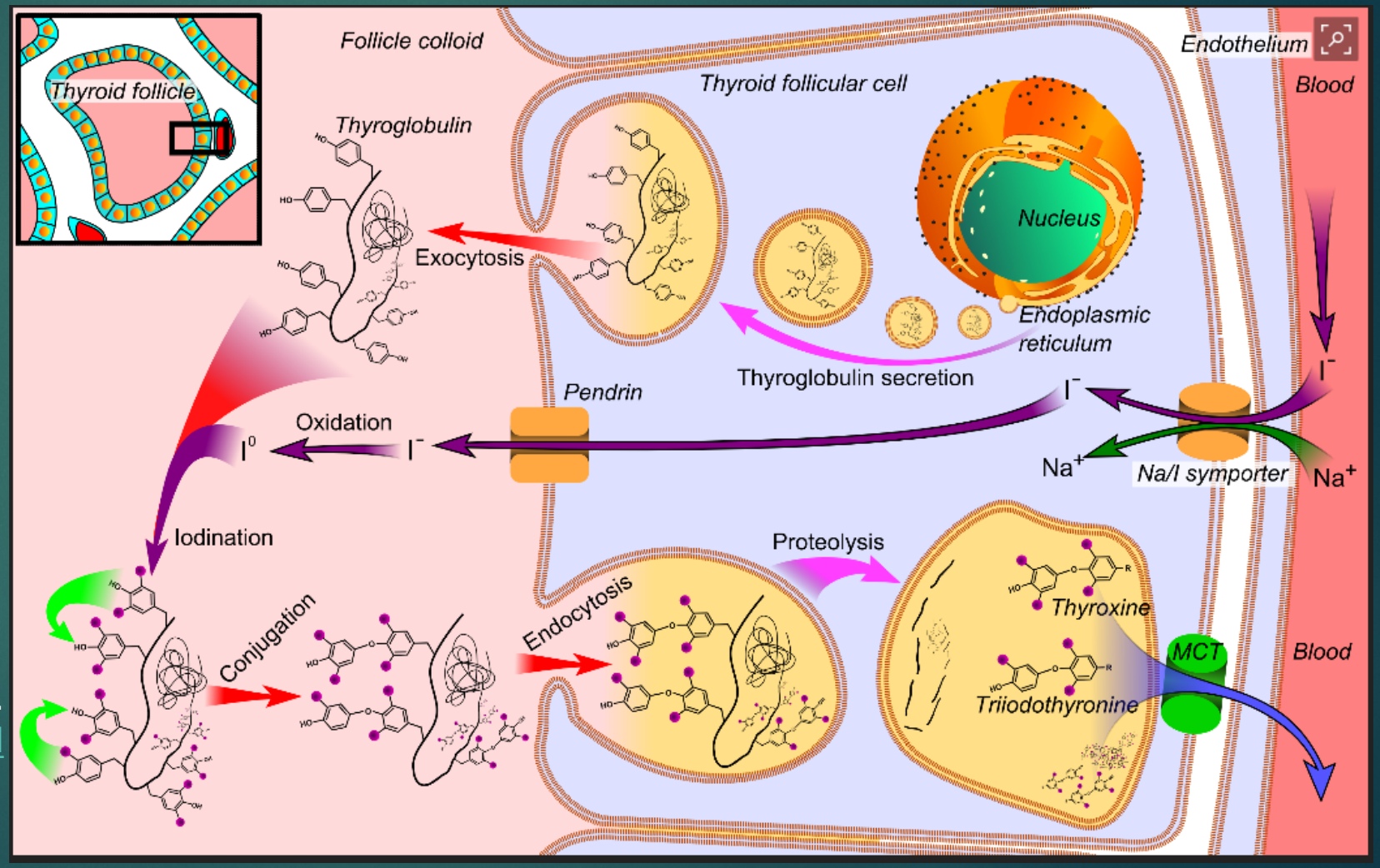
Thyroid Hormone Synthesis

- Monoiodotyrosine: Tg + 1 Iodine
- Diiodotyrosine: Tg + 2 Iodine

- Reaction performed by Thyroid Peroxidase (TPO)

- MIT + MIT: T2
- MIT + DIT: T3
- DIT + DIT: T4

Thyroid Hormone Synthesis



- Häggström, Mikael (2014). "Medical gallery of Mikael

Case

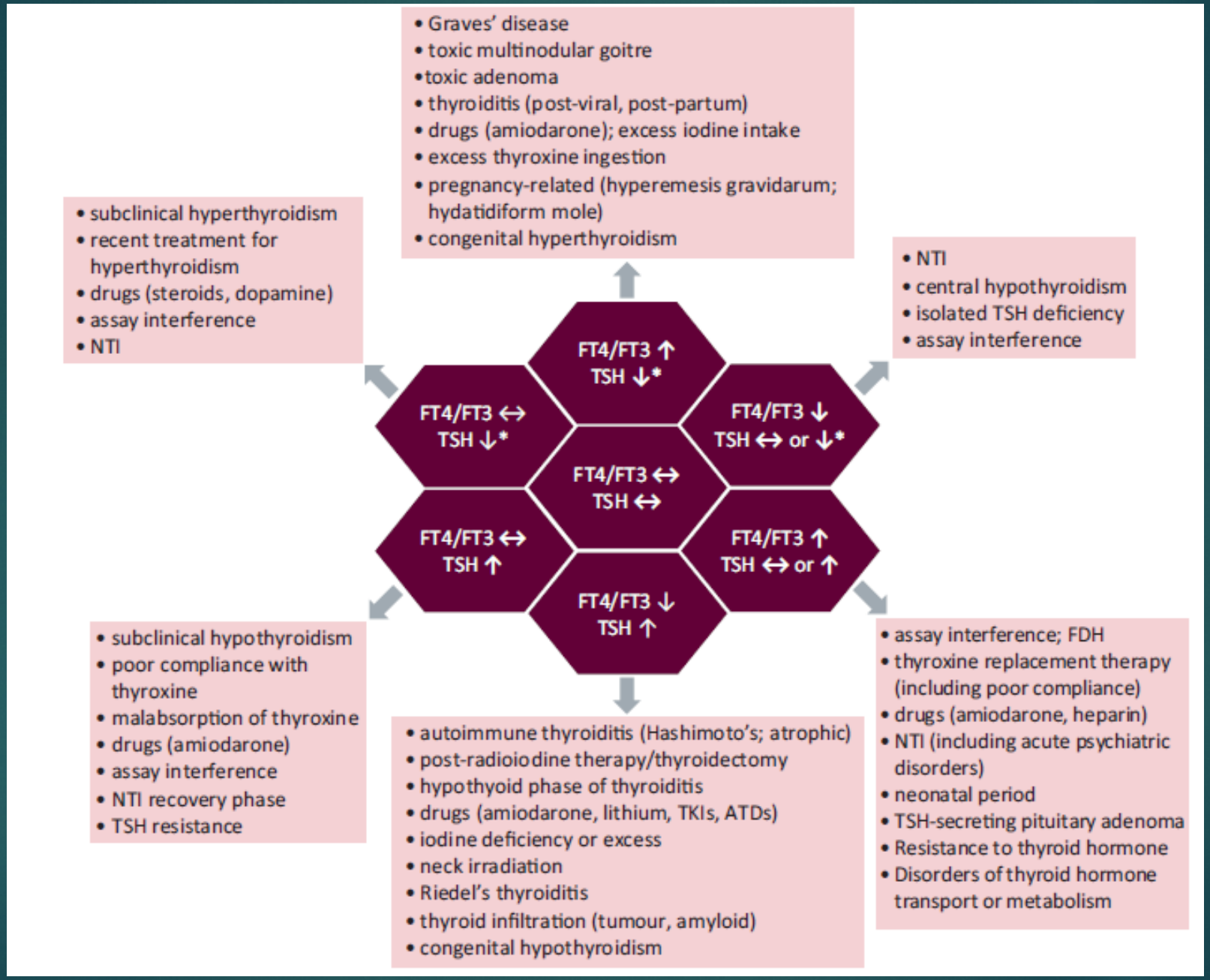
- 39 year old woman with no past medical history presents to your clinic for follow up visit. She complains of fatigue, 15 lb weight gain over 3 months, being cold despite summer temperatures in Phoenix, dry skin, enlargement of her neck, and heavier periods.

- What laboratory test should you order to screen for her likely condition?
  - Free T4 (thyroxine)
  - Total T3 (triiodothyronine)
  - Reverse T3
  - Thyroid-stimulating hormone
  - Thyroid stimulating immunoglobulin

Box 1. Conditions in which measurement of TSH alone might be misleading.

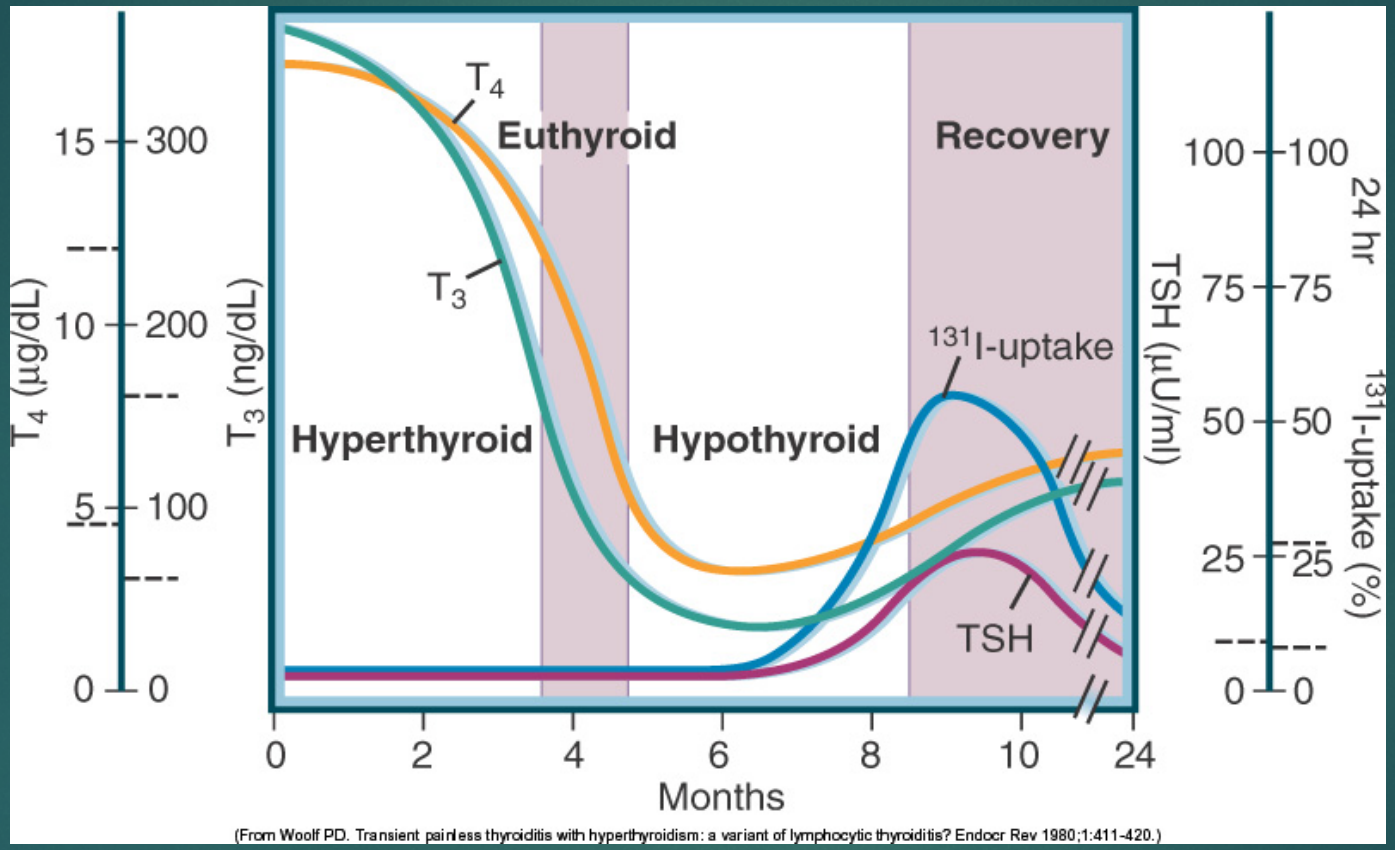
- Central hypothyroidism (eg hypothalamic and/or pituitary disorders)
- Non-thyroidal illness
- Recent treatment for thyrotoxicosis (TSH can remain suppressed even when thyroid hormone levels have returned to the reference range)
- Resistance to thyroid hormone
- TSH-secreting pituitary adenoma (thyrotropinoma or TSHoma)

TSH = thyroid-stimulating hormone; TSHoma = TSH-secreting pituitary adenoma.


• Graves' disease
• toxic multinodular goitre
• toxic adenoma
• thyroiditis (post-viral, post-partum)
• drugs (amiodarone); excess iodine intake
• excess thyroxine ingestion
• pregnancy-related (hyperemesis gravidarum; hydatidiform mole)
• congenital hyperthyroidism
• subclinical hyperthyroidism
• recent treatment for hyperthyroidism
• drugs (steroids, dopamine)
• assay interference
• NTI
• NTI
• central hypothyroidism
• isolated TSH deficiency
• assay interference
FT4/FT3 ↑ TSH ↓*
FT4/FT3 ↔ TSH ↓*
FT4/FT3 ↓ TSH ↔ or ↓*
FT4/FT3 ↔ TSH ↔
FT4/FT3 ↔ TSH ↑
FT4/FT3 ↑ TSH ↔ or ↑
FT4/FT3 ↓ TSH ↑
• subclinical hypothyroidism
• poor compliance with thyroxine
• malabsorption of thyroxine
• drugs (amiodarone)
• assay interference
• NTI recovery phase
• TSH resistance
• autoimmune thyroiditis (Hashimoto's; atrophic)
• post-radioiodine therapy/thyroidectomy
• hypothyoid phase of thyroiditis
• drugs (amiodarone, lithium, TKIs, ATDs)
• iodine deficiency or excess
• neck irradiation
• Riedel's thyroiditis
• thyroid infiltration (tumour, amyloid)
• congenital hypothyroidism
• assay interference; FDH
• thyroxine replacement therapy (including poor compliance)
• drugs (amiodarone, heparin)
• NTI (including acute psychiatric disorders)
• neonatal period
• TSH-secreting pituitary adenoma
• Resistance to thyroid hormone
• Disorders of thyroid hormone transport or metabolism

Test	Graves Disease	MNG	Thyroiditis	Toxic Adenoma
TSH	LOW	LOW	Low/Normal/High	LOW
Free T4	HIGH	HIGH	Low/Normal/High	HIGH
Free T3	HIGH	Normal/HIGH	Low/Normal/High	Normal/HIGH
RAI Uptake	Diffuse Increased Uptake	Patchy increased uptake	Decreased	Single Focus with suppressed rest of gland
TRAbs	++	--	-- (possibly + TPO)	--

Silent Thyroiditis: Course



(From Woolf PD. Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? Endocr Rev 1980;1:411-420.)

Williams Textbook of Endocrinology, Fig 11-16, 2008

Hypothyroidism Epidemiology

- Prevalence:
  - Overt hypothyroidism:
    - 0.1-2%
  - Subclinical Hypothyroidism
    - 4-10% of population
- Most commonly affects mid-age to older women
- Women > Men (5 X higher)

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 Mental retardation (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

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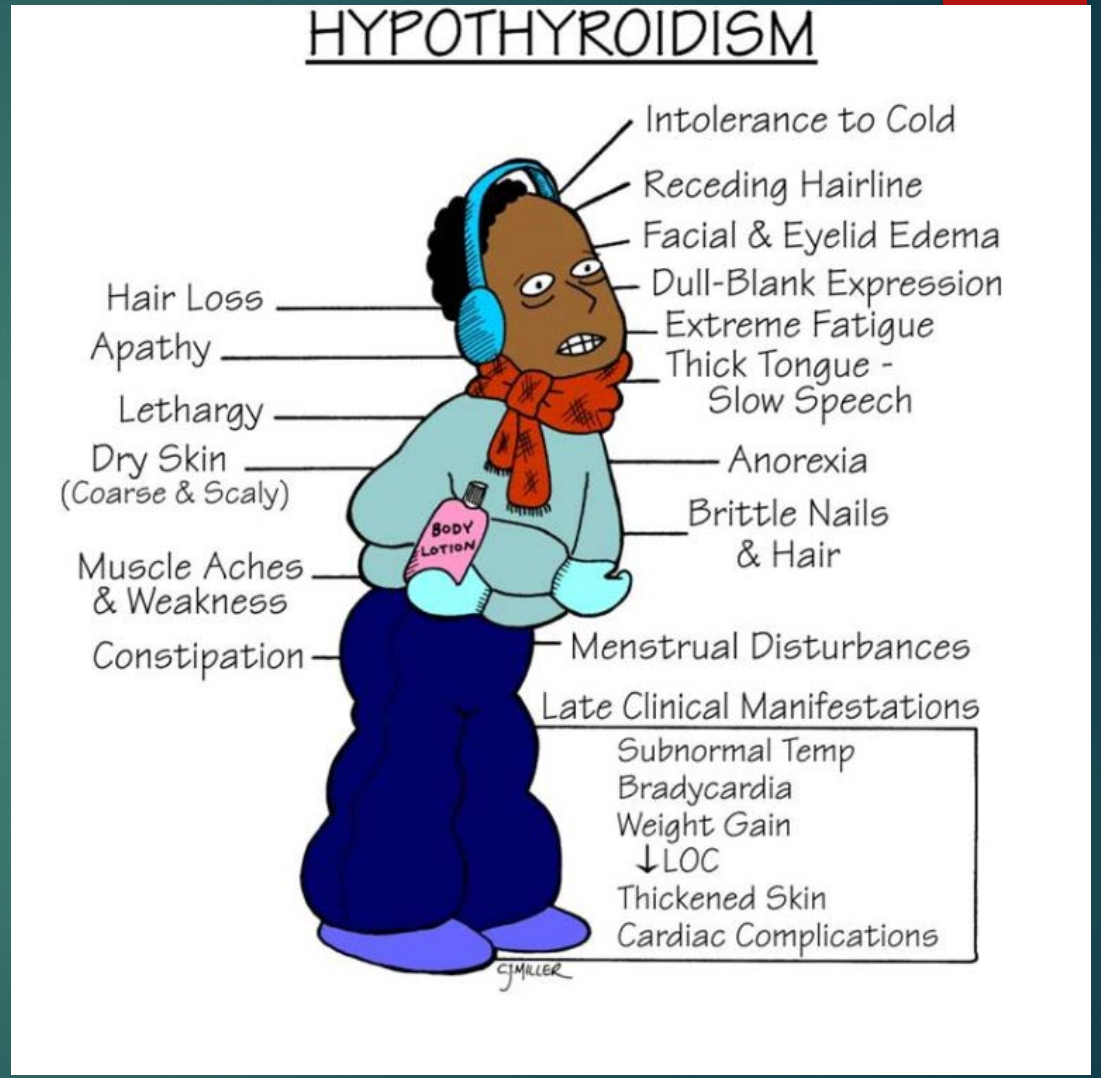
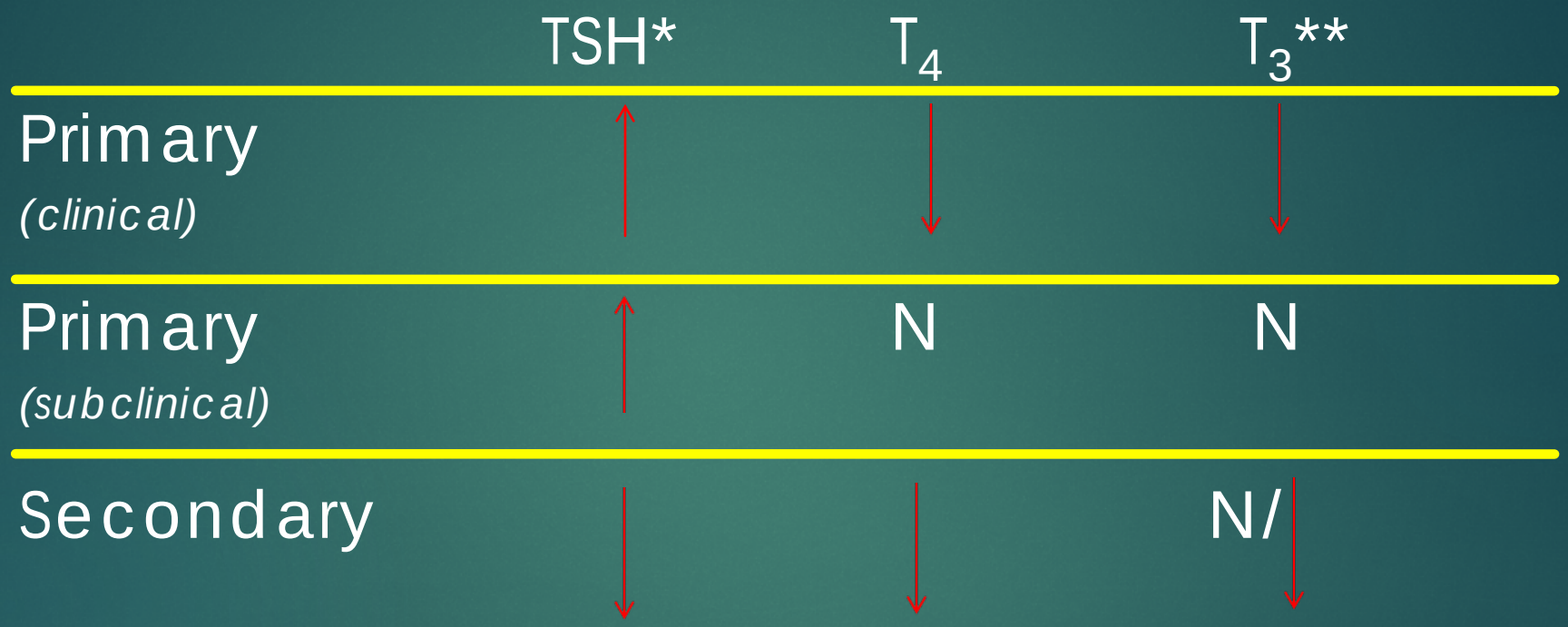


Levels in Hypothyroidism



*TSH = most sensitive test for diagnosis of primary hypothyroidism

**Measurement of T3/ free T3 rarely helpful

Indications for Treatment

- 1st: Always Repeat TSH and T4.
- Overt or Central Hypothyroidism
  - Symptomatic or Asymptomatic
  - High TSH
  - Low Free T4
- Levothyroxine Therapy (Synthetic T4)
- Goal: Normalize TSH levels.

Indications for Treatment

- Subclinical Hypothyroidism
  - TSH > 10 mU/L
  - Age < 65 with TSH 7-10 mU/L with symptoms
  - Anyone with TSH < 7 mU/L: Consider monitoring unless severely symptomatic

Levothyroxine

- Starting dose
  - Young healthy individual:
    - 1.6 mcg/kg/day
    - 50-200 mcg daily
  - Elderly patient or risks for heart disease
    - Lower starting dose (1.0 mcg/kg/day)
    - 25-50 mcg daily and titrate as needed

- Timing of Dose
  - Empty stomach
  - No other medications particularly calcium, Iron Supplements
  - 1 hour prior to eating, Water only.

Monitoring Dose

- Primary Hypothyroidism
  - Monitor every 6 weeks after dose adjustment
  - Goal TSH within normal limits
- Central Hypothyroidism
  - Goal T4 in upper 1/3 of normal range
- Always ask about compliance with medication before dose changes.
- If patient becomes pregnant, increase of dose is needed by 30%

Case

- 28 yr old woman with history or Prader-Willie syndrome, hypothyroidism presents to your emergency room with altered level of consciousness, lethargy, and lower extremity edema. She is taken care of exclusively by her care giver. She ran out of levothyroxine 3 months prior.
- Vital Signs: Temperature 92.9 degrees, HR: 49, BP: 110/90, RR: 8, O2 Sat: 94%
- Physical Exam: Appears lethargic, bradycardic and with significant nonpitting lower extremity edema. Otherwise unremarkable exam

Case Continued

- Laboratory Data:
- Sodium 129
- Blood glucose: 54
- TSH 110, T4, T3 Undetectable.
- + TPO antibodies
- Normal renal function, normal CBC, cortisol level.

- What is the most likely diagnosis?

Myxedema Coma

- Most severe form of Hypothyroidism
  - Altered level of consciousness
  - Hyponatremia
  - Hypothermia
  - Hypoventilation
  - Hypoglycemia
  - Hypotension
  - Rarely heart failure

Treatment

- Call Endocrinology!
- *** Corticosteroids Initially ***
- IV levothyroxine then oral Levothyroxine
- T3
- Supportive Care

Table 1. Causes of anomalous thyroid function tests in patients receiving levothyroxine therapy.[12,13]

Cause	TFT patterns and LT4 dosage requirements	Comments
Normal physiological variant	Normal TSH, mildly ↑FT4; ± higher than predicted LT4 requirements*	To abolish symptoms and normalise TSH, some individuals require a mildly elevated FT4 (possibly reflecting less efficient deiodination of T4 to T3); FT3 is typically normal
'Inappropriate' administration	↑TSH, low normal or ↓FT4; requirement for high LT4 dosages to normalise TSH*	LT4 should be taken on an empty stomach; certain foodstuffs (eg fibre or espresso coffee) and some medication (eg iron, calcium, proton-pump inhibitors, sucralfate, aluminium hydroxide and cholestyramine) might impair absorption
Malabsorption	↑TSH, low normal or ↓FT4; requirement for high LT4 dosages to normalise TSH*	LT4 malabsorption occurs with coeliac disease, achlorhydria, lactose intolerance (lactose is a constituent of some LT4 preparations) and with certain medication (see above)
Increased TH metabolism or excretion	↑TSH, low normal or ↓FT4; requirement for high LT4 dosages to normalise TSH*	Phenytoin, carbamazepine, rifampicin and some tyrosine kinase inhibitors (eg imatinib) increase LT4 requirements through enhanced metabolism; occasional cases of increased urinary TH loss complicating nephrotic syndrome have also been reported

Increased TH-binding capacity	↑TSH, low normal or ↓FT4; requirement for high LT4 dosages to normalise TSH*	Oral oestrogen therapy results in a marked increase in TBG levels and, hence, TH binding capacity, necessitating an increase in LT4 therapy
Change in LT4 preparation	Increase or reduction in LT4 dosage required to maintain clinical and biochemical euthyroidism	Not all LT4 preparations are of comparable potency and/or bioavailability; changes in preparation are generally best avoided but, if necessary, should prompt more frequent TFT monitoring‡
TSH assay interference	↑TSH, normal FT4	Heterophilic antibody interference in the TSH assay can yield falsely elevated results; FT4 and FT3 are normal, and the patient is clinically euthyroid
Poor compliance	Persistent ↑TSH, ↓ ↑ or normal FT4, despite treatment with high LT4 dosages	Owing to their differing half-lives, intermittent hormone ingestion can result in normal or even elevated TH levels, but fails to normalise TSH
Resistance to TH	Supraphysiological LT4 required to normalise TSH, but with resultant ↑FT4 (and ↑FT3)	Typically seen following inappropriate thyroid ablation in a patient harbouring a mutation in the human TH receptor β (*THRB*) gene

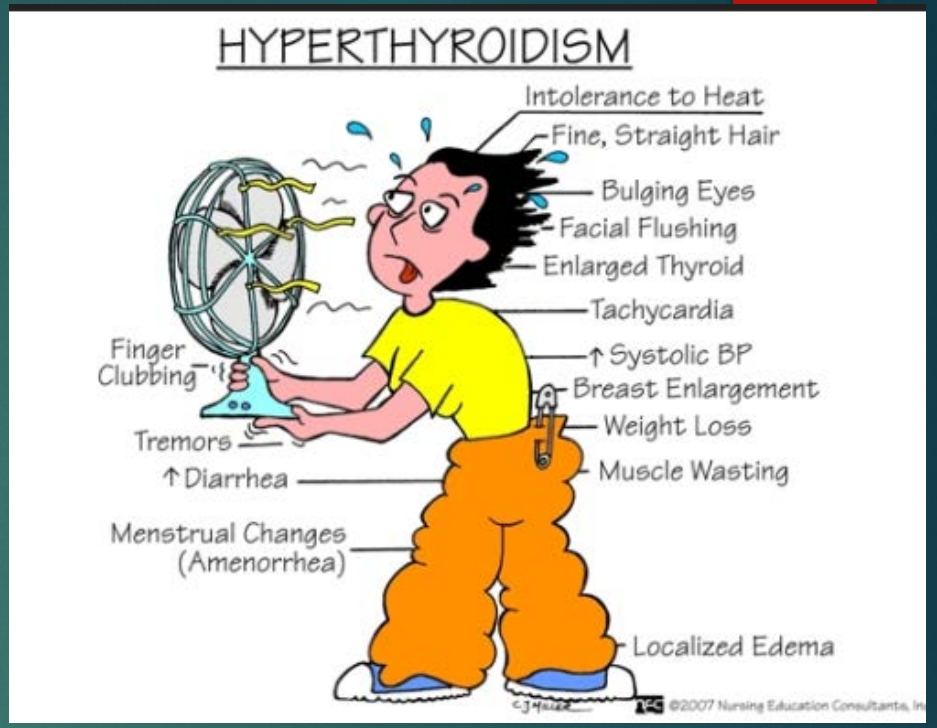
Case

- 34 yr old man with no significant medical history comes to your emergency department with palpitations, sweating, being hot all the time despite winter conditions in Flagstaff, tremor in hands, and significant anxiety.
- Vital signs: Afebrile, P: 122 BP: 125/79. O2 Sat: 99% on RA.
- Physical Exam shows: anxious gentleman, no acute distress, Tachycardia with flow murmur at LUSB, enlarged thyroid gland, lid lag, conjunctival injection, bilateral tremor, hyperreflexive DTRs and mild nonpitting edema.

- Given his most likely diagnosis what will his thyroid labs look like?
- 1. TSH elevated, Free T4 Low
- 2. TSH elevated, Free T4 elevated
- 3. TSH low, Free T4 Elevated
- 4. TSH and Free T4 normal
- 5. I didn't check his thyroid labs because he doesn't have a thyroid condition.

Clinical Symptoms

- Tremor
- Heat intolerance
- Weight Loss
- Loose bowel movements
- Sweating
- Lower extremity edema
- Anxiety
- Palpitations
- Menstrual irregularities (lighter period)
- Elderly patient may experience depression-like symptoms



https://nclexies.files.wordpress.com/2011/01/hyperthyroidism.jpg

Clinical Signs

- Goiter
- Bruit in thyroid gland (Graves Disease)
- Tremor
- Tachycardia (Atrial fibrillation)
- Moist skin
- Hair loss
- Exopthalmos (Graves disease)
- Non-pitting Edema (Graves disease)
- Hyperreflexia
- Lid Lag (Stare)

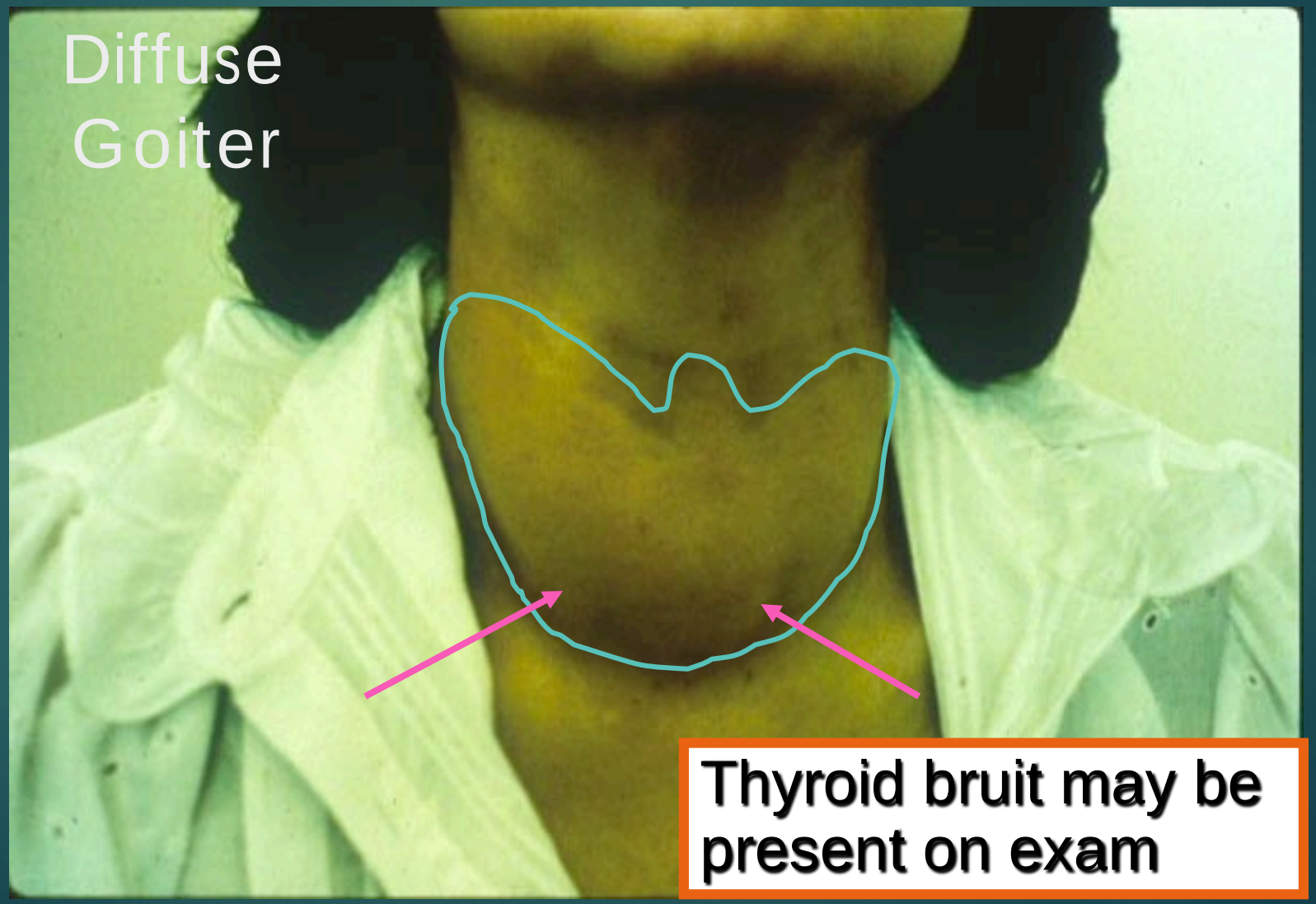
Graves' Disease

- Exopthalmos

Graves' Physical Exam Findings:

Infiltrative Ophthalmopathy

Graves' Physical Exam Findings:



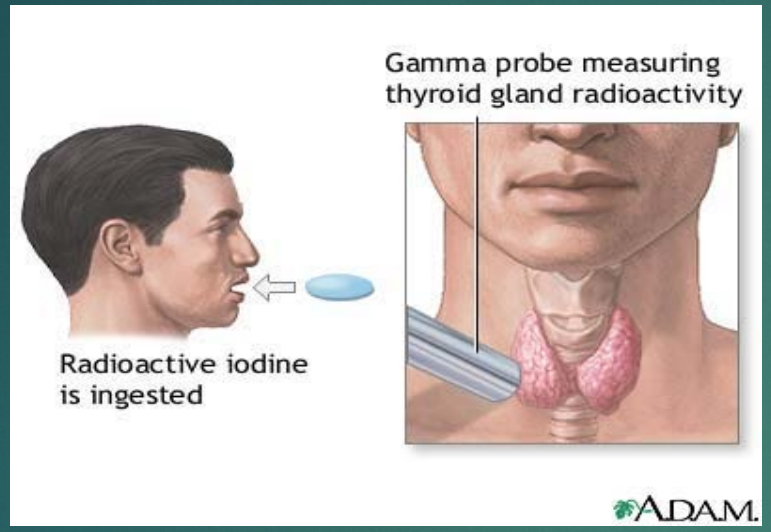
Graves' Physical Exam Findings:

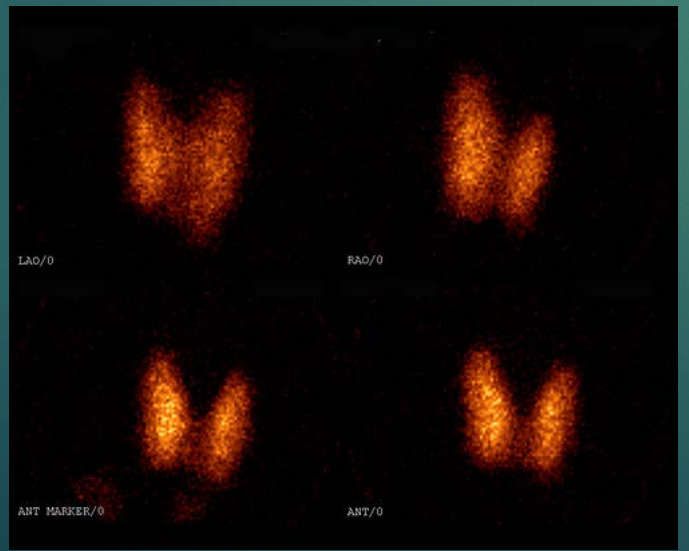
Pre-Tibial Myxedema

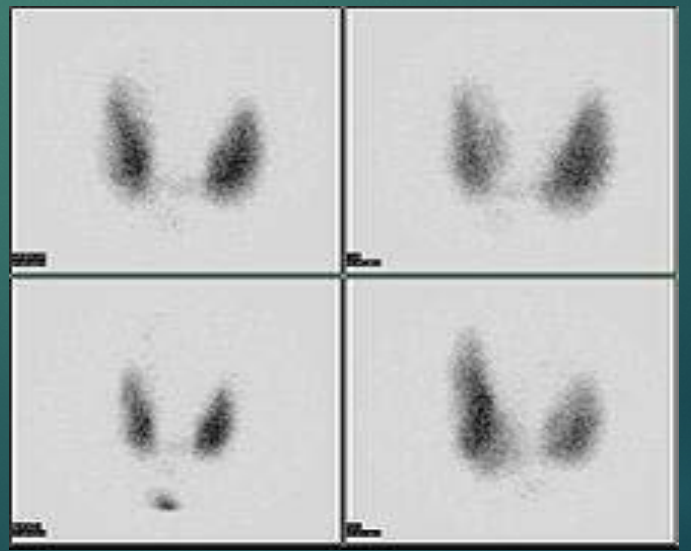
What shall I order?

- TSH—Low to undetectable
- Free T4—Normal to High
- Free T3—Normal to High
- Radioiodine Uptake and Scan
- Thyrotropin Receptor Antibodies
  - TRAB, TSI, TBI
- Thyroid Ultrasound
  - Useful if nodules present
  - Also looking at blood flow to thyroid gland

Thyroid uptake and scan

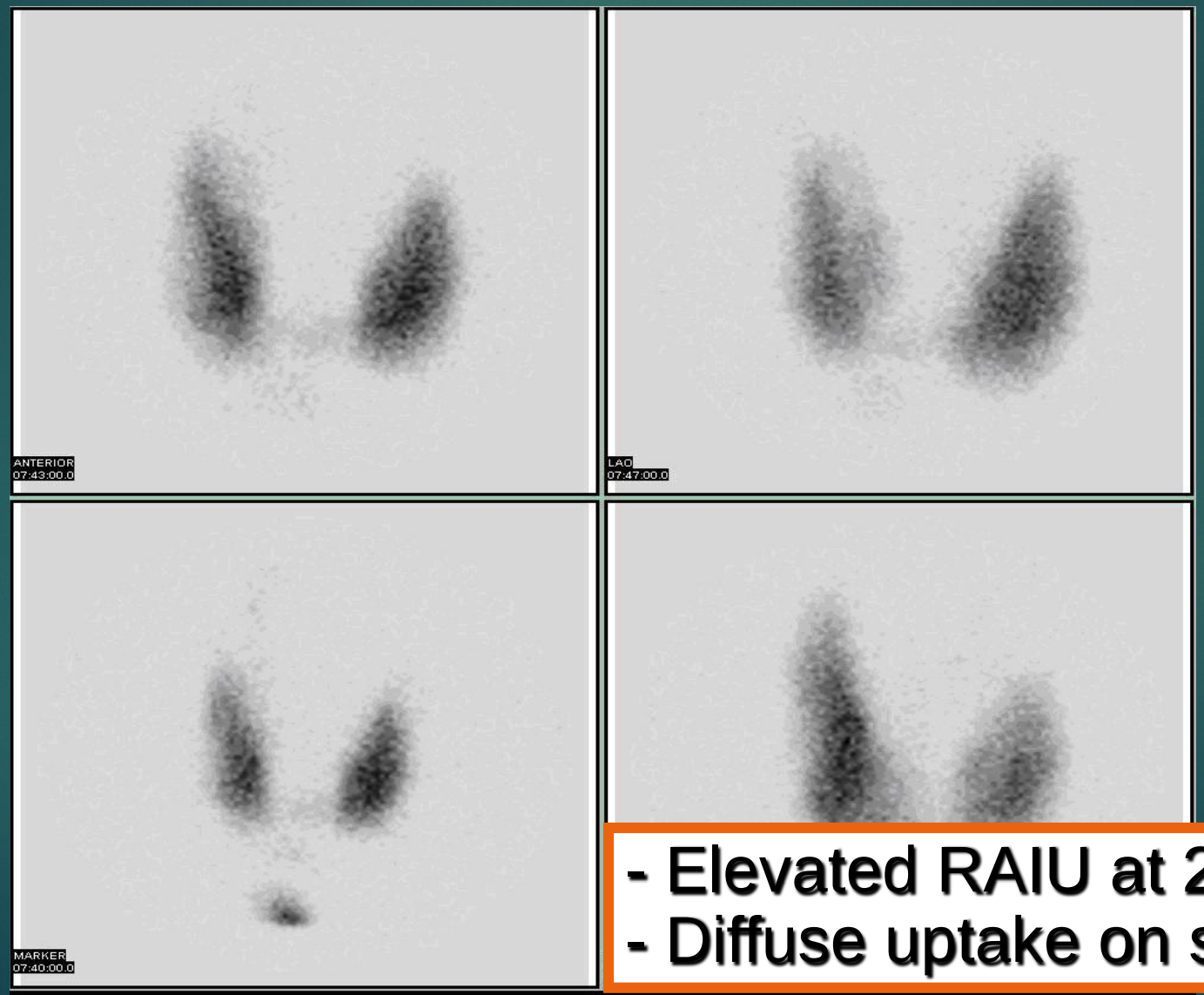






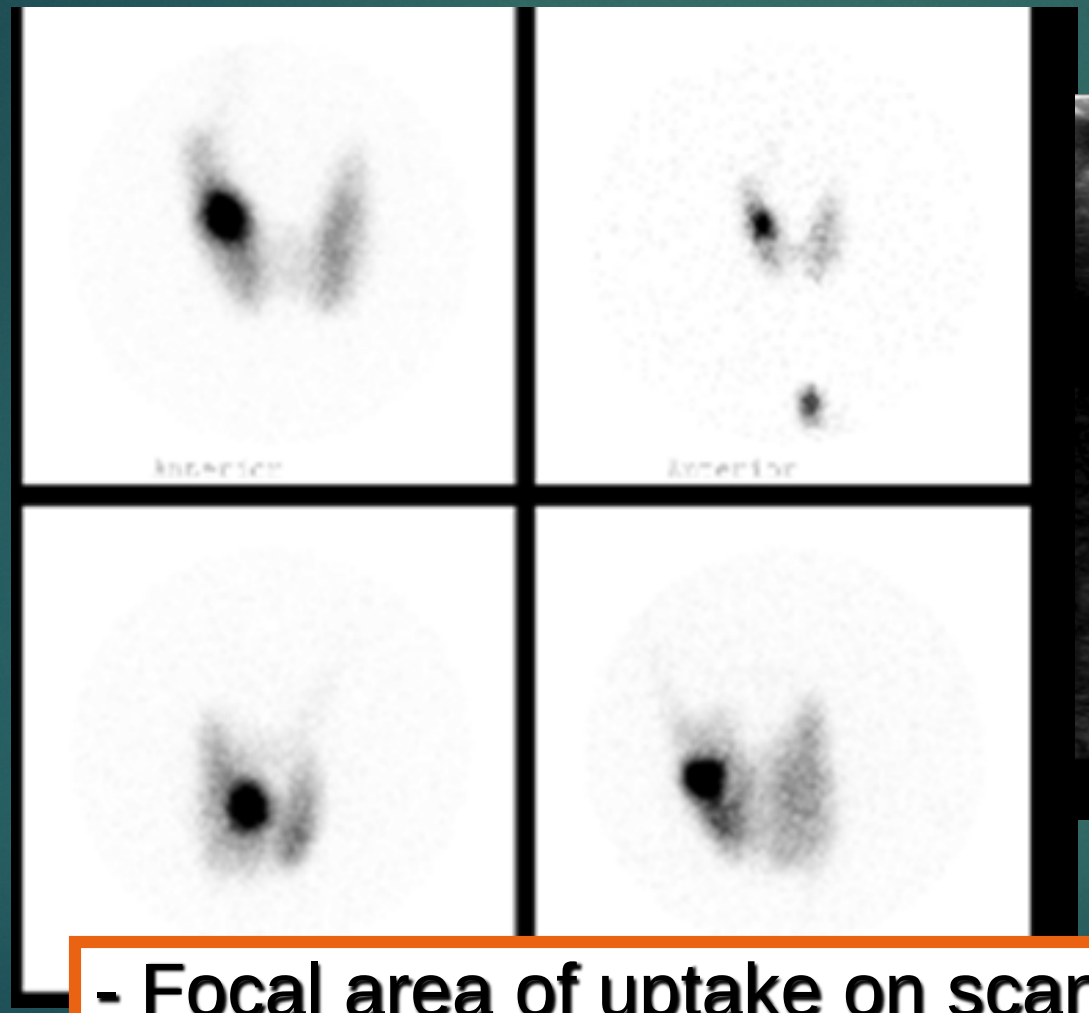
Images from Google.com

What is the diagnosis?



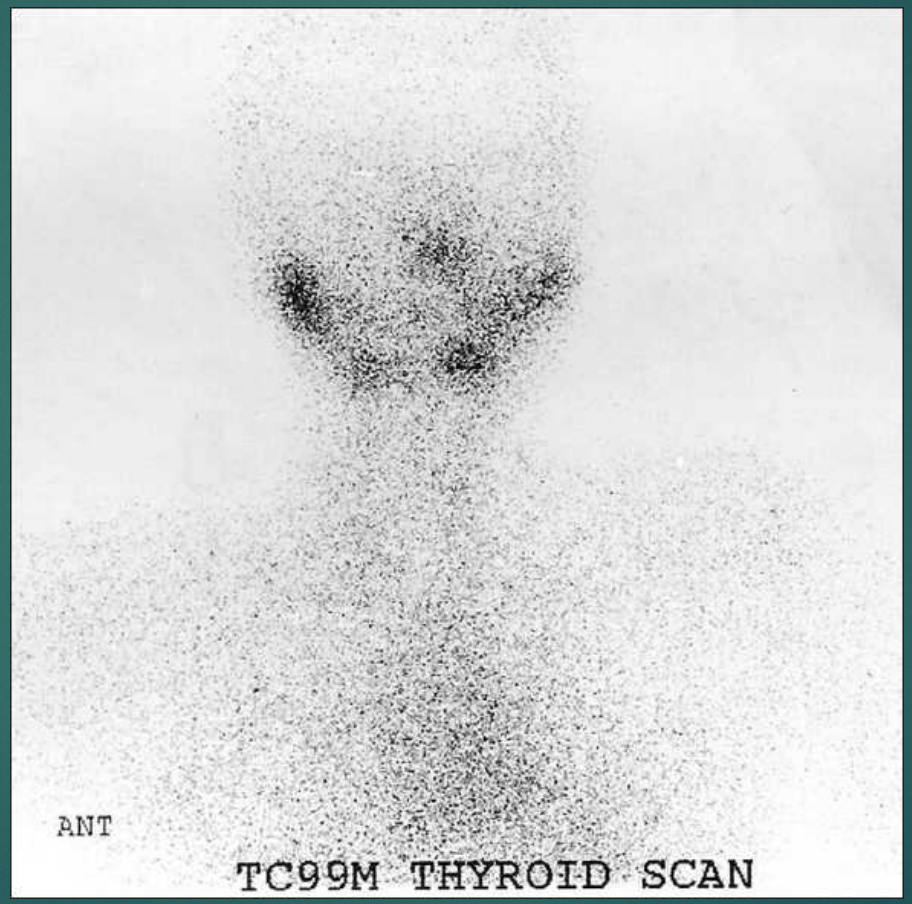
- Elevated RAIU at 24 hours
- Diffuse uptake on scan

What is this diagnosis?



- Focal area of uptake on scan (left panel) corresponding to nodule on ultrasound (right)

Diagnosis?



- Low RAIU at 24 hours
- None or limited uptake on scan

Treatments

- Medical Treatment
  - Beta Blockers (propranolol, metoprolol, atenolol)
  - Thionamides (Methimazole, PTU)
    - Adverse reactions: hepatic toxicity, agranulocytosis, rash
  - Monitor TSH and T4
  - Goal within normal limits

- RAI ablation (I-131)
  - Takes up to 6 months
  - Often hypothyroidism requiring Levothyroxine
  - Use caution in exophthalmos
  - Contraindicated in pregnancy

- Surgical Resection
  - Immediate
  - Requires Levothyroxine

Table 2. Examples of drugs affecting thyroid function in previously euthyroid individuals.

Drug	TFT patterns	Comments
Amiodarone		Average daily dosages of amiodarone provide a large excess of 'dietary' iodine; it is highly lipophilic with a large volume of distribution, has structural similarity to TH, and inhibits T4→T3 conversion by type 1 DIO
	Transient ↑TSH; ↑FT4, normal FT3	Short-lived rises in TSH are common during the first few months of treatment with amiodarone; inhibition of type 1 DIO leads to persistent elevation of FT4, but normal FT3
	↓TSH, ↑FT4	Two main types of thyrotoxicosis are recognised: type 1 (large iodine load precipitating latent thyroid autonomy); and type 2 (destructive thyroiditis). Amiodarone inhibits T4→T3 conversion such that T4 is typically more markedly elevated than T3
	↑TSH, ↓FT4	Hypothyroidism occurs in up to 15% of patients (particularly women and those with positive antithyroid antibodies); it can signify a failure to escape from the Wolff–Chaikoff effect*
Lithium	↑TSH, ↓ or normal FT4	Overt or subclinical hypothyroidism
	↓TSH, ↑FT4	Thyroiditis occurs in a few patients and is typically self-limiting
Tyrosine kinase inhibitors	↑TSH, ↓FT4	Primary hypothyroidism (possibly owing to a direct toxic effect on the thyroid gland) has been observed with some tyrosine kinase inhibitors (eg sunitinib and sorafenib)
	↓TSH, ↑FT4	A prodromal thyrotoxic phase is occasionally seen in patients taking sunitinib
Immune modulators	↓TSH, ↑FT4	Graves' disease has been reported in patients receiving: alemtuzumab (a humanised monoclonal antibody directed against CD52) for multiple sclerosis; HAART for HIV infection; or INFα for chronic hepatitis C
	↑TSH, ↓FT4	Hashimoto's thyroiditis can complicate INFα therapy (± prodromal thyrotoxic phase)

DIO = deiodinase; FT4 = free thyroxine; FT3 = free triiodothyronine; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; INFα = interferon alpha; T4 = thyroxine; T3 = triiodothyronine; TFTs = thyroid function tests; TSH = thyroid stimulating hormone (thyrotropin).
*The Wolff–Chaikoff effect is the temporary impairment of T4 and T3 synthesis by high intrathyroidal concentrations of iodine (eg following ingestion of a large iodine load).

Other points to add

- Binding globulins change levels
  - Exogenous estrogen,
  - Pregnancy
    - Need to increase LT4 by 30% once pregnancy due to binding globulins
    - ESAP question.
    - Different Goals for pregnancy

- Central hypothyroidism TSH becomes obsolete
  - Leads to under-replacement of levothyroxine

Euthyroidal Illness

- Low to Low normal TSH
- Low to low normal T4, T3

Key points

The results of thyroid function tests (TFTs) must always be interpreted in light of the clinical status of the patient: hypothyroid, euthyroid or hyperthyroid

Awareness of the conditions and/or disorders that can be associated with different patterns of TFTs guides further investigation and management

Confounding factors that may might influence thyroid status (eg intercurrent non-thyroidal illness or medications) should be excluded before embarking on further biochemical, radiological or genetic testing

Screening for interference in thyroid hormone (T4 and T3) and/or thyrotropin (TSH) laboratory assays should be considered in any patient with apparently anomalous or discordant TFTs

Referral to a specialist laboratory and/or endocrine service is required when anomalous or discordant TFTs cannot be readily explained by confounding intercurrent illness, medication or assay interference

KEY WORDS: Thyroid function tests (TFTs), interpretation, anomalous or discordant TFTs

References

- Koulouri O, Gerunell M. How to interpret thyroid function tests. Royal College of Physicians 2013. 282-286.
- Uptodate articles
  - Diagnosis of hyperthyroidism
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  - Diagnosis of and screening for hypothyroidism in nonpregnant adults
  - Treatment of primary hypothyroidism in adults
  - Clinical Manifestations of hypothyroidism
- Williams Textbook of Endocrinology 13th edition

Thank You!!

- Any Questions:
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