Managing/Diagnosing Hypo/Hyperthyroidism and Interpreting Thyroid Function Tests

Part 1: Hypothyroidism

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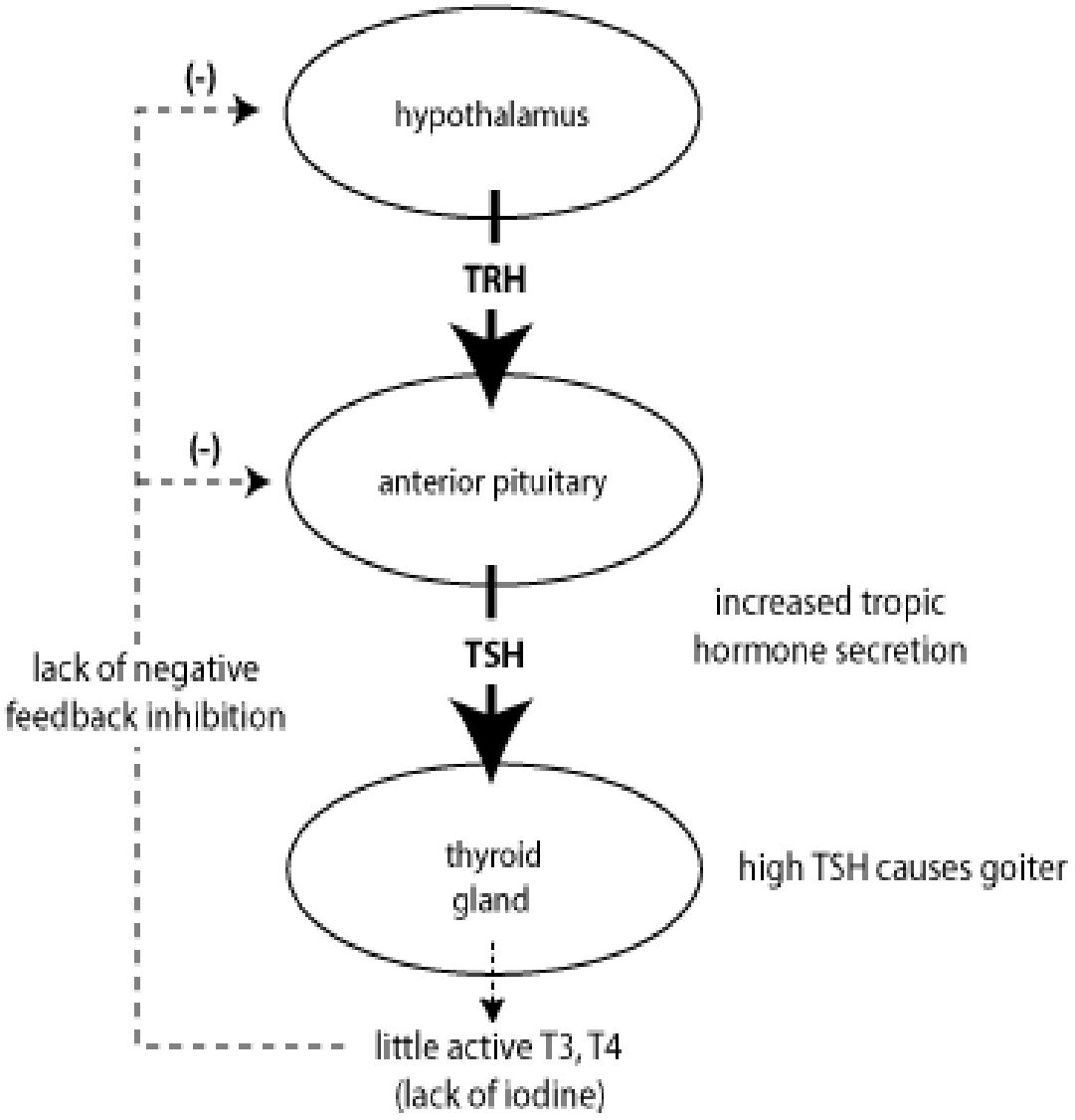
Definition and Epidemiology

- **Hypothyroidism** is traditionally defined as deficient thyroidal production of thyroid hormone

- Prevalence of overt hypothyroidism varies from 0.1 to 2 percent.

- Hypothyroidism is five to eight times more common in women than men.



Primary

- **Autoimmune disease (Hashimoto thyroiditis)–most common in US**
- **Iodine deficiency–most common world wide**
- Surgery/Radiation therapy
- Medications (eg, lithium, tyrosine kinase inhibitors)

Secondary

- Tumors (pituitary adenoma, craniopharyngioma, meningioma)
- Trauma (surgery, irradiation, head injury)
- Infections (abcess, tuberculosis, syphilis, toxoplasmosis)
- Infiltrative (sarcoidosis, histiocytosis, hemochromatosis)
- Chronic lymphocytic hypophysitis
- Drugs (dopamine, glucocorticoids)

Peripheral

- Consumptive hypothyroidism (massive infantile hemangioma)
- Mutations in genes encoding for MCT8, SECISBP2, TRα or TR β (thyroid hormone resistance)

Diagnosis of Primary Hypothyroidism

- **Primary hypothyroidism** indicates decreased thyroidal secretion of the thyroid hormone by factors affecting thyroid gland itself.

- Fall in serum concentrations of thyroid hormone causes an increased secretion of TSH resulting in elevated serum TSH concentrations.

- Characterized by high TSH and low Free T4

- Thyroid peroxidase (TPO) antibodies are elevated in majority of patients with chronic autoimmune thyroiditis.

Manifestations of Hypothyroidism

- **Common symptoms:** fatigue, cold intolerance, weight gain, constipation, dry skin, myalgia, and menstrual irregularities

- **Physical examination:** goiter, bradycardia, diastolic hypertension, and a delayed relaxation phase of the deep tendon reflexes

- **Metabolic abnormalities:** hypercholesterolemia, macrocytic anemia, elevated creatine kinase, and hyponatremia

Case Study Knowledge Check

A patient with hypothyroidism comes to you and requests a switch to Armour (combined T4/T3) thyroid because she was told it was more natural and better than levothyroxine.

You tell her:

A. Yes, it is has been proven to be better

B. There is clear proof that patients don't like it

C. Some patients prefer it but there is higher risk of TSH suppression and monitoring is needed

D. A combination of T3 and T4 separately is better

Case Study Knowledge Check

A patient with hypothyroidism comes to you and requests a switch to Armour (combined T4/T3) thyroid because she was told it was more natural and better than levothyroxine.

Answer is C:

Some patients do prefer combination therapy. There is no clear proof of superiority in blinded studies and there is a greater risk of TSH suppression. Triiodothyronine (T3) or desiccated thyroid should not be used in pregnancy.

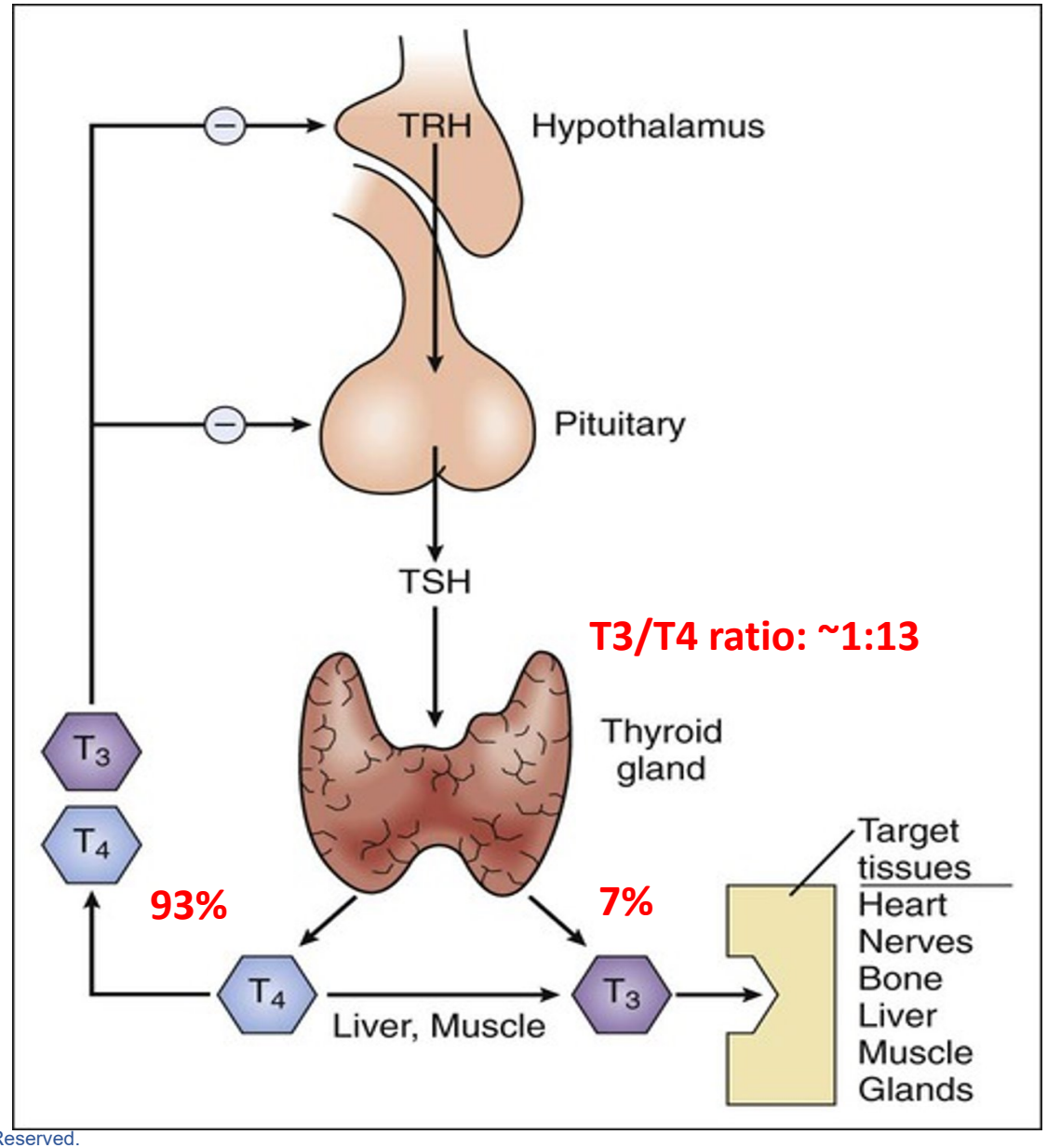
T3/T4 Pharmacology

Thyroxine (T4)

- Half life = 7 days
- Stable/long acting
- Intestinal absorption of oral T4 is ~80%

Triiodothyronine (T3)

- Half life = 0.75 days
- Onset of action: 2–4 hours
- Rapidly absorbed
- Marked blood level fluctuations
- May falsely suppress TSH if taken close to bloodwork



Treatment of Primary Hypothyroidism

- Goal to normalize TSH
- T4 (levothyroxine, Synthroid) drug of choice
- Generic/brand-name bioequivalent but altered bioavailability reported
- Full replacement dose usually about 1.6 mcg/kg
- Absorption more complete/ less erratic in fasting state
- Patients advised to take L-T4 tablets in morning or late evening

Treatment of Primary Hypothyroidism

- Some patients don't need full replacement at first; never wrong to start low and titrate up
- Careful in CAD, elderly: start with lower dose~25-50 mcg/day
- Avoid taking with iron/calcium - impairs absorption
- Dose titrated up to normalize TSH
- Recheck 6-8 weeks after dose changes and 6-12 months thereafter

What About T3?

Treatment of choice: levothyroxine (LT4)*

Evidence does not support use of LT3/LT4 combinations†

LT3 = liothyronine

*Strong recommendation. Moderate quality evidence (Jonklaas J et al. *Thyroid*. 2014;24(12):1670-1751).

†Grade B recommendation because of unresolved issues raised by studies that report some patients prefer, and some patient subgroups may benefit from, LT4 and LT3 combination (Garber J, et al. *Endocr Pract*. 2012;18(6):988-1028).

T3/T4 Combinations

- Armour thyroid / NP thyroid
  - 1 grain = 60 mg–contains T3 9 mcg, T4 38 mcg
  - Nature-throid and Westhroid
  - 1 grain = 65 mg: contains T3 9 mcg, T4 38 mcg
  - Pharmacologic equivalence: 74 mcg of T4
- T3 is four times more potent than T4
- (9 x 4 = 36… 36+38 = 74)
- Clinically 90-100 mcg of Levothyroxine

Conditions Requiring Dose Adjustment

Increased dose requirement

1. Decreased intestinal absorption of T4

- Dietary fiber supplements
- Reduced gastric acid secretion: H.pylori infection, atrophic gastritis, proton-pump inhibitors
- Malabsorption: coeliac disease, short bowel syndrome, lactose intolerance, bariatric surgery
- Bile-acid sequestrants
- Agents that bind L-T4: sucralfate, aluminum hydroxide, ferrous sulfate, calcium carbonate, sevelamer

Conditions Requiring Dose Adjustment

Increased dose requirement

2. Increased need for T4

- Weight gain
- Estrogens
- Pregnancy

3. Increased metabolic clearance of T4

- Antiepileptic drugs (phenobarbital, phenytoin, carbamazepine)
- Tuberculostatic drugs (rifampicin)

Conditions Requiring Dose Adjustment

Decreased dose requirement

1. Decreased need for T4

- Weight loss
- Androgens

2. Decreased metabolic clearance of T4

- Old age

Central Hypothyroidism

- Decreased thyroidal secretion of hormone caused by insufficient stimulation of thyroid gland by TSH.
  - Pituitary TSH release (secondary hypothyroidism)
  - Hypothalamic TRH release (tertiary hypothyroidism)
- Characterized by Low T4 concentration/ TSH not appropriately elevated
- **Central hypothyroidism less common than primary hypothyroidism**

Central Hypothyroidism

- Should be suspected in the following circumstances:
  - There is known hypothalamic or pituitary disease
  - A mass lesion is present in the pituitary
  - When symptoms/signs of hypothyroidism associated with pituitary hormonal deficiencies
- Goal of replacement therapy is to Titrate FT4/FT3 to mid-upper normal.
- TSH not monitored as it is unreliable.

Case Study Knowledge Check

50-year-old man had splenectomy after motor vehicle accident 10 years ago. He is admitted with pneumococcal sepsis to the intensive care unit. During admission, thyroid function studies show decreased levels of total serum T3 and T4, low-normal TSH, and increased levels of reverse T3.

Select the Next Step:

A. Initiate thyroxine

B. Radioactive iodine thyroid uptake test

C. Thyroid ultrasound

D. Start Dexamethasone

E. Continue to monitor patient and recheck thyroid function after illness resolve

Case Study Knowledge Check

50-year-old man had splenectomy after motor vehicle accident 10 years ago. He is admitted with pneumococcal sepsis to the intensive care unit. During admission, thyroid function studies show decreased levels of total serum T3 and T4, low-normal TSH, and increased levels of reverse T3.

Correct Answer is E:

Continue to monitor patient and recheck thyroid function after illness resolves.

This clinical and biochemical picture is suggestive of Euthyroid Sick Syndrome/ Non- thyroidal illness syndrome.

Thyroid Function in Nonthyroidal Illness

- Euthyroid Sick Syndrome/ Non-thyroidal illness syndrome/ Low T3 syndrome.
- Many hospitalized/ill patients have low/low-normal serum T4, low T3, and low/low-normal/normal TSH.
- Similar to pattern in central hypothyroidism.
- Changes possibly protective in severe illness -prevent excessive tissue catabolism.
- Patients receiving glucocorticoids, dopamine, dobutamine may have low serum TSH.
- Unusual for TSH to be undetectable in the absence of thyrotoxicosis.

Thyroid Function In Non-Thyroidal Illness

- Thyroid function should not be assessed in seriously ill patients unless a strong suspicion of thyroid dysfunction.
- TSH, Free T4, and Free T3 needed to differentiate non-thyroidal illness from thyroid disorder.
- Possibility of adrenal insufficiency must be considered and ruled out, since treatment of hypothyroidism might accelerate cortisol metabolism.
- In critically ill patients with low free T4 and total T3 who do not appear to have an underlying primary thyroid disorder.
  - Do not treat with thyroid hormone
  - Repeat thyroid tests (TSH, free T4), typically in one to two weeks

Myxedema Coma

- Myxedema coma represents decompensated state of severe untreated hypothyroidism.
- The prognosis is poor with a reported mortality between 20% and 50%.
- **Triad of hypothermia, hyponatremia, and hypercapnia.**
- Common precipitating factors include cold exposure, infection, trauma, or anesthesia.

Myxedema Coma

- **Physical manifestations** include hypotension, bradycardia, macroglossia, delayed deep-tendon reflexes. cold, clammy, and dry skin, nonpitting edema, and periorbital edema.
- Laboratory examination may reveal anemia, hyponatremia, hypoglycemia, hypercholesterolemia, and high serum creatine kinase concentrations.
- Most patients have low serum FT4 and high serum TSH.

Myxedema Coma

MANAGEMENT OF MYXEDEMA COMA	
Hypothyroidism	Large initial iv dose of 300-500 µg T4, if no response add T3
	Alternative- initial IV dose of 200-300 µg T4 plus 10-25 µg T3
Hypocortisolemia	IV hydrocortisone 200-400 mg daily
Hypoventilation	Don't delay intubation and mechanical ventilation too long
Hypothermia	Blankets, no active rewarming
Hyponatremia	Mild fluid restriction
Hypotension	Cautious volume expansion with crystalloid or whole blood
Hypoglycemia	Glucose administration
Precipitating event	Identification and elimination by specific treatment, liberal use of antibiotics

Myxedema Coma

Therapeutic endpoints in Myxedema coma should be:

- Improved mental status
- Improved cardiac function
- Improved pulmonary function

Measurement of thyroid hormones every 1-2 days to ensure a favorable trajectory in the biochemical parameters.

Subclinical Hypothyroidism

- Defined as elevated serum thyrotropin (TSH) level with normal levels of free thyroxine (FT_4).
- Affects up to 10% of the adult population.
- **Most often caused by autoimmune (Hashimoto) thyroiditis.**
- Greater risk of progression from subclinical to overt hypothyroidism in patients with circulating thyroid peroxidase antibodies.

Subclinical Hypothyroidism

- May be associated with an increased risk of heart failure, coronary artery disease events, and mortality from coronary heart disease.
- Patients may have cognitive impairment, fatigue, and altered mood.
- No evidence it is beneficial to treat persons aged 65 years or older
- Treatment usually indicated for patients with subclinical
- hypothyroidism and serum thyrotropin levels of 10 mU/L or higher.

Subclinical Hypothyroidism

TSH VALUE	Patient age› 65 years	Patient age ‹ 65 years
4.5-6.9	Measure TPO antibodies Follow TSH measurement in asymptomatic patients Consider treatment: • Plan for pregnancy • Significant hypothyroid symptoms • Positive TPO antibodies • Goiter	No treatment
7.0-9.9	Treat with levothyroxine	Consider treatment with levothyroxine
›10	Treat with levothyroxine	Treat with levothyroxine

Adapted from Subclinical Hypothyroidism: A Review. *JAMA. 2019;322(2):153-160. doi:10.1001/jama.2019.9052.*

ATA Guidelines
Hypothyroidism in Pregnancy

- Maternal hypothyroidism defined as TSH concentration elevated beyond upper limit of pregnancy-specific reference range.
- Pregnancy-specific TSH reference range should be defined as follows:
  - Population / trimester-specific reference ranges for serum TSH during pregnancy should be defined by a provider's institute / laboratory.
  - If TSH reference ranges not available, upper reference limit of ~ 4.0mU/l may be used.
- Treatment of overt hypothyroidism recommended during pregnancy.

ATA Guidelines
Hypothyroidism in Pregnancy

- Oral levothyroxine recommended treatment.
- Triiodothyronine (T3) or desiccated thyroid should not be used.
- Patients should be monitored with a serum TSH measurement every four weeks until mid-gestation, and at least once near 30 weeks gestation.
- Target TSH in the lower half of the trimester specific reference range or below 2.5 mU/L.

ATA Guidelines
Subclinical Hypothyroidism in Pregnancy

- Pregnant women with TSH concentrations ›2.5 mU/L should be evaluated for TPO antibody status.
- Levothyroxine therapy recommended for:
  - TPO antibody positive women with TSH greater than pregnancy specific reference range
  - TPO antibody negative women with TSH greater than 10.0 mU/L

ATA Guidelines
Subclinical Hypothyroidism in Pregnancy

- Levothyroxine therapy may be considered for:
  - TPO antibody positive women with TSH concentrations › 2.5 mU/L and below upper limit of pregnancy specific reference range
  - TPO antibody negative women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L

ATA Guidelines
Subclinical Hypothyroidism in Pregnancy

- Levothyroxine therapy not recommended for TPO antibody negative women with a normal TSH (TSH within the pregnancy specific reference range, or ‹ 4.0 mU/L if unavailable).
- Isolated hypothyroxinemia (free thyroxine concentration in the lower 2.5th -5th percentile of a given population, in conjunction with a normal maternal TSH) should not be routinely treated in pregnancy.

ATA Guidelines
Pre-conception Counseling

- Hypothyroid women should contact caregiver immediately upon confirmed or suspected pregnancy.
- Serum TSH should be evaluated preconception, levothyroxine dose adjusted to achieve TSH value between lower reference limit and 2.5 mU/L.
- Hypothyroid patients receiving LT4 treatment with suspected or confirmed pregnancy should increase their dose of LT4 by ~20-30% (administer 2 additional tablets weekly of the patient's current daily levothyroxine dosage).

ATA Guidelines
Pre-conception Counseling

Postpartum:

- LT4 should be reduced to patient's preconception dose following delivery.
- Thyroid function testing should be performed at approximately six weeks postpartum.

References

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