



# Managing/Diagnosing Hypo/Hyperthyroidism and Interpreting Thyroid Function Tests

## Part 3: Interpreting Thyroid Function Tests

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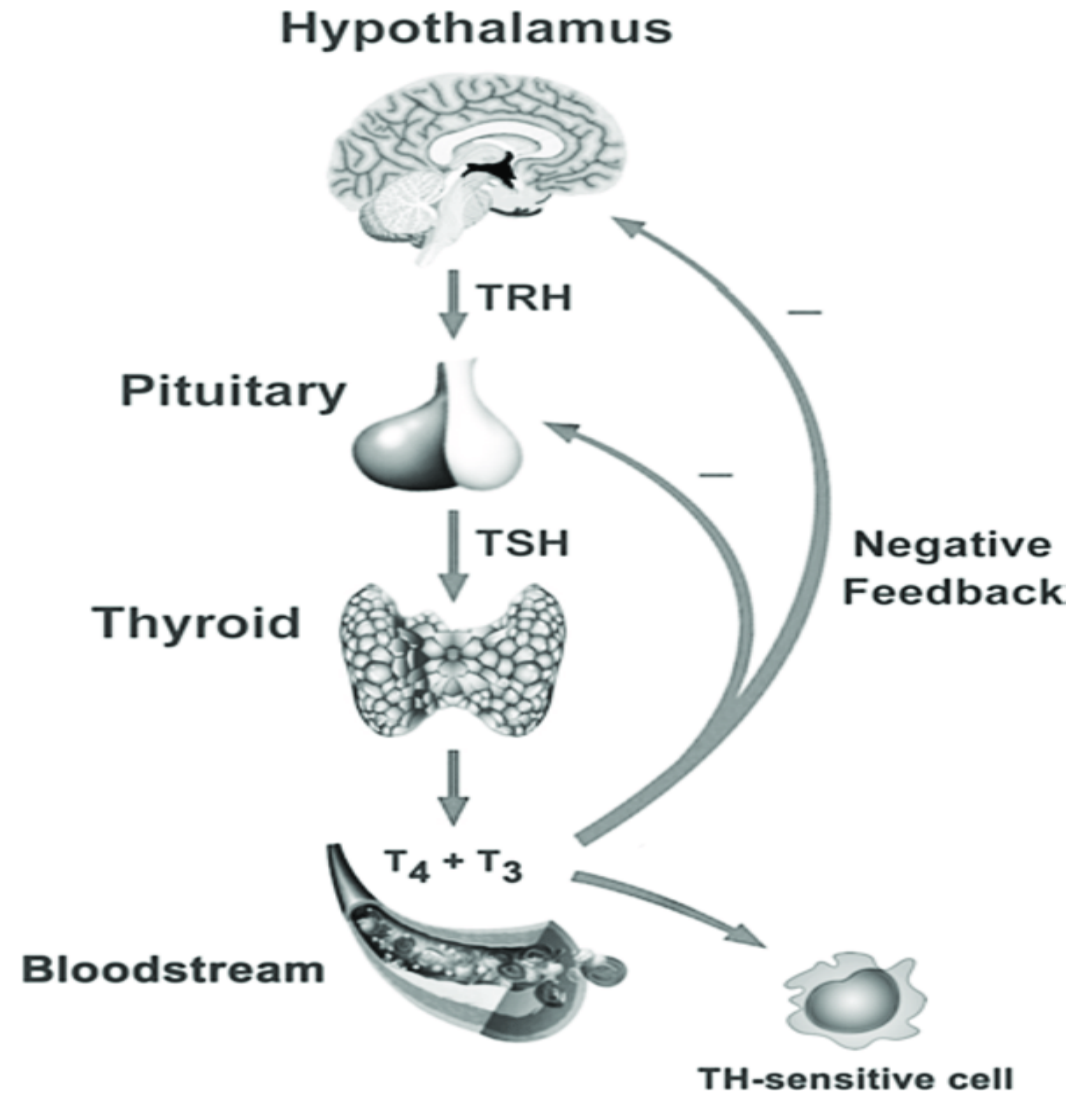
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# Hypothalamic-Pituitary Thyroid Axis



# Screening Guidelines for Thyroid Disease: Who Should be Tested?



- USPSTF: No data for routine screening in primary care; identify at risk pts with hx, PE, use TSH
- ATA: Screen  $>35$  and every five years, more often if risk factors
- ACP: Screen women  $>50$  with one or more symptoms
- AAACE: TSH in childbearing women
- ACOG: Consider signs/symptoms of postpartum thyroid disease
- AAFP: No routine screening if asymptomatic and  $<60$

# Tests Used to Detect Thyroid Dysfunction



<b>TSH</b>	Cost effective, accurate, and considered the best screening tool
<b>FT<sub>4</sub></b>	Used in conjunction with TSH to differentiate between subclinical and overt disease
<b>TT<sub>3</sub></b>	Used to assess degree of hyperthyroidism Not useful for diagnosing hypothyroidism

# Defining Ranges for Serum TSH

## Individual's range

- Much narrower than reference range

## Lab reference range

- Defined by values in “normal” population

## Target range

- Goals for thyroxine treatment of specific conditions
- Hypothyroidism: normalization of TSH within age-specific reference range
- Thyroid cancer: undetectable to 0.5-2 mIU/L, depending on disease status and clinical risk

# Measurement of Thyroid Hormones

- T4: thyroxine and T3: triiodothyronine
- 99.99% T4 and 99.5% T3 circulate bound to proteins
  - 70-80% bound to thyroxine binding globulin (TBG)
  - 15-20% bound to albumin
  - 8-10% bound to transthyretin
- Bound T4 and T3 are inactive and should not be used as the sole measures of thyroid function
- Illnesses and medications greatly alter T4/T3 bound to protein

# Measurement of Thyroid Hormones

- Total T4 / T3: measure bound hormone
- Measured Free T4/T3:
  - Not always accurate due to alterations in protein binding; equilibrium dialysis most accurate method of measuring free hormone
- Free thyroxine index (FTI): Calculated estimate of free thyroid hormone
  - Corrects for alterations in protein binding
  - $FTI = T4 \times T3\text{-Uptake}$



# T3 Uptake / T3 Resin Uptake

- T3 Uptake: Indirect measure of serum thyroid hormone binding capacity, accounts for binding protein alterations
- Performed by incubating patient's serum with radiolabeled T3 tracer and subsequently adding resin that traps remaining unbound radiolabeled T3:
  - Value reported is the percent tracer bound to the resin, which varies inversely with the number of available free binding sites;
  - Number of free binding sites is determined both by levels of binding protein and endogenous hormone production
- T3 Uptake Alterations occur in Hypo- and Hyperthyroidism, pregnancy, nephrotic syndrome, TBG excess or deficiency

# Thyroid Antibodies

- Thyroid Peroxidase (TPO) and Tg Ab:
  - Hashimoto's Disease: predictor of hypothyroidism progression from subclinical to overt
- Thyroid Stimulating Immunoglobulin (TSI) and Thyroid Binding Inhibitor Immunoglobulin (TBII) comprise TSH receptor Abs (TRAb)
  - Graves' Disease

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# Thyroglobulin and Calcitonin

- Thyroglobulin (Tg): protein made by thyroid cells; used as a tumor marker in differentiated thyroid cancer; measurements affected by the presence of Tg antibodies (Abs)
- Calcitonin: hormone produced by the thyroid parafollicular (C-cells); used as a marker in medullary thyroid cancer

# Patterns of Abnormal TFTs

- Elevated TSH 4.5-10 with normal T4 / FTI / Free T4 =  
Subclinical hypothyroidism
- Elevated TSH 10+ with either normal or low T4 / FTI / Free T4 =  
Hypothyroidism
- Low TSH with normal T4 / FTI / Free T4 =  
Subclinical hyperthyroidism

# Patterns of Abnormal TFTs

- Low TSH with elevated T4 / FTI / Free T4 or T3 =
  - Hyperthyroidism
- High TSH with elevated T4 / FTI / Free T4 or T3 =
  - TSH-producing pituitary adenoma
  - Thyroid hormone resistance syndrome
  - Interfering antibodies

# Patterns of Abnormal TFTs

- Low TSH with low T4 / FTI / Free T4 or T3
  - Central hypothyroidism
  - Interfering antibodies
- Normal TSH with elevated T4 / FTI / Free T4 or T3
  - Biotin interference
  - TBG excess
  - Familial Dysalbuminemia

# Suboptimal Thyroxine Therapy

## What Causes It?



### TFTs: Mild Hypothyroidism

- Low Rx dose
- Poor compliance
- Drug interaction
- Dietary interference with absorption
- Malabsorption syndromes
- Pregnancy
- Decreased residual gland function
- Formulation switch

### TFTs: Mild Hyperthyroidism

- High Rx dose
- Factitious ingestion
- Aging with decreased requirement for  $LT_4$
- Nonsuppressed endogenous gland function
- Stopping estrogen therapy
- Formulation switch



# Drug Effects on the Thyroid

## Broad Categories:

- Interference with Thyroid Function
- Interference with Thyroid Hormone Therapy
- Interference with Thyroid Laboratory Testing in Euthyroid Persons

# Drug Effects on the Thyroid Gland

- Via hypothalamic-pituitary effects: Bexarotene, mitotane, Immune checkpoint inhibitors (CTLA-4 inhibitors > PD-1 inhibitors), glucocorticoids, dopamine agonists, somatostatin analogues, metformin
- Via effects on hormone synthesis or release: Iodinated contrast, amiodarone, kelp, lithium
- Via thyroid autoimmunity: Immune checkpoint inhibitors (PD-1 inhibitors > CTLA-4 inhibitors), interleukin-2, interferon alfa or beta-1a, alemtuzumab
- Via direct thyroid damage: Amiodarone, tyrosine kinase or multikinase inhibitors

# Drug Effects on the Thyroid and on Thyroid Hormone Therapy

Via protein binding of thyroid hormone:

➤ **Increased TBG- oral estrogen**

- SERMs
- Methadone
- Heroin
- Mitotane
- Fluorouracil

➤ **Decreased TBG**

- Androgens
- Glucocorticoid
- Niacin

➤ **Displacement from binding proteins:**

- Phenytoin
- Carbamazepine
- Salsalate
- High dose furosemide
- Heparin

# Drug Effects on the Thyroid and on Thyroid Hormone Therapy

Via thyroid hormone activation, metabolism or excretion:

- Amiodarone
- Glucocorticoids
- High dose propranolol
- Ipodate
- Phenobarbital
- Carbamazepine
- Rifampin
- Tyrosine kinase inhibitors
- Cholestyramine
- Colestipol
- Colesevelam

# Drug Effects on the Thyroid and on Thyroid Hormone Therapy

Via absorption of thyroid hormone:

- Proton pump inhibitors
- $\text{FeSO}_4$
- Calcium carbonate
- Aluminum hydroxide
- Sucralfate
- Bile acid sequestrants
- Raloxifene
- Foods:
  - Soy formula
  - Milk
  - Coffee

# Drugs Affecting Thyroid Laboratory Tests in Euthyroid Persons

- Biotin
- Amiodarone
- Heparin
- Salsalate
- Phenytoin
- Carbamazepine

# Interference with Thyroid Function Immunoassays



- May result in delay in diagnosis, unnecessary testing or treatment, or inappropriate discontinuation of therapy
- Immunoassays are the method of choice for measuring thyroid function tests: rapid, automated, sensitive/specific

# Interference with Thyroid Function Immunoassays

- When to suspect interference:
  - Divergence with previous results
  - Discrepancy with clinical or other biochemical parameters
  - Patient risk factors: autoimmune disease, contact with pets/animals, monoclonal Ab therapy, recent immunization or transfusion
- Interferences may be unique to an individual or change over time



# Major Types of Assay Interference

- Macro-TSH: large, bio-inactive molecule leading to isolated, falsely high TSH
- Biotin interference: hair/skin/nail supplements or high dose therapy in multiple sclerosis and inherited disorders of metabolism. Impact depends on the assay/platform used and can affect TSH, T4, T3 and anti-TSH receptor Abs

# Major Types of Assay Interference

- Anti-streptavidin and Anti-Ru antibody interference: less common, can affect TSH, fT4, fT3
- TH autoAb interference: rare antibody production to T4, T3, more common in patients with thyroid autoimmunity
- Heterophile and Human anti-animal Ab interference: Abs directed against animal epitopes- goats, rabbits, sheep, horses, mice; includes Rheumatoid factor

# Biotin and TFTs

- Biotin can cause spurious results in TFT assays when ingested in higher doses
- May cause falsely low values in immunometric TSH assays
- May cause falsely high values in competitive binding assays like those used to measure Total T3, Total T4, and TSH receptor binding inhibitor immunoglobulin
- Patients should be asked if they are taking biotin prior to testing

# How to Detect Thyroid Immunoassay Interference



- Comparison with another lab platform
- Use another method: PEG precipitation or Chromatography for macro-TSH, Anti-Ru or thyroid hormone Abs; equilibrium dialysis for free T4 in suspected binding protein defects
- Serial dilution and Blocking agents for suspected Ab interference
- Hold biotin for 2-7 days for suspected biotin interference prior to repeat testing

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