Faculty

Leslie S. Eldeiry, MD, FACE, ECNU
Department of Endocrinology
Harvard Vanguard Medical Associates/Atrius Health
Assistant Professor, Part-Time, Medicine, Harvard Medical School
Boston, MA
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
- AACE: 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

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>TSH</strong></td>
<td>Cost effective, accurate, and considered the best screening tool</td>
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<tr>
<td><strong>FT₄</strong></td>
<td>Used in conjunction with TSH to differentiate between subclinical and overt disease</td>
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<tr>
<td><strong>TT₃</strong></td>
<td>Used to assess degree of hyperthyroidism</td>
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<tr>
<td></td>
<td>Not useful for diagnosing hypothyroidism</td>
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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 x T3-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 LT4
• 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
- FeSO4
- 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
References


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