Hyperthyroidism and Hypothyroidism: The Ups and Downs

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated: Organic iodide radiographic contrast agents used block peripheral conversion of T4 to T3 and inhibit release.

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Dr. Mayeaux lives and practices in Columbia, South Carolina. He has received the American Society for Colposcopy and Cervical Pathology (ASCCP) Award of Merit four times and has also received numerous faculty teaching awards. He focuses on women's health and skin diseases, noting that the most important trends in the field are the rise and fall of methicillin resistant Staphylococcus aureus (MRSA); changes in Pap test recommendations and follow up; and changes in human papillomavirus (HPV) testing recommendations. Dr. Mayeaux considers keeping up with the rapidly changing knowledge base in medicine and physician burnout to be family medicine's most critical challenges. Other professional interests include health care quality, preventive medicine, and returning joy to medical practice.
Learning Objectives

1. Develop a screening protocol to identify patients with risk factors for developing hypo/hyper-thyroidism, particularly pregnant patients or those planning to become pregnant.

2. Order appropriate laboratory and radiologic tests to diagnose hypo/hyper-thyroidism based on symptomatology.

3. Prescribe appropriate therapy for patients with hypo/hyper-thyroidism symptomatology and monitor patients accordingly.

4. Identify the clinical signs, symptoms and required laboratory tests for diagnosing acute viral thyroiditis.

5. Recognize indications for referral and possible admission and coordinate care and follow-up as necessary.

AES Question
Poll Question 1

Which of the following is NOT a common symptom of hyperthyroidism?

A. Emotional lability
B. Weakness
C. Palpitations
D. Diarrhea

Hyperthyroidism Symptoms

• Anxiety, emotional lability
• Weakness, tremor, "apathetic thyrotoxicosis"
• Palpitations
• Heat intolerance, increased perspiration
• Weight loss despite normal or ↑ appetite
  • Hyperdefecation (not diarrhea), urinary frequency, oligomenorrhea or amenorrhea, gynecomastia and erectile dysfunction

Hyperthyroidism Signs

- Hyperactivity and rapid speech
- Sympathetic hyperactivity
- Warm, moist skin and/or thin fine hair
- Tachycardia and/or systolic hypertension
- Tremor
- Proximal muscle weakness
- Hyperreflexia


Thyroid Regulation

Image courtesy of E.J. Mayeaux, Jr., MD
Serum T4 and T3

• Both are highly bound to proteins
• Total measures free + bound
  • Normal range is variable between labs
• Serum free T4 and free T3
  • Free hormone is available for uptake into cells and interaction with nuclear receptors
  • Bound hormone is storage pool
  • T4 10x more bound


Subclinical Hyperthyroidism

• Normal serum free T4 & T3 with a suppressed TSH level
• Symptoms mild and nonspecific
• Often toxic nodular goiter or mild Graves ds
• Associated with a 2-fold increase in the risk of atrial fibrillation in older persons and decreased bone mineral density in postmenopausal women

Drugs Causing Hyperthyroidism

- Stimulation of thyroid hormone - iodine, amiodarone
- Immune dysregulation - interferon-alfa, interleukin-2, denileukin diftitox, ipilimumab, alemtuzumab
- ↓ TBG - androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), l-asparaginase
- ↑ TBG - estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane
- ↓ T4 binding to TBG - salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
- Increased T4 clearance - phenytoin, carbamazepine, rifampin, phenobarbital
- ↓ TSH secretion - dobutamine, glucocorticoids, octreotide
- Impaired conversion of T4 to T3 - amiodarone, glucocorticoids, contrast agents for oral cholecystography, PTU, propranolol, nadolol

Hyperthyroidism Diagnosis

- T3-toxicosis - Graves’ ds or nodular goiter
  - ↓ TSH, ↑ serum T3 > ↑ serum T4
    - ↑ thyroidal T3 secretion and ↑ extrathyroidal conversion T4
  - In early disease, patient may have normal serum T3 and free T4 levels
Graves’ Disease Signs

- Exophthalmos
- Periorbital & conjunctival edema
- Limitation of eye movements
- Infiltrative dermopathy (pretibial myxedema)


Graves’ Disease Dx

- Clinical signs
- Measurement of thyrotropin receptor antibodies
  - Sensitivity/specificity = 97/99% for Graves
- Radioactive iodine uptake
- Quantitative thyroid blood flow by ultrasonography (skill dependent)

Thyroid Scan

- Graves’ disease produces a more uniform increased uptake

Hyperthyroidism Diagnosis

- T4-toxicosis - ↓ TSH,
  ↑ free T4, & normal T3
  - Hyperthyroidism in pts with concurrent nonthyroidal illness that ↓ extrathyroidal conversion of T4 to T3
  - Despite the nonthyroidal illness, patients remain hyperthyroid and with ↓ serum TSH

Courtesy of the CDC
Hyperthyroidism Diagnosis

Signs or symptoms
Serum TSH & fT4

↓ TSH ↑ fT4
Primary hyperthyroidism

↑ TSH ↑ fT4
Secondary hyperthyroidism
Image pituitary gland

↓ TSH NI fT4

Serum fT3

High T3

T3 toxicosis
Graves or nodular goiter

NI T3
Subclinical hyperthyroid
Resolving hyperthyroid
Medication
Pregnancy
Nonthyroid illness

Thyroid uptake

Low

Exogenous hormone

Thyroiditis, iodine exposure, extraglandular production

High

Thyroglobulin

High diffuse
Graves’ ds

High nodular

Toxic adenoma or multinodular goiter

AES Question
Poll Question 2

True statements about the treatment of hyperthyroidism include which of the following?

A. Beta blockers treat palpitations and tachycardia but not other symptoms
B. Iodides are contraindicated because of increased hormone synthesis
C. Methimazole is preferred in all non-allergic patients due to lower cost, longer half-life, and lower incidence of hematologic side effects
D. PTU is preferred in pregnancy

Hyperthyroidism Treatment

- **Beta blockers** *(propranolol) 10 - 20 mg Q 6 hours*
  - Prompt relief of adrenergic S/S (tremor, palpitations, and nervousness)
- **CCBs** *(diltiazem)* used to reduce heart rate
- **Iodides** block peripheral conversion of T4 to T3 and inhibit release
  - Adjunctive therapy before emergency nonthyroid surgery if beta blockers are ineffective and to reduce gland vascularity before Graves’ surgery
  - Iodides are not used routinely because of paradoxical increases in hormone release with prolonged use
  - Organic iodide *radiographic contrast* agents (1 g per day for up to 12 weeks) used more commonly

Antithyroid Drugs

• Interfere with iodine organification
  • **Methimazole** (15-30 mg/day) drug of choice in **nonpregnant patients** - lower cost, longer half-life, and lower incidence of hematologic side effects but associated with rare congenital abnormalities
  • **PTU** (100 mg TiD maintenance of 100-200 mg daily) is preferred during the **first trimester of pregnancy**
• **Remission rates** of up to 60% when therapy continued for 2 years
• **Relapse** can occur in up to 50% of patients
  • Relapse more likely in patients who smoke, have large goiters, or had elevated thyroid-stimulating antibody levels at end of therapy


Radioactive Iodine

• **US tx of choice** for Graves’ disease and toxic nodular goiter
• **Contraindicated in pregnant patients!!**
• It is inexpensive, highly effective, easy to administer, and safe
• **Theoretical risk** of cancer of the thyroid, leukemia, or genetic damage in future offspring of pregnant women but long-term follow-up of patients has **not validated** these concerns
• **Higher-dose ablative therapy** increases the chance of successful treatment
  • Allows resulting early hypothyroidism to be diagnosed and treated while the patient is undergoing close monitoring
Hyperthyroidism in Pregnancy

- Overt hyperthyroidism relatively uncommon during pregnancy
  - Occurs in 0.1 to 0.4 percent of all pregnancies [1,2]
- During pregnancy: ↑TBG, ↑ total T4 / T3 but normal free T4 / T3
- Clinical manifestations - same
  - Many are same as nonspecific symptoms associated with pregnancy

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Hyperthyroidism in Pregnancy

Overt hyperthyroidism associated with: ¹
- Spontaneous abortion
- Premature labor
- Low birth weight
- Stillbirth
- Preeclampsia
- Heart failure

Subclinical hyperthyroidism – no adverse pregnancy outcomes ²

Common Causes, Diagnosis, and Initial Management of Hypothyroidism

AES Question
Poll Question 3

What is the most common cause of hypothyroidism in the US?

A. Congenital abnormalities  
B. Autoimmune disease  
C. Iodine deficiency  
D. Infiltrative diseases  
E. Neck irradiation

Hypothyroidism

• Failure of gland to produce sufficient hormone to meet body metabolic demands
• ~1/300 persons in U.S. ¹  
  • Prevalence increases with age  
  • Higher in females than in males ²  
  • ~13 million Americans have undiagnosed disease ³

Untreated Hypothyroidism

• Can contribute to
  • Hypertension
  • Dyslipidemia
  • Infertility
  • Cognitive impairment
  • Neuromuscular dysfunction


Drugs Causing Hypothyroidism

• ↓ thyroid hormone synthesis and/or release - thionamides, lithium, perchlorate, aminogluthethimide, thalidomide, and iodine and iodine-containing drugs including amiodarone, radiographic agents, expectorants, kelp tablets, potassium iodine solutions (SSKI), povidone-iodine (Betadine) douches, topical antiseptics
• ↓ absorption of T4 - cholestyramine, colestipol, colesvelam, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole, and possibly other medications that impair acid secretion, sevelamer, lanthanum carbonate, and chromium; malabsorption syndromes
• Immune dysregulation - interferon-alfa, interleukin-2
• Suppression of TSH - dopamine
• ↑ type 3 deiodination - sorafenib
• ↑ T4 clearance and suppression of TSH - bexarotene
Hypothyroidism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Lab</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Bradycardia</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Difficulty concentrating</td>
<td>Increased CRP, CK</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Weakness</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Constipation</td>
<td>Weight gain</td>
<td>Normocytic anemia</td>
</tr>
<tr>
<td>Depression</td>
<td>Myalgias</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Thin L. Eyebrow</td>
<td>Increased LDL, TG,</td>
</tr>
<tr>
<td>Hair thinning/hair loss</td>
<td>Memory impairment</td>
<td>Low-voltage electrocardiography</td>
</tr>
</tbody>
</table>

Subclinical Hypothyroidism

- Biochemical diagnosis
- Normal-range free T4 and elevated TSH
  - May or may not have symptoms
  - On repeat testing, TSH may spontaneously normalize
- Incidence ranges from 3 to 15%
  - Increasing with age, female sex, and low iodine status
- Associated with progression to overt hypothyroidism \(^1\)
  - Especially with ↑ thyroid peroxidase abs

Hypothyroidism – Screening

• AAFP supports USPSTF - insufficient evidence 1
  • No asymptomatic adult screening
  • All newborns screened
• Consider screening with risk factors
  • Hx of autoimmune disease
  • Hx head/neck irradiation, radioactive iodine
  • Goiter
  • Family hx thyroid disease
  • Drugs known to influence thyroid function


Hypothyroidism Diagnosis

Signs or symptoms

Serum TSH

TSH > 5.5 mIU/L

Serum free T4

Low Free T4

Primary hypothyroidism

TSH in normal range

Patient is euthyroid

NI Free T4

Subclinical hypothyroidism

Confirm TSH/T4 in 2-3 months

TSH < 0.35 mIU/L

Consider hyperthyroid state

High Free T4

Central hyperthyroidism
Hypothyroidism Treatment

• Most patients require lifelong therapy
• Once-daily synthetic thyroxine T4
• Normal thyroid makes T4 and T3
  • T4 produced in greater amounts
  • T3 biologically active
    • ~80% T3 derived from peripheral T4 conversion
  • T3 preps have short half-life
• Do not switch generics or switch to/from Brand


Hypothyroidism Treatment

• Start levothyroxine
  • Healthy adults is 1.6 mcg/kg/day
    • Morning or evening 30 minutes before eating
    • No calcium or iron supplements within 4 hours
    • Poor adherence most common cause of ↑ TSH
  • Older or cardiac disease – 25-50 mcg/day then ↑ 25 mcg Q3-4 wks
• Subclinical hypothyroidism
  • TSH < 10 mIU/L or Age > 70 years: based on patient
    • 50 mcg/day, ↑ by 25 mcg Q6 wks
    • TSH ≥ 10 mIU/L: adult dosage

Reverse T3?

• rT3 is the stereoisomer T3
• Most rT3 is formed by peripheral deiodination of T4 (thyroxine)
• In hospitalized or sick patients with low T3, elevated rT3 is consistent with "sick euthyroid" syndrome
  • Finding an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism
• The rT3 is high with propylthiouracil, ipodate, propranolol, amiodarone, dexamethasone, and halothane
• Some theorize rT3 competes with T3 binding – minimal evidence

Hypothyroidism in Pregnancy

• Women need more thyroid hormone in pregnancy
  • ~75 – 85% of women with preexisting hypothyroidism need a higher dose of T4
  • Increase ~5th week of gestation
• All newborns should be screened
• Consider referrals if positive

Thyroiditis

Hashimoto Thyroiditis

- Nontender goiter, hypothyroidism, and an elevated thyroid peroxidase antibody level
- Rarely thyrotoxicosis secondary to alternating stimulating & inhibiting thyroid autoantibodies
- Measure serum TSH and TPO antibody levels
- Elevated TSH and low free T4 levels
  - Levothyroxine starting with 1.6 mcg/kg/day
  - Incremental changes made every 10 to 12 weeks

Suppurative Thyroiditis

- Thyroid pain, high fever, leukocytosis, and cervical lymphadenopathy; focal inflammation
- Compressive symptoms such as dysphonia or dysphagia; patients may assume a posture to limit neck extension
- Palpation may reveal focal or diffuse swelling of the thyroid
- Overlying skin warm and erythematous
- Multiple infectious organisms, most commonly bacterial Streptococcus pyogenes; Staphylococcus aureus and Pneumococcus are among the most common isolates


Subacute Thyroiditis

- Thyroid pain, hyperthyroidism or hypothyroidism
- Postviral
- Thyroid function tests; elevated TPO antibody levels; low radioactive iodine uptake in the hyperthyroid phase
- Euthyroidism generally by 18 months - rarely recurs
  - Up to 15% of patients become permanently hypothyroid
- Beta blockers for significant hyperthyroid symptoms
- Levothyroxine for symptomatic hypothyroidism
- NSAIDS for pain

Riedel (Fibrous) Thyroiditis

- Very firm goiter
- Compressive symptoms (dyspnea, stridor, dysphagia), which appear disproportionate to the size of the thyroid
- Hypocalcemia may occur - fibrosis of the parathyroid glands
- Viral +/- Autoimmunity


Thyroiditis Treatment

- Initial hyperthyroid phase - Beta blockers for symptoms
- Subsequent hypothyroid phase, levothyroxine should be considered in women with a serum thyroid-stimulating hormone level greater than 10 mIU per L, or in women with a thyroid-stimulating hormone level of 4 to 10 mIU per L who are symptomatic or desire fertility.
- Treatment with high-dose NSAIDs is directed toward relief of thyroid pain

Thyroid Nodules

AES Question
Poll Question 4

True statements about thyroid nodules include which of the following?

A. About ½ are malignant
B. FNA gives best nonsurgical diagnosis
C. They are rarely associated with multinodular goiter
D. Cancers are more common in the 40- to 50-year-old group

Thyroid Nodules

• 4-7% population
• Most are benign
  • 1.5-17% malignant
• ~23% are actually dominant nodules in a multinodular goiter
• ~1,300 US deaths

Courtesy of E.J. Mayeaux, Jr., MD

Types of Thyroid Nodules

- Adenoma
- Macrofollicular adenoma (simple colloid)
- Microfollicular adenoma (fetal)
- Embryonal adenoma (trabecular)
- Hürthle cell adenoma
- Atypical adenoma
- Adenoma with papillae
- Signet-ring adenoma

- Carcinoma
- Cyst
- Colloid nodule
- Inflammatory thyroid disorders
  - Subacute thyroiditis
  - Chronic lymphocytic thyroiditis
  - Granulomatous disease
- Developmental abnormalities
  - Dermoid
  - Rare unilateral lobe agenesis

Higher Prevalence of Cancer

- Children
- Adults < 30 years or > 60 years old
- Patients with a history of head and neck irradiation
- Patients with a family history of thyroid cancer
Thyroid Nodule Diagnosis

- Solitary thyroid nodule
  - Serum TSH
  - Euthyroid
    - FNA
    - Cold nodule
      - Insufficient
        - Solid
          - Recur/Persist
        - Cystic
          - Observe
      - Benign
        - Repeat in six months
    - Hyperthyroid
      - Scan
      - Total or partial thyroidectomy

Diagnostic Thyroid/Neck US

- Thyroid sonography with survey of cervical lymph nodes should be performed in all patients with known or suspected nodules (Strong recommendation, High-quality evidence)

- Report should convey
  - Nodule size (in 3 dimensions) & location (e.g., right upper lobe)
  - Description of features (solid, cystic proportion, or spongiform)
  - Echogenicity, margins, presence and type of calcifications, vascularity
  - Sonographic pattern defines malignancy risk and with nodule size, guides FNA decision-making

Haugen BR, et al. Thyroid 2016 26: 1-133
Best Practice Recommendations

• Methimazole is the drug of choice in nonpregnant patients
• PTU is preferred during the first trimester of pregnancy
• Most hypothyroidism treated with once-daily synthetic thyroxine
• Most thyroid nodules are benign and FNA is often best way to make diagnosis
Answers

1. D
2. D
3. B
4. B

Questions