Managing Thyroid Disease in Primary Care

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Best Practices Pearls

- Have a low threshold to test for thyroid disease
- Treatment of both subclinical and overt disease should be individualized and monitored
- Manage issues around variable therapeutic equivalence of levothyroxine products
- Appropriately counsel, screen, and monitor thyroid function in pregnancy to improve outcomes

Susan Slow: 1st Visit for WWE

- Susan Slow
  - 54 year old female presents for annual well woman exam (WWE)
  - Your medical assistant advises you to be prepared for multiple concerns

Definitions and Diagnosis

Thyroid system

- Positive feedback
- Negative feedback
- Thyroid hormones (T3 and T4)
- Thyroid-stimulating hormone (TSH)
- Thyrotropin-releasing hormone (TRH)
- Anterior pituitary gland

Physiology

- Increased metabolic rate
- Growth and development
- Increased bone mineralization effect
Definitions and Diagnosis

Underactive

- Hypothyroidism
  - Primary: high serum thyrotropin (TSH) and a low serum free thyroxine (FT4)
  - Secondary and Tertiary (central): low FT4 and TSH not elevated
- Subclinical Hypothyroidism
  - Only an elevated TSH with a normal FT4 level
- Both overt and subclinical disease can be symptomatic


Overactive

- Hyperthyroidism
  - Usually excess production of free thyroid hormones (either T3 or T4 or both) in serum with suppressed HS-TSH or highly sensitive (3rd generation) TSH (<0.01mU/L)
- Thyrotoxicosis includes hyperthyroidism but also excess release of hormone in thyroiditis or excess exogenous T4
- Subclinical Hyperthyroidism (SH)
  - Low or undetectable (HS-TSH) but normal range for both triiodothyronine (T3) and free thyroxine (FT4)
- Both overt and subclinical disease may lead to characteristic signs and symptoms


Prevalence

NHANES III: 13,344 people (54% female) without known thyroid disease had TSH, T4, thyroglobulin antibodies, and thyroid peroxidase antibodies measured

- Hypothyroidism in 4.6% (0.3% overt and 4.3% subclinical)
- Hyperthyroidism was found in 1.3% (0.5% overt and 0.7% subclinical)
- Serum thyroid peroxidase antibody concentrations elevated in 11%


Higher Prevalence in 70-79 Years Old

<table>
<thead>
<tr>
<th>Hyperthyroidism and Hypothyroidism Study Results</th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black women</td>
<td>9.7%</td>
<td>6.2%</td>
</tr>
<tr>
<td>White women</td>
<td>6.0%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Black men</td>
<td>2.2%</td>
<td>1.7%</td>
</tr>
<tr>
<td>White men</td>
<td>2.2%</td>
<td>5.6%</td>
</tr>
</tbody>
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- 3 to 8 times more common in women than men
- Mean TSH is lower in blacks than whites or Hispanics
- Mean TSH rises as we age


Etiology
Etiology of Hypothyroidism

- Hashimoto’s Thyroiditis (Chronic Lymphocytic Thyroiditis)
  - Most common in the USA
  - Historic Note: 1st discovered Auto-Immune Disorder
  - Diagnosed with antithyroid peroxidase (antiTPO) antibodies or antimicrosomal antibodies (AMA)
- Post Treatment Graves’ Disease
  - No function after radiation or surgery
- Iodine Deficiency
  - Most common worldwide associated with a goiter
  - Rare in North America but re-emergence with “natural” salt
- Hypothalamic-pituitary Disease (secondary or central)

Etiology of Hyperthyroidism

- Graves’ Disease
  - Most common
  - Auto-immune: long-acting thyroid stimulating antibodies (LATS)
- Thyroid Nodules
  - “Toxic” nodules (become autonomous)
  - Benign or malignant, single or multiple
  - Toxic nodular goiter- most common cause in the elderly

Etiology of Hyperthyroidism

- Excessive Thyroid Supplementation
  - Iatrogenic
  - Exogenous
- Thyroiditis (excessive release, not production)
  - Early Hashimoto’s, radiation, palpation, post partum
- Rare Causes: pituitary adenoma, teratomas

Etiology of Subclinical Hyperthyroidism Exogenous

- 10,000,000 Americans and 200,000,000 worldwide take thyroid hormone
  - All are at risk for subclinical hyperthyroidism, whether intentional or unintentional
  - In patients on LT4 (levothyroxine), up to 25% may have low TSH
    - Associated with lower bone density
    - Associated with atrial fibrillation
  - BUT subclinical hyperthyroidism is the goal of thyroid hormone therapy in thyroid cancer, in some thyroid nodules, multinodular or diffuse goiters, or a history of head and neck irradiation

Euthyroidism Symptoms

- Hypothyroidism and Subclinical Hypothyroidism Signs & Symptoms
  - Fatigue
  - Weight gain from fluid retention (but usually not morbid obesity)
  - Dry skin and satiety/intolerance
  - Yellow skin
  - Coarseness or loss of hair
  - Hoarseness
  - Gastrointestinal
    - Anemia
  - Reflex delay, relaxation phase
  - Ataxia

- Hypothyroidism
  - Memory and mental impairment
  - Decreased concentration
  - Depression
  - Irregular or heavy mensturation and infertility
  - Myxedema
    - Fluid infiltration of tissues
  - Constipation

Hyperthyroid Symptoms

Overt Hyperthyroidism and Subclinical Hyperthyroidism Signs & Symptoms

- Nervousness and irritability
- Tachycardia
- Heat intolerance or increased sweating
- Tremor
- Weight loss
- Altered appetite
- Frequent bowel movements or diarrhea
- Dependent lower extremity edema
- Sudden paralysis

Hyperthyroidism Work-Up

Pre and Post Treatment

History
- Radiation and Surgery
- Infections
  - TB, Pneumocystis carinii
- Infiltrative Disease
  - Riedel’s, leukemia, scleroderma, hemochromatosis
- Medi...
  - Lithium
  - Prednisone
  - Methimazine
  - Androgens and Anabolic Steroids
  - Heparin
  - Tyrosine Kinase Inhibitors
  - Interferon, Interleukin
  - Amiodarone (3 mg iodine per 100 mg)

Physical
- +/- Goiter
- Slowed movement and speech
- Hoarse voice
- Bradycardia
- Carotenemia
- Hung deep tendon reflex
- Coarse skin
- Puffy eyes and faces
- Enlarged tongue
- Galactorrhea
- Diastolic Hypertension
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Hypothyroidism Work-Up

- **Lab**
  - TSH, FT4
  - No need to check thyroid antibodies
  - CBC, CMP, lipids

- **Imaging**
  - No need for thyroid imaging unless abnormal palpations or pain
  - No need of pituitary MRI unless signs of central hypothyroidism (<1%)

Susan: Follow-up Visit 1 Week Later

- Susan returns after WWE and lab work is back
  - VS: Hgt: 5’4” Wgt: 157 lbs BMI: 26.95 (overweight)
  - T 97.6, BP 130/92, P 60
  - Normal exam except bilateral Tinel’s at wrists (no goiter, eye changes, edema or hung reflexes)
  - ECG, cardiac stress test, mammography, colonoscopy, all WNL

- **LAB**
  - CBC, CMP, UA all WNL
  - Lipids: LDL cholesterol: 135, otherwise OK
  - TSH: 8.8 (N = 0.5-5), FT4: 0.9 (N = 0.7 to 2)

Hyperthyroidism Work-Up

- **History**
  - Thyroiditis including trauma
  - Meds
    - Amiodarone
  - Iodine

- **Physical**
  - Hyperactivity and rapid speech
  - Stare (lid retraction) and lid lag
  - Sweaty
  - Fine hair
  - Tachycardia and Atrial Fibrillation
  - Hypertension
  - Hyperreflexia
  - Muscle weakness
  - Tremor

- **Thyroid**
  - Size, nodularity, tenderness

Hyperthyroidism Work-Up

- **Lab**
  - 3rd generation TSH (< 0.05 mU/L)
  - T4 (RIA), FT4, T3(RIA), FT3
  - CBC, CMP including alkaline phosphatase

- **Imaging**
  - Radioiodine uptake and scan
    - If high, increased production such as Graves’ or nodule(s)
    - If low, thyroiditis or source is outside of thyroid (struma ovarii or exogenous)

Radioiodine Scan

Treatment

Susan: Follow-up Visit 10 Months Later

- Little change in symptoms or TSH at 6 weeks
- LT4 increased to 0.125 to get TSH down <5.0
- Feeling better with TSH of 3.2 at 6 month recheck
- Lab and prescription unchanged
- Returns early for her annual check complaining of recently feeling less energetic
Managing Thyroid Disease in Primary Care

Controversy
Hypothyroidism and Subclinical Hypothyroidism

- Decision to treat subclinical disease is controversial and should be individualized
- Recommended if TSH >10 or patient is symptomatic
- Individual decision when no symptoms of TSH only slightly elevated
- Levothyroxine (LT4) is the recommended replacement
- Average replacement dose is 112 mcg/daily or 1.6 mcg/Kg/day

Special Cases and Considerations
Hypothyroidism and Subclinical Hypothyroidism

- In some older patients and those with CAD start at 25 or 50 mcg as T4 increases myocardial O2 demands and risk of angina and arrhythmia
- Take on empty stomach (ideally 1 hour before breakfast)
- Coffee, antacids, and calcium interfere with absorption

Hypothyroidism and Subclinical Hypothyroidism

- Patients may feel better as soon as two weeks, but it can take months
- Changes are often incremental, not dramatic
- Takes 6 weeks to see blood levels change
- FT4 rises first, TSH is slower to fall
- Recheck FT4 and TSH at 6 weeks
- If still sub-therapeutic, increase by 12.5 or 25 mcg, and recheck in 6 weeks
- Once stable, check every 6 months for first year, then annually

Controversy
Bioavailability, Bioequivalence, Therapeutic Equivalence

- The American Association of Clinical Endocrinologists (AACE)
  - Advocates the use of a single consistent branded LT4
  - Need to measure Area Under Curve (AUC) and maximum concentration (Cmax) in thyroid patients to equate
  - Need to measure TSH to equate
  - Bioavailability ≠ bioequivalence ≠ therapeutic equivalence
  - Up to 25% variation found between products, but change from 125 mcg and 137 mcg is only 9%
  - At minimum need to measure thyroid function at 6 weeks if brand changed (same as if dose changed)

US Food and Drug Administration (FDA)
- Does not see any risk with brand switching
- Uses AUC and Cmax determinations in normal subjects with normal thyroid function for bioavailability
- Bases approval of all generics and the 5 branded LT4 on only total level of T4 but not TSH
- Accepts formulations that deviate from each other by < 25% but > 12.5% as equivalent


Controversy
T3 and “Natural” Therapy

Arguments PRO and CON for T3 Supplementation

- The thyroid produces both T3 and T4
- LT4 therapy has no T3
- Patients on T4 alone have higher than normal T4/T3 ratios
- Peripheral conversion of T4 to T3 may be inadequate in some patients → tissues have deficient T3 level
- So is T4 monotherapy = “Tissue hypothyroidism”
- BUT T3 has short half life, may need extended release
- Data doesn’t support use of T3 or dessicated thyroid

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Controversy
T3 and “Natural” Therapy

- Mood better with T3: 7 of 8 tests P<0.04
- No difference in:
  - Neuropsychological tests
  - BP and serum lipids
- Eur J Endocrinol 2009
  - 49% preferred combination of T4 and T3 and 15% T3 alone, 36% had no preference

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Controversy
T3 and "Natural" Therapy

- But no benefit demonstrated in over nine studies\(^1\)
- Meta-analysis of >1,200 patients randomized to LT4 monotherapy\(^2\) or combination therapy with T3 showed no difference in body pain, depression, lipids, anxiety, fatigue, quality of life, body weight

\(^2\) Elam P, et al. J Clin Endocrinol Metab. 2002;87:4505-4509

Controversy
T3 and "Natural" Therapy

- 1891: Dr. George Murray 1st used sheep thyroid extract to successfully treat his patient with myxedema for 28 years
- Same issues with naturally desiccated thyroid or NDT (a mixture of T3 and T4 made from porcine or beef thyroid glands) as with T3
- Must use TSH for monitoring
- NDT contains all thyroid hormones: T4, T3, T2 and T1 and calcitonin which is present in natural thyroid and usually lacking after total thyroidectomy, which removes the parathyroid glands
- Synthetic T4 alone is the recommended therapy by AACE as there is no proven evidence of benefit with NDT
- Daily dose of 100 μg of LT4 = biologic activity to 101 mg of NDT

Protein Binding

- Thyroid hormone is highly protein bound so changes in the amount of binding protein and drugs that compete for binding change the amount of available active free thyroid hormone
- The thyroid replacement dosage must be changed in response to alterations in binding status
- **HIGH BINDING**: High estrogen states (pregnancy, oral contraceptive use, or postmenopausal estrogen replacement), so the dose of LT4 must be increased
- **LOW BINDING**: Low androgens, nephrosis, protein-losing enteropathies, cirrhosis, and aging may decrease levels of thyroid binding proteins, and so require a reduced dose

Drug Interactions
Multiple Complex Mechanisms of Actions

- Iodine and iodide-containing drugs such as radiographic contrast (may cause both hypothyroidism and hyperthyroidism weeks later)
- Lithium (therapeutic levels cause thyroid enlargement in half the patients and hypothyroidism in 20%, but may also cause hyperthyroidism)
- Oral tyrosine kinase inhibitors (blocks clearance)
- Proton pump inhibitors
- Concomitant use of calcium, iron, and bile acid sequestrants (interfere with absorption)

Drug Interactions
Multiple Complex Mechanisms of Actions

- Selective estrogen receptor modulators (SERMs), anabolic steroids, and glucocorticoids (decrease protein binding so dose may need to be reduced)
- Amiodarone (multiple causes for both hypothyroidism and hyperthyroidism)
- Phenobarbital, rifampin, phenytoin, and carbamazepine (increase the metabolism of both T4 and T3 so patients on T4 supplementation may need higher dosages)
- Beta adrenergic antagonists including high-dose propranolol (inhibit T3 production)
- NSAIDs including salicylates, heparin, and furosemide (decrease T4 binding)
- Dopamine (suppresses TSH)

Graves’ Disease Treatment
Two Step Process

- >95% satisfaction with all three therapy choices, but relapse risk higher with med
- **1ST STEP**: Rapid amelioration of symptoms with a beta-blocker
  - Palpitations, tachycardia, anxiety, tremor, heat intolerances
  - 2nd STEP: Decreasing thyroid hormone synthesis
    1. Methimazole and propylthiouracil (PTU)
    - Inhibit the enzyme thyroid peroxidase
    - 3-8 weeks to work, often a step before permanent ablation, but may be well tolerated long term - 37% relapse
    2. Radiiodine ablation
    - 60% of endocrinologists prefer to treat with a capsule of I131
    - 6-18 weeks to work, worsening of Graves’ ophthalmopathy, 21% relapse
    3. Surgery
    - 1% use, lowest relapse (8%) surgical risk (recent laryngeal nerve injury)
    - Obstructive goiter or suspicious nodule, ophthalmopathy, contraindications to meds or radiiodine
Anatomy Review

In 1866, Samuel David Gross said, "If a surgeon should be so foolhardy as to undertake it [thyroidectomy] … every step of the way will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery."

Controversy
Subclinical Hyperthyroidism Treatment

- Treat if high risk patient
  - >65 years old
  - Heart disease
  - Osteoporosis
- Treat low risk if TSH value is <0.1 mU/mL
- Same treatment options as in Graves’

Susan: Follow-up Visit 2 Years Later

Susan tells you that her 29 year old daughter is now planning to start a family and she is worried that she and the baby might be at risk for thyroid problems.

Pregnancy

- Maternal and fetal hypothyroidism associated with risks to fetal neural development
- Maternal hypothyroidism at increased risk for anemia, myopathy, congestive heart failure, preeclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage
- Maternal thyrotoxicosis is associated with fetal tachycardia, fetal hyperthyroidism, small for gestational-age babies, prematurity, preeclampsia, and stillbirths

Pregnancy

- Thyroid size increases 10% to 15% during pregnancy in patients who live in countries with adequate iodine and by 20% to 40% where there is an iodine deficiency
- T4 and T3 production increases by 50%
- The daily iodine requirement goes up by 50% due to > T4 production and > renal clearance
- WHO recommends 250 mcg of iodine daily
- TSH drops the most in the first trimester under the impact of placental human chorionic gonadotropin (hCG), which itself has a weak thyrotropic effect-> possible transient hyperthyroidism
- Thyroid Binding Globulin (TBG) increases

Abalovich M, et al. J Clin Endocrinol Metab. 2007;92(8 Suppl);S1-S47.
Third

Women with recurrent pregnancy loss

- Symptoms or clinical signs suggestive of thyroid dysfunction
- Women in whom the last delivery was preterm
- Thyroid antibodies (when known)

2009;200:260.e1

1.1.1. Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus. Therefore,

1.1.3. The T4 dose usually needs to be incremented by 4 to 5 μg/kg/day. A history of hyperthyroid or hypothyroid disease,

1.1.5. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of

A family history of thyroid disease

Type 1 diabetes

Infertility should have screening with TSH as

Women in the childbearing age should have an average iodine intake of 150 μg/day. The

1.1.6. Subclinical hypothyroidism (serum TSH concentration above the upper limit of the reference range with a

A history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid surgery

A goiter

Prior therapeutic head or neck irradiation

Previous history of thyroid disease

Controversy

Screening

- American Thyroid Association, American College of Obstetricians and Gynecologists, and The Endocrine Society all recommend targeted rather than universal screening

- BUT may miss 1/3 pregnancy with hypothyroidism

Screening for Thyroid Disease

Suggested indicators for targeted thyroid care finding in pregnancy, where the incidence of clinical hypothyroidism disease is high and benefit of therapy is clear, women with:

- A history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid surgery

- A family history of thyroid disease

- A goiter

- Thyroid antibodies (when known)

- Symptoms or signs suggestive of thyroid under function

The following conditions screening may be considered since the incidence might be high enough but no known benefit of treatment has yet been determined:

- Women in whom the last delivery was preterm


Controversy

Management Consult an Experienced Endocrinologist

- hCG-mediated hyperthyroidism is usually transient and does not require treatment

- PTU is 1st choice and ATA recommends treatment saying benefits > risks, but is category 4

- Surgery if PTU is contraindicated

PTUpropylthiouracil

Controversy

Management Consult an Experienced Endocrinologist

- Subclinical Hypothyroidism

- Lower pregnancy risk than with overt disease

- RX with LT4 may improve baby’s neuro development

- The Thyroid Dysfunction during Pregnancy and Postpartum Guideline Task Force recommends treatment

- Elevated antithyroid peroxidase antibody (TPO antibodies) in euthyroid pregnant patients

- Increased risk of fetal loss, perinatal mortality, and large-for-gestational-age

- High risk to become hypothyroid, so need monitoring

- LT4 may lower miscarriage rates

- ATA does not recommend for or against treatment

Controversy

Management Consult an Experienced Endocrinologist

- Hypothyroidism Treatment Recommendations

- Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus. Therefore,

- If not provided, then for TSH use

- 1. First trimester 0.1 to 2.5

- 2. Second trimester 0.2 to 3.0

- 3. Third trimester 0.3 to 3.0

- TBG is higher so total T4 is higher as total T4 reflects the increased protein binding in pregnancy

- FT4 however is more likely to be normal but can be technically difficult to accurately measure


Baldasso M, et al. J Clin Endocrinol Metab. 1991;73:130-


Controversy

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