A Practical Approach to the Diagnosis and Management of Thyroid Disorders

All you wanted to know about thyroid disease but were afraid to ask

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Learning objectives

• Understand the regulation of the hypothalamo-pituitary-thyroid axis
• Develop an approach to screening and evaluation of patients with suspected thyroid dysfunction
• Recognize causes of hyper and hypothyroidism and how to manage them
• Develop an approach to the patient with thyroid nodular disease
Regulation of thyroid hormone secretion
Thyroid Function Tests

• To *diagnose* thyroid dysfunction
  • The first step is to identify the patient who has an abnormality of thyroid function

• To diagnose the *cause* of thyroid dysfunction
  • Then determine cause of the problem to determine best treatment
What Does the TSH Level Mean?

- **TRH**
- **TSH**
- **T4/T3**
- **End Organ**

- **< 0.01-0.1**
  - hyperthyroid
- **0.1-0.5**
  - hyperthyroid (sub-clinical)
- **0.5-5.0**
  - euthyroid
- **> 5.0**
  - hypothyroid
Suspected Primary Thyroid Dysfunction

**Free T3 indicated if FT4 normal**

If measure Total T4 need measurement of TBG or T3 uptake
TSH alone is not a diagnostic test

- Unreliable in hypopituitarism - TSH levels inappropriately normal because of secretion of biologically inactive hormone
- May be unreliable post radioiodine treatment or during therapy with antithyroid drugs
- Secondary hyperthyroidism may be missed
- Unreliable in acutely ill patients or those on dopamine or steroids
Screening For Thyroid Disease: Who Should be Screened?*

1. Symptoms suggestive of thyroid disease
2. Family history of thyroid disease
3. Women over the age of 50
4. Pregnant women
5. Post-Partum
6. Nodular thyroid disease

* USPSTF does not recommend routine screening for thyroid disease
Tests Used to Diagnose the **Cause** of Thyroid Dysfunction

- Radioiodine uptake
- Radioiodine scan
- Thyroid ultrasound
- Thyroid antibodies
  - Thyroid peroxidase (TPO)
  - Thyroglobulin
  - TSH receptor antibody (Thyroid stimulating IgG)
- Thyroglobulin
Evaluation of the Patient with Hyperthyroidism

Goiter*  
Orbitopathy  
Dermopathy

GRAVES’  
No further tests

No goiter  
123I uptake/scan

Elevated  
Graves’

Suppressed  
Thyroiditis

Other

Nodule  
123I scan

Hot nodule  
Toxic adenoma

*Multinodular goiter – no further tests necessary for diagnosis
Graves’ Disease

A. TT4, TT3, free T4
   ↓ TSH

B. Exopthalmos

C. Pre-Tibial Myxedema

D. 1. Adrenergic
    2. Wt loss
    3. Sweating
    4. Diarrhea
    5. Tremor
    6. Lid Lag
    7. Proximal Muscle
Ophthalmopathy In Graves’ Disease

• Up to 25% of eye disease occurs before or after the diagnosis of thyrotoxicosis.

• Most common presentation is a staring appearance (>60%) due to contraction of Müller’s muscle of the upper eyelid

• Smoking and perhaps RAI treatment may worsen eye disease (Tallstedt et. al. NEJM 1992, 326:1733)

• Treatment: local, antiinflammatory, and surgery (last option)
Exopthalmos
Exopthalmos
Pretibial Myxedema
Graves’ Disease

I-123 Thyroid Scan

RAO  Ant  LAO

Uptake = 85.4%

April 9, 1999
Graves’ Disease – Treatment

• Factors to consider when deciding on therapy
  • Natural history
  • Predictors of outcome

• Treatment options:
  • Medical - thionamides, beta blockers, iodine
  • Radioiodine
  • Surgery
Antithyroid Drugs

• Advantages
  • Relatively safe
  • Not permanent
  • Can be used in pregnancy - PTU
  • ? Immunosuppressive effects
  • Concomitant use of antithyroid drugs and thyroxine decreases production of antibodies to TSH receptor and recurrence of hyperthyroidism
Antithyroid Drugs (continued)

• Disadvantages
  • "Minor" side effects
  • Skin rash/hives 5%
  • Arthralgia 5%
  • Major side effects
    • Agranulocytosis 1/1000
    • Hepatotoxic 1/1000
  • Not permanent
  • Low remission rates of disease
Antithyroid Drugs – Which One?

Methimazole:
1. Only has to be given once daily.
2. Similar side effect profile to PTU.
3. Should not be given during pregnancy.

PTU:
1. Blocks peripheral conversion of T4 to T3.
2. Used during pregnancy.
3. Severe liver toxicity – FDA boxed warning
Propylthiouracil should be reserved for patients who cannot tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

Because of the risk of fetal abnormalities associated with methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy.
Radioiodine Therapy for Graves’ Disease

• Advantages
  • Permanent
  • Safe - no increase in teratogenicity, cancer, infertility

• Disadvantages
  • Acute thyroiditis
  • Permanent hypothyroidism (up to 80% or more)
  • May be associated with worsening of ophthalmopathy (± 3% risk)
Radioiodine Therapy for Graves’ Disease

• Absolutely contraindicated in pregnancy
• Patients should not become pregnant for 6 months following radioiodine therapy
• Always check HCG before administering radioiodine and counsel patients about pregnancy
Surgery for Graves’ Disease

• Advantages
  • Relatively safe

• Disadvantages
  • Morbidity - recurrent laryngeal nerve palsy, hypoparathyroidism
  • Hypothyroidism
  • Relapse of hyperthyroidism
Graves’ Disease: Natural History

• Low remission rates (20 - 30%)
• Greater chances of remission
  • Female
  • Older
  • Small goiter, no orbitopathy or dermopathy
  • Short duration of illness and "milder" disease
  • Low iodine diet
  • Treatment with antithyroid drugs for a year or more
Graves’ Disease – My Approach to Therapy

• Antithyroid drugs if tolerated for 12 months
• If no remission then RAI
• Thyroid function tests are followed every 5 – 6 weeks on antithyroid drugs
• Women with moderate to severe Graves’ disease who are planning a pregnancy
  • RAI preferred prior to pregnancy
Other Causes of Hyperthyroidism
Thyroiditis

• Subacute
  • Often follows URI
  • Pain and tenderness of thyroid
  • Symptoms of thyrotoxicosis
  • Elevated ESR
  • Thyroid antibodies negative
  • Self limiting
  • Full recovery in more than 90%

• Chronic
  • Painless
  • Self limiting usually
44 Year Old Male With Hyperthyroidism and a Tender Thyroid
Thyroiditis - Treatment

• Self limiting
• Treatment symptomatic
• Beta blockers
• NSAID for pain
• Steroids (for severe pain)
• Radioiodine contraindicated
• Antithyroid drugs usually not used
Postpartum Thyroiditis

Affects 5-10% of all pregnancies. Approaches 25% if another autoimmune condition is present.

**Diagnosis:** TSH, free T4, anti-TPO abs
No uptake on a RAI scan.

Should we screen all post-partum women?
Postpartum Thyroiditis: Treatment

1. Symptomatic hyperthyroidism - beta blocker
2. Symptomatic hypothyroidism - T4 therapy

Full recovery can occur but PPT will recur after subsequent pregnancies.
Hot Nodule

OVERPRODUCTION OF T4 AND T3 SUPPRESSION OF TSH

TREATMENT
Radioactive iodine usually

MOLECULAR DEFECT
TSH RECEPTOR ACTIVATING MUTATIONS

123I Scan

Hot Nodule
19 Year Old Female With Hyperthyroidism and a Hot Thyroid Nodule
Drugs and the Thyroid

Thyrotropin suppression
Hypophysitis
↓ Conversion of T₄ to T₃
Autoimmunity
Thyroiditis
↓ Release of T₄ and T₃
Iodine-induced hyperthyroidism
↓ Conversion of T₄ to T₃
↓ Binding proteins
↓ LT₄ tablet dissolution
T₄ and T₃ conjugation
↓ Conversion of T₃ to T₄
Biliary excretion
↓ LT₄ absorption
Urinary excretion
↓ Fecal excretion
Classification of drug effects on the thyroid

Interference with endogenous thyroid function
Disruption of hypothalamic–pituitary control
Decreased thyroid hormone production or release
Increased thyroid hormone production
Enhanced thyroid autoimmunity
Destructive thyroiditis
Changes in thyroid hormone–binding proteins
Inhibition of thyroid hormone activation (T$_4$-to-T$_3$ conversion)
Displacement of thyroid hormone from binding proteins
Increased thyroid hormone metabolism or elimination
Drug effects on the thyroid

- Disruption of hypothalamo-pituitary control
  - Suppression of TSH – bexarotene
  - Hypophysitis – immune check point inhibitors

- Decreased thyroid hormone production or release
  - Iodine, lithium

- Increased thyroid hormone production
  - Iodine, drugs containing iodine (Amiodarone)

- Increased thyroid autimmunity
  - Immune check point inhibitors, alemfuzamab, PD-1 inhibitors, CTLA-4 inhibitors
Drug effects on the thyroid

- **Destructive thyroiditis**
  - Amiodarone, interferon, interleukin 2
- **Changes in thyroid hormone binding proteins**
  - Estrogen, SERM – increase TBG
  - Androgens, steroids, niacin – decrease TBG
- **Decreased T4 to T3 conversion**
  - Propranolol, PTU, dexamethasone, amiodarone
- **Displacement of thyroid hormone from binding proteins**
  - Aspirin
- **Increased metabolism or elimination**
  - Phenytoin, rifampin, carbamazepine
Amiodarone and the Thyroid

- May cause hyper- or hypothyroidism
- **Amiodarone induced thyrotoxicosis** can be severe
- **Mechanisms**
  - Iodine induced
  - Thyroiditis secondary to amiodarone therapy
    - Associated with increased levels of interleukin 6
- **Treatment**
  - Stop drug if possible
  - Antithyroid drugs
  - Prednisone
- My approach: methimazole 10 mg bid and prednisone 10 mg bid.
Classification of drug effects on the thyroid

Interference with thyroid hormone therapy
Decreased pill dissolution
Decreased thyroid hormone absorption
Decreased free thyroid hormone levels
Increased thyroid hormone metabolism or elimination
### Table 2. Drugs That Cause Spurious Thyroid Test Results in Euthyroid Persons.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Test Results</th>
<th>Condition Mimicked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Class III antiarrhythmic agent</td>
<td>High end of normal range</td>
<td>High Low end of normal range Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance</td>
</tr>
<tr>
<td>Biotin</td>
<td>Micronutrient</td>
<td>Low</td>
<td>High High Primary hyperthyroidism</td>
</tr>
<tr>
<td>Carbamazepine and oxcarbazepine</td>
<td>Antiepileptic agent</td>
<td>Normal Low</td>
<td>Low end of normal range Central hypothyroidism</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Anticoagulant</td>
<td>Normal High</td>
<td>High Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant</td>
<td>Normal High</td>
<td>High Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Antiepileptic agent</td>
<td>Normal Low</td>
<td>Low end of normal range Central hypothyroidism</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>Normal Low end of normal range Low end of normal range</td>
<td>Central hypothyroidism</td>
</tr>
</tbody>
</table>
Hypothyroidism: Causes

• Autoimmune
  • Hashimoto's thyroiditis

• Ablative
  • Post radioiodine
  • Post surgery
  • Post radiation therapy to head/neck

• Drugs
  • Thionamides
  • Iodine containing preparations (Amiodarone)
  • Lithium

• Pituitary or hypothalamic lesions
Hypothyroidism - Treatment

• Start low - Go slow!

• Use L-Thyroxine
  • 0.05mg qd for one to two weeks, then increase dose slowly up to 0.1 - 0.125mg qd
  • Usual dose requirement is 1.6 mcg/kg/day
  • May need to start elderly patients with active underlying coronary artery disease on a lower dose - 0.012 mg to 0.025 mg qd - and increase dose more slowly
  • May start at a higher dose in young individuals
Hypothyroidism – Treatment

• Repeat TSH after 6 weeks of therapy, or 6 weeks after adjusting dose of thyroxine
• Aim to normalize TSH
• No evidence that one brand of thyroxine supplementation any “better” than another
• Do not substitute one form of thyroxine for another
Cytomel (T3) and Hypothyroidism

• No evidence that cytomel use adds benefit or results in improved symptomatology

  • Clyde PW et al. JAMA. 2003; 290: 2952-8
  • Sawka AM et al. J Clin Endocrinol Metab. 2003; 88: 4551-5.
# Thyroxine Therapy – Increased Dose Requirements

<table>
<thead>
<tr>
<th>Medication/Condition</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin, Carbamazepine, Rifampin</td>
<td>Increased clearance of thyroxine</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Interference with absorption of thyroxine</td>
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<tr>
<td>Cholestyramine</td>
<td></td>
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<tr>
<td>Aluminum hydroxide</td>
<td></td>
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<tr>
<td>Ferrous sulphate, calcium</td>
<td></td>
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<tr>
<td>Pregnancy</td>
<td>Increased concentration of TBG</td>
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<tr>
<td>Women taking estrogen</td>
<td>Increased body mass (pregnancy)</td>
</tr>
<tr>
<td>Condition</td>
<td>Mechanism</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Aging</td>
<td>Decreased clearance of thyroxine</td>
</tr>
</tbody>
</table>
Hypothyroidism in Pregnancy: Recommendations

• Screen for hypothyroidism at the first pre-natal visit
• In those with known hypothyroidism recheck TFTs early in pregnancy
• Treat new hypothyroidism with LT4 (1.6-1.8 ug/kg)
• Consider increasing the dose of treated patients by 15-25% in autoimmune hypothyroidism and 25-50% in post ablative or surgical hypothyroidism
• After a dose change re-check the TSH in 3-4 weeks.
Subclinical Thyroid Disease

- Abnormal TSH with normal thyroid functions in a clinically "asymptomatic" individual
  - Usually progress to "clinically overt" disease at a rate of 4 - 5% per year

- Subclinical hypothyroidism
  - Indications for treatment
    - Hyperlipidemia, depression, fatigue, weight gain, goiter
    - Positive antibodies
    - TSH more than 2X upper limit normal
  - Treat with as low a dose of thyroxine as possible to normalize TSH
Progression of Subclinical Hypothyroidism to Overt Hypothyroidism

Cumulative Incidence of Hypothyroidism

- TSH >12
- TSH 6-12
- TSH 4-6

From Braverman et al, JCEM, 2002.
Case study

- 70 year old male
- Fatigue, some weight gain
- TSH 5.6 (normal 0.3 to 4.0)
- Free T4 0.9 (normal 0.8 to 1.8)

Would you treat this person with thyroid hormone replacement?
Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism


This article was published on April 3, 2017, at NEJM.org.

N Engl J Med 2017;376:2534-44. DOI: 10.1056/NEJMoa1603825
METHODS
We conducted a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults who were at least 65 years of age and who had persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter; free thyroxine level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the body weight was <50 kg or the patient had coronary heart disease), with dose adjustment according to the thyrotropin level; 369 patients were assigned to receive placebo with mock dose adjustment. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related quality-of-life questionnaire at 1 year (range of each scale is 0 to 100, with higher scores indicating more symptoms or tiredness, respectively; minimum clinically important difference, 9 points).

CONCLUSIONS
Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126.)
Subclinical Hyperthyroidism

• Indications for therapy
  • Concern about bone status (increased risk of osteopenia)
  • Concern about cardiac status (increased risk of atrial fibrillation)
  • TSH less than 0.05 uU/mL associated with 2-3 fold increased risk for atrial fibrillation*

• Evaluate with iodine uptake and scan prior to any therapy

• Follow patients if TSH between 0.1 and 0.5 uU/mL

  Coppola et al JAMA, 2006
Thyroid Nodules

• Cumulative incidence of developing a thyroid nodule over one's lifetime is 5 - 10%
• More than 50% of people have a thyroid nodule at the time of death
• Women affected 3-5 times more than men
• 5 - 15% of all nodules are malignant
• Thyroid carcinomas are slow growing and treatable
When Are Thyroid Nodules Malignant?

- High suspicion
  - MEN
  - Rapid growth
  - Presence of mets
  - Vocal cord paralysis
  - Fixation
  - Very firm nodule

- Moderate suspicion
  - < 20 or > 60 yrs
  - Male
  - Single nodule
  - Head or neck irradiation

14% risk of malignancy

71% chance with 1 finding
100% chance with 2 or more findings

Hamming et. Al. Arch Intern Med 1990:113
Thyroid Nodule – Diagnostic Approach

Palpated nodule
or
Incidentaloma (>1.0 cm)

TSH
Low
Thyroid Scan
Hot
Observe

Cold
Normal-High
FNA
Benign
Observe

suspicious
cancer
Remove
Thyroid Ultrasound

70 yr old male with a new left thyroid nodule

1. Well circumscribed nodule.
2. Microcalcifications

DIAGNOSIS
Papillary Carcinoma
What Should One Do About Thyroid Nodules with Indeterminate Cytology?

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology


NEJM 2012; 367:705-715
Use of Gene Expression Classifier to Diagnose Indeterminate Nodules

• 15 – 30% of nodules are indeterminate on cytology – most of these are benign but surgery currently recommended

• Use of gene expression classifier using molecular analysis found to have negative predictive value of 85-95% and correctly identified suspicious nodules with a sensitivity of 95% and specificity of 52%
Multicenter Study Evaluating Afirma GEC in Thyroid Nodules with Indeterminate Cytology

339 Thyroid Nodules with Indeterminate FNA Cytology

- 174 Afirma GEC "Benign" - 4 of 174 (2%) surgery recommended, 11 of 174 (6%) surgery performed
- 17 of 339 "Non-Diagnostic" - surgery recommended
- 148 Afirma GEC "Suspicious" - 141 of 148 (95%) surgery recommended, 121 of 148 (82%) surgery performed

Alexander E et al. JCEM 2014; 99: 119-125
Results

141 of 148 (95%) surgery recommended

121 of 148 (82%) surgery performed

53 (44%) proven malignant

Alexander E et al. JCEM 2014; 99: 119-125
Therapy of Thyroid Nodules

• Careful monitoring essential

• Thyroid hormone suppression not advocated because most benign nodule do not shrink after $T_4$ therapy
  Gharib et. al. NEJM 1987, 317:70.

• Clinical exam (+/- ultrasound) every six months.
  • If growth occurs repeat FNA or remove surgically

• Hot nodules associated with hyperthyroidism best treated by radioactive iodine (RAI)
Treatment of small (< 2cm) papillary ca
What We Have Covered

• Physiology
• Screening for thyroid disease
• Hyperthyroidism
• Hypothyroidism
• Subclinical thyroid disease
• Thyroid nodules
Remember – sometimes you can only see the tip of iceberg