THYROID DYSFUNCTION REVISITED: WHAT’S NEXT AFTER TSH

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Faculty/Presenter Disclosure

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  - **NONE**
Mitigating Potential Bias

- N/A
OBJECTIVES

✧ Review thyroid physiology and the pertinent lab tests for family practice management of common thyroid disorders.

✧ Understand the role of the TSH test in patient screening - when to screen; pitfalls and cost-benefit.

✧ Become aware of conditions and substances that can interfere with thyroid function and interpretation of results.

✧ Evaluate the role of other thyroid tests using case-based examples for common thyroid disorders.
Regulation of Thyroid Hormone Synthesis

70:30 T4/T3
THE FACE OF HYPOHYROIDISM

❖ Old, Cold & Slow
HYPOTHYROIDISM
## Prevalence of Hypothyroidism

<table>
<thead>
<tr>
<th>Study</th>
<th>Subclinical</th>
<th>Overt</th>
<th>TSH</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES III</td>
<td>4.3%</td>
<td>0.3%</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>ColoradThyroid Disease Prevalence</td>
<td>8.5%</td>
<td>0.4%</td>
<td>5.0</td>
<td>not on thyroid hormone</td>
</tr>
<tr>
<td>Framingham</td>
<td></td>
<td></td>
<td>10.0</td>
<td>Over age 60 years: 5.9% women; 2.3% men; 39% of whom had subnormal T4</td>
</tr>
<tr>
<td>British Whickham</td>
<td></td>
<td></td>
<td>10.0</td>
<td>9.3% women; 1.2% men</td>
</tr>
</tbody>
</table>

Sources: Hollowell et al., 2002; Canaris et al., 2000; Sawin et al., 1985; Vanderpump et al., 1995; Vanderpump and Tunbridge, 2002.

Abbreviations: NHANES = National Health and Nutrition Examination Survey.
CAUSES OF HYPOTHYROIDISM

Primary: - Auto-immune

- Iatrogenic
  - Drugs (iodine contrast, amiodarone, lithium, sunitinib, interferon alpha, aminogluthethimide, antithyroid drugs, p-amino salicylic acid)

- Congenital Hypothyroidism

- Infiltrative (amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel’s thyroiditis, lymphoma, metastatic, primary thyroid CA)

- Overexpression of type 3 deiodinase in infantile hemangioma
CAUSES HYPOTHYROIDISM CONTINUED

**Transient:**  
- Silent Thyroiditis, including Post-Partum Thyroiditis
  - Sub-Acute Thyroiditis
  - after I\textsubscript{131} treatment or sub-total thyroidectomy for Graves’ Disease
  - after thyroxine withdrawal in a patient with an intact thyroid

**Secondary:**  
- Hypopituitarism
  - Isolated TSH deficiency or inactivity
  - Bexarotene treatment (cutaneous T cell lymphoma)
  - Hypothalamic causes
Serum thyrotropin (TSH) is the single best screening test for primary thyroid dysfunction for most out-patient clinical settings - but not when central hypothyroidism is present or suspected

(American Association of Clinical Endocrinologists AACE / American Thyroid Association ATA)
general agreement TSH > 10 should be treated

no clinical out-come data to support treating patients with sub-clinical hypothyroidism with TSH levels 2.5 - 4.5 (except pregnancy)

at values of 4.5 - 10, the data is less certain

for treatment, NHANES 111 suggest a reference range of 0.45 - 4.12 if no third generation assay available
PITFALLS ENCOUNTERED WHEN INTERPRETING SERUM TSH LEVELS

- TSH levels vary diurnally by up to 50% of mean values (lowest in late afternoon, highest around the hour of sleep)
- TSH secretion is exquisitely sensitive to minor fluctuations in free T4 (can see before overt T4 abnormalities are detectable)
- TSH increases with age - 95% of “normal” individuals have TSH < 2.5; elderly (>80 yrs) have TSH >3.0
- TSH can be suppressed in critically ill patients especially if on dopamine infusion or receiving glucocorticoids
- Pregnancy / Anorexia - have lower TSH
- Upper normal range does not apply to Iodine insufficient regions
- Patients with non-functioning pituitary adenomas with central hypothyroidism or secondary hyperthyroidism
CASE STUDY 1

- 61 y.o. female with a past history for Hypertension, smoker, Family history for Type 2 DM and ovarian cancer
- gradual progressive swelling around eyes and some ankle swelling, low energy, myalgias and cold intolerance
- develops daily low grade headache and notices if she bends forward or lifts arms above her head, she feels pressure and has trouble breathing
- on physical exam she has a large firm irregular goitre with no lymphadenopathy
- TSH is 7.25 mIU/L
What would you do next?

1. Treat with levo-thyroxine 0.100 mg a day

✓ 2. Order a TSH first

3. Order a free T4 and free T3 only

4. Treat with 1.6 mcg/kg levo-thyroxine daily

5. Order free T4 and thyroid antibodies

6. Order a thyroid ultrasound
TSH is elevated at 7.26 mIU/L  

What next?

- free T₄
- Anti TPO
- thyroid ultrasound
- (free T₃)
EVALUATION OF FREE T4

❖ T4 is bound to specific proteins in serum: TBG, transthyretin or prealbumin and albumin

❖ 99.97% is bound; free T4 is metabolically active

❖ a sub-normal assessment of free T4 is a good indicator of hypothyroidism (except in pregnancy due to an increase in binding proteins)
## Factors that Alter Thyroxine and Triiodothyronine Binding in Serum

<table>
<thead>
<tr>
<th>Increased TBG</th>
<th>Decreased TBG</th>
<th>Binding Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited</td>
<td>Inherited</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Androgens</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Neonatal state</td>
<td>Anabolic Steroids</td>
<td>Free Fatty Acids</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Glucocorticoids</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Severe Illness</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Hepatic failure</td>
<td>NSAIDs (variable, transient)</td>
</tr>
<tr>
<td>Heroin</td>
<td>Nephrosis</td>
<td>Heparin</td>
</tr>
<tr>
<td>Methadone</td>
<td>Nicotinic Acid</td>
<td></td>
</tr>
<tr>
<td>Mitotane</td>
<td>L-Asparaginase</td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SERMS (tamoxifen, raloxifene)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EVALUATION OF FREE T3 IS NOT ROUTINELY RECOMMENDED

- also bound to serum proteins including TBG, but to a lesser extent.
- limited utility in evaluation of hypothyroidism - these levels are frequently normal due to hyperstimulation of residual functional thyroid tissue by TSH.
- up-regulation of type 2 iodothyronine deiodinase in hypothyroidism keeps levels normal.
- levels of T3 can be low in the absence of thyroidal disease.
WHEN SHOULD ANTI-THYROID ANTIBODIES BE MEASURED?

- Anti-thyroid peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism. Grade B, BEL 1

- The best evidence is only predictive in nature. If positive, hypothyroidism occurs at a rate of 4.3% per year vs 2.6% per year if negative. Therefore, the presence of TPOAb may influence the decision to treat.

- TPOAb measurement may identify autoimmune thyroiditis when nodular thyroid disease is suspected to be due to autoimmune thyroid disease. Grade D, BEL 4

- TPOAb should be done when evaluating patients with recurrent miscarriage with or without infertility. Grade A, BEL 2
Case Study 1

- Free T4 is 11 pmol/L (N 9.0 - 22.0)
- Free T3 is 3.0 pmol/L (N 3.5 - 6.5)
- Anti-microsomal Abs (TPOAb) is positive - titre 1:409,600
- Thyroid ultrasound is reported as a very large irregular, lobulated and heterogeneous gland
When is the appropriate time to start treatment? (for all with TSH > 10 mIU/L)

If treatment is initiated, what should the therapeutic endpoints be?
PATIENTS WITH NORMAL THYROID TESTS

- Patients with symptoms of hypothyroidism but normal levels of thyroid function tests **Do Not** benefit from treatment with L-thyroxine. 2001 BMJ 323:891–895.

A REVIEW OF THE CLINICAL CONSEQUENCES OF VARIATION IN THYROID FUNCTION WITHIN THE REFERENCE RANGE

Peter N. Taylor et al, J Clin Endocrinol Metab 98: 3562 - 3571, 2013

- a Medline review
Benefits of treating sub-clinical hypothyroidism, TSH 4.5 - 10 mIU/L or sub-clinical hyperthyroidism, TSH ≤ 0.5 mIU/L

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Association</th>
<th>Parameter</th>
<th>Comment</th>
<th>Refs.</th>
<th>Evidence Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Yes</td>
<td>TSH</td>
<td>Positively associated with blood pressure, approximately a 5-mm Hg increase in systolic blood pressure across the reference range.</td>
<td>20–22</td>
<td>Good</td>
</tr>
<tr>
<td>Cholesterol and lipid levels</td>
<td>Yes</td>
<td>TSH</td>
<td>Positively associated with cholesterol and lipid levels although effect modest, approximately 0.2 mmol/L increase in total cholesterol across the reference range.</td>
<td>23, 24</td>
<td>Good</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Possible</td>
<td>TSH</td>
<td>Positively associated with cardiovascular mortality in women, but not men. No association identified between TSH and hospitalization for myocardial infarction.</td>
<td>27, 28</td>
<td>Moderate</td>
</tr>
<tr>
<td>BMI</td>
<td>Yes</td>
<td>TSH</td>
<td>Positively associated with BMI and odds of obesity. Those with TSH levels in the upper 1/3 of reference range have a BMI of approximately 1.9 kg/m², higher than the lower 1/3. Increasing TSH over time is also associated with increased weight gain.</td>
<td>34–37</td>
<td>Good</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Yes</td>
<td>TSH</td>
<td>Positively associated with increased odds of fulfilling the diagnostic ATP III criteria.</td>
<td>24, 38</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnancy outcomes</td>
<td>Yes</td>
<td>TSH</td>
<td>The proportion of spontaneous pregnancy loss in individuals with a TSH less than 2.5 mIU/L was 3.6%, vs 6.1% in individuals with a TSH between 2.5 and 5.0 mIU/L; ( P = .006 ).</td>
<td>66</td>
<td>Moderate</td>
</tr>
<tr>
<td>BMD</td>
<td>Probable</td>
<td>TSH</td>
<td>TSH was positively associated with BMD at both the spine and the hip and reduced odds of osteoporosis/osteopenia and vertebral fracture. However, 1 study with the highest proportion of men found no evidence of association between TSH and BMD.</td>
<td>46, 48–51, 84</td>
<td>Good in females. Moderate in males</td>
</tr>
<tr>
<td>BMD</td>
<td>Probable</td>
<td>( fT_3 ), ( fT_4 )</td>
<td>( fT_3 ) consistently associated with low BMD; ( \beta = -0.08; P = 0.02 ), but not ( fT_4 ).</td>
<td>47, 53</td>
<td>Moderate</td>
</tr>
<tr>
<td>Depression</td>
<td>Unclear</td>
<td>TSH</td>
<td>Inverse association between serum TSH and depression score in males but not in females. Also appears to be a different relationship between TSH and depression in individuals on levothyroxine. Other studies are conflicting.</td>
<td>56</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Odds of adverse outcomes for higher TSH within the reference range

CARDIOVASCULAR OUTCOMES
- Hypertension (F) N=18221 (18)
- Hypertension (M) N=9565 (18)
- Hypertension (C) N=5918 (19)
- Hypertension (M+F) N=6435 (19)
- CVS mortality (F) N=17311 (24)
- CVS mortality (M) N=8002 (24)

Cardiovascular outcomes combined

METABOLIC OUTCOMES
- Metabolic syndrome N=7270 (21)
- Metabolic syndrome N=1333 (43)
- Obesity (F) N=16395 (40)
- Obesity (M) N=8167 (40)
- CKD N=29480 (46)

Metabolic outcomes combined

BONE OUTCOMES
- Osteoporosis (F) N=581 (31)
- Osteoporosis (F) N=950 (34)
- Osteoporosis (M) N=1478 (33)
- Vertebral fracture (F) N=130 (35)

Bone outcomes combined

% Weight
- 8.1
- 4
- 18.6
- 66.8
- 1.5
- 1.1

\[ \text{OR} = 1.21 \text{ (95\% CI 1.15–1.27) p=7.99x10^{-15}} \]

\[ \text{OR} = 1.37 \text{ (95\% CI 1.27–1.48) p=5.99x10^{-15}} \]

\[ \text{OR} = 0.55 \text{ (95\% CI 0.41–0.72) p=1.93x10^{-05}} \]
<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Thyroid Association</td>
<td>women &amp; men &gt; age 35, screened every 5 yrs</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>Older, especially women</td>
</tr>
<tr>
<td>American Association of Family Physicians</td>
<td>All patients &gt; 60 yrs</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>women ≥ 50 with an incidental finding suggestive of thyroid disease</td>
</tr>
<tr>
<td>U.S. Preventative Services Task Force</td>
<td>Insufficient evidence for or against screening</td>
</tr>
<tr>
<td>Royal College of Physicians - London</td>
<td>Screening of the healthy adult population unjustified</td>
</tr>
</tbody>
</table>
CO-MORBID CONDITIONS THAT MAY WARRANT TSH SCREENING

- ICD 9 Codes to support
  - auto immune disease or first degree relative with it, incl. pernicious anemia
  - H & N Irradiation
  - abnormal exam
  - previously abnormal function
  - psychiatric disorders
  - amiodarone or lithium

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>255.41</td>
</tr>
<tr>
<td>Alopecia</td>
<td>704.00</td>
</tr>
<tr>
<td>Anemia, unspecified deficiency</td>
<td>281.9</td>
</tr>
<tr>
<td>Cardiac dysrhythmia, unspecified</td>
<td>427.9</td>
</tr>
<tr>
<td>Changes in skin texture</td>
<td>782.8</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>428.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>564.00</td>
</tr>
<tr>
<td>Dementia</td>
<td>294.8BA</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>250.01</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>625.3</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>272.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401.9</td>
</tr>
<tr>
<td>Mixed hyperlipidemia</td>
<td>272.2</td>
</tr>
<tr>
<td>Malaise and fatigue</td>
<td>780.79</td>
</tr>
<tr>
<td>Myopathy, unspecified</td>
<td>359.9</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>794.31</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>709.01</td>
</tr>
<tr>
<td>Weight gain</td>
<td>783.9M</td>
</tr>
</tbody>
</table>
L-THYROXINE TREATMENT OF HYPOTHYROIDISM

- synthetic levo-thyroxine preferred
- desiccated thyroid has not been systematically studied and to date has shown variable absorption and concentration - not recommended at all in pregnancy or preg. planning
- replacement doses for adults is 1.6 mcg / kg if little or no thyroid reserve - slightly more if thyroidectomy
- for SCH: if TSH is 5 - 8 25 mcg, 8 - 12 50 mcg, > 12 75 mcg
- do not re-evaluate sooner than 8 weeks if making small dose adjustments
- some clinical features may take 3-6 months to improve.
Agents & Conditions Having an Impact on L-thyroxine Therapy & Interpretation of Thyroid Tests

### 10.1. Interference with absorption

<table>
<thead>
<tr>
<th>Agents/Conditions</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants (cholestyramine, colestipol, colesevelam)</td>
<td>• Ingestion with a meal</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>• Grapefruit juice&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cation exchange resins (Kayexelate)</td>
<td>• Espress coffee</td>
</tr>
<tr>
<td>Oral bisphosphonates</td>
<td>• High fiber diet</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>• Soybean formula (infants)</td>
</tr>
<tr>
<td>Raloxifene&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Soy</td>
</tr>
</tbody>
</table>
| Multivitamins (containing ferrous sulfate or calcium carbonate) | |}

### 10.2. Thyroid gland hormone production and secretion

<table>
<thead>
<tr>
<th>Agents/Conditions</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium salts (carbonate, citrate, acetate)</td>
<td>• Antiangiogenic (lenalidomide, thalidomide)</td>
</tr>
<tr>
<td>Chromium picolinate</td>
<td>• Lithium</td>
</tr>
<tr>
<td>Charcoal</td>
<td>• Alemtuzumab</td>
</tr>
<tr>
<td>Orlistat&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Denileukin diftitoxin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>• Ameliorates (if autoimmune)</td>
</tr>
<tr>
<td>H2 receptor antagonists&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Glucocorticoids</td>
</tr>
<tr>
<td>Malabsorption syndromes</td>
<td>• Development of Graves’</td>
</tr>
<tr>
<td>• Celiac disease</td>
<td>• Interferon alpha</td>
</tr>
<tr>
<td>• Jejunoileal bypass surgery</td>
<td>• HAART (highly active antiretroviral therapy)</td>
</tr>
<tr>
<td>• Cirrhosis (biliary)</td>
<td>• Alemtuzumab</td>
</tr>
<tr>
<td>• Achlorhydria</td>
<td>• Amelioration of Graves’</td>
</tr>
<tr>
<td></td>
<td>• Glucocorticoids</td>
</tr>
</tbody>
</table>

### 10.3. Direct and indirect effects on the hypothalamic-pituitary-thyroid axis

<table>
<thead>
<tr>
<th>Agents/Conditions</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine uptake</td>
<td>• Hypoadrenalism</td>
</tr>
<tr>
<td>• Iodine (including kelp supplements)</td>
<td>• Interleukin 2</td>
</tr>
<tr>
<td>• Amiodarone</td>
<td>• Amphetamine</td>
</tr>
<tr>
<td>• Ethanamidine</td>
<td>• Ritonavir&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Iodinated contrast (ipodate, iopanoic acid)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>• St. John’s Wort&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Perchlorate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hypophysitis</td>
</tr>
<tr>
<td>• Hormone production</td>
<td>• Iprilimumab</td>
</tr>
</tbody>
</table>
| • Iodine (including kelp supplements) | |}

### 10.4. Increased clearance

<table>
<thead>
<tr>
<th>Agents/Conditions</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Primidone</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Beta blockers (e.g., propranolol, nadolol)</td>
</tr>
<tr>
<td>Oxacarbazepine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Iodinated contrast (ipodate, iopanoic acid)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Clomipramine</td>
</tr>
</tbody>
</table>

<sup>a</sup> Interferon alpha.
<sup>b</sup> HAART (highly active antiretroviral therapy).
<sup>c</sup> St. John’s Wort.
<sup>d</sup> Iprilimumab.
SPECIAL CONSIDERATIONS FOR THYROXINE REPLACEMENT

- the most reliable therapeutic end-point is the serum TSH
- regardless of the degree of hypothyroidism, patients 50+ with known or suspected coronary heart disease start low, go slow (≤ 50 mcg/day)
- elderly require 20 - 25% less / pregnancy needs more (50%)
- if adrenal insufficiency is suspected, treat before the thyroid to avoid adrenal crisis
- not recommended for weight loss
- target value differ for those with differentiated thyroid carcinomas. (TSH ≤ 0.1 mIU/L)
THYROID DISEASE AND THE ELDERLY

KEY POINTS

- TSH distribution curve shifts to higher values in older adults.

- There is no conclusive evidence that subclinical hypothyroidism has adverse cognitive, metabolic, or cardiovascular outcomes in the elderly.

- A considerable proportion of elderly patients with subclinical hypothyroidism or hyperthyroidism revert to normal values over time without any intervention.

- Physicians should be cautious about making therapeutic decisions in elderly patients with subclinical thyroid dysfunction.
ELDERLY

- In 60 to 90 yr olds
- effect of subtle changes in thyroid function on cognitive & metabolic outcomes is questionable
- no doubt that overt hypo or hyperthyroidism has detrimental effect on cognition
TSH shifts to higher levels with advancing age (age-specific reference levels for the lab)

60% revert to normal TSH over 5 years; only 2.9% progressed to overt hypothyroidism

subtle changes in TSH occur due to concurrent illness &/or medication that does not reflect true thyroid disease.

no relationship between SCH and cardiovascular events or mortality
CHILDREN

- consult an endocrinologist or pediatrician
- requirements vary with age:
  - directly affect growth and development (cognitive and pubertal), so needs to be monitored more closely
- often associated with other genetic / congenital defects
EVALUATION OF HYPOTHYROIDISM

Measure TSH

Elevated

Measure unbound T₄

Normal

Mild hypothyroidism

TPOAb⁺ or symptomatic

T₄ treatment

TPOAb⁻, no symptoms

Annual follow-up

Low

Primary hypothyroidism

TPOAb⁺

Autoimmune hypothyroidism

T₄ treatment

TPOAb⁻

Rule out other causes of hypothyroidism

Normal

Pituitary disease suspected?

No

No further tests

Yes

Measure unbound T₄

Low

Rule out drug effects, sick euthyroid syndrome, then evaluate anterior pituitary function

Normal

No further tests
While there is no consensus about population screening for hypothyroidism, there is compelling evidence to support in:

- Autoimmune disease, such as Type 1 DM
- Pernicious Anemia
- Those with first degree relative with auto-immune thyroid disease
- History of Head & Neck radiation incl. RAI therapy
- Prior thyroid surgery or dysfunction
- Abnormal Thyroid exam
- Psychiatric Disorders, including Dementia
- Patients taking amiodarone or lithium
THE FACE OF HYPERTHYROIDISM

Hot, “Hyper”, & Hysterical
HYPERTHYROIDISM
THYROTOXICOSIS

- First test is TSH - confirmatory
- In the absence of a TSH-producing pituitary tumor or TSH resistance, the TSH is almost never normal.
- Diagnostic accuracy improves when TSH and free T4 are assessed at the same time (inverse log-linear relationship), but TSH is more sensitive.
- when the clinical presentation is not diagnostic of Graves’ Disease, radionucleotide scan.
- Differential Diagnosis: with positive radionucleotide scan; with negative radionucleotide scan
### Causes of Thyrotoxicosis

<table>
<thead>
<tr>
<th>Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>GD</td>
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<td>TA or TMNG</td>
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<td>Trophoblastic disease</td>
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<tr>
<td>TSH-producing pituitary adenomas</td>
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<tr>
<td>Resistance to thyroid hormone (T&lt;sub&gt;3&lt;/sub&gt; receptor mutation)&lt;sup&gt;b&lt;/sup&gt;</td>
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<th>Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck</th>
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<td>Painless (silent) thyroiditis</td>
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<td>Amiodarone-induced thyroiditis</td>
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<td>Subacute (granulomatous, de Quervain’s) thyroiditis</td>
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<td>Iatrogenic thyrotoxicosis</td>
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<td>Factitious ingestion of thyroid hormone</td>
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<td>Struma ovarii</td>
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<tr>
<td>Acute thyroiditis</td>
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<tr>
<td>Extensive metastases from follicular thyroid cancer</td>
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OTHER TESTS

- ESR (>50 in subacute thyroiditis) or CRP
- TRAbs specific for Graves’ Disease
- Ultrasound does NOT contribute to diagnosis
- Free T3? - rarer entities of T3 toxicosis
CASE STUDY 2

❖ 34 y.o male East Indian descent

❖ history of Graves’ Disease in 2008, treated for one year on suppression therapy (methimazole), now presents with symptoms of low grade headache, heat intolerance, vague pre-prandial nausea and occasional palpitations.

❖ on exam the thyroid is palpable, smooth, slightly tender

❖ TSH is 0.25 mIU/L (0.35 - 5.00)
HOW SHOULD CLINICALLY OR INCIDENTALLY DISCOVERED THYROTOXICOSIS BE EVALUATED AND INITIALLY MANAGED?

- begin with assessment of disease severity - history & physical: cardiovascular and neuromuscular complications
- the severity of thyrotoxic symptoms is not proportional to the elevation of T3 and T4
- age is big determinant in severity of symptoms
- evaluation for signs of Graves’ Disease - gland size, ophthalmopathy, pretibial myxedema
What would you do next?

1. Reassure

2. Reassure and repeat TSH in 8 to 12 weeks

√ 3. Measure free T4

4. Radionucleotide Scan &/or TRAbs

5. Measure free T3

6. Thyroid Ultrasound
Free T4 is 17 pmol/L (12 - 22)

TPOAbs are negative

4 weeks later he returns: TSH is < 0.01

Free T4 is 35 and free T3 is 12.7 (3.5 - 6.5)

What has happened?
WHAT IS THE NATURAL HISTORY OF SUB-CLINICAL HYPERTHYROIDISM

- prevalence varies from 0.7 to 12.4%
- rate of progression to overt hyperthyroidism is 1 to 5%
- 30 to 38% get better in 2 to 5 years
- the rest stay the same

TSH RECEPTOR ANTIBODIES - AKA TBII, TBI, TSHRAB

- Measurement of TSHR Abs using a sensitive assay should be considered in hypothyroid pregnant patients with a history of Graves’ Disease who were treated with radioactive iodine or thyroidectomy prior to pregnancy. (done at 20–26 weeks gestation) Grade A, BEL 2

- Strong correlation between a high titre of TSHR Abs and the development of fetal or neonatal Graves’.
CASE STUDY 3

28F 18 weeks post partum presents with fatigue, cold intolerance, weight gain, and constipation. Also, she recalls having mild tremors, heat intolerance, and hyperdefecation approximately 4 weeks ago. TSH is 28 and FT4 is 6.
CASE STUDY

• Hypothyroid phase Post Partum thyroiditis.

• Treatment:
  1. Beta blocker ☛ only for symptoms
  2. None ☛ will resolve spontaneously
  3. Life long levothyroxine
  4. Levothyroxine for 6-12 months, then attempt to wean
POST-PARTUM THYROIDITIS (PPT)

- Destructive autoimmune thyroiditis within 1 year post-partum, results in:
  - Transient hyperthyroidism alone
  - Transient hypothyroidism alone
  - Transient hyper followed by hypo then recovery
    - 20-30%
POST-PARTUM THYROIDITIS (PPT)

- Prevalence about 7.5%

- Risk Factors:
  - Previous PPT (42%)
  - Positive anti-TPO (40-60%)
  - Type 1 diabetes (25%)
1-4 months post delivery

Lasts 2-8 weeks

Symptoms are usually mild
Follows hyperthyroid phase

i.e. about 2-6 months post-partum

“Hyperthyroid” phase may be subclinical or not even enough to lower TSH below normal
PPT DIAGNOSIS

- Insufficient evidence for screening general population

- Case Finding:
  - TSH at 3 months and 6 months:
    - Type 1 diabetes
    - Previous PPT
    - Anti-TPO +
    - Post-partum depression
PPT Diagnosis

- High index of suspicion in general population
- If clinical suspicion, measures TSH and FT₄
Graves’ Disease

Can Evaluate with Radioactive iodine (if not contraindicated - breast feeding) or TSH receptor antibodies

- Ophthalmopathy
- Persistent hyperthyroidism (>1 month)
- Severe hyperthyroidism with FT$_3$ $>$ FT$_4$
- No improvement in 3-4 wks
Repeat TSH, FT₄, FT₃ every 4-8 wks until normalization

About 30% will have permanent hypothyroidism
Hyperthyroid

- Asymptomatic or mild symptoms
  - No treatment
- Symptomatic
  - Beta blocker
    - Propranolol preferred ☛ Lowest breast milk concentration
PPT TREATMENT

✦ Hypothyroid

✦ Asymptomatic
  • TSH 5-10 ➔ Monitor
  • TSH >10 ➔ Consider levothyroxine

✦ Symptomatic
  • Levothyroxine
    • Start 50 - 100 mcg daily and adjust as necessary
    • Wean Levothyroxine after 6-12 months
    • Can discontinue and check TSH and FT₄ in 3 - 6 wks OR halve dose and check in 6 - 8 wks before stopping
POST-PARTUM THYROIDITIS

- If recovery occurs ➡ Check TSH yearly (for at least 5 - 10 years)
CASE STUDY 3

• Hypothyroid phase Post Partum thyroiditis. (Symptomatic and Significant)

• Treatment:
  1. Beta blocker ☛ only for symptoms
  2. None ☛ will resolve spontaneously
  3. Life long levothyroxine
  4. Levothyroxine for 6–12 months, then attempt to wean
WHEN TO CONSULT AN ENDOCRINOLOGIST

Although most physicians can diagnose and treat hypo/hyperthyroidism, consultation is recommended in the following situations:

- Children and Infants
- Patients in whom it is difficult to render and maintain a euthyroid state
- Pregnancy
- Women Planning Conception
- Cardiac Disease
- Presence of goitre, nodule or other structural changes in the thyroid
- Presence of other Endocrine Disease such as adrenal or pituitary disorders
- Unusual constellation of thyroid function tests
- Unusual causes of hypothyroidism induced by other agents
SUMMARY

- A serum thyrotropin is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations.

- The standard treatment is replacement with L-thyroxine using serum TSH as the reference guide.

- The decision to treat sub-clinical hypothyroidism when the serum TSH is < 10 mIU/L should be tailored to the individual patient.