Thyroid Hormone: Too little?

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The Thyroid Gland

Diseases of the Thyroid Gland
Among the most common endocrine disorders
- Over/underactive
- Growth (goiter)
- Nodules
- Cancers

Thyroid Hormone
- Primary function: regulation of metabolism
- Synthesized and stored within the thyroid gland
- Dietary iodine extracted from circulation
- Combined with amino acid tyrosine
- Circulates (99%) bound to TBG
- In peripheral tissues, T4 de-iodinated to T3
- Disorders
  - Hypothyroidism (too little)
  - Hyperthyroidism (too much)
**Hypothalamic-Pituitary-Thyroid Axis**

Adapted from Merck Manual of Medical Information, ed. R Berkow. 704:1997; courtesy of G. Brent

**Prevalence of Thyroid Disorders in Women**

- **SWAN**
  - 3,000 multiethnic women ages 42 to 52 yr
  - TSH abnormal in 10%
    - 2/3 above normal
    - 1/3 below normal

- **NHANES III**: presence of thyroid antibodies
  - 40 to 49 yr 15.8 %
  - > 80 yr 26.5 %


**Screening Recommendations**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Age to Begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA</td>
<td>Adults &gt; 35 yrs</td>
<td>every 5 yr</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Evidence insufficient</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Peri- or PMP women with ? findings</td>
<td></td>
</tr>
<tr>
<td>AAFP</td>
<td>Evidence insufficient</td>
<td></td>
</tr>
<tr>
<td>AACE</td>
<td>Older patients, esp. women</td>
<td></td>
</tr>
<tr>
<td>ACP</td>
<td>Women &gt; 50 yrs with ? Findings</td>
<td></td>
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Garber JR, Endocr Pract 2012;18:988

**Clinical Hypothyroidism**

- Most common thyroid disorder in women
  - Prevalence adult women 1.9 %
    - > 60 years 5.0 %

- Associated with:
  - Family history, postpartum thyroiditis, Type 1 DM, adrenal insufficiency, POI, celiac disease
  - Previous treatments for thyroid disorders

Suspicious for Hypothyroidism...

- Absence of typical symptoms does not exclude the diagnosis—especially in the elderly
- Memory and mental impairment, dementia, anemia, depression, heart failure, CHD
- Labs provide additional clues:
  - Hypercholesterolemia, hypertriglyceridemia, hyperprolactinemia, hyperhomocysteinemia, hyponatremia, anemia, elevated CPK

Laboratory Evaluation of Hypothyroidism

<table>
<thead>
<tr>
<th>Determination</th>
<th>Value in overt hypothyroidism</th>
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<tbody>
<tr>
<td>TSH</td>
<td>usually &gt; 10 mIU/L</td>
</tr>
<tr>
<td>Free T4</td>
<td>subnormal</td>
</tr>
<tr>
<td>TPOAb</td>
<td>Identify autoimmune thyroiditis when evaluating nodular thyroid disease</td>
</tr>
<tr>
<td></td>
<td>When evaluating subclinical hypothyroidism</td>
</tr>
</tbody>
</table>

Causes of Primary Hypothyroidism

- Thyroid destruction
- Autoimmune or non-autoimmune thyroiditis
- Radioactive iodine treatment
- Partial or total thyroidectomy
- External RT of head and neck
- Infiltrative disorders: amyloid, sarcoid, lymphoma

Medications
- Iodine excess, amiodarone, radiographic contrast
- Lithium, cytokines (interferon-α)

TSH: Thyroid Stimulating Hormone; TPOAb: Anti-thyroidperoxidase Ab
2013 Survey of Clinical Practice
Management of Primary Hypothyroidism

- Document current practices
  - Diagnostic evaluation
  - Choice of therapy
  - Follow-up
- Compare with 2012 ATA/AACE Clinical Practice Guidelines
- Respondents (percent of members polled)
  - 13.6% American Thyroid Association
  - 10.9% The Endocrine Society
  - 9.0% American Association of Clinical Endocrinologists


Treating Primary Hypothyroidism
Preparations: AACE/ATA Guidelines

- Treat with L-thyroxine monotherapy
- Evidence does not support T4/T3 combination therapy
  - Some patients prefer and some patient subgroups may benefit from combination therapy
  - Area for future research
- Desiccated thyroid hormone should not be used
- Recommend against compounded thyroid hormones unless suspected allergy to standard preparations

Jonklaas J, Thyroid 2014; Sept 29; Garber JR. Endocrine Practice 2012; 18:988-1028.

Why is levothyroxine monotherapy standard of care?

- Efficacy in resolving symptoms of hypothyroidism
- Long-term experience of benefits
- Favorable side effect profile
- Ease of administration
- Good intestinal absorption
- Long serum half-life
- Low cost


Dietary Supplements and Nutraceuticals
AACE/ATA Guidelines

Patients taking dietary supplements and nutraceuticals for hypothyroidism or euthyroidism should be advised:

- Commercially available thyroid-enhancing products are not a remedy for hypothyroidism
- Potential side effects of various preparations containing
  - Iodine
  - Sympathomimetic amines
  - L-thyroxine and/or L-triiodothyronine

### Treating Primary Hypothyroidism

**Dosing: AACE/ATA Guidelines**

- Dependent on age, lean body mass, etiology of hypothyroidism, TSH elevation, and general clinical context
- Young healthy adults: Full replacement dose
  - 1.6 mcg/kg of L-thyroxine daily
- > 50 to 60 yr without CHD: Start 50 mcg/d
- Known CHD: Start 12.5 to 25 mcg/d

Jonklaas J, *Thyroid* 2014; Sept 29; Garber JR. *Endocrine Practice* 2012; 18:988-1028.

### Thyroxine Administration

**ATA/AACE Guidelines**

- L-thyroxine should be taken:
  - With water, consistently
  - 60 minutes before breakfast, or
  - At bedtime, >3 hours after the last meal
- Not with substances or medications that interfere with absorption
  - Oral bisphosphonates, proton pump inhibitors, raloxifene, MVI, ferrous sulfate, calcium salts, soy


### Treating Established Hypothyroidism

**Monitoring: AACE/ATA Guidelines**

- TSH should be measured 4-6-8 weeks after:
  - Initiating treatment
  - Changing dose or preparation
  - Starting treatment with drugs that affect binding
- Target TSH (+FT4 level) within the normal range
- Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months, and then at 12-month intervals, or more frequently if the clinical situation dictates

Jonklaas J, *Thyroid* 2014; Sept 29; Garber JR. *Endocrine Practice* 2012; 18:988-1028.

### Central Hypothyroidism

- Insufficient TSH stimulation of normal thyroid gland
- Secondary to disorders of pituitary or hypothalamus
- 1:1000 incidence of primary hypothyroidism
- Characterized by:
  - Low FT4 with low or normal TSH
  - Consider combined pituitary hormone deficiencies
  - Treatment: titrate FT4 to upper half of normal range

Laboratory Evaluation of Thyroid Disorders

- Primary hypothyroidism
- Central hypothyroidism
- Subclinical hypothyroid

TSH free T4

Subclinical Thyroid Disorders

Thyroid Stimulating Hormone (mIU/L)
(FT4 in normal range)

- SUBCLINICAL HYPERTHYROIDISM
- NORMAL RANGE
- SUBCLINICAL HYPOTHYROIDISM

<0.1 0.1 - 0.4 0.4 – 4.5 4.5 – 10 >10

Subclinical Hypothyroidism

- TSH above normal with normal FT4 concentration
- Prevalence in women
  - Age 55 to 60 10%
  - > 60 years 20%
- Challenges in diagnosis
  - Race, age, sex, BMI, and dietary iodine intake contribute
  - Requires normal HA-pit axis and absence of severe illness
  - Fluctuations of TSH over time (often normalizes)
- Repeat in 3 to 6 months prior to treatment decision

Subclinical Hypothyroidism

Treatment of Subclinical Hypothyroidism?

AACE/ ATA Guidelines

- Patients whose serum TSH levels > 10 mIU/L
- Increased risk for heart failure and CVD mortality
- Should be considered for L-thyroxine treatment

Subclinical Hypothyroidism
Risk of CHD and Mortality

- 11 prospective cohorts
  - US, Europe, Australia, Brazil, Japan
- Data on 55,287 participants
  - 542,494 person-years of follow-up
- 6.2% had subclinical hypothyroidism
  - TSH 4.5 to 19.9 mIU/L
  - Normal thyroxine levels
- Increased risk of CHD events and CHD mortality with TSH > 10 mIU/L; not associated with TPOAb


Subclinical Hypothyroidism: MI Risk Among Postmenopausal Women

- Population-based nested case-cohort design
- WHI observational study (mean age 67.5 y)
- Association between subclinical hypothyroidism and first-time MI over 7 years
- Normal FT4 with TSH 4.68 – 6.99 mU/L, or > 7 mU/L
- No evidence to suggest association with MI


Subclinical Hypothyroidism: Risk of CHD and Mortality

<table>
<thead>
<tr>
<th>TSH Level (mIU/L)</th>
<th>No. of Events</th>
<th>No. of Participants</th>
<th>HR Ratio (95% CI)</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 - 6.0</td>
<td>204</td>
<td>2051</td>
<td>1.03 (0.90 - 1.18)</td>
<td></td>
</tr>
<tr>
<td>6.1 - 10.0</td>
<td>70</td>
<td>239</td>
<td>1.27 (1.06 - 1.52)</td>
<td></td>
</tr>
<tr>
<td>TSH &gt; 10.0</td>
<td></td>
<td></td>
<td>1.99 (1.59 - 2.49)</td>
<td></td>
</tr>
</tbody>
</table>

CHD Events and Mortality increase with TSH > 10 mIU/L


Subclinical Hypothyroidism: MI Risk Among Postmenopausal Women

- No association
- No effect of severity

Is subclinical hypothyroidism a CVD risk factor in the elderly?

Cardiovascular Health Study All Stars Study (age 85)
- Significant 13% increase in TSH with time
- No association between subclinical hypothyroidism and mortality, but FT4 was positively associated with death
- Hypothesis?
  - Age-associated alteration in pituitary TSH set point
  - A decrease in TSH bioactivity
  - Decreased responsiveness of thyroid gland to TSH

Waring AC, J Clin Endocrinol Metab 2012; 97:3944-3950.

Is subclinical hypothyroidism a CVD risk factor in the elderly?

The negative effect of subclinical hypothyroidism on CV events and mortality appears:
- Well established in young adults < 55 to 60 y
- Less evident in moderately old people < 70 to 75 y
- Could vanish in the oldest old! > 80 to 85 y


Treatment of Subclinical Hypothyroidism?

AACE/ ATA Guidelines
- TSH between the upper normal limit and 10 mIU/L
Consider:
- Symptoms of hypothyroidism
- Positive TPOAb: predicts progression?
- Atherosclerotic CVD, heart failure, associated risks
- Age? < 65 y might derive > benefit with < risk


Levothyroxine Rx of Subclinical Hypothyroidism

Fatal and Nonfatal CVD Events and Mortality
- UK Gen Practice Data Base
- Subclinical hypothyroidism: TSH 5 – 10 mIU/L; FT4 nl
- Treatment was associated with fewer fatal and nonfatal IHD events and mortality in persons < 70 y
- In group > 70, no difference by levothyroxine treatment

Treatment of Subclinical Hypothyroidism?
AACE/ATA Guidelines
- TSH between the upper normal limit and 10 mIU/L
- Unresolved key issues:
  - Whether or not L-thyroxine treatment will prevent CVD or heart failure
  - Whether age is a critical determinant of risk for cardiac morbidity
  - Perils of inducing hyperthyroidism

Do not use thyroid hormones...
AACE/ATA Guidelines and ATA Task Force
- If symptoms are suggestive of hypothyroidism without biochemical confirmation of diagnosis
- To treat obesity in euthyroid patients
- To treat depression in euthyroid patients

When to Consult an Endocrinologist?
AACE/ATA Guidelines
Patient characteristics:
- Difficult to render and maintain euthyroid state
- Goiter, nodule, other structural change in gland
- Adrenal insufficiency and/or pituitary disorders
- Unusual constellation of TFT
- Drug induced hypothyroidism
- Cardiac disease

Thyroid Hormone: Too little?
Summary and Conclusions
- Hypothyroidism is common in women, with incidence increasing with age
- Aggressive case-finding is an appropriate strategy
- Treatment of overt hypothyroidism is indicated
- Subclinical hypothyroidism should be monitored prior to a treatment decision as it may spontaneously resolve
- Given the age-associated increase in TSH, a cautious approach to treating older persons seems merited