Hypothyroidism: Practice Guidelines

"Advances in Diabetes and Thyroid Disease 2013" presented by Joslin Diabetes Center and Harvard Medical School

November 2013

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Clinical Practice Guidelines for Hypothyroidism in Adults: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN THYROID ASSOCIATION 2012

Garber JR et al. Thyroid December 2012 Endocrine Practice November-December 2012

Advisory

AACE-ATA Guideline is Key Reference for talk
Repetition will be employed on purpose
HIPAA Compliance. All cases are fictitious. However, resemblance to real patients is not coincidental.
Objectives

- 1) The role of clinical scoring systems in diagnosing and managing hypothyroidism
- 2) TSH normal range(s): impact of age, ethnicity, and stage of pregnancy
- 3) Subclinical Hypothyroidism: When to treat it and its impact on the development of cardiac disease

Highlights

- Treating early
- Symptom based treatment pitfall
- TSH and other tests
- Hypothyroidism and the heart
- Weight control
- Pregnancy ranges
- T4/T3 combinations/supplements/prenatal vitamins
Focus mostly on ambulatory adult patients, gravid and non-gravid

Levels of Evidence
- Level 1
  - Prospective, randomized, controlled trials (large)
- Level 2
  - Prospective controlled trials, with or without randomization – limited body of outcome data
- Level 3
  - Other experimental and non-experimental or observational data
- Level 4
  - Expert opinion

Recommendation Grades
- Grade A
  - BEL 1 or 2 with positive upgrade
- Grade B
  - BEL 2, 1 with (-) factor or 3 with (+) factor
- Grade C
  - BEL 3, 2 with (-) factor or 4 with (+) factor
- Grade D
  - BEL 4, 3 with (-) or NO committee consensus
Hypothyroidism

Before

After

BEFORE
What Used to be “Before & After”

What is Now “Before and After”

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Clinical Signs and Symptoms

• How useful are they?

Utility of Thyroid Exam: Identifies Disease But Does Not Specify Thyroid Status

Percentage of Euthyroid Patients, Subclinical and Hypothyroid Patients Reporting Symptoms
Clinical Scoring Systems: NOT for Diagnosis

- R5. Clinical scoring systems should not be used to diagnose hypothyroidism. Grade A, BEL 1

Causes of Hypothyroidism

- Primary:
  - Principal Cause and Largely Autoimmune
- Central
  - Secondary + Tertiary
- More recently recognized
  - Chemotherapeutic Agents
    - Ipilimumab, Bexarotene, Sunitinib (tyrosine kinase inhibitors)
  - Consumptive hypothyroidism

Hypothyroidism (2° AITD)\

Hypothyroidism (2° Graves' Disease)
PRINCIPAL LABS TESTS EMPLOYED IN THE DIAGNOSIS AND MONITORING OF PATIENTS WITH HYPOTHYROIDISM

FREE HORMONE HYPOTHESIS

• ONLY FREE HORMONE IS METABOLICALLY ACTIVE.
• THEREFORE ONLY FREE HORMONE, NOT TOTAL WHICH IS LARGELY BOUND TO BINDING PROTEINS, DETERMINES THYROID STATUS

T4: Total and Free

Free Thyroxine Measurement Key
“Free Hormone Hypothesis”
Gold Standard: Equilibrium Dialysis Estimates
• Free Thyroxine Assays
• Use and T4 Antibodies
• Free Thyroxine Index
• Total T4 x T3 UPTAKE
• T3U ESTIMATES % free hormone
Hypothyroidism

**T3: Total and Free**

- **TOTAL T3**
  - Principal use is diagnosing and following Thyrotoxic patients, *NOT* Hypothyroid patients
- **Free T3**
  - Not as reliable as Total T3
  - Can estimate with Total T3 x T3 UPTAKE

**Anti-Thyroid Antibodies**

- Markers of Chronic Thyroiditis
- Anti-Thyroglobulin Antibodies
  - Does not Correlate with hypothyroidism
- Anti-Thyroid Peroxidase Antibodies (formerly known as Anti-microsomal Antibodies)
  - Correlate with the development of hypothyroidism

**Anti-TSH Receptor Antibodies (TSHRAb)**

- Used in the diagnosis and monitoring of Graves’
- TSI (Thyroid Stimulating Immunoglobulin)
- TBII (TSH Binding Inhibitory Immunoglobulin)
Severity of Hypothyroidism by Thyroid Levels

McDermott and Ridgway

Lab Tests

- The **Good**: FTI
- The **Bad**: free thyroxine by kit and even worse in pregnancy
- The **Ugly and even uglier**: T3 followed by Free T3
Lab Tests

- TSH
  - The “fairest of them all”
  - But, alas, even she is not perfect

But does = FREE T4 imply = TSH?

<table>
<thead>
<tr>
<th>I FEEL LOUSY</th>
<th>I FEEL GREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 4.5 (4.5-12)</td>
<td>T4 4.5 (4.5-12)</td>
</tr>
<tr>
<td>T3 U 30 (25-35)</td>
<td>T3 U 30 (25-35)</td>
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<tr>
<td>FTI 4.5 (4.5-12)</td>
<td>FTI 4.5 (4.5-12)</td>
</tr>
<tr>
<td>Free T4 0.8 (0.8-1.8)</td>
<td>Free T4 0.8 (0.8-1.8)</td>
</tr>
<tr>
<td>TSH 30</td>
<td>TSH 9</td>
</tr>
</tbody>
</table>

• HOW DOES THIS HAPPEN
  ASSUMING THAT THEY ARE NOT STARTING AND STOPPING
  THYROID MEDICATION AND THEIR TESTS ARE CONFIRMED
  OVER A 3 WEEK PERIOD?
Hypothyroidism

Different Free T4 set points, different degrees of disease

When Disease becomes overt

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Setpoint 6.5

Free T4 Index

Population Reference Range

Overt Hyperthyroidism

Free T4 Index

Setpoint 13.0

Overt Hypothyroidism

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Hypothyroidism

SUBCLINICAL
- Normal Free T4 Estimate
- TSH usually below 10
- 5% or more USA

OVERT
- Low Free T4 Estimate
- TSH usually above 10
- Less than 1% USA

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T3 to Diagnose Hypothyroidism: NO

- R10. Serum total T3 or assessment of serum free T3 should not be done to diagnose hypothyroidism Grade A, BEL 2; Upgraded because of many independent lines of evidence and expert opinion.

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ASSOCIATED AUTOIMMUNE
DISORDERS

See Autoimmune
Think Thyroid;
See Thyroid
Think Autoimmune

When to Treat?

40 year old female: TSH 3, FTI 8.0
negative Anti-TPO antibodies
comes to you for counseling about
whether she should be treated with
thyroid hormone
Family history: thyroid or
autoimmune disease is negative
Asymptomatic
Thyroid exam is unremarkable as is
the remainder of her exam
Should she be treated now?

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What Used to be “Before & After”

What is Now “Before and After”

What’s is the big deal?
Thyroid Hormone is one of the safest things we prescribe
Why not treat anyone who might benefit from it?
Hypothyroidism

Hazards of Overtreatment

- Heart
- Bone
- Psychiatric
Hazard: Overtreatment

- Colorado Prevalence Study, 2000
  - 20.7% (316) of patients on thyroid medication were subclinically hyperthyroid!
  - 0.9% (13) Overt
- Stelfox, 2004
  - Only 56% received standard monitoring
  - More adverse effects (afib, unstable angina) with poor monitoring

Patients With Hypothyroid Symptoms and Normal TFTs Treated Hypothyroidism

**Saravanan, Clinical Endo 2002:**
- Hypothyroid patients with normalized TSH—still more likely to feel poorly.

**Boeving, Thyroid 2011**
- Confirmatory Study

No Clinical Evidence that Adjusting TSH from (2.0-4.8)--> (0.3-1.99)-->(<0.3) Produces Benefit

**NON-PREGNANT TARGET TSH**

- R17. In patients with hypothyroidism who are not pregnant, the target range should be the normal range of a third generation TSH assay. If an upper limit of normal for a third generation TSH assay is not available, an upper limit of normal of 4.12 should be considered and if a lower limit of normal is not available, 0.45 should be considered. Grade B, BEL 2

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**What are the odds that she will become hypothyroid?**

TPOAb (+) patients with TSH of 3-4 have less than 50% chance of developing hypothyroidism over 20 years; if Negative, <20%!

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**20 Year % Probability of Developing Hypothyroidism**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>TSH (mIU/liter)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
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<td>3</td>
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<td>25</td>
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<tr>
<td>60</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>17</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>70</td>
<td>4</td>
<td>21</td>
<td>4</td>
<td>21</td>
<td>9</td>
<td>37</td>
</tr>
</tbody>
</table>

TPOAb (+) patients with TSH of 3-4 have less than 50% chance of developing hypothyroidism over 20 years; if Negative, <20%!

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Value of Treating Patients with TSH Values Between 2.5 and 4.5

- Most studies used to invoke the benefit of treating or preventing atherosclerotic disease used markers and not cardiovascular events as endpoints.
- No prospective study has shown that levels lower than 5-10 are associated with more cardiovascular disease.
- With marginal evidence of treating those with TSH's between 5 and 10, there is virtually no evidence for treating those below 4.5 and an RCT arguing against it.


Half empty / Half full argument from the perspective: “primum non nocere” and “if it ain’t broke, don’t fix it”

- While 50% of individuals with TSH in the 2.5 - 4.5 mIU/L range may have thyroid disease, 50% may not!
- Many who do are mild, at low risk for progression, and may even remit.
- The risk of overtreatment is not trivial (20% or so).


What about TSH of 5-10 or >10?

More to Follow
10 years later—she is now 50 years old-- her thyroid tests are repeated TSH 3.0, FTI 8.0 Positive Anti-TPO Antibodies Family history unchanged Still asymptomatic Thyroid exam is unremarkable as is the remainder of her exam

Should she be treated? If so, what do you give her and how much do you start with? How long would you treat her for?

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>TPOAb (+)</th>
<th>TPOAb (-)</th>
<th>TSH (mIU/liter)</th>
<th>20 Year % Probability of Developing Hypothyroidism</th>
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<td></td>
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<td>70</td>
<td>4</td>
<td>21</td>
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<td>21</td>
</tr>
</tbody>
</table>

TPOAb (+) patients with TSH of 3-4 have less than 50% chance of developing hypothyroidism over 20 years; if Negative, <20%!

10 more years elapse—she is now 60 years old—she is tired, cannot lose weight, feels cold, and cannot concentrate. Family of thyroid disease is still negative.

TSH 6.0, FT4 7.0, Cholesterol is 180, HDL is 70, LDL 95, TG 75

Thyroid exam is unremarkable as is the remainder of her exam including her BP.

Should she be treated? If so, what do you give her and how much do you start with? How long would you treat her for?

R16. Treatment should be considered particularly if they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.

Grade B, BEL 1; evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.


TSH 5-10? DEPENDS

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Overt: How much?

- **Recommendation 22.7.1**: When initiating therapy in *young healthy adults with overt hypothyroidism*, begining treatment with *full* replacement doses should be considered. *Grade B, BEL 2*

- **Recommendation 22.7.2**: When initiating therapy in *patients older than 50-60 years with overt hypothyroidism, without evidence of coronary heart disease*, an L-thyroxine dose of 50 µg daily should be considered. *Grade D, BEL 4*

Subclinical: How much?

- **Recommendation 22.8**: In patients with *subclinical hypothyroidism* initial L-thyroxine dosing is generally lower than what is required in the treatment of overt hypothyroidism. A daily dose of **25 to 75 µg** should be consid-ered, depending on the degree of TSH elevation. Further adjustments should be guided by clinical response and fol-low up laboratory determinations including TSH values. *Grade B, BEL 2*

2 months after starting therapy, her symptoms are unchanged, tests normal what do you do?
What do you do now that thyroid hormone did not help?

• Consider other causes for her symptoms

Pregnancy
Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy provides strong physiological evidence to support redefining the TSH upper limit of normal in the first trimester to 2.5 mIU/liter.

Negro, J Clin Endocrinol Metab. 2010 Sep;95(9);
Pregnancy Thyroid Testing

• R9. In pregnancy, the measurement of total T4 or a free thyroxine index (FTI), in addition to TSH, should be done to assess thyroid status. Because of the wide variation in the results of free T4 assays, should only use when method-specific and trimester-specific reference ranges are available. Grade B, BEL 2

Pregnancy TSH values

• R. 14.2 In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; third trimester, 3.5 mIU/L. Grade B, BEL 2.

Treatment prior to Pregnancy

• R19. Treatment with L-thyroxine should be considered in women of child bearing age with serum TSH levels between 2.5 mIU/L and the upper limit of normal for a given laboratory’s reference range if they are in the first trimester of pregnancy or planning a pregnancy including assisted reproduction in the near future. Grade B, BEL 2
Pregnancy Dose Requirements

- Hypothyroidism: average increase is 50% over pre-partum dose
- The increase occurs early and generally plateaus around the end of the first trimester
- Several approaches:
  - Increase in advance; Increase by 30% at outset; or follow closely and adjust
  - Resume pre-partum dose at the time of delivery

CATS – Controlled Antenatal Thyroid Study

- Large, well done, long prospective randomized controlled trial of T4 treatment vs. no treatment in hypothyroid mothers starting in the 1st trimester.
- PRIMARY OUTCOME:
  - IQ of children tested between 3yr 2mo and 3yr 6mo
  - % IQ < 85 in children from treated vs non treated mothers

International Thyroid Congress, Paris 2010

Main results
(Intention-to-treat analysis)

From John Lazarus CATS PI
**CATS - Conclusions**

- No benefit of screening for hypothyroidism in pregnancy with respect to intellectual development of the child “although there does remain some uncertainty”

**Screening: Is there benefit?**

- Aggressive case finding? Yes
- Screening populations? Society positions differ, based on age, sex
  - Mixed results and timing of intervention in CATS—up to 16 weeks—may be too late
- National Institute of Child Health and Human Development Trial Ongoing

**Screening: Pregnancy?**

R20.1.1 Universal screening is not recommended for patients who are pregnant or are planning pregnancy, including assisted reproduction.

Grade B, BEL 1; limitations to the evidence and therefore insufficient evidence for lack of benefit to recommend Grade A

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24 year old female with 2 year history of hypothyroidism diagnosed after she presented with secondary amenorrhea and found to have T4 1.4 and TSH 114. 6 months ago when she was not feeling well she was switched from Levothyroxine 112 mcg to 75 mg of desiccated thyroid, lost 4 lbs and feels better.

After learning that demands for thyroid hormone will rise during pregnancy, she seeks your advice.

How will you counsel her?

T4 T3 Combinations
T4-T3 Combinations

- What are they?
  - Combinations of T4 and T3 given as 1 or more formulation
- What is the rationale for prescribing them instead of T4 alone?
  - Make up for T3 deficit
  - "Natural"

Mean Serum Free T₄ by IMA before and after Thyroidectomy

Normal T3 Production and Physiology

- Average woman:
  - Thyroid secretes: 101 mcg T4
  - 6 mcg T3
  - Peripheral Conversion from T4:
    - 20 mcg T3
  - Total T3 production
    - 26 mcg T3
  - Levels are steady throughout day
  - Production varies from organ to organ

Figure 3. Mean serum free T₄ levels are measured by immunometric assay (IMA). P = 0.46 comparing time points. Jonklaas et al JAMA 2008: 299:769
80% of T3 is made from T4 by Deiodinase

T4-T3 Combinations
- Formulations
  - Desiccated Thyroid: T4: T3 ratio: ~4:1
    - (~16:1 is physiologic and continuous)
  - Customized by clinician with synthetic T4 and T3
  - Compounded by Specialty Pharmacy:
    - Safety Concerns
    - Slow release not proven

T3: Unmet Needs
Has a Role in the Treatment of Hypothyroidism Been Demonstrated?
- Endpoints have been mostly affective ones
- Trials have been relatively short
- Studies to date mixed...and meta-analyses negative, but not entirely so
- We don’t yet understand patient preferences for combinations
IS THE T4-T3 CHAPTER CLOSED?

• MAYBE NOT!

Does the DIO2 gene play a role?

Why Might some Prefer T4/T3?

The rarer CC genotype of the rs225014 polymorphism in the deiodinase 2 gene (DIO2) was present in 16% of the study population (552) and was associated with:

- worse baseline GHQ scores in patients on T4
- enhanced response to combination T(4)/T(3) therapy, but did not affect serum thyroid hormone levels.

Desiccated Thyroid

• Should be viewed as T4/T3 combination
• First randomized, double-blind crossover study: Hoang, JCEM March 28, 2013 RCT
• 70 patients: 49% preferred vs 19% T4 vs 33% neither
• Predictors of preference: Reduce Thyroid Symptoms, Weight loss
• TSH comparable

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Game Changer?

- 1 Study
- Relatively small
- Modest duration
- No significant improvement in Quality of Life

L-T4 Rx of Choice

- R22.1 Patients with hypothyroidism should be treated with L-thyroxine monotherapy Grade A, BEL1.

T4/T3?

“Evidence does not support using”

R22.2 The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. Grade B, BEL1.

Not considered Grade A because of unresolved issues raised by studies reporting some patients prefer and some patient subgroups may benefit from L-thyroxine and L-triiodothyronine combination.
Question 3.12 How should hypothyroidism be treated and monitored?

R22.3 L-thyroxine and L-triodothyronine combinations should not be administered to pregnant women or those planning pregnancy. Grade B, BEL 3; upgraded because of potential for harm of hypothyroxinemia during pregnancy.

Overt: How much?

- **Recommendation 22.7.1:** When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with full replacement doses should be considered. Grade B, BEL 2

- **Recommendation 22.7.2:** When initiating therapy in patients older than 50-60 years with overt hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50 µg daily should be considered. Grade D, BEL 4

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Subclinical: How much?

- **Recommendation 22.8:** In patients with subclinical hypothyroidism initial L-thyroxine dosing is generally lower than what is required in the treatment of overt hypothyroidism. A daily dose of 25 to 75 µg should be considered, depending on the degree of TSH elevation. Further adjustments should be guided by clinical response and follow-up laboratory determinations including TSH values. *Grade B, BEL 2*

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**Question 3.12** How should hypothyroidism be treated and monitored?

R23. L-thyroxine should be taken with water consistently 30 to 60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption.

*Grade B, BEL 2.*

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**Some More on TSH**
Joslin Diabetes Center
Advances in Diabetes and Thyroid Disease 2013

Hypothyroidism

TSH Population Reference Range

Reasons for the skew BESIDES AGE

- Euthyroid Outliers - inherent TSH liability
- Measurement of bioactive TSH isoforms
- TSH receptor polymorphisms - TSH sensitivity
- Occult autoimmune thyroid dysfunction (AITD)

TSH mIU/L

~ 4-5

95% Limits

TSH and some Pitfalls

- The patient with central disease
- Abnormal isoforms, TSH receptor polymorphisms
- Drugs (glucocorticoids, dopaminergic drugs [metoclopramide], metformin)
- Diurnal Variation
- Heterophilic antibodies - particularly low titer
- Requires steady state: pitfalls in a inpatient population and early phases of pregnancy
- Adrenal Insufficiency (may raise TSH)

Thyroid Function in the Elderly

Serum TSH Level in Disease-free

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Subclinical Hypothyroidism: \[ \Delta \text{TSH} \geq 40\% \text{ to Establish Change} \]

![Graph showing subclinical hypothyroidism](image)

Karmisholt Thyroid 2008; 18:303

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**DIURNAL VARIATION:** 50% UP-DOWN

![Graph showing diurnal variation](image)

Caron, 1986

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**TSH 2011**

- An Approach for Development of Age-, Gender-, and Ethnicity-Specific Thyrotropin Reference Limits Boucai, Hollowell, Surks
  - THYROID Volume 21, Number 1, 2011

- **Examples Age + Ethnicity Differences**
  - African Americans between 30-39: upper normal \( > 24 \)
  - Mexican Americans \( \geq 80 \): upper normal \( < 5.0 \)

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Normal range of TSH values?

R14.1 The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. TSH levels may rise with age. If an age based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 should be considered. Grade A, BEL 1.

You are asked to do a Shared Medical Appointment (SMA)—for asymptomatic hypothyroid patients comprised of 7 members of the Joslin BIDMC Geriatric Track & Field Club who were screened for thyroid disease. They are all very competitive and want to know if taking thyroid hormone will improve their athletic performance.

TSH 5: Will she lift it higher?
TSH 6: Will they throw it further?

TSH 7: Will they run faster?

TSH 8: Will she be able to focus better?
Why Not Treat Everyone?

Hazards of Overtreatment

- Heart
- Bone
- Psychiatric

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Hypothyroidism

- Colorado Prevalence Study, 2000
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  - 0.9% (13) Overt

- Stelfox, 2004
  - Only 56% received standard monitoring
  - More adverse effects (afib, unstable angina) with poor monitoring
Sites of Action of Thyroid Hormone on the Heart

Based on Klein and Danzi, In: The Thyroid 2004

Sites of Action of Thyroid Hormone on the Heart: Hypothyroidism

Based on Klein and Danzi, In: The Thyroid 2004

Hypothyroidism and the Heart

- Hypertension (Diastolic)
- Diastolic Dysfunction
- Elevated Cholesterol*
- Long Q-T Syndrome
- Serum CK Elevation (*Statin Hazard?)
- Coagulopathy

Hypothyroidism

- Tissue Thermogenesis
- Systemic Vascular Resistance
- Diastolic Blood Pressure
- Renin/Angiotensin/Aldosterone System
- Preload
- Cardiac Output
- Afterload
- Cardiac Chronotropy, Inotropy, & Lusiotropy

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**SUBCLINICAL HYPOTHYROIDISM**

**METHANALYSES CHD and Mortality**

- **OCHS--AIM, 2008**
  - 10 Studies looked at Subclinical Hypothyroidism
    - CHD RR 1.2
    - Higher quality studies: LOWER: RR (1.02-1.06)
    - Older than 65: LOWER: RR (0.98-1.05)
    - Younger than 65: HIGHER: RR (1.09-2.09)
  - **Conclusion:** May increase risk, particularly in younger than 65

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**Subclinical Hypothyroidism**

**Impact on Ischemic Heart Disease Events**

- **BIONDI, COOPER ENDOR REV 2008**
- **FROM LADENSON**
  - Age (years)
  - Studies Since Ochs: Elderly May Not be spared
    - CHF: Rodondi, 2008 *J Am Coll Cardiol*
      Cardiovascular Health Study (yet 2013 Hyland, JCEM follow up no impact regardless of TSH !)
    - CHD Rodondi, 2010, JAMA;
    - ASCVD Razvi, 2010 JCEM Whickham Study
    - CHF Gencer, 2012 Circulation
Best to Date NON RCT--
Observational: Benefit of Treatment?

- **UK General Practitioner**: In the ~50% of individuals 40-70 treated with L-thyroxine, (TSH 4.5-10) the hazard ratio for cardiac events was reduced (0.67, CI 0.49 – 0.92). Arch IM 2012

- **Cleveland Clinic**: high risk ASCVD Clinic (TSH 6.1-10 + >10) who were under 65 and not treated with thyroid hormone had higher all-cause mortality McQuade, Thyroid 2011

Heart Failure Events by TSH

<table>
<thead>
<tr>
<th>TSH (mU/L)</th>
<th>Events / Participants</th>
<th>HRa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH 10.0-19.9</td>
<td>40 / 224</td>
<td>1.86 (1.37-2.52)</td>
</tr>
<tr>
<td>TSH 7.0-9.9</td>
<td>54 / 422</td>
<td>1.65 (0.84-3.33)</td>
</tr>
<tr>
<td>TSH 4.5-6.9</td>
<td>156 / 1422</td>
<td>1.01 (0.61-1.62)</td>
</tr>
</tbody>
</table>

Gencer Circulation 2012; 126:1040

What to do?

- Until RCTs done
- Preponderance of data favors treating
  - Younger
  - Higher TSH values (>10)
TSH 5-10?

**DEPENDS**

R16. Treatment should be considered particularly if they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.

Grade B, BEL 1; evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.


TSH >10?

**YES**

R15. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.

Grade B, BEL 1; not generalizable and meta-analysis does not include prospective interventional studies.

• SHIFTS IN THYROID STATUS AND WEIGHT LOSS

Before and 41 days After

Plummer: Does Rx Hypothyroid Patients result in weight loss?
• Yes if patients are overtly hypothyroid
• What type?: EDEMA
• For how long?: NOT KNOWN BUT SEVERELY HYPOTHYROID and UNDERWEIGHT MAY TEND TO GRAVITATE TOWARDS THE MEAN
Baseline Subclinical Hyper and Hypo & REE

Al-Adsani, JCEM 1997; 82:1118 Fig 4a

Weight and Baseline TSH

Fox, Archives Internal Medicine, 2008

Weight and Change in TSH

Fox, Archives Internal Medicine, 2008

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WEIGHT and TSH

• Weiss in Accompanying Editorial:

• Cause or Effect?

Weight Loss Studies in those without hypothyroidism

Why is thyroid hormone a “lousy” weight loss drug?

• Although it increases metabolism, it also increases appetite!
A 42 year old woman wants to lose weight. She assures you that nothing has worked. “Eats like a bird.” Exercises 12 ½ hours a week. Thyroid evaluation normal. Wants thyroid anyway.

Thyroid Hormone Therapy for Obesity

- INCONCLUSIVE BENEFIT
- INDUCES SUBCLINICAL HYPERTHYROIDISM

TREATING OBESITY: NO

- R30. Thyroid hormone should not be used to treat obesity in euthyroid patients. Grade A, BEL 2
- Upgraded to A because of potential harm—

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Impact of T4 on TPOAb(+) Pregnancy

Negri et al 2006

Role for TPOAb?

• R3. TPOAb measurement should be considered when evaluating patients with infertility, particularly recurrent miscarriage. Grade A, BEL 2; upgraded because of favorable risk-benefit potential.
Treatment of TPOAb+ Women?

- R20. Treatment with L-thyroxine should be considered in women of child-bearing age with normal thyroid hormone levels when they are pregnant or planning a pregnancy including assisted reproduction if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or past history of hypothyroidism Grade B, BEL 2

Who Should be referred to an Endocrinologist?

- Non-Endocrinologists who are familiar with the diagnosis and treatment of hypothyroidism should be able to care for most patients with primary hypothyroidism

- Infants and children
- Unable to maintain euthyroid state
- Planning and being Pregnant
- Unstable cardiac status
- Goiter, nodule
- Pituitary, Adrenal Disease
Supplements

27 y.o. planning pregnancy and would like to take a “thyroid support” product seen on the internet based on her understanding that her demands for thyroid hormone will rise during pregnancy.

Hazards of Supplements

- Supra-physiologic amounts of iodine may alter thyroid status, particularly in those with disease
- Many thyroid-enhancing products have sympathomimetic amines and iodine
- Many thyroid support products have significant amount of thyroid hormone
- Kang et al, 2011, ATA

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“Dietary Supplement” Example
Ingredients include: 130 mg Thyroid Tissue. "May cause a reaction with other thyroid medications. If heart palpitations occur, discontinue use."

Counsel Patients taking alternative therapies
• R34 Patients...should be counseled about the potential side effects of...preparations containing iodine...sympathomimetic amines..."thyroid support" since they could be adulterated with L-thyroxine or L-triiodothyronine
• Grade D BEL 4

Which thyroid support product do you prescribe?
QUIZ?
ONLY IF THERE IS ENOUGH TIME

Question 1

• True False

• Over a 20 year period, the presence of elevated Anti-TPO Ab’s regardless of TSH levels at the outset virtually always predict the development of hypothyroidism
Question 2
• True False
• In the USA the TSH normal range is the same regardless of age and ethnic background

Question 3
• True False
• TSH levels normally go down significantly during the first trimester of pregnancy

Question 4
• True False
• Randomized control trials have shown that treating patients whose TSH values are greater than 10 improves cardiac outcomes
Question 5

• True or False: 2 parts
• More people (absolute #) with 4 or more symptoms of hypothyroidism have overt hypothyroidism than
• A) Subclinical Hypothyroidism
• B) Euthyroid Population

Question 6

• True or False
• In primary hypothyroidism, which accounts for the vast majority of cases of hypothyroidism, the earliest stage is characterized by a drop in T3 before a rise in TSH levels

THANK YOU FOR YOUR ATTENTION!