Management of Hypothyroidism—an Evidence Based and Practical Approach

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Learning Objectives

- Apply guideline-directed and evidence-based approaches for the diagnosis and management of hypothyroidism
- Describe clinical presentation and patient factors associated with hypothyroidism
- Outline treatment for patients with hypothyroidism, including those experiencing residual symptoms
- But first, just 2 slides on physiology (with more to come later)

Hypothalamic-Pituitary-Thyroid Axis

TSH is the Most Sensitive Test for Thyroid Status

From: Spencer et al JCEM. 70: 453, 1990

Etiologies of Primary Hypothyroidism

- Chronic autoimmune (Hashimoto’s thyroiditis)
- Ablative therapy
  - 131-I
  - Surgery
- Pharmacologic agents
  - Amiodarone (and other iodides)
  - Lithium carbonate
  - Interferons, interleukins
  - Tyrosine kinase inhibitors

Symptoms of Hypothyroidism

- Arthralgias
- Cold intolerance
- Constipation
- Decreased appetite
- Impaired memory
- Decreased perspiration
- Depression
- Dry skin
- Fatigue
- Hoarseness
- Lethargy
- Menstrual disturbances
- Muscle cramps
- Paresthesias
- Sleepiness
- Weight change

Signs of Hypothyroidism

- Bradycardia
- Coarse hair
- Dry, cool, pale skin
- Goiter
- Hoarseness
- Nonpitting pre-tibial edema
- Puffy eyes and face
- Slow movements
- Slow speech
- Delayed relaxation of deep tendon reflexes
- Thinning lateral third of eyebrows

Case Study: JP—Mildly Elevated TSH

- 73-year-old woman with elevated cholesterol of 278 detected at routine health fair. On questionnaire, responded with:
  - Fatigue
  - Becoming forgetful
  - Depression (husband died 6 months prior)
- Exam: pulse: 68, BP: 152/96, placid appearance, exam otherwise normal
- Saw her physician, who checked TSH: 7.2 µu/L(0.4-4.0); FT4: 1.2 ng/dL (0.8-2.0)
- An antidepressant was prescribed, and she was asked to return if no improvement

Questions

- Should TPO antibodies have been measured?  
  - CPG Grade B, BEL 1  
    - If Ab’s +, mprogress to overt hypothyroidism
- Should her subclinical hypothyroidism (normal T4 and elevated TSH) have been treated with L-T4?  
  - We’re still arguing!
- Should clinical scoring systems be used in the diagnosis of hypothyroidism?  
  - NO! Grade A, BEL 1

Natural History for the Development of SCH: 10-Year Follow-Up

- Over 10-year follow-up:  
  - 34% overt hypothyroidism
  - 57% SCH
  - 9% euthyroid
- Greatest predictors of overt disease  
  - Initial TSH level
  - Presence of antithyroid antibodies (4.3 %/yr v 2.6 % if neg)


Progression of Subclinical to Overt Hypothyroidism

- Do not measure T3!
Prevalence of Elevated Serum TSH by Decade of Age and Gender (n = 798)

![Graph showing Prevalence of Subclinical Hypothyroidism (SCH) in Women in Different Age Groups](image)

Clinical Effects of SCH
- Progression to overt hypothyroidism
- Symptoms of hypothyroidism
- Effects on mood and cognition
- Effects on lipid levels
- Effects on the heart
- Effects on children of hypothyroid mothers

Mild Thyroid Failure: Cognitive Function with LT4 Therapy
- 14 patients
- TSH ~8.8
- Wechsler Memory Scale

*P<0.05

On the other hand……

  40 women with mean TSH ~8 and normal FT4, divided into L-T4 and control groups studied for 6 months
  - Results: neuropsych and other symptoms showed no difference with L-T4 Rx to normal TSH

  89 individuals (45 men, 44 women) with TSH <10, and 154 euthyroid controls (72 men, 82 women). 69/89 with SCH entered into placebo controlled, double blind L-T4 Rx.
  - Results: no difference in neuropsych or QOL with Rx

Colorado Study: TSH and Cholesterol

TC (mg/dL) | TSH (mIU/L)
---|---
<0.3 | 0.3-5.1
5.2-10 | >10
15-20 | >20
40-60 | >80

All TC values were significantly different from euthyroid TSH values (P<.003).
LDL increased P<.001

TC = total cholesterol.
HDL-C = high-density-lipoprotein cholesterol; MI = myocardial infarction.

Subclinical Hypothyroidism, Lipids, and the Heart

- Normal or slightly ↑ total cholesterol
- ↑ LDL-C
- ↓ HDL-C
- Endothelial dysfunction
- Aortic atherosclerosis
- MI

HDL-C = high-density-lipoprotein cholesterol.

Colorado Thyroid Disease Prevalence Study (N=25,862)

% Abnormal Total CHOL, LDL-C, HDL-C

![Graph showing percentage of abnormal cholesterol levels]

Subclinical Hypothyroidism, Lipids, and the Heart

Basel Thyroid Study (N=63)

Reduction in Total Cholesterol with LT4 in SCH

![Graph showing reduction in total cholesterol with LT4]

SCH as Risk Factor for Cardiovascular Disease: The Rotterdam Study

- Euthyroid
- SCH
- SCH and antibodies

![Graph showing odds ratio for cardiovascular disease]

1Adjusted for patient age; 2Thyroid peroxidase; Reference risk.

**Does treatment of SCH make a difference?**

<table>
<thead>
<tr>
<th>TSH 4.5-10</th>
<th>Strength of Association</th>
<th>Benefit of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid sx</td>
<td>None</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Neuropsych sx</td>
<td>None</td>
<td>Insufficient</td>
</tr>
<tr>
<td>CV endpoints</td>
<td>Insufficient</td>
<td>No evidence</td>
</tr>
<tr>
<td>Lipids</td>
<td>Insufficient</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Cardiac dysfx</td>
<td>Insufficient</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

**Surks, M et al. JAMA 2004**

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**So, to treat or not to treat with L-T4**

- **TSH < 10**
  - little evidence to support for age >70
  - ok for younger, if symptoms, positive TPO AB,s, goiter, desire pregnancy

- **TSH > 10**
  - treat

- **Caveat—clinical judgment prevails!**  
Cooper DS and Biondi B. Lancet 2012: 379; 1142-1154

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**Hypothyroidism and Pregnancy**

<table>
<thead>
<tr>
<th>Mothers</th>
<th>IQ of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal TSH (n=124)</td>
<td>107 +/- 12</td>
</tr>
<tr>
<td>Hypothyroid Rx LT4 (n=14)</td>
<td>*111 +/- 12</td>
</tr>
<tr>
<td>Hypothyroid no Rx (n=48)</td>
<td>#100 +/- 15</td>
</tr>
</tbody>
</table>

*Normal vs Rx, P=0.2, #Normal vs no Rx, P=0.005  

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**Is Screening for Pregnancy Recommended?**

- Very controversial, but AACE/ATA CPG’s:  
  - Grade B, BEL 1

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**Society Guidelines for Treatment of SCH**

- AACE/ATA—unclear, but for TSH >10, Grade B, BEL 1.
- Endocrine Society--ditto
Treatment of Patients with Subclinical Hypothyroidism
Thyroidologist Practice Patterns

Survey of ATA & AMA members

Hypothetical cases:
- Young vs. Older
- TSH 8.2
- + Ab’s

McDermott MT et al. Thyroid. 2001.

What About Screening Recommendations, with TSH?
- American Thyroid Association (ATA)—at age 35 and every 5 years, at routine examination.
- American Association of Family Physicians —insufficient evidence to screen
- American College of Physicians —women > 50 years of age, if symptoms
- US Preventative Services Task Force—insufficient evidence for or against screening
- AACE/ATA CPG’s—consider for people >60 yrs
  - Grade B, BEL 1

What About Case Finding? Stratification of At-Risk Populations*
- Psychiatric diagnosis
- Women <35 years of age
- Men <60 years of age
- Hyperlipidemia
- Women >35 years of age
- Men >60 years of age
- Gestation
- Postpartum
- Family history of thyroid disease
- Recent change in symptoms
- Women >60 years of age
- Type 1 diabetes
- Autoimmune disease
- Lithium, interferon alpha, amiodarone, TKIs
- Thyroid surgery/radiation

What about case finding?
- AACE/ATA CPG’s—Grade B, BEL 2

Case Study: JP—SCH, 2-Year Follow Up
- JP struggled for the next 2 years and her family felt she was going “downhill”
- Thyroid tests were repeated:
  - TSH: 28.2 mu/L (0.4-4.0)
  - FT4: 0.8 ng/dL (0.8-2.0)
  - TPOAb 198 (<0.5) (so, might have been predictive)?
Progression of Subclinical to Overt Hypothyroidism

Clinical Effects of Overt Hypothyroidism—Subclinical Amplified

- Symptoms and signs of hypothyroidism
- Effects on mood and cognition
- Effects on children of hypothyroid mothers
- Effects on lipid levels
- Effects on the heart

Treatment of Overt Hypothyroidism

- Goal: normalize TSH level
- Starting dose for healthy patients: <50 to 60 years of age may begin at full replacement—1.6 µg/kg/day (Grade B, BEL 2)
- Starting dose for healthy patients ≥50 to 60 years of age should begin at ≤50 µg/day (Grade B, BEL 4). Dose should be increased by 25 µg/day, if needed, at 6- to 8-week intervals, depending on the TSH concentration (Grade B, BEL 2).
- Starting dose for patients with CAD should begin at 12.5 to 25 µg/day and increase by 12.5-25 µg/day, if needed, at 6- to 8-week intervals (Grade B, BEL 2).
**TSH Distribution in Normal Population**

![TSH Distribution Graph](image)

- **Mean TSH Goal (on LT4 treatment): 0.5-2.0 mU/L**

**Determinants of L-Thyroxine Requirements**
- Age
- Severity and duration of hypothyroidism
- Weight
- Concomitant drug therapy
- Pregnancy
- Presence of cardiac disease

**Increasing Thyroid Hormone Dose Requirements: Differential Diagnosis**
- Non-compliance
- Pharmacy error
- Other medications
- Weight gain
- Change of LT₄ brands
- Malabsorption (celiac disease)

**Increasing Thyroid Hormone Dose Requirements: Medications**
- Iron
- Calcium
- Proton Pump Inhibitor
- Antacids
- Sucralfate
- Estrogen
- Sertraline
- Bile acid resins
- Anticonvulsants

**What about treated patients who still feel poorly?**

A 46-year-old woman with treated hypothyroidism, due to Hashimoto’s, on L-T₄. She still has severe, unrelenting fatigue; continues to have depression, difficulty concentrating, poor memory, and difficulty losing weight but insists she takes her medications. She wants T4:T3 combination—"I’m not a converter!"

**Past medical history:** Fibromyalgia

**Physical exam:** BP: 128/75; pulse: 72; height: 5’4”; weight: 156 lb
Complete exam normal

**Lab:** TSH: 1.1 mU/L; Free T4 1.4 ng/dL (nl: 0.8-1.8)
TPO Ab’s 995 (<0.5)

**Colorado Thyroid Disease Prevalence Study (N = 25,862)**

**Thyroid Status among Treated Participants (n = 1525)**

<table>
<thead>
<tr>
<th>Status</th>
<th>Participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroid</td>
<td>0.9</td>
</tr>
<tr>
<td>Subclinical Hypothyroid</td>
<td>20.7</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>60.1</td>
</tr>
<tr>
<td>SCTH</td>
<td>17.6</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>0.7</td>
</tr>
</tbody>
</table>

McDermott MT, In Werner and Ingbar’s The Thyroid (Braverman L, Cooper D), 2012 (in press)
**Persistent Symptoms on LT4 Rx**

Community Based Questionnaire Study:

- 397 Hypothyroid Patients with normal TSH on LT4
- 397 Control Subjects (matched for gender and age)

<table>
<thead>
<tr>
<th>Abnormal Survey Score</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health Questionnaire</td>
<td>26%</td>
<td>34%</td>
<td>&lt;.014</td>
</tr>
<tr>
<td>Thyroid Symptom Questionnaire</td>
<td>35%</td>
<td>35%</td>
<td>.41</td>
</tr>
</tbody>
</table>

Saravanan P, Clin Endo 2002; 57:577-85

**Hashimoto’s Thyroiditis**

Coexisting Autoimmune Diseases

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Symptom (% of) Men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>4.7</td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>4.5</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>2.8</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1.2</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>0.7</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1.2</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>0.7</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.7</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>1.2</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Any other autoimmune disease: 14.3%


**Are Some Symptoms Due to Hashimoto’s Thyroiditis?**

426 Euthyroid women with goiter undergoing thyroidectomy

Assessments: symptoms, thyroid antibodies, thyroid histology

<table>
<thead>
<tr>
<th>TPO Ab Positive</th>
<th>TPO Ab Negative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mU/L</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Symptom Score</td>
<td>6.7 ± 2.5</td>
<td>4.1 ± 2.8</td>
</tr>
</tbody>
</table>

Symptoms associated with TPO Ab (Hashimoto’s Disease)

Fatigue, irritability, nervousness, lower quality of life, dry hair, early miscarriage, history of breast cancer

NS = non-significant. Ott J et al. Thyroid. 2011;21(2):161-167

**Would a T4/T3 Combination Help Her?**

(Time for a little more physiology)

- T4 101 ug/day
- T3 6 ug/day
- T3 20 ug/day
- T3 26 ug/day

20% secreted
80% converted from T4


**Deiodinases**

- T4
  - D2, D1
  - D3, (D1)
  - D1: Liver, distal (circulating T3)
  - D2: Brain, pituitary (brain T3)
- T3
  - D3, (D1)
  - D1, D2
- T2

McDermott MT, Endocrine Practice 2012; May 1; 1:30 (e-pub ahead of print)

**Maybe L-T4 alone isn’t enough?**

Response of L-T4 vs LT4/T3, and effect on psychological well-being

Study:

- 532 hypothyroid patients (84T, 166M)
- Mean age 57 yrs; mean LT4 dose 123-127 mcg/day
- RCT: LT4 × LT4 (usual dose – 50 mcg) × LT3 10 mcg × 3 months

Polymorphisms:

- 16 tested across all 3 Deiodinase genes: 16 % Thr92Ala D2
- Polymorphism homozygotes

General Health Questionnaire:

- Those patients with the Thr92Ala D2 polymorphism (16%) were worse at baseline on L-T4 alone, and improved more with LT4/LT3 c/w LT4 alone (p = .03)

Panicker V, J Clin Endocrinol Metab. 2009; 94;1823:9
Type 2 Deiodinase Polymorphisms
Effect on Response to LT4 and to LT4/LT3

Subjects: 552 hypothyroid patients (84% women, 16% men; mean age: 57);
mean LT4 dose: 123-127 mcg/day
Randomized controlled trials: LT4 vs LT4 (usual dose: 50 mcg) + LT3 10 mcg x 3 months
Polymorphisms: all deiodinase genes tested for 16 polymorphisms
Thr92Ala homozygotes = 16%

General Health Questionnaire
Thr92Ala Homozygotes
Baseline: worse compared with no polymorphisms (P = .03)
LT4/LT3 treatment: improved more compared with LT4 alone (P = .03)


Combined LT/LT3 Therapy
Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective Benefit</th>
<th>Subjective Benefit</th>
<th>Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunevicious 1999</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Walsh 2003</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sawka 2003</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Clyde 2003</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Siegmund 2004</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Saravanan 2005</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Escobar-Morreale 2005</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Apelhof 2005</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rodriguez 2005</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Regalbuto 2007</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Slawik 2007 (central)</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Escobar-Morreale 2005 review</td>
<td>No benefit of T4/T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grozinsky-Glasberg 2006 meta-analysis</td>
<td>No benefit of T4/T3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA = not applicable.

Why Do Some Treated Hypothyroid Patients Still Feel Poorly?

n Symptoms may persist in hypothyroid patients even after they are biochemically euthyroid on levothyroxine therapy
n This may be due to a coexisting nonendocrine illness
n This may be due to Hashimoto’s thyroiditis itself
n This may be due to a coexisting autoimmune condition
n Some patients may have a D2 polymorphism that subtly impairs T4 to T3 conversion in the brain; no test available

LT4/LT3 Therapy for Hypothyroidism
Summary

Should all hypothyroid patients be treated with combination LT4/LT3 therapy?
– No

Should any hypothyroid patients be treated with combination LT4/LT3 therapy?
– Reasonable if symptoms persist on optimal LT4 therapy

Clinical use of combination LT4/LT3 therapy
– The optimal T4:T3 ratio is ~10:14:1
– LT3 is best taken twice daily or as slow release
– Avoid thyroid hormone excess (low TSH)

McDermott MT, Endocrine Practice 2012; May 1: 1-30 (e-pub ahead of print)

Singer’s Rule for Treatment of Hypothyroidism

– No contraindication for T4/T3, but monitor TSH to make sure you’re not overtreating.
– If you want a busy practice, don’t argue!

Returning to Case JP……..

– L-thyroxine 0.025 mg/day was initiated, and the dose was gradually increased at 6-week intervals
  – Within 4 months she like “her old self”
– TSH: 1.2 μu/L; FT4: 1.4 ng/dL

Page
Thank you!

Questions?