“Women’s Health Forum”: Hormones and Thyroid Disorders

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Thanks

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USC School of Medicine
Tony Parker, M.D., Ph.D., Larry Barbaras, Kevin Donohoe, M.D.
Harvard Medical School
Scope

- Focus mostly on ambulatory adult patients, gravid and non-gravid
- Emphasize hypothyroidism, the most commonly treated thyroid condition
Female Preponderance for common thyroid disorders in the United States (iodine sufficient)

Structural: Nodular disease and Cancer

Functional: Hypothyroidism and Hyperthyroidism [including extra-thyroidal manifestations]

Autoimmunity (reviewed earlier today)

Estrogen bases for Preponderance

Nodules/Thyroid Cancer

Nodules Much more Common (4-10:1). FTRL-5 (functional thyroid cells) and thyroid cancer lines affected by estrogen may play a role

Pregnancy and multi-parity promote nodule and thyroid growth, particularly in areas of suboptimal iodine intake

Evolution towards functional autonomy leading to toxic adenoma and toxic multinodular and differentiated thyroid cancer, both much more common in women believed to be part of same process
THYROID NODULES

Potential for Increasing Thyroid Nodule Incidence is Enormous!

- Multiply Clinically apparent disease by 10+!
  - Adult males 1.5%→ 15%+
  - Adult females 6.5%→65%+
PREVALENCE OF THYROID NODULES—Compiled Series: 1955-1989

Lessons From 1955: 60+ Years Later

- A great deal of thyroid nodular disease:
  - Exists
  - Is missed
  - Is unimportant
Thyroid carcinoma is more common in women (all ages)

Ratio of Female to Male Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000
Thyroid carcinoma is “common” in women

Jemal et al., 2004

Thyroid carcinoma is becoming more common in women

Source: SEER Program Database, NCI
RISING INCIDENCE

- Increasing use of FNA?
- Incidentalomas?
- Role of Ultrasound examinations and multiple FNA's of sub-clinical lesions?

BIDMC, BWH, UPENN “NODULE CLINICS” - -
HYPERTHYROIDISM

Hyperthyroidism: The common forms

- Uptake 85%
- Uptake 25%
- Uptake 32%
- Uptake 1%
Lab tests

- Choice of TFTs
- Role of Total T3
- TSH receptor antibodies
- Other:
  - Baseline CBC
  - Baseline LFTs

TRAb—Monitor Pregnancy

Hall & Evered Fig 256 & 257
Pretibial Myxedema

Acropachy
Obstruction

SINGLE STANDARD DOSE of RADIOACTIVE IODINE UNLIKELY TO WORK
COSMETIC REASONS?

Keys to choosing Rx

• Cause of thyrotoxicosis which predicts course, comorbidities, goals (pregnancy) severity, time frame for control, goiter status (size, nodularity, obstructive)
• Pros and cons of Rx
• Patient input
Therapy

- Antithyroid drugs
- Radioactive Iodine
- Surgery
- Observation
  - Subclinical (selected cases)
  - Thyroiditis (self-limited)

Adjunctive RX

- Other:
  - Beta Blockade to temporize
  - Iodine
  - Glucocorticoids
PTU INDICTMENT

- ACUTE LIVER FAILURE
  - 1/10,000 ADULTS
  - 1/2,000 CHILDREN
- 16 LIVER TRANSPLANTS: UNOS
- 22 SERIOUS LIVER EVENTS: 5 TRANSPLANTS: FDA

PTU ROLE

- Methimazole (or carbimazole outside the United States) should be used in virtually every patient who chooses ATD therapy, except in 1st trimester pregnancy when propylthiouracil is preferred.
Clinical Practice Guidelines for Hypothyroidism in Adults: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN THYROID ASSOCIATION Garber JR et al. Thyroid & Endocrine Practice 2012
Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. Jonklaas J, Thyroid. 2014
Aggressive case finding: a clinical strategy for the documentation of thyroid dysfunction. Hennessey JV, Ann Intern Med. 2015
ITALIAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS STATEMENT: REPLACEMENT THERAPY FOR PRIMARY HYPOTHYROIDISM: A BRIEF GUIDE FOR CLINICAL PRACTICE. Guglielmi R, Endocrine Practice 2016
Highlights

- Treating early or not?
- Symptom based treatment pitfall
- TSH and other tests
- Hypothyroidism and the heart
- Weight control
- Pregnancy ranges
- T4/T3 combinations/supplements/prenatal vitamins

What we hope for
What Used to be “Before & After”

What is Now “Before and After”

Evered, Hall

Evered, Hall
Clinical Signs and Symptoms

• How useful are they?

Utility of Thyroid Exam: Identifies Disease But Does Not Specify Thyroid Status
Percentage of Euthyroid, Subclinical and Hypothyroid Patients Reporting Symptoms

60% euthyroid have ≥ 1 symptom
15% ≥ 4 symptoms

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

Causes of Hypothyroidism

- Primary:
  - Principal Cause and Largely Autoimmune
  - Post Surgical
- Central
  - Secondary + Tertiary
- More recently recognized
  - Chemotherapeutic Agents
    - Ipilimumab, Bexarotene, Sunitinib (tyrosine kinase inhibitors), Pembrolizumab, Nivolumab
  - Consumptive hypothyroidism
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 anti T4 Antibodies
• Free Thyroxine Index
  • Total T4 x T3 UPTAKE
    • T3U ESTIMATES % free hormone
**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

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**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’ NOT
- Hypothyroidism
  - TSI (Thyroid Stimulating Immunoglobulin)
  - TBII (TSH Binding Inhibitory Immunoglobulin)

Severity of Primary Hypothyroidism by Thyroid Levels

- TSH rises first and abruptly
- Decline of T4 and T3 slower and later
Central hypothyroidism: TSH declines first

- Some important details
  - Age
  - Ethnicity
  - Time of Day
  - Some variation with repeated measurements
  - Iodine sufficiency
Thyroid Function in the Elderly
Serum TSH Level in Disease-free

Surks MI, Hollowell JG. J Clin Endocrinol Metab. 2007;92:4575-82 –FROM
LADENSON

DIURNAL VARIATION:
50% UP-DOWN

Caron, 1986
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.


But does = FREE T4 imply = TSH?

I FEEL LOUSY
- T4 4.5 (4.5-12)
- T3 U 30 (25-35)
- FTI 4.5 (4.5-12)
- Free T4 0.8 (0.8-1.8)
- TSH 30

I FEEL GREAT
- T4 4.5 (4.5-12)
- T3 U 30 (25-35)
- FTI 4.5 (4.5-12)
- Free T4 0.8 (0.8-1.8)
- TSH 9
• HOW DOES THIS HAPPEN ASSUMING THAT THEY ARE NOT STARTING AND STOPPING THYROID MEDICATION AND THEIR TESTS ARE CONFIRMED OVER A 3 WEEK PERIOD?

Different Free T4 set points, different degrees of disease

When Disease becomes overt

From Andersen Thyroid 13:1069, 20
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

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.
ASSOCIATED AUTOIMMUNE DISORDERS

See Autoimmune
Think Thyroid;
See Thyroid
Think Autoimmune

Evered, Hall

When to Treat?
Case 1: 30 year old female: TSH 3, FTI 8.0 positive Anti-TPO antibodies positive comes to you for counseling about whether she should be treated with thyroid hormone. *Not* considering pregnancy
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?

What’s the big deal? Thyroid Hormone is one of the safest things we prescribe
Why not treat anyone who might benefit from it?
Increased risk of developing atrial fibrillation in patients with subclinical hyperthyroidism

Mcdermott and Ridgeway
Hazard: Overtreatment

- **Heart**
- **Bone**
- **Psychiatric**

**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

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


<p>| TABLE 3. Clinical parameters (descriptive mean ± standard error) analyzed by treatment (T₃ dosage) and by serum TSH at the end of treatment periods |</p>
<table>
<thead>
<tr>
<th>TSH (mIU/liter)</th>
<th>Low (n = 23)</th>
<th>Middle (n = 47)</th>
<th>High (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0-4.8</td>
<td>73 ± 3.0</td>
<td>73 ± 2.0</td>
<td>72.8 ± 2.1</td>
<td>0.97</td>
</tr>
<tr>
<td>0.3-1.99</td>
<td>65 ± 1</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>0.98</td>
</tr>
<tr>
<td>&lt;0.3</td>
<td>65 ± 1</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>0.21</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73 ± 3.0</td>
<td>73 ± 2.0</td>
<td>72.8 ± 2.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>0.98</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>123 ± 2</td>
<td>123 ± 2</td>
<td>122 ± 2</td>
<td>0.70</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73 ± 2</td>
<td>73 ± 2</td>
<td>73 ± 2</td>
<td>0.54</td>
</tr>
<tr>
<td>Ankle jerk relaxation time (ms)</td>
<td>363 ± 7</td>
<td>357 ± 7</td>
<td>343 ± 7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Zawalinski score</td>
<td>2.9 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Post hoc testing using the Scheffe procedure showed that middle and high doses were significantly different from low dose (P < 0.01).

What are the odds that she will become hypothyroid?
30 YEAR OLD: TPOAb (+): TSH of 3 \( \rightarrow \) 17% chance of developing hypothyroidism over 20 years

Autoimmune Thyroid Disease: 20 Year % Probability of Developing Hypothyroidism

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>TSH (mIU/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
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<td>50</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>70</td>
<td>4</td>
</tr>
</tbody>
</table>


10 years later—she is now 40 years old: is tired, cannot lose weight, feels cold, and cannot concentrate. *Not* planning pregnancy
-- her thyroid tests are repeated
TSH 6.0, FTI 8.0 Positive
Anti-TPO Antibodies
Family history unchanged
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?

L-T4 Rx of Choice

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

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

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
2 months after starting therapy, her symptoms are unchanged, tests normal what do you do?

Percentage of Euthyroid, Subclinical and Hypothyroid Patients Reporting Symptoms

60% euthyroid have ≥ 1 symptom
15% ≥ 4 symptoms

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

Canaris et al.
What do you do now that thyroid hormone did not help?

• Consider other causes for her symptoms

Video: “It’s Not Your Thyroid”
https://www.youtube.com/watch?v=zgL4055crpA&t=68s
No other causes determined
Back to her thyroid?

T3 Hypothesis

- “T3 is important as the main iodothyronine with significant binding to nuclear TRs at physiological concentrations, and T4 is important as a precursor of T3”
  - T4 pro-hormone
  - T3 active hormone
Treated athyreotic hypothyroidism:

Free thyroid hormones and FT3/FT4 ratio frequency distribution.

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
  – Production varies from organ to organ
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
• Slow release formulations elusive
• 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
• Suggestion of DIO2 gene polymorphisms may play a role, but not strong predictors

We don’t yet understand patient preferences for combinations
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.


Pregnancy

TSH: Pregnant vs. Non-Pregnant
TPO Ab Status
Pregnancy

- TSH upper limits of normal are lower
- Need more thyroid hormone and iodine (role of prenatal vitamin with iodine)
- Anti-TPO antibodies are associated with:
  - Impaired thyroid reserve
  - Increased risk of miscarriage, which may be due to other factors other than impaired thyroid reserve
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.

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Alexander, Pearce, 2017
Thyroid
R22.3 L-thyroxine and L-triiodothyronine 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**

How should hypothyroidism be treated and monitored?

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
Thyroid Hormone Therapy for Obesity

• INCONCLUSIVE BENEFIT
• POOR CHOICE WEIGHT LOSS: Increases metabolic rate AND appetite!
• INDUCES SUBCLINICAL HYPERTHYROIDISM

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
Thank You!