Approach to Thyroid Disorders: A Primer for Primary Care

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Objectives

• Review thyroid gland physiology, regulation, and hormone production

• Review diagnosis and treatment of hypothyroidism

• Review rationale and potential role for T3 therapy

• Follow-up the finding of a low serum thyrotropin (TSH) level with appropriate diagnostic investigations

• Review the etiologies of a low serum TSH and how to make a diagnosis

• Realize that a low serum TSH is not always the result of suppression by elevated thyroid hormones (T4 and/or T3)
Thyroid Hormone Production

Hypothalamic - Pituitary - Thyroid Axis

TRH = Thyroid Releasing Hormone
TSH = Thyroid Stimulating Hormone

+ Stimulation
- Inhibition
Thyroid Hormone Production

Primary Hypothyroidism

- Hashimoto’s Disease (Autoimmune)
- Post-surgical Hypothyroidism
- Post-RAI treatment (Graves, Toxic MNG)
Primary Hypothyroidism Diagnosis

• Elevated serum TSH in routine clinical practice

• Very few other disorders than can cause an elevated TSH
  – Lab interference (HAMA)
  – TSH secreting pituitary adenoma (rare)
  – Recovery from Euthyroid Sick Syndrome
  – Adrenal Insufficiency
Diagnosis
Per the “experts”

• In most patients with symptoms or signs suggestive of hypothyroidism the serum TSH should be the initial test

  – ↑TSH, repeat the TSH with a serum free T4 to make the dx
    • Repeat ↑TSH and ↓FT4
      – Consistent with primary hypothyroidism, replacement therapy with T4 should be initiated
  – Repeat ↑TSH but normal range FT4
    • May indicate subclinical hypothyroidism
      – The decision about T4 replacement is made on a case by case basis and depends partly upon the degree of TSH elevation and symptoms reported by the patient
Diagnosis

• If TSH is within the normal reference range, but the patient has convincing symptoms of hypothyroidism
  – Repeat serum TSH and obtain free T4 to assess for central hypothyroidism (hypothalamic/pituitary disorder)

• Do not always assume that because the TSH is normal they do not have a thyroid problem (see later case)
Central Hypothyroidism

• Low or “normal range” TSH, in setting of Low FT4/FT3
  – Rarely a slightly high TSH can be observed

• Pituitary or Hypothalamic Process
  – Mass lesions
  – Infiltrative disorders
  – Pituitary irradiation history
  – Pituitary surgery
  – Infarction/Apoplexy (Sheehan Syndrome)
  – Genetic diseases - pit-1 mutation
  – Empty sella syndrome
Central Hypothyroidism

• Isolated central hypothyroidism would be very unlikely

• Usually occurs with other anterior pituitary hormone deficiencies

• If a diagnosis of central hypothyroidism is suspected
  – Complete an evaluation of the remaining hypothalamic/pituitary axes
  – Refer to an endocrinologist
  – Likely will require pituitary imaging (MRI)
Signs & Symptoms of Hypothyroidism

**Symptoms**
- Weight gain
- Cold intolerance
- Fatigue
- Hair loss
- Constipation
- Depression

**Signs**
- Delayed DTR
- Amenorrhea
- Nail pitting
- Dry skin
- Periorbital puffiness
- Slowed speech/movement
- Hair loss
- Unusual loss of hair in the outer edge of the eyebrow
Treatment of Primary Hypothyroidism

• Levothyroxine (generic, name brand, etc.)
  – Remind them how to take it correctly!

• T3 therapy (Liothyronine, Cytomel®)

• Desiccated Thyroid Extracts [Pig thyroid (T4 and T3)]
  – Armour® Thyroid and others variants
Do Patients Really Need T3 Therapy?

- Most patients do well with just T4/Levothyroxine
- Symptoms of hypothyroidism are vague and non-specific
  - Often times, residual symptoms, despite appropriate treatment, are unrelated to the thyroid condition
- A minority of patients may feel better with T3 therapy
Case 1:

A 38 year old female
Diagnosed with hypothyroidism a year ago
Takes 112 mcg of T4
  TSH – 2.197  (0.5-5.5)
  Free T4 – 1.2  (0.9-1.8)
  Free T3 – 2.9  (2.6-4.6)

Energy is not good, + fatigue; wants to try Armour thyroid…..
SomePatientshavePersistentSymptomsDespiteAdequateT4Therapy

•SomepatientshavesymptomsconsistentwithhypothyroidismdespiteadquatetSHandT4levels

Some Patients have Persistent Symptoms Despite Adequate T4 Therapy

• Some of these patients ask for addition of T3 to the treatment regimen
  – Many of them have found claims of need for T3 on the internet

  – Some have friends whose doctors claim that only combination therapy works
It Is Not Your Thyroid (usually)!!!
A significant number of these patients will have other conditions responsible for these residual symptoms

- Sleep disorders (Untreated OSA)
- Depression
- Medications causing fatigue
- Obesity
- Anemia
- Vitamin D deficiency
- Lack of EXERCISE!!!!
- Adrenal Insufficiency (rare)
  - Note, I did not mention Adrenal Fatigue!

- Treatment of these may lead to clinical improvement
But, is there more to this story?
How many with persistent symptoms?

Community based health questionnaire:
397 patients with normal TSH and T4
397 age and sex matched controls

Abnormal Survey score

- General Health Questionnaire
  - Controls: 26%
  - Patients: 34%
  - P = 0.014

- Thyroid Health Questionnaire
  - Controls: 36%
  - Patients: 49%
  - P < 0.01

T3 Therapy Needed Theory:

No T3 Therapy Needed Theory:

Hypothalamus

TRH

TSH

T3 + T4

However

- T3 is the major feedback regulator of TSH secretion
- If TSH is normal, brain T3 must be normal

# Early Randomized Controlled Trials of T4/T3 Combination Therapies

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<th>Study</th>
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<th>Subjective Benefit</th>
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- Escobar-Morreale 2005 Review: No benefit of T4/T3
- Grozinsky-Glasberg 2006 Meta-Analysis: No benefit of T4/T3
Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study

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Objective: Our objective was to investigate the effectiveness of DTE compared with l-T₄ in hypothyroid patients.

Design and Setting: We conducted a randomized, double-blind, crossover study at a tertiary care center.

Patients: Patients (n = 70, age 18–65 years) diagnosed with primary hypothyroidism on a stable dose of l-T₄ for 6 months were included in the study.

Intervention: Patients were randomized to either DTE or l-T₄ for 16 weeks and then crossed over for the same duration.

Outcome Measures: Biochemical and neurocognitive tests at baseline and at the end of each treatment period were evaluated.

Results: There were no differences in symptoms and neurocognitive measurements between the two therapies. Patients lost 3 lb on DTE treatment (172.9 ± 36.4 lb vs 175.7 ± 37.7 lb, P < .001). At the end of the study, 34 patients (48.6%) preferred DTE, 13 (18.6%) preferred l-T₄, and 23 (32.9%) had no preference. In the subgroup analyses, those patients who preferred DTE lost 4 lb during the DTE treatment, and their subjective symptoms were significantly better while taking DTE as measured by the general health questionnaire-12 and thyroid symptom questionnaire (P < .001 for both). Five variables were predictors of preference for DTE.

Conclusion: DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over l-T₄. DTE therapy may be relevant for some hypothyroid patients. (J Clin Endocrinol Metab 98: 1982–1990, 2013)
Follow-up Testing

• TSH is all that is required unless there is something that does not make sense

• In most circumstances, there is very little information gained from checking FT4 or FT3 once the patients have started thyroid hormone therapy
  – Patients (and Dr. Google) will very frequently disagree
Low TSH

• Most commonly suggestive of a hyperthyroid state
  – BUT NOT ALWAYS!
The Low TSH

• A low serum TSH is a commonly encountered finding, of which there are many etiologies

• A low TSH is not always the result of suppression by elevations in circulating thyroid hormones
  – Particularly in the hospitalized patient
The Low TSH

• A low TSH (<0.4 μIU/mL)
  – Slightly low: (0.1 to 0.4)
  – Frankly suppressed (<0.1)

• Different etiologies/conditions can yield various levels of TSH lowering
  – However, the approach to a correct diagnosis can be integrated into a solitary algorithm

• Overt hyperthyroidism is usually associated with a frankly suppressed TSH (<0.1)
Key Points

• The history is vital to correctly interpret TFTs

• The trend of TFTs can be invaluable in correctly interpreting TFTs
  – One good thing that results from using an EHR!
Approach

• A low TSH should always be followed by an evaluation of the T4 and/or T3 status
  – T4-thyroxine and T3-triiodothyronine
  – Free thyroid hormone levels preferred

• Free vs. Total
  – Use free thyroid hormones, especially in the acute/inpatient setting

  – Low Albumin/TBG in malnourished patients may make total levels low, and not reflect a patient’s true thyroid status

  – Likewise, total levels can be high during pregnancy or in women taking OCPs (estrogen)
Approach

• A low TSH in the setting of normal levels of the free thyroid hormones should always be reassessed 4-6 weeks later prior to making a definitive diagnosis or pursuing more involved testing.

• Frankly low TSH values should be evaluated in a more expedited manner, regardless of the levels of free thyroid hormones.
Lab tests will place patient in a particular category

But it is the history, physical, trend of thyroid function tests, and imaging results (iodine uptake(scan) that are crucial in making the correct diagnosis.
Key Points
History & Physical

• Important to incorporate clinical context when interpreting abnormal TFTs
  – Signs and Symptoms
    • Suggestive of Hypo vs. Hyperthyroidism
  – Past Medical History
  – ? Reason tests were ordered
  – Previous TFT results
  – Other pituitary hormone deficiencies suspected
Signs & Symptoms of Hyperthyroidism

**Symptoms**
- Palpitations
- Weight loss
- Tremor
- Sweating
- Anxiety
- Insomnia
- Heat Intolerance
- Diarrhea

**Signs**
- Exophthalmos (Graves)
- Brisk Reflexes
- Tremor
- Tachycardia
- Oligomenorrhea
- Hair Loss
Hyperthyroidism

- ↓ TSH, ↑ FT3 and/or FT4
  - In T3 toxicosis, FT4 may be within reference range
  - Subclinical hyperthyroidism
    - TSH may be low but the FT3 and FT4 are within reference range

- Next Step: Iodine radioisotope imaging
  - AKA “uptake and scan” with I\(^{123}\)
  - Rule out pregnancy first!
  - The patient needs to be off any anti-thyroid drug (methimazole or propylthiouracil) for at least 1 week prior to the uptake/scan
Uptake: % uptake of tracer dose
Scan: Image

A) Normal

B) Graves disease
   - diffuse increased uptake in both thyroid lobes

C) Toxic multinodular goiter
   - “hot” and “cold” areas of uneven uptake

D) Toxic adenoma
   - increased uptake in a single nodule with suppression of the surrounding thyroid

E) Thyroiditis
   - decreased or absent uptake

Iodine Uptake

• Recent iodine load (IV iodine containing contrast medium utilized in CAT scan imaging) can result in transient worsening of the thyrotoxicosis, but result in a low I-123 uptake

• The gland becomes saturated with cold (non-radiolabeled) iodine, thus minimal I-123 is taken up by the saturated gland

• It is for this reason that I-123 imaging should not be performed for approximately 6-8 weeks after an exogenous load of iodine
  – Could check a 24 hour urine iodine level
High Iodine Uptake (%)

1) Graves Disease
   ±TRAB
   ±Ophthalmopathy

2) Toxic Nodular Goiter
   Negative TRAB
   No Ophthalmopathy

3) Marked Elevations of hCG (Rare)


TSH secreting adenoma
Graves

Anti-thyrotropin-receptor antibodies also recognize the thyrotropin receptor on orbital fibroblasts and in conjunction with the secreted type 1 helper T cytokines interferon-γ and tumor necrosis factor (TNF), initiate the tissue changes characteristic of Graves ophthalmopathy.

The extraocular muscles are widely separated by an amorphous accumulation of granular material consisting primarily of collagen fibrils and glycosaminoglycans.

http://bjr.birjournals.org/cgi/content/full/75/894/514/F3
Treatment

• Patients with overt hyperthyroidism should be referred to an endocrinologist for a thorough evaluation and discussion of the diagnosis and the treatments that are available

• Beta-blockers can be used to ameliorate the symptoms of thyrotoxicosis such as palpitations, anxiety, and tremor
Treatment

- Treatment options for the usual causes of hyperthyroidism (toxic nodular goiter or Graves disease) include:
  - Radioactive Iodine Ablation
    - Unless the patient was exposed to a recent cold iodine load
  - Anti-thyroid Drugs
    - Methimazole or Propylthiouracil
  - Surgical Resection
    - Partial or Complete

Low Iodine Uptake (%)

- Thyroiditis

- Ectopic Hyperthyroidism

- Recent Iodine Load (Jod Basedow)

- Amiodarone
  - AIT-1: Iodine
  - AIT-2: Thyroiditis

Central Hypothyroidism

Natural history of thyroid function tests in patients with thyroiditis

Disequilibrium state = the period during the hypothyroid phase of thyroiditis in which the thyroid-stimulating hormone (TSH) level transiently remains low or inappropriately normal in the setting of low levels of free thyroid hormones; $T_4$ = thyroxine; $T_3$ = triiodothyronine

Disequilibrium State

• Seen in the hypothyroid phase of resolving thyroiditis
  – Low or inappropriately normal TSH in the setting of low T4/T3

• There are 3 phases of thyroiditis
  – Hyperthyroid phase
  – Euthyroid then Hypothyroid phase
  – Recovery
Ectopic Hyperthyroidism

• Exogenous T4/T3

• Endogenous
  – Struma Ovarii
    – Large deposits of functioning thyroid cancer metastases

• ? Exogenous vs. Endogenous
  – Check Thyroglobulin (Tg) level
Iodine (Jod Basedow)

• Develops in patients with underlying thyroid disease
  – Toxic nodular goiter or Graves disease
    • Often undiagnosed/subclinical disease

• Causes an exacerbation of autonomous (TSH-independent) thyroid function
  – Usually seen a few weeks after iodine exposure

• Iodine load
  – IV contrast medium that contains iodine
  – Amiodarone therapy

Amiodarone Induced Thyrotoxicosis

- Two types:
  - Type 1 - Jod Basedow
    - Amiodarone contains 37% iodine by weight
  - Type 2 - Destructive Thyroiditis
    - Occurs in patients with no underlying thyroid disease and is probably a consequence of a drug-induced destructive thyroiditis

- Mixed or indeterminate forms of AIT encompassing several features of both type 1 and type 2 may also be observed

Euthyroid Sick Syndrome (ESS)

• A low FT3 with normal FT4 and low-normal TSH are the most common abnormalities seen in ESS

• Although the FT3 is usually low in ESS; in severe cases, the FT4 can also be low

## Changes in Thyroid Hormone During Illness

<table>
<thead>
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<th>Severity of Illness</th>
<th>Free T&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Free T&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Reverse T&lt;sub&gt;3&lt;/sub&gt;</th>
<th>TSH</th>
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<td>Mild</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
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<tr>
<td>Moderate</td>
<td>↓↓</td>
<td>N, ↑↓</td>
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<tr>
<td>Severe</td>
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<td>↑</td>
<td>↓↓</td>
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<tr>
<td>Recovery</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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Table 10.9 Williams Textbook of Endocrinology, 11th edition
Euthyroid Sick Syndrome

• The TSH levels have been reported
  - Normal in approximately 50%
  - Decreased in about 30%
  - Increased in approximately 12%
  - Level varies based on severity of illness

• The TSH levels are markedly suppressed (<0.1 µIU/mL) in about 7% of patients
  – Predominantly in those patients treated with corticosteroids

What happens to TFTs with recovery from ESS

- A mild elevation of TSH is seen in patients who are recovering from their illness
  - However, serum levels > 25 to 30 μU/mL strongly suggests the diagnosis of primary hypothyroidism

- TSH >30 μU/mL is rarely seen
- TSH >20 μU/mL is found in <3%
- TFTs should return to baseline with resolution of illness
Severe Euthyroid Sick Syndrome

• Some advocate treatment, especially when FT4 is low

• A low FT4 is a significant predictor of mortality

• Available literature suggests some improvement in clinical parameters with treatment (e.g. cardiac output) but no mortality benefit has been found
  – Most have shown an increase in mortality with treatment
Remember….all you need to know is...............
Lab tests will place patient in the correct category

BUT, it is your knowledge and skill that will make the correct diagnosis!

A 34 year old female presents to the outpatient endocrinology clinic 4 months post-partum

She reports that approximately 2 months post-partum she developed palpitations, heat intolerance and difficulty sleeping

Her primary care physician diagnosed her with post-partum thyroiditis after laboratory evaluation revealed a TSH of 0.005 (0.4-5.5 μIU/mL) and a free T4 (FT4) of 2.4 (0.7-1.8 ng/dL)

She was placed on atenolol for symptomatic treatment. However, follow-up thyroid function testing performed six weeks later revealed a TSH of 0.085 and a FT4 of 0.6
Question 1

What do her current TFTs represent?

A) Central Hypothyroidism
B) Disequilibrium State
C) Euthyroid Sick Syndrome
D) Primary Hypothyroidism
E) Graves Disease
Question 1

TFTs two weeks later at Endo appointment:
TSH 3.5 (0.4-5.5 μIU/mL)
FT4 0.8 (0.7-1.8 ng/dL)

Diagnosis:
Resolving Thyroiditis/Disequilibrium state
Question 2

- A 42 year old female comes to your office complaining of fatigue for the past 4 years. She has a history of sarcoidosis, which has been under control since the time of her diagnosis 10 years ago.

- She reports her TSH has been checked at least 5 times, and all of them were in the normal range (she brings these records for your review).

- On further review of her laboratory test results, you note an FSH (follicle stimulating hormone) and LH (luteotropic hormone) that are within the normal range, and an estradiol level that is very low.
Question 2

TSH checked by PCP:

10/02 11/05 7/06 10/06 1/09

TSH: 0.400-5.500 uU/mL 3.720 2.440 4.810 3.890 4.390

All within normal range
Question 2

She reports she has not had any periods for 8 years, and that she was told by her previous doctor that she had premature ovarian failure. What would be the next best step in her evaluation?

A) Order free T4 and free T3
B) Order microsomal antibodies
C) Complete an evaluation of each of her hypothalamic-pituitary-axes
D) Check a serum angiotensin-converting-enzyme (ACE)
MRI was consistent with sarcoidosis involvement of the hypothalamus/pituitary

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<td>&lt;12</td>
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</table>
• Central Hypothyroidism/Panhypopituitarism

• Patient was too young for menopause

• LH/FSH would be high in menopause or premature ovarian failure
  – This should have been tip off for possible central process
  – If concerned for central process, must get FT4/FTI with TSH
  – If patient has symptoms, should get TSH/FT4, TSH is only indicated as a screening test
  – By definition, screening tests are those that are completed to detect disease in asymptomatic patients, she was clearly not asymptomatic

• She has a history of an infiltrative disorder which can involve pituitary/hypothalamus
Question 3

- A 23 year old woman presents to your office with the complaints of palpitations and insomnia. She currently weighs 212 lbs and her height is 5’ 6”. She has struggled to lose weight in her attempt to get back to her pre-pregnancy weight of 140 lbs.

- Concerned her symptoms are related to hyperthyroidism, you order a set of TFTs which find a TSH level of 0.005 µIU/mL (0.4-5.5), FT4 of 0.5 ng/dL (0.7-1.8), and FT3 8.4 pg/mL (1.5-3.5).

- You ask the patient if she is using any weight loss medications, which she adamantly denies.
Question 3

• What laboratory test could be ordered help determine if the source of her thyrotoxicosis is endogenous or exogenous?

  A) Microsomal Ab
  B) Free Thyroid Index (FTI)
  C) Thyroglobulin
  D) Thyroid Stimulating Antibodies
Thank You!