**Common and Uncommon Thyroid Disorders**

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**CONFLICTS OR INTEREST**

NONE

**Understanding Thyroid Disease**

Thyroid Disease Can Affect Every System of the Body

- **The Thyroid**: Thyroid disease can have widespread effects
- **The Liver**: Increased LDL cholesterol, elevated triglycerides
- **The Intestines**: Constipation, increased GI activity
- **The Reproductive System**: Decreased fertility, menstrual abnormalities
- **The Brain**: Depression, decreased concentration, general lack of interest
- **The Heart**: Decreased heart rate, increased/decreased blood pressure, decreased cardiac output
- **The Kidneys**: DecreasedInsufficiency
depression, increased/decreased blood pressure, decreased cardiac output
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References:

Prevalence of Thyroid Disease

The Colorado Study

- At a statewide health fair in Colorado (N=25,862), participants were tested for TSH and total T4 levels.
- 9.5% of subjects had elevated TSH; most were subclinically hypothyroid (in this study, normal T4 with TSH >5.1).
- Among the subjects already taking thyroid medication (almost 6% of study population), 40% still had abnormal TSH levels.
- Among patients not taking thyroid medication, 9.9% had a thyroid abnormality that had been unrecognized.
- There may be an excess of 13 million cases of undetected thyroid gland failure nationwide. In addition, there are nearly 14 million patients on thyroid hormone replacement.

Recent Studies


Prevalence of Thyroid Disease

Thyroid Disease and Aging

The incidence of thyroid disease increases with age. 1

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>25</td>
<td>4.5%</td>
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<tr>
<td>35</td>
<td>5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>45</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>55</td>
<td>10%</td>
<td>13.5%</td>
</tr>
<tr>
<td>65</td>
<td>16%</td>
<td>15%</td>
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<tr>
<td>75</td>
<td>21%</td>
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(Adapted from Canaris, et al.)

Physiological changes in organ systems and higher prevalence of other diseases may make older patients more vulnerable to consequences of even mild thyroid deficiency. 2

Recent Studies


Case 1

- 26 YO white male referred for treatment of hyperthyroidism. Presented to PCP 3 months ago with weight loss, fatigue, palpitations, heat intolerance.
- Labs with undetectable TSH, Free T4 2.8, 1-123 scan and uptake of 45% (15-32%), diffuse pattern.
- Was on methimazole 15 mg daily and f/u TSH 1.5 with now normal free T4. Still some fatigue.
- Labs reassessed CBC, comprehensive chemistry. Methimazole decreased to 10 mg, PE normal except to upper normal size thyroid gland. Any thoughts?
Case 1

- Patient was scheduled for labs in 1 and 3 months and F/U in 3 months.
- Missed several appointments, then called in and stated needed to reschedule his planned appointment in one week secondary to upcoming surgery for testicular tumor
- Any recommendations?

Diseases that Cause Hyperthyroidism

- Diffuse toxic goiter – Graves’
- Subacute thyroiditis
- Hashitoxicosis
- Toxic MNG or autonomous nodule
- Iatrogenic
- Medication induced
- Iodine induced

Hyperthyroidism and hCG

- Germ cell tumors in men
  - hCG level >50,000 IU/L
  - Ligand-receptor cross reactivity with TSH
- Rare occurring in < 5% of seminoma patients
- Hyperthyroidism resolves with successful treatment

hCG - hyperthyroidism

- hCG induced hyperthyroidism also seen in trophoblastic disease in women
- Hyperthyroidism responds to thioamide therapy
- Was seen in this case
- Post orchectomy hCG was normal and TPO and TSI were also normal as was thyroid function off methimazole

Case 2

- 32 yo female 2-3 months, anxiety, weight loss, sweats, palpitations, eye irritation
- PE: HR 110, stare present, lid lag, diffuse goiter, tremor
- What is the diagnosis?
- What labs?
- What scans?

Case 2

- Labs TSH, Free T4, TPO, TSI optional
- Scan and uptake to confirm and potentially direct therapy
- CBC and liver prior to thioamide therapy
- Choice of therapy
  - Medical
  - I-131
  - Surgical
"Common and Uncommon Thyroid Disorders"

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Methimazole acts faster than PTU in Graves' hyperthyroidism

Time required for patients with Graves' hyperthyroidism to become euthyroid (normal serum T4 and T3 concentrations) after therapy with methimazole (10 mg three times daily, n = 96) or PTU (100 mg three times daily, n = 17). The euthyroid state was achieved more quickly with methimazole (3.6 versus 16.8 weeks).

PTU (propylthiouracil): T3: thionamides; T2: triiodothyronine.


Methimazole dose in hyperthyroidism

The proportion of patients with hyperthyroidism who became euthyroid at two different doses of MM: The euthyroid state was defined as normalization of the serum T4 and T3 concentrations. Both doses were equally effective; similar results (not shown) were achieved with 10 mg given three times daily.

MM: methimazole; T4: thyroxine; T3: triiodothyronine.


Treatment of Graves' hyperthyroidism

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantage</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroidectomy</td>
<td>Choice of immediate procedure</td>
<td>Major side effects, cosmetic, skin reactions, transient hypothyroidism.</td>
</tr>
<tr>
<td>Radioiodine</td>
<td>Permanent ablation of thyroid hormone production</td>
<td>Major side effects: apathy, anorexia, weight loss, transient hypothyroidism.</td>
</tr>
<tr>
<td></td>
<td>Permanent hypothyroidism</td>
<td>Risk of fatal goiter, hypothyroidism, and both sides of thyroid remnant.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Potential permanent cure of hyperthyroidism</td>
<td>Permanent hypothyroidism.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient cannot delay radical surgery for life-threatening complications and urgent surgical intervention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complications due to long-term suppressive effects of radiation.</td>
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</table>

Major of the advantages and disadvantages of the three major therapeutic modalities used in the treatment of Graves' hyperthyroidism.

Data from: UpToDate.
Treatment – Graves’

• Symptom control - beta blocker - atenolol 25-200 mg daily
• Hyperthyroidism - methimazole exclusively (1st trimester)
  – More rapid, fewer SE’s, once daily
• Once euthyroid consider definitive rx – I-131 preferred
• Surgery - Malignancy, large gland, orbitopathy
• Initial I-131 therapy - option in mild presentations
• Avoid pregnancy for 6 months post I-131 - PTU 1st tri.

• 2016 ATA Guidelines. Thyroid 2016;26(10):1343

Case 3

• 60 YO female diagnosed with MNG 2 years ago. Noted to have low TSH on routine labs. No prior history of thyroid disease. No history of radiation exposure, FHMx of benign nodular disease in her father.
• No neck symptoms, complains of fatigue, hair loss, heat intolerance
• Labs 3/2014 - TSH 0.02, free T4 0.96, Tg Ab <20, Quant. Tg level 48 ng/ml (2.0-35.0)
  4/2016 – TSH <0.01, free T4 0.94 ng/dl

Case 3

• Thyroid US
  – R lobe 4.3 x 1.9 x 1.8cm
  – 1.3 x 0.8 x 0.8 cm hypoechoic
  – 2.3 x 1.8 x 1.6 cm hypoechoic with calcifications
  – L lobe 4.7 x 2.0 x 2.0 cm
  – 2.7 x 1.6 x 1.7 cm hypoechoic with calcifications
  – 1.0 x 0.7 x 0.8 cm
  – I-123 scan - 7 of hyperfunction R inf nodule, 24 hour uptake 32.9% (12-35%)
Case 3

- 60 YO female with subclinical hyperthyroidism secondary to toxic MNG
- Should she be treated?
- What are potential problems of observation?
- What are the treatment options?
- Should aspiration of thyroid nodules be carried out and if so which nodules?

Case 3 – Toxic MNG

- Mortality – 29% increase with TSH < 0.1 iU/L, nonsignificant increase with TSH 0.1 to 0.44
- Cortical bone loss and increase fracture risk correlating with degree of TSH suppression
- Atrial fibrillation – TSH 0.1 - 0.44 – 68% increase, TSH < 0.01 – 2.54 fold increase
- 10 year prospective study – Sawin et al
  - TSH normal – 11%, TSH 1. - 4 – 16%, <1 – 28%
  
  Collet et al Arch Intern Med 2012, 172:799
  Swan et al NEJM 1994, 331:1249

Increased incidence of atrial fibrillation in subclinical hyperthyroidism

Cumulative incidence of atrial fibrillation in subjects over age 60 years according to the serum concentration of TSH. The risk of atrial fibrillation was increased almost twofold in the subjects with marked suppression of TSH (left panel) as compared with those who had normal serum TSH concentrations and were presumably euthyroid (right panel). Patients with slightly low serum TSH concentrations (middle panel) had a lesser increase in risk.

TSH: thyroid stimulating hormone.

Toxic Nodular Goiter or Toxic Nodule

- Physical and ultrasound reveals single larger nodule or MNG
- Toxic nodules can occur in younger patients, MBG classically in older
- Suppressed TSH with normal or elevated T4/T3
- I-123 scan consistent with diagnosis
- Indications for therapy
  - Fully suppressed TSH
  - Depressed but detectable TSH in elderly, cardiac/bone
Indications for I-123 Scanning

- DDx of hyperthyroidism
  - Increased uptake in diffuse pattern c/w Graves’
  - Patchy increased uptake c/w toxic MNG
  - Decreased uptake c/w thyroiditis (<5%)

Assess nodule function: Hot or Cold

A thyroid nodule in a chemically euthyroid patient does not require scanning. Proceed to FNA

2015 ATA Guidelines
Changing Diagnostic and Treatment Recommendation

- Less aggressive detection
- Less aggressive surgery for low risk PTC
- Less RAI therapy for remnant ablation
- Lower dose RAI for remnant ablation
- Central compartment node excision optional for Low risk PTC
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2015 ATA Guidelines for Thyroid

- Less than 1 cm suspect nodule no FNA and observe particularly in older
- When diagnosed R/O metastasis, if unifocal, no radiation history or syndromal PTC: lobectomy and no lymph node sampling
- May consider active surveillance, in certain situations
- 1-4 cm no other risks lobectomy a consideration

2015 ATA Guidelines for Micro-papillary Thyroid cancer
Case 4

- 68 YO male presents with new onset atrial fibrillation.
- Symptoms: chest pressure, SOB/DOE, mild diffuse wheezing, palpitations
- HR 150 irregular, lungs clear, neck is normal
- PMHx: HTN, CHD, obesity, lipids, COPD, no hx of thyroid disease

Case 4

- Chemistry is normal, H/H - 13/38, CK/troponin - normal
- CXR - mild cardiac enlargement
- Pt was treated in the ED and admitted

Case 4

- Next day atrial fibrillation resolved. Added labs: TSH - 0.21 (0.45-4.5 iU)
- How to pursue from here?
  - Obtain free T4/T3?
  - I-123 scan and uptake?
  - Endocrine consult?
  - None of the above?
**Case 4**

- Seriously ill patients frequently present with low but detectable TSH levels. Multiple medications can contribute. Steroids/dopamine common
- When low but detectable TSH, > 95% normalize with recovery
- No further evaluation is indicated in this case, except TSH upon recovery

**Case 4- Principles**

- Use caution in measuring thyroid function in critically ill patients
- TSH alone is inadequate in evaluation of severely ill patients
- High sensitivity assays (0.01mU/L) should be used
- Almost all patients with low but detectable TSH levels with recovery
- Endocrine consult not indicated

> Ross et al. Thyroid Function in Nonthyroid Illness. UptoDate Nov 2016
Case 5

- 45 yo male presents for evaluation. Onset of nervousness, anxiety, palpitations, sweats several months ago, had a sore throat. Labs revealed TSH < 0.01, free T4 3.8 (<1.7)
- Symptoms began to improve after several weeks
- What is your suspicion and what would you do now several months later?

C/W subacute thyroiditis
- Reassess labs and anticipate?
- Do you scan?
- Etiology?
- Outcome?
- Therapy?

Subacute thyroiditis
- Viral etiology
- Presents acute hyperthyroidism
- Suppressed TSH, increased T4/T3, suppressed I-123 uptake
- Self resolving, can use beta blocker, thioamide not effective
- Return to euthyroid status is the rule
Case 6

- 53 YO female being treated for progressive MS
- No history of thyroid disease and previously normal TFT’s
- Follow up screening TSH <0.006 uU/ml
- Repeat TSH 0.01 and free T4 >651 (71-180 ng/dl)
- PE- normal, no goiter, clinically appears euthyroid
  - US thyroid- normal
  - I-123 scan /uptake- normal at 16%
  - TPO negative, TSI normal

Case 6

- Repeat TFT’s
  - Free T4 >7.77 (0.82-1.77 ug/dl)
  - Free T3- 9.6 (2-4.4 pg/ml)
  - TSH- 0.014 mU/dl
  - Total T4- 10.4 (4.2-13 ucg/dl)

  - Questions/ideas

Case 6

- Patient had been started on biotin 300 mg for MS
- Biotin interferes with thyroid immunoassay tests
- Some immunoassays employ biotinylated antibody in “capture” system. Will lead to marked aberrant results
- Stopped biotin supplement
  - Free T4- 1.72, TT3- 124 and TSH 0.766
  - Rechallenge- Free T4- >7.77, TT3 >651 and TSH 0.01
Biotin Interference- Effected Assays

- CPK- low level in acute MI
- HCG- low HCG in ectopic pregnancy
- ACTH/Cortisol- low ACTH and elevated cortisol in Addison’s crisis
- TFT’s- low TSH and elevated free T3 in myxedema

CASE REPORT

- 22 yo white male
- Seen for 2nd opinion for hyperthyroidism
- PMHx- Asthma
- FMHx- DM, CHD, HTN, Adrenal adenoma in father
- Complaints- low BW and no wt gain, anxiety, pruritis, fatigue
Case- Slide 2

- 5'11", 169#, 134/82, P-100
- No stare or protosis, VF's- normal
- Thyroid- 1 ½ x, smooth, no bruit or thrill,
- DTR’s- brisk, mild tremor
- No gynecomastia

Case- Slide 3

- T3- 881, 910 (<420 pg/dl)
- Free T4- 3.7, 4.0 (<3.7 ng/dl)
- TT4- 17.3 (<12.0)
- T3RU- 45%
- Scan I-123- Diffuse uptake at 44.7%
- Rx with tapazole and no help
- Recommendation for I-131 rx; Any thoughts?

Case- Slide 4

- TSH- 6.2, 1.63, 2.25 iU/ml
- MRI- 6x5x5 pit. Adenoma
- Alpha subunit was normal
- What is the DDx?
Case- Slide 5

- F/U MRI was normal
- Sequencing of the TSH beta receptor revealing a point mutation at position 268 of exon 8

Case- Slide 6

- Dx – Thyroid hormone resistance
- Auto. Dominant disorder with 50% pene.
- Treatment is generally not indicated
- Treatment with thioamides, surgery or I-131 is contraindicated.
- Generally picked up on routine screening labs

Refetoff et al. Impaired Sensitivity to Thyroid Hormone. Up To Date, Nov 2016

Case 6

- 26 YO female presenting at 6 weeks IUP
- Hx of hypothyroidism dating to age 15 years and on thyroid hormone therapy
- Feels ok, TSH is 14 uU/ml
Maternal Hypothyroidism – Fetal Effects

- Maternal
  - Gestational HTN
  - Preeclampsia
  - Abruptio placenta
  - Anemia

- Fetal
  - Prematurity
  - Low birthweight
  - Stillbirths
  - Fetal distress

ATA Guidelines - 2011

- Recommendation 6:
  - Overt hypothyroidism should be treated in pregnancy. This includes women with a TSH above the trimester-specific reference interval with a decreased FT4, and all women with a TSH above 10.0 mIU/L irrespective of the level of FT4.

Recent Studies

Haddow Pregnancy Study (N=62)

The 1999 Haddow Study showed that euthyroid children of hypothyroid mothers also suffer adverse effects.1

- Early studies showed that when both mother and fetus have hypothyroidism, fetal brain development and IQ are affected
- Before 12 weeks’ gestation, the mother is the sole source of thyroid hormones
- Screening for hypothyroidism early in pregnancy may prevent poor mental and motor development
- American Association of Clinical Endocrinologists (AACE) recommends that women with histories of infertility or miscarriage be given a TSH test before and during pregnancy2

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Recent Studies

Haddow Pregnancy Study: Results

124 matched pairs of children aged 9 to 11 were tested for intelligence, attention, language, reading ability, school performance and visual-motor skills.¹

- Children of untreated hypothyroid women averaged 7 points lower on IQ tests (Wechsler) than control group (P=0.005)
- 19% of children in this group scored 85 or lower on IQ tests, as compared with 5% of control children
  - Below-normal IQ suggests learning difficulties that may limit employment and income opportunities in adulthood


Maternal Subclinical Hypothyroidism

Effect of Offspring IQ (4-14.5 yr)

<table>
<thead>
<tr>
<th>SCH (19)</th>
<th>Euthyroid on LT4 (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mean (range)</td>
<td>11.3 (5.9-27)</td>
</tr>
<tr>
<td>T4 mean (range)</td>
<td>9.0 (7.1-12)</td>
</tr>
<tr>
<td>Gest. Age (wk)</td>
<td>39.3</td>
</tr>
<tr>
<td>IQ: total</td>
<td>120 +/- 14</td>
</tr>
<tr>
<td>Perform</td>
<td>117 +/- 12</td>
</tr>
<tr>
<td>Verbal</td>
<td>121 +/- 16</td>
</tr>
<tr>
<td>IQ &lt; 85</td>
<td>0%</td>
</tr>
<tr>
<td>Behrooz et al. Thyroid</td>
<td>2011;21:1143</td>
</tr>
</tbody>
</table>

Does 1st Trimester TSH Predict Pregnancy Outcome?

- TSH @ 9-14 wks gestation – Outcomes at 20 weeks
- 2411 tests: TSH > 2.15 (5.5%); >4 (1.0%); >10 (0.2%)
- No effect of increased TSH on prematurity, SGA, stillbirth, obstetric complications, any fetal abnormality

Ong Gsy et al, J Clin Endo Metabolism 2014 (Epub)
Recent Studies

Endocrine Society Recommendations

- A cost-effective strategy for screening before or during first trimester of pregnancy
- Immediate hormone replacement in women who are hypothyroid during pregnancy
- Monitoring and adjustment of therapy throughout gestation

AACE Recommendations

- Routine TSH testing in early pregnancy is reasonable
- Test all high risk patients, goiter, TPOab+, FMHx, symptoms, IDDM or other autoimmune diseases
- If TSH elevated, promptly treat even if mild
- Monitor closely and assure TSH at goal, LT4 requirement is increased during pregnancy
- In women who are TPOab+, follow closely post delivery
- TSH screening in all women considering pregnancy

ATA Guidelines - Stagnaro et al, Thyroid 2011

- Recommendation 7:
- Isolated hypothyroxinemia should not be treated in pregnancy.
Standard Recommendation - Pregnancy

- TSH goal 0.5 to 2.5 at conception
- With pregnancy increase replacement dose approximately 30-45%, ie 2 extra daily doses weekly
- Assess TSH monthly for first 20 weeks gestation
- Maintain TSH
  - First trimester under 2.5
  - Second and third trimester under 3.0

CASE

- 71 yo male, long history IRDM, also PMHs of CAD/PVD, VHD post replacement, advanced neuropathy, HTN, stage 3-4 CKD.
- Recent screening TSH 4.8 uU/ml
- PCP recommends LT4 replacement?
- Do you agree?

Age Adjusted Norms for TSH in 16,533 Subjects – NHANES III

- 97.5 centile for TSH
  - Age 20-29 - 3.56
  - Age >80 - 7.49
- 70% of subjects in old group with TSH > 4.5 were within normal range for age
- Subjects with + thyroid antibodies were excluded
- Controversy exists in treatment of subclinical hypothyroidism
American Thyroid Association

- Recommends replacement with synthetic levothyroxine products
- Suggests raising TSH goal to 4-6 mIU/L in people 70 to 80 years of age