Hypothyroidism 2013
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Professor, Mayo Clinic College of Medicine
President, American Thyroid Association
Past President, American Association of Clinical Endocrinologists
Disclosure & Thanks

- Nothing to disclose
- My sincere thanks for the invitation to participate at this meeting & speak to you today
CLINICAL PRACTICE GUIDELINES FOR HYPOTHYROIDISM IN ADULTS:
COSPONSORED BY THE AMERICAN ASSOCIATION OF CLINICAL
ENDOCRINOLOGISTS AND THE AMERICAN THYROID ASSOCIATION

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Irwin Klein, MD, FACP\textsuperscript{5}; Jeffrey I. Mechanick, MD, FACP, FACE, FACN\textsuperscript{6};
Rachel Pessah-Pollack, MD\textsuperscript{6,7}; Peter A. Singer, MD, FACE\textsuperscript{8}; Kenneth A. Woeber, MD, FRCPE\textsuperscript{9}
for the American Association of Clinical Endocrinologists
and American Thyroid Association Taskforce on Hypothyroidism in Adults

Thyroid 22:1200, 2012
Subclinical Hypothyroidism

- A 34-year-old woman with BMI 30, fatigue and hyperlipidemia, is referred because a recent TSH is 5.6. Thyroid gland palpation is normal. Repeat TSH is 6.0, FT4 1.0 & TPOAb is positive.

  *Do you Rx with T4?*    *Yes ~ No ~*

- A 76-year-old woman has a screening serum TSH of 7.0 & FT4 1.2. Thyroid palpation is normal.

  *Do you Rx with T4?*    *Yes ~ No ~*
Normal Serum TSH

• A changing target & a matter of debate
• Lab *reference* range 0.5 to 5.0 mIU/L; lab *normal* range is 0.5-4.1
• Factors influencing TSH levels include age, ethnicity, I-intake and autoimmune disease
Serum TSH and Age

Upper TSH concentration

% vs. Upper TSH concentration

Age 20-29
Age 50-59
Age ≥80

TSH group (%) vs. TSH concentration groups (mIU/L)

JCEM 92:4575, 2007
Serum TSH Variation in Normals
±0.5 mIU/L Over 1 Year

Range 0.4-4.1; mean 1.3 mIU/L

Population reference range

Andersen S et al: JCEM 87:1068, 2002
Subclinical Hypothyroidism

• TSH ≥5.0 mIU/L with normal FT4
• In 80% of cases, TSH is between 5-10 mIU/L
• TPO antibodies (TPOAb), present in 60-80%, are more likely positive with higher TSH levels
• Sometimes referred to as "mild" or "early" hypothyroidism
Consequences of SCHypothyroidism

- Progression to overt (symptomatic) hypothyroidism
- Symptoms include fatigue, mood & excess weight
- High serum cholesterol
- CV morbidity/mortality
Risk of Overt Hypothyroidism in a 60-Year-Old Woman

Vanderpump M et al, 2003
### CHD Events and Mortality

**Individual Patient Meta-Analysis from 7 Prospective Cohort Studies**

Hazard ratios (HRs) for coronary heart disease (CHD) events, CHD mortality, and total mortality according to elevated (TSH) categories and subclinical hypothyroidism stratified by age vs euthyroidism

<table>
<thead>
<tr>
<th>CHD events by TSH level (mIU/L)</th>
<th>Events (no.)</th>
<th>Participants (no.)</th>
<th>HR ratio (95% CI)</th>
<th>Decreased risk</th>
<th>Increased risk</th>
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<tbody>
<tr>
<td>0.5-4.49</td>
<td>4,040</td>
<td>23,957</td>
<td>1 (reference)</td>
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<tr>
<td>4.5-6.9</td>
<td>264</td>
<td>1,844</td>
<td>1.00 (0.86-1.18)</td>
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<tr>
<td>7.0-9.9</td>
<td>96</td>
<td>441</td>
<td>1.17 (0.96-1.43)</td>
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<tr>
<td>10-19.9</td>
<td>70</td>
<td>235</td>
<td>1.39 (1.28-2.80)</td>
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</table>

**CHD mortality by TSH level (mIU/L)**

<table>
<thead>
<tr>
<th>CHD mortality by TSH level (mIU/L)</th>
<th>Events (no.)</th>
<th>Participants (no.)</th>
<th>HR ratio (95% CI)</th>
<th>Decreased risk</th>
<th>Increased risk</th>
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<tr>
<td>0.5-4.49</td>
<td>1,958</td>
<td>50,953</td>
<td>1 (reference)</td>
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<tr>
<td>4.5-6.9</td>
<td>132</td>
<td>2,363</td>
<td>1.09 (0.91-1.30)</td>
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<td>7.0-9.9</td>
<td>50</td>
<td>652</td>
<td>1.42 (1.03-1.95)</td>
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<tr>
<td>10-19.9</td>
<td>28</td>
<td>833</td>
<td>1.58 (1.10-2.27)</td>
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</table>

P<0.001 for trend

Rodondi et al: JAMA, 2010
## Incident Cardiovascular Disease in Subclinical Hypothyroidism

<table>
<thead>
<tr>
<th>Prospective studies</th>
<th>Effect of SH on incident CHD</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Whickham survey 1977</td>
<td>No</td>
<td>20 year F/U</td>
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<tr>
<td>Rotterdam study 2000</td>
<td>No</td>
<td>5 year F/U</td>
</tr>
<tr>
<td>Atomic Bomb Survivors 2004</td>
<td>Yes</td>
<td>Middle aged men</td>
</tr>
<tr>
<td>Leiden Plus 2004</td>
<td>No</td>
<td>Age &gt;85</td>
</tr>
<tr>
<td>Busselton study 2005 (Walsh)</td>
<td>Yes</td>
<td>Mean age 50</td>
</tr>
<tr>
<td>Health Aging study 2005</td>
<td>No</td>
<td>Mean age 75; increased risk of CHF</td>
</tr>
<tr>
<td>Cardiovascular Health study 2006 (Cappola)</td>
<td>No</td>
<td>&gt; age 65</td>
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</tbody>
</table>
Subclinical Hypothyroidism

- A 34-year-old woman with BMI 30, fatigue and hyperlipidemia is referred because a recent TSH is 5.6. Thyroid gland palpation is normal. Repeat TSH is 6.0, FT4 1.0 & TPOAb is positive.

  Do you Rx with T4? Yes ✓ No

- A 76-year-old woman has a screening serum TSH of 7.0 & FT4 1.2. Thyroid palpation is normal.

  Do you Rx with T4? Yes ~ No ✓
Subclinical Hypothyroidism

Recommendation 16

- Treatment of TSH 5-10 mIU/L should be considered particularly if they have symptoms of hypothyroidism, positive TPOAb or atherosclerotic CV disease as risk factors
Subclinical Hypothyroidism

Arguments against Rx

- Impact on CV morbidity and mortality is unclear, especially in elderly
- Data on improved symptoms equivocal
- Benefits of improved cognitive outcomes unproven
- Complications of overtreatment
- Cost & inconvenience
Approach to SCHypothesism

Serum TSH

5-10 mIU/L
- Repeat TSH, FT4, TPOAb
  - Normal tests: Follow
  - TSH & TPOAb+: Follow

>10 mIU/L
- Begin T4 Rx
  - T4 Rx if ...
    - Goiter
    - Hyperlipidemia
    - Infertility
    - Young pt
Screening for Thyroid Disease in Pregnancy

A 24-year-old woman was just diagnosed with her first pregnancy. She enjoys good general health. There is no h/o thyroid disease.

Q: Should she have screening TSH?

Yes ~ No ~
What are the recommendations for TSH and T4 Screening in Pregnancy

- Recommendation 20.1.1
  Universal screening is not recommended for patients who are pregnant or planning pregnancy
Screening for Thyroid Disease in Pregnancy

- Although the benefits of universal screening for thyroid dysfunction may not be justified at this time, aggressive case finding should be considered.

- Positive FHx thyroid disease
- Goiter
- Post TPO Ab
- Symptoms
- Type 1 DM
- Miscarriage

- Other autoimmune disease
- Infertility
- Morbid obesity
- Age >30 years

Thyroid, 2012
Screening for Thyroid Disease in Pregnancy

A 24-year-old woman was just diagnosed with her first pregnancy. She enjoys good general health. There is no h/o thyroid disease.

Q: Should she have screening TSH?

Yes ~ No ✅
TSH Levels in Normal Pregnancies
n=343

Median and 95% TSH

<table>
<thead>
<tr>
<th>TSH (mIU/L)</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
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<tbody>
<tr>
<td>3.5</td>
<td>2.3</td>
<td>3.1</td>
<td>3.5</td>
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<tr>
<td>3.5</td>
<td>0.8</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>1.2</td>
<td>0.03</td>
<td>0.03</td>
<td>0.13</td>
</tr>
<tr>
<td>0.4</td>
<td>0.03</td>
<td>0.03</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Weeks gestation: 10, 20, 30, 40

Serum TSH In Pregnancy

Recommendation 14.2

- In pregnancy, the upper limit of normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available in the lab, the following upper normal ranges are recommended: 1\textsuperscript{st} trimester, 2.5 mIU/L; 2\textsuperscript{nd} trimester, 3.0 mIU/L; 3\textsuperscript{rd} trimester, 3.5 mIU/L
Pregnancy, TSH & LT4 Rx

A 26-year-old woman is planning pregnancy. She enjoys good health and has no thyroid disease. Thyroid gland is normal on palpation. Serum TSH is 4.3 mIU/L & FT4 1.0 ng/dL

Q: Should she be treated with LT4?

Yes ✓ No ~

Recommendation 19.1:

Rx with LT4 should be considered in women with TSH >2.5 in 1st trimester of pregnancy or planning pregnancy

Thyroid, 2012
Increased Pregnancy Loss in TPOAb-Neg Women with TSH 2.5-5.0

4,562 First trimester pregnant women

4,123 TPOAb-

3,481 TSH <2.5
Pregnancy loss 3.6%

642 TSH 2.5-5.0
Pregnancy loss 6.1%

P=0.006

Negro R et al: JCEM 95:E44-8, 2010
Pregnancy, TSH & LT4 Rx

A 26-year-old woman is planning pregnancy. She is in good health. Thyroid gland is normal on palpation. Serum TSH is 4.3 mIU/L; FT4 is 1.0 ng/dL; & TPOAb is positive.

Q: Should she be treated with LT4?

Yes ✔️  No ~

Recommendation 19.3:

Women who are pregnant or plan pregnancy, should be treated with LT4 if TSH is >2.5 & TPOAb positive.
Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence

30 articles with 31 studies (19 cohort and 12 case-control) involving 12,126 women assessed the association between thyroid autoantibodies and miscarriage.

Cohort studies: OR 3.90 (95% confidence interval 2.48 to 6.12; P<0.001).

Case control studies: OR 1.80 (1.25 to 2.60; P=0.002).

There was a significant doubling in the odds of preterm birth with the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; P=0.01).

Conclusion: The presence of maternal thyroid autoantibodies is strongly associated with miscarriage and preterm delivery. There is evidence that treatment with levothyroxine can attenuate the risks.

TSH Changes in TPOAb (+) Pregnancy Women During Gestation

Vanderpump M et al, 2003
Treatment with LT4 in Pregnant Women with TAI: Effects on Obstetrical Complications

984 pregnant women

58 TPOAb + No treatment

57 TPOAb + LT4

115 TPOAb +

869 TPOAb-

LT4: 0.5 μg/kg.d TSH <1.0 mIU/l
0.75 μg/kg.d TSH 1.0-2.0 mIU/l
1 μg/kg.d for TSH >2.0 mIU/l or TPOAb >1,500 kIU/L

Treatment with LT4 in Pregnant Women with TAI: Effects on Obstetrical Complications

- Miscarriage
  - TOPAb-: 3%
  - TOPAb+: 18%
  - TOPAb+ LT4: 15%

- Preterm Delivery
  - TOPAb-: 5%
  - TOPAb+: 25%
  - TOPAb+ LT4: 10%

Recommendations for TPOAb Screening in Pregnancy

- There is insufficient evidence to recommend for or against screening for thyroid antibodies in the first trimester of pregnancy, or treating TPOAb+ euthyroid women with LT4 to prevent preterm delivery

- Women with TAI (TPOAb pos) who are euthyroid in the early stages of pregnancy are at risk for developing hypothyroidism, and should be monitored carefully
MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD

JAMES E. HADDOW, M.D., GLENN E. PALOMAKI, B.S., WALTER C. ALLAN, M.D., JOSEPHINE R. WILLIAMS, GEORGE J. KNIGHT, PH.D., JUNE GAGNON, M.A., CHERYL E. O’HEIR, M.ED., ED.S., MARVIN L. MITCHELL, M.D., ROSALIE J. HERMOS, M.P.H., SUSAN E. WAISBREN, PH.D., JAMES D. FAIX, M.D., AND ROBERT Z. KLEIN, M.D.
Antenatal Thyroid Screening and Childhood Cognitive Function

21,846 pregnant women at 11-14 weeks

Control
Screen

TSH >97.5th%
FT4 <2.5th%

Follow
T4Rx

IQ test in all children at age 3 were similar

Thyroid Hormone Therapy

• Up to 3% of population in Western Countries is on thyroid hormone Rx (JCEM 89:3879, 2004)

• Replacement Rx is for hypothyroidism: Keep TSH normal

• LT4 dose requirement is less for primary hypothyroidism compared to central hypo-, postop- or post$^{131}$I hypothyroidism

• Generic LT4 is in common use nowadays
Primary Hypothyroidism

- A 50-year-old woman complains of recent wt gain, fatigue, sleepiness and cold intolerance; one sister has Graves’ disease and another hypothyroidism

Tests
- TSH 62.0 mIU/L
- FT4 0.2 ng/dL
- TPOAb 560 (<9)
Hypothyroidism

- What is the most likely cause of hypothyroidism in this patient?
- When is TPO measurement useful?
- How do you select LT4 dose?
Hakaru Hashimoto
1881-1934
Hypothyroidism

- Hashimoto thyroiditis is the most common cause
- 95% of pt are women
- Goiter is nontender, diffuse, firm (rubbery) and bosselated
- Additional helpful tests include TPOAb, FNA, & US
Thyroid Peroxidase Antibody (TPOAb)

- Sensitive test for detecting thyroid autoimmune disease (TAID)
- Order in pt with subclinical hypothyroidism
- Order when TAID is suspected in pt with nodular thyroid
- Consider in woman with recurrent miscarriage
Levothyroxine (LT4) Therapy

- Average daily dose is about 100 mcg
- Initial dose is influenced by severity & duration of hypothyroidism, as well as presence of CAD
- Obesity (↑ BMI) increases requirement
- Replacement therapy (TSH 0.3-3.0) is life-long treatment
LT4 Rx

Recommendation 13

- Pt treated for hypothyroidism should have TSH measurement at 4-8 wk

Recommendation 22.8

- When initiating Rx in pt older than 50-60 yr, without CAD, LT4 dose of 50 mcg daily should be considered

Recommendation 23

- LT4 should be taken 30-60 min before breakfast or 4 hr after pm meal
Target TSH

Recommendation 17

• In pt with hypothyroidism who are not pregnant, the target should be the normal range of a sensitive TSH assay
Hypothyroidism With Low TSH

A 52-year-old man reports fatigue, lethargy, 5 lb wt gain and decreased libido. Thyroid is small on exam. Serum TSH is 2.0 (0.5-5.0) & FT4 0.5 (0.8-1.8)

Q: Differential diagnosis? Additional tests?

Causes: Pituitary/hypothalamic tumor lymphocytic hypophysitis Sheehan’s syndrome surgery radiation
Hypothyroidism With Low TSH

Additional test
- Serum T3 55 ng/dL
- Serum cortisol 2.1 ng/dL
- Serum testosterone 60 ng/dL
- LH/FSH ↓
- Prolactin normal

Imaging
- Head MR showed on 2 cm smaller mass

Rx
- Placed on T4, testosterone & prednisone
- Pituitary surgery
Central Hypothyroidism

Recommendation 12

- In patient with central hypothyroidism, assessment of FT4 or FTI, not TSH, should be done to Dx & Rx hypothyroidism
Symptomatic Hypothyroidism With Normal TSH

- A 42-year-old nurse complains of fatigue, cold intolerance, constipation and depression
- She has been on T4 for 12 years since $^{131}$I Rx for hyperthyroidism
- Exam is normal; serum TSH is 3.6 mIU/L (0.5-5.0) & FT4 1.3 ng/dL (0.8-1.8)
Why Some Patients With Hypothyroidism Continue to Complain Despite Normal TFTs?

- Non-thyroid causes
- T4 dose inadequate
- Need for combination T4 plus T3
- Other explanations
Common Features of Hypothyroidism and Depression

Depression
- Sleep decrease
- Suicidal ideation
- Weight loss
- Constipation
- Decreased concentration
- Decreased libido
- Depressed mood
- Diminished interest
- Fatigue
- Sleep increase
- Weight gain
- Delusions

Hypothyroidism
- Bradycardia
- Cardiac & lipid abnormalities
- Cold intolerance
- Delayed reflexes
- Goiter
- Hair and skin changes

Possible Other Causes

- Obesity
- Sleep disorder
- Stress
- Depression
- Menopause
- Iron or vit D deficiency
56 hypothyroid patients on T4
Randomized to receive 3 T4 doses & outcomes measured
Mean serum TSH levels were: 2.8±0.4 mU/L, 1.0±0.2 mU/L, and 0.3±0.1 mU/L for the 3 treatments
There were no significant treatment effects on any of the instruments of well-being, symptoms, quality of life, cognitive function, or treatment preference
Thyroxine-Triiodothyronine Combination Therapy Versus Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

- Meta-analysis of 11 studies and 1,216 patients
- Randomized trials comparing T4 & T3 to T4 therapy
- End points included bodily pain, depression anxiety, fatigue, QOL, B wt, and lipid profiles
- Adverse effects were similar
- No difference between T4 & T3 vs T4 therapy
- T4 monotherapy should remain the Rx of choice for hypothyroidism

JCEM 89:2099, 2004
LT4 Rx in Hypothyroidism

Recommendation 22.1

• Pt with hypothyroidism should be treated with LT4 monotherapy

Recommendation 22.2

• The evidence does not support using LT4 and LT3 combinations to treat hypothyroidism

Recommendation 22.4

• There is no evidence to support using DTE in preference to LT4 monotherapy in hypothyroidism, therefore DTE should not be used
# Results of Randomized, Controlled
Trials of T4+T3 vs T4 Alone

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Outcome</th>
<th>Pt preference</th>
</tr>
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<tbody>
<tr>
<td>Bunevicius et al, 1999</td>
<td>T4 + T3 &gt; T4</td>
<td>T4 + T3 &gt; T4</td>
</tr>
<tr>
<td>Walsh et al, 2002</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Escobar-Morreale et al, 2005</td>
<td>No difference</td>
<td>T4 + T3 &gt; T4</td>
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<tr>
<td>Appelhof et al, 2005</td>
<td>No difference</td>
<td>T4 + T3 &gt; T4</td>
</tr>
</tbody>
</table>

*Review of Endo 2:32, 2008*
Combination T4 & T3 Therapy

- 70 pt, age 18-65 yr
- RCT using Dessicated Thyroid Extract (DTE) vs LT4 treatment in hypothyroidism
- DTE did not result in significant QOL improvement but did cause moderate weight loss
- Combination T4 + T3 is safe but not better than LT4
Thyroid Hormone Metabolism

T4 = Thyroxine
T3 = Triiodothyronine
D = Deiodinase
D1 = liver, kidney, thyroid
D2 = CNS, pituitary
D3 = brain, placenta
Why LT4 Monotherapy May Not be Enough?

- Type 2 deiodinase (Dio2) controls T4 $\rightarrow$ T3
- Dio2 polymorphism could influence T3 level in brain and mood
- Increasing LT4 levels result in ↓ Dio2 and ↓ T3
- Some patients on T4 Rx do not feel normal because of ↓ T3 level in brain

Elevated TSH in LT4 Therapy

A 50-year-old biology teacher reports recent fatigue, lethargy and decreased libido; has been on LT4 for hypothyroidism for 20 years. Last yr TSH was 2.2; current TSH 11.7 mIU/L with FT4 0.7 ng/dL. He is on 15 other drugs and supplements

Q: Cause of ↑ TSH?
Drug-Induced Abnormal TSH

↑ TSH due to ↓ GI absorption of T4

- Aluminum hydroxide
- Calcium
- Carafate
- Ferrous sulfate
- Lovastatin
Drug-Induced Abnormal TSH

↑ TSH due to ↑ T4 metabolism

- Dilantin
- Phenobarbital
- Rifampin
- Tegretol
## Drug-Induced Abnormal TSH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypo-/hyper-</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Bexarotene</td>
<td>Y/N</td>
<td>Central</td>
</tr>
<tr>
<td>Lithium</td>
<td>Y/?Y</td>
<td>Autoimmune</td>
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<tr>
<td>Amiodarone</td>
<td>Y/Y</td>
<td>Iodine</td>
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<tr>
<td>Interferon</td>
<td>Y/Y</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Y/N</td>
<td>?</td>
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</table>
Conclusions (1)

- Subclinical hypothyroidism in the young pt should be treated with LT4
- Aggressive case finding rather than routine screening in recommended in pregnancy
- Normal serum TSH is $\leq 2.5$ in early & $\leq 3.5$ in late pregnancy
- Commonest cause of hypothyroidism is Hashimoto thyroiditis
Conclusions (2)

- Use FT4 or FTI, rather than TSH, to Dx & Rx central hypothyroidism
- LT4 monotherapy is recommended for most pt with hypothyroid
- Deiodinase polymorphism is one explanation for hypothyroid pt being unhappy with T4 Rx
- Consider interfering drugs when TSH is abnormal in established, hypothyroid pt
Thank You