MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM

Prof. Dato’ Dr. Mafauzy Mohamed
Professor of Medicine /
Senior Consultant Endocrinologist
Health Campus, Universiti Sains Malaysia
Subclinical Hypothyroidism

Hypo

• TSH >4.0 mIU/L
• FT4, T₃ - normal

2 Categories
• mildly increased TSH levels (4.0–10.0 mU/l)
• severely increased serum TSH levels (>10.0 mU/l)
TSH assay

- TSH < 0.001
  - FT4
    - Raised
      - Thyrotoxic
    - Normal
      - FT3
        - Normal
          - Sub-clinical Hyperthyroidism
        - Raised
          - T3 toxicosis

- TSH normal
  - Euthyroid

- TSH raised
  - FT4
    - Low
      - Hypothyroid
    - Normal
      - Sub-clinical Hypothyroid
Epidemiology

• ~ 5% of population
• prevalence increases with age
• more common in women, whites
• more likely in those with
  - previous hyperthyroidism
  - family history of thyroid disease
  - type 1 diabetes mellitus
  - previous radiotherapy to head & neck
Subclinical Hypothyroidism

Causes

• Autoimmune thyroiditis
• Subacute thyroiditis
• Post $^{131}$I or surgery
• Postpartum thyroiditis
• Medications (ATD, Lithium, I)
Thyroid Antibody Testing

• Anti-thyroid peroxidase antibodies (TPOAb)
  - most sensitive serological test for thyroid autoimmunity
  - useful in patients with goitre or with other autoimmune diseases to diagnose AIT
  - in patients with elevated serum TSH to identify cause

• Anti-thyroglobulin antibodies (TgAb)
Subclinical Hypothyroidism
Whickham Study: Risk of Progression

<table>
<thead>
<tr>
<th>Positive test</th>
<th>Annual risk (%)</th>
<th>20-yr cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH N, Ab⁺</td>
<td>2.1</td>
<td>27</td>
</tr>
<tr>
<td>TSH ↑, Ab⁻</td>
<td>2.6</td>
<td>33</td>
</tr>
<tr>
<td>TSH ↑, Ab⁺</td>
<td>4.3</td>
<td>55</td>
</tr>
</tbody>
</table>

Vanderpump M: Clin Endocrinol 43:55, 1995
Subclinical Hypothyroidism

Whickham Study: Follow-Up

• 1,877 subjects

• Lower risk with young age, lower TSH, Ab neg

• Prevalence increased in women with age: 4.5% in <44; 17.4% in >75

• Prevalence in men >65 was 6.2%
Risk of Overt Hypothyroidism in a 60-Year-Old Woman

Vanderpump M et al, 2003
Subclinical Hypothyroidism

Colorado Study

• 25,862 subjects surveyed at health fair

• Mean age 55

• TSH >5.1 in 9.5% (8.9% not on T4)

• TSH 5.1–10 µU/mL in 74%

• TSH >10 µU/mL in 26%

Colorado Study
Mean Cholesterol Levels

P<0.001

TSH levels

Arch Intern Med 160:526, 2000
Colorado Study
Mean Cholesterol Levels

P<0.003

Arch Intern Med 160:526, 2000
Imaizumi M: 
JCEM 89:336, 2004

257 pt with SCH, TSH >5.0
2,293 controls, TSH <5.0
Screening for subclinical hypothyroidism

• previous thyroid dysfunction
• family history of thyroid disease
• type 1 diabetes mellitus
• previous radiotherapy to head & neck
• symptoms of thyroid dysfunction
• abnormal thyroid gland
• history of autoimmune disorder
Subclinical Hypothyroidism

Why Treat?

- Prevent progression to overt hypothyroidism
- Reduce TC and CV risk
- Improve symptoms
Subclinical Hypothyroidism

BaseL Study

• RCT, 63 F
• 34 with SCH
• Mean TSH 11-14 (range 5-50)
• Mean LT4 dose 86 µg/d
• Duration 48 wk
• TC ↓ 3.8%, LDL C ↓ 8.2%
• Risk reduction of CAD mortality 17%

Subclinical Hypothyroidism

Effect of T4 on LDL Cholesterol

• 49 pt; 33 controls

• 6 mo normal TSH after T4 Rx

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>Rx</td>
</tr>
<tr>
<td>TSH (mU/mL)</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>128</td>
<td>132</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/mL)</td>
<td>6.0</td>
<td>1.5*</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>139</td>
<td>120**</td>
</tr>
</tbody>
</table>

*P=0.0001; **P=0.003

Caraccio N et al: JCEM 87:1533, 2002
TPOAb
When to Check?

- Whickham Study showed that 87% of pt with TSH >10, 68% of pt with TSH 5.3-10, and only 14% of pt with TSH 0.5-5.2 were positive for TPOAb.

- Since positive TPOAb and ↑TSH are highly predictive of hypothyroidism, TPO should be checked when TSH is 3.0-5.0.
Consequences of SCH

• mild impairment of declarative memory, working memory and mood
• weight gain
• insulin resistance and components of the metabolic syndrome
• elevated total cholesterol & LDL cholesterol
• functional cardiac abnormalities, such as left ventricular diastolic dysfunction, and reduced resting and exertional systolic function
• CHD events and mortality
When to Treat?

- TPO positive
- Goiter
- Pregnancy
- ↑ TC
- Infertility
- Symptoms
Management of Subclinical Hypothyroidism

High TSH

Repeat TSH; check TPOAb, FT4

TSH >10

T4 Rx

TSH 4-10

TPOAb

TPOAb+
Sx
Goiter
Lipids ↑

TPOAb-
No goiter
Lipids nl

Recheck 1 yr
ETA Guideline 2013

**Age ≤ 70**

- **Serum TSH < 10**
  - Hypothyroid symptoms?*  
    - No: Observe and repeat TFT in 6 months  
    - Yes: 3-Month trial of LT₄, then assess response to treatment

- **Serum TSH ≥ 10**
  - Treat with LT₄

**Age > 70**

- **Serum TSH < 10**
  - Observe and repeat TFT in 6 months

- **Serum TSH ≥ 10**
  - Consider LT₄ if clear symptoms of hypothyroidism or high vascular risk
Treatment

• For those patients older than 50 years, or in younger patients with a history of cardiac disease, a lower initial dosage is indicated, starting with 0.025 to 0.05 mg of l-thyroxine daily

• Clinical and biochemical reevaluations at 6- to 8-week intervals until the serum TSH concentration is normalized.
I-thyroxine

• to be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal)
• should be separated from other potentially interfering medications and supplements (e.g., calcium carbonate and ferrous sulfate). A 4-hour separation is traditional
Goal of Treatment

• To alleviate symptoms (if symptomatic)
• Aim for serum TSH in lower half of reference range (0.3–2.5 mU/l)
• For older individuals (>70 years), more relaxed targets acceptable, aim for serum TSH between 1.0 - 5.0 mU/l
Follow-Up of Untreated Patients

- 5–8% per year progress to overt hypothyroidism, depending on the degree of serum TSH elevation
- normalise in 6–35% depending on initial TSH levels, thyroid autoantibody status
- repeat thyroid function test should be re-checked within 8–12 weeks along with thyroid autoantibodies
- those who have persistent SCH, thyroid function should be tested 6 monthly at least for the first 2 years & then yearly thereafter
Summary

• 2 categories of SCH according to TSH elevation
  - mildly increased TSH levels (4.0–10.0 mU/l)
  - more severely increased TSH levels (>10 mU/l)

• Initially raised serum TSH with normal FT 4 should be investigated with repeat measurement of TSH, FT4 & TPOAb

• T4 Rx recommended for younger patients (<70 yrs) with serum TSH >10 mU/l
• T4 Rx recommended for younger patients (<70 yrs) with serum TSH 4-10 mU/l if symptomatic - if no improvement in symptoms, T4 therapy should generally be stopped

• For older patients (>70yrs) with serum TSH >10 mU/l, T4 Rx if symptomatic or high vascular risk

• Aim - serum TSH 0.3–2.5 mU/l (for older patients 1-5 mU/l)

• T4 should be taken on empty stomach; start with low dose in elderly patients or patients with CVD