Subclinical hypothyroidism: to treat or not to treat? Cons
Conflict of interest statement

Gabriela Brenta
Cesar Milstein Hospital
Buenos Aires, Argentina

Declared receipt of honoraria or consultation fees from Merck Serono.
Case 1: 34-year-old female

- Patient describes coldness, poor memory and constipation
- BP: 130/70 mmHg; weight: 60 kg; height: 163 cm
- Pulse: 62 bpm; dry skin observed
- Thyroid: non-palpable

Is there a reason to suspect hypothyroidism?
Please check that the pulse is correct. Other slide says 72 bpm
Clinical practice guidelines for the management of hypothyroidism

Diretrizes clínicas práticas para o manejo do hipotiroidismo

Gabriela Brenta¹, Mario Vaisman², José Augusto Sgarbi³, Liliana Maria Bergoglio⁴, Nathalia Carvalho de Andrade⁵, Pedro Pineda Bravo⁶, Ana Maria Orlandi⁷, Hans Graf⁸, on behalf of the Task Force on Hypothyroidism of the Latin American Thyroid Society (LATS)

Arq Bras Endocrinol Metab. 2013;57/4
Recommendation 2

Clinicians cannot rely exclusively on physical examination to confirm or rule out hypothyroidism. Patients with physical signs such as deeper voice (LR + = 7.1), hoarser voice (LR + = 5.2), puffy eyes (LR + = 4.0), bradycardia (LR + = 3.88), constipation (LR + = 3.6), coldness (LR + = 3.5), delayed ankle reflex (LR + = 3.4), poor memory (LR + = 2.6), coarse skin (LR + = 2.3), puffy face (LR + = 1.15), pretibial edema (LR + = 1.13) and slow movements (LR + = 1) are suspected of hypothyroidism and require a diagnostic workup that includes thyroid hormone assays. Grade B.

If the patient has clinical findings or a high probability of overt hypothyroidism, the measurement of both TSH and free T4 are required. However, one must take into account that clinical findings of hypothyroidism are very unspecific. Grade D.
Editor has added the reference. Please check it is appropriate
Linda Edmondson; 01/06/2015
Case 1: 34-year-old female

- Patient describes coldness, poor memory and constipation
- BP: 130/70 mmHg; weight: 60 kg; height: 163 cm
- Pulse: 62 bpm; dry skin observed
- Thyroid: non-palpable
- TPOAb: 10 IU/l; **TSH: 6.4 mIU/l; T4L: 0.9 ng/ml**

Should levothyroxine therapy be initiated?
Assessment of TSH values in a community setting: 5 years’ follow-up

n=422,242*

- 95% normal TSH
- 3.0% high TSH (<10.0)
- 0.7% high TSH (>10.0)
- 1.2% low TSH

*346,549 without thyroid disease or other factors interfering with thyroid tests

Speaker to check addition by editor - 2.0% became abnormal. Is that correct?
Linda Edmondson; 01/06/2015
Case 1: 34-year-old female

3 months later...

TSH: 3.4 mIU/l
Case 2: 59-year-old female

- Gained 15 kg in weight in the last year
- Weight: 90 kg; height: 163 cm
- BMI: 34
- Thyroid: palpable
- TSH: 4.7 mIU/l and 5 mIU/l (3 months later)
- TPOAb negative
## TSH and obesity (BMI >30)

<table>
<thead>
<tr>
<th>TSH</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td>0.67</td>
<td>0.4, 1.11</td>
</tr>
<tr>
<td>0.4–1</td>
<td>1.06</td>
<td>0.85, 1.32</td>
</tr>
<tr>
<td>1–2</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>2–3</td>
<td>1.20</td>
<td>0.94, 1.55</td>
</tr>
<tr>
<td>&gt;3.6</td>
<td>2.13</td>
<td>1.44, 3.14</td>
</tr>
</tbody>
</table>

T3, positively associated with weight

\[ r=0.36; \ P<0.01 \]

\[ n=97 \]

speaker, consider redoing axes labels?
Thyroid function is related to weight

- 20 girls with anorexia
- 32 normoweight girls
- 100 obese girls

All thyroid values normalized when weight disorder was corrected

Cholesterol values differ between morbid-obese and lean patients at similar TSH elevated values

Speaker to check alignment of TSH values - there are three values but these don't seem to align properly. Is the 0.388 a P-value?

Linda Edmondson; 05/06/2015
Obesity: effects on thyroid status

Increased levels of T3 and TSH in obesity

Thermogenic adaptative phenomenon with modification of thyroid axis?

LE6  Speaker to check that these reference details are OK
Linda Edmondson; 05/06/2015

MS8  Speaker please check all text is correct in the graphic
Maxine Skipp; 09/06/2015
Obesity and high levels of TSH

Screening for and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force

BMI and weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>BMI 1</th>
<th>BMI 2</th>
<th>p-value</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duman 2007</td>
<td>RCT</td>
<td>8 months</td>
<td>LT4</td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Iqbal 2006</td>
<td>RCT</td>
<td>12 months</td>
<td>LT4</td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Kong 2002</td>
<td>RCT</td>
<td>6 months</td>
<td>LT4</td>
<td></td>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Monzani 2004</td>
<td>RCT</td>
<td>10.5 months</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Nagasaki 2005</td>
<td>RCT</td>
<td>5 months</td>
<td>LT4</td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Razvi 2007</td>
<td>RCT crossover</td>
<td>12 weeks</td>
<td></td>
<td></td>
<td></td>
<td>Good</td>
</tr>
</tbody>
</table>

Speaker to provide full reference details
Linda Edmondson; 05/06/2015
Case 3: 80-year-old male

- Presents with depression and neurocognitive symptoms
- Neurologist refers the patient, due to increased TSH levels

TSH: 6.40 mIU/l
fT4: 0.94 ng/dl
Case 3: 80-year-old male

3 months later...

TSH: 7.40 mIU/l
fT4: 0.97 ng/dl
ATPO: <0.5 Ul
Speaker please check units for ATPO
Maxine Skipp; 09/06/2015
TSH distribution by age groups in the USA excluding individuals with +FH, +Ab or goitre

70% of older patients with TSH >4.5 mIU/l were within their age-specific reference range

<table>
<thead>
<tr>
<th>Age</th>
<th>TSH 97.5 percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>3.56 mIU/l</td>
</tr>
<tr>
<td>50–59</td>
<td>4.03 mIU/l</td>
</tr>
<tr>
<td>80+</td>
<td>7.5 mIU/l</td>
</tr>
</tbody>
</table>

speaker is percentiles correct?
Maxine Skipp; 09/06/2015

And please check X axis label is correct
Maxine Skipp; 09/06/2015
Serum TSH increase not associated with persistent or true hypothyroidism

- Heterophilic or interfering antibodies, including human anti-animal (most commonly mouse) antibodies, rheumatoid factor and autoimmune anti-TSH antibodies
- Bioinactive forms of TSH in central hypothyroidism
- Adrenal insufficiency
- Transient subhypo following subacute, painless or postpartum thyroiditis
- Impaired renal function
- TSH-secreting pituitary adenoma
- Isolated pituitary resistance to thyroid hormone
- Recovery phase from non-thyroidal illness
- Loss-of-function mutations in gene encoding for TSH receptor

- Obesity
- Age
# Screening for and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force

## Health-related quality of life

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Design</th>
<th>Study Duration</th>
<th>Country</th>
<th>Mean Age</th>
<th>Mean TSH Level (LT4 vs. Placebo)</th>
<th>Intervention and Duration, n</th>
<th>Results, LT4 vs. Placebo</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abul-Tealah 2010</td>
<td>RCT crossover (at 2 months)</td>
<td>4 months</td>
<td>United Kingdom</td>
<td>55 years overall (NR by group) 4.1 to 9.0 mIU/L (mean NR)</td>
<td>LT4 7.2 µg (mean) for 2 months: 33 Placebo: 51</td>
<td>JOL: odds of feeling better after taking thyroxine than placebo</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Jorde 2008</td>
<td>RCT</td>
<td>12 months</td>
<td>Norway</td>
<td>62 vs. 63 years 5.8 vs. 5.3 mIU/L</td>
<td>LT4 109.7 µg for 12 months (mean): 36 Placebo: 33</td>
<td>HDL: 1.3 ± 3.6 vs. 3.3 ± 4.0; p=NS</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Kong 2002</td>
<td>RCT</td>
<td>6 months</td>
<td>United Kingdom</td>
<td>53 vs. 45 years 8.0 vs. 7.3 mIU/L</td>
<td>LT4 (mean NR) for 6 months: 23 Placebo: 17</td>
<td>Mean change in thyroxine group minus mean change in placebo group: HADS-anxiety 1 (95% CI, −1 to 3); p=NS HADS depression: −1 (95% CI, −3 to 1); p=NS GHQ-30: 2 (95% CI, −5 to 7); p=NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Parie 2010</td>
<td>RCT</td>
<td>12 months</td>
<td>United Kingdom</td>
<td>73.5 vs. 74.2 years 0.6 vs. 0.6 mIU/L</td>
<td>LT4 50 µg (median) for 12 months: 52 Placebo: 42</td>
<td>HADS depression: 3.55 (0.27) vs. 3.37 (0.31); p=0.82</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Nazvi 2007</td>
<td>RCT crossover (at 2.0 months)</td>
<td>5.5 months</td>
<td>United Kingdom</td>
<td>53.5 vs. 54.2 years 5.4 vs. 5.3 mIU/L</td>
<td>LT4 1000 µg for 12 weeks: 50 Placebo: 50</td>
<td>ThyUOCL: −1.1 ± 1 vs. −1.2 ± 0.9; p=0.24 SF-36-sex: −2.3 ± 2.7 vs. −2.7 ± 2.8; p=0.18 SF-36-motivation: 3.1 ± 2.7 vs. 3.7 ± 2.7; p=0.16 SF-36-women: −2.5 ± 3 vs. −2.8 ± 2.9; p=0.23 Average weighted impact of all 18 QOL domains: −2.7 ± 2.4 vs. −2.8 ± 2.3; p=0.15</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

Cognitive function

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>Jorde 2006&lt;sup&gt;44&lt;/sup&gt;</th>
<th>Parle 2010&lt;sup&gt;45&lt;/sup&gt;</th>
<th>LT4 109.7 μg for 12 months (mean): 36 Placebo: 33</th>
<th>LT4 50 μg (median) for 12 months: 52 Placebo: 42</th>
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<tr>
<td>RCT</td>
<td>62 vs. 63 years 5.8 vs. 5.3 mIU/L</td>
<td>73.5 vs. 74.2 years 6.6 vs. 6.6 mIU/L</td>
<td>Composite cognitive function score: 1.5 ± 3.7 vs. -0.9 ± 4.8; p=NS</td>
<td>MEAMS—cognitive skills and performance: 11.67 (0.09) vs. 11.60 (0.11); p=0.57</td>
</tr>
<tr>
<td>12 months Norway</td>
<td>LT4 109.7 μg for 12 months (mean): 36 Placebo: 33</td>
<td>LT4 50 μg (median) for 12 months: 52 Placebo: 42</td>
<td>Trail Making A—psychomotor test of executive function: 39.0 ± 14.8 vs. 44.1 ± 17.7; p=NS</td>
<td>MMSF—cognitive status: 28.24 (0.38) vs. 28.22 (0.43); p=0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trail Making B—psychomotor test of executive function: 94 ± 62 vs. 103 ± 49; p=NS</td>
<td>SCOLP—speed of cognitive processing and accounting: 1.29 (0.30) vs. 0.84 (0.35); p=0.59</td>
</tr>
</tbody>
</table>

Thyroid status, disability, cognitive function and survival in old age

All individuals aged 85 years living in Leiden 1997–1999
558 participants followed for 4 years

Recommendation 14

The panel recommends against routine treatment for elderly (> 65 yr) and very-elderly (> 80 yr) patients with subclinical hypothyroidism at TSH levels < 10 mU/L. Grade A.

The panel also recommends against treatment of SH if the aim is to improve cognitive function in elderly people. However in > 65 years old, treatment can be considered on an individual basis. Grade D.
Does treatment of screen-detected subclinical thyroid dysfunction improve morbidity or mortality?
Subclinical hypothyroidism and coronary disease: meta-analysis of observational studies stratified by age

<table>
<thead>
<tr>
<th>Ochs N et al.</th>
<th>Razvi S et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years RR: 1.51; 95%CI: 1.09, 2.09</td>
<td>&lt;65 years OR: 1.68; 95%CI: 1.27, 2.23</td>
</tr>
<tr>
<td>&gt;65 years RR: 1.05; 95%CI: 0.90, 1.22</td>
<td>&gt;65 years OR: 1.02; 95%CI: 0.85, 1.22</td>
</tr>
</tbody>
</table>

In this slide we only have the ages as 'below and above' 65 years. Which category included patients aged 65 years? We will change the symbol to \( \leq \) or \( \geq \) accordingly.

Linda Edmondson; 01/06/2015
### Subclinical hypothyroidism and mortality: meta-analysis of observational studies stratified by age and comorbidities

<table>
<thead>
<tr>
<th>Haentjens et al.</th>
<th>Razvi S et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with comorbidities</strong>&lt;br&gt;HR: 1.76; 95%CI: 1.36, 2.30</td>
<td><strong>&lt;65 years</strong>&lt;br&gt;OR: 1.37; 95%CI: 1.04, 1.79</td>
</tr>
<tr>
<td><strong>Rest of the cohort</strong>&lt;br&gt;HR: 1.03; 95%CI: 0.78, 1.35</td>
<td><strong>&gt;65 years</strong>&lt;br&gt;OR: 0.85; 95%CI: 0.56, 1.29</td>
</tr>
</tbody>
</table>

Speaker to check slide notes, which end in the middle of a sentence

Linda Edmondson; 05/06/2015
# Thyroid studies collaboration

## Meta-analysis with individual data

55,287 subjects; 11 observational studies

<table>
<thead>
<tr>
<th>CHD Events by TSH Level, mIU/L&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No. of Events</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-4.49</td>
<td>4040</td>
<td>23,957</td>
</tr>
<tr>
<td>4.5-6.9</td>
<td>264</td>
<td>1344</td>
</tr>
<tr>
<td>7.0-9.9</td>
<td>96</td>
<td>441</td>
</tr>
<tr>
<td>10-19.9</td>
<td>70</td>
<td>235</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHD Mortality by TSH Level, mIU/L&lt;sup&gt;c&lt;/sup&gt;</th>
<th>No. of Events</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-4.49</td>
<td>1059</td>
<td>50,052</td>
</tr>
<tr>
<td>4.5-6.9</td>
<td>132</td>
<td>2363</td>
</tr>
<tr>
<td>7.0-9.9</td>
<td>50</td>
<td>652</td>
</tr>
<tr>
<td>10-19.9</td>
<td>28</td>
<td>333</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Mortality by TSH Level, mIU/L&lt;sup&gt;d&lt;/sup&gt;</th>
<th>No. of Events</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-4.49</td>
<td>8749</td>
<td>51,837</td>
</tr>
<tr>
<td>4.5-6.9</td>
<td>640</td>
<td>2431</td>
</tr>
<tr>
<td>7.0-9.9</td>
<td>170</td>
<td>672</td>
</tr>
<tr>
<td>10-19.9</td>
<td>105</td>
<td>347</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR Ratio (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference]</td>
<td>1.00 (0.86-1.16)</td>
<td></td>
</tr>
<tr>
<td>1.17 (0.96-1.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.89 (1.28-2.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt; .001 for trend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR Ratio (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference]</td>
<td>1.09 (0.91-1.30)</td>
<td></td>
</tr>
<tr>
<td>1.42 (1.03-1.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.58 (1.10-2.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = .005 for trend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR Ratio (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference]</td>
<td>1.06 (0.96-1.17)</td>
<td></td>
</tr>
<tr>
<td>1.02 (0.84-1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.22 (0.80-1.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = .39 for trend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment with levothyroxine was associated with reduced ischaemic events in patients <70 years old

- Cohort followed up for 7.5 years (UK GPRD)
- TSH 5.01 and 10 mIU/l

HR for ischaemic events 0.61
95%CI: 0.49, 0.92
in patients treated with LT4 between 40 and 70 years

Speaker to confirm that the notes are correct. There appear to be references missing in the notes.

Linda Edmondson; 05/06/2015
Screening for and treatment of thyroid dysfunction: 
an evidence review for the US Preventive 
Services Task Force

- One fair-quality cohort study found that treatment of 
  subclinical hypothyroidism was associated with decreased 
  risk for CHD events vs no treatment
- No studies found that treatment was associated with 
  improved HRQoL, cognitive function, BP or BMI vs no 
  treatment
- Effects of treatment vs no treatment showed potential 
  beneficial effects on lipid levels of uncertain clinical 
  significance (difference, –28 to 0 mg/dl for total cholesterol 
  [nine studies] and –22 to 2 mg/dl for low-density lipoprotein 
  cholesterol [10 studies])

Lack of definitive evidence for a benefit does not equate to evidence for lack of benefit
Treatment algorithm proposed by LATS for subclinical hypothyroidism excluding pregnancy

Persistent subclinical hypothyroidism

> 10 mIU/l
- Treat

≥ 4.5 to 10 mU/L
- m/l 10 mIU/l
- Cardiovascular risk and/or preexistent cardiovascular disease
  - No
    - Typical sonographic appearance ofAITD and/or positive TPOAb
      - No
        - Hypothyroidism symptoms and/or depression
          - No
            - Only observational monitoring of thyroid function
          - Yes
            - Short LT4 course
              - Yes
                - Improved
                  - Keep on LT4 therapy
              - No improved
                - Stop LT4 therapy
          - Yes (not mentioned in the flowchart)

* In patients over 65 years of age, this algorithm should be applied on an individual basis.

Concluding remarks

- Before treating subclinical hypothyroidism make sure TSH was measured twice with 2-3 months interval.
- Treatment is not recommended when TSH is below 10 mU/L in:
  - Patients >65 years old
- Treatment is not recommended in patients <65 years old when TSH is below 7 mU/L in:
  - Patients without cardiovascular risk factors
  - Patients without AITD or ultrasound finding of AITD
  - Patients without signs or symptoms of hypothyroidism
Thank you for your attention
2015 Latin American conference on cardiometabolic diseases management