Subclinical thyroid disorders

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Definitions:

- Individuals with elevation of TSH but normal thyroid hormone levels have sub-clinical hypothyroidism*.

*Some authors consider patients with high-normal TSH and abnormal response to TRH as having SCH.

Definitions:

- Individuals with TSH lower than normal but with normal thyroid hormone levels have sub-clinical hyperthyroidism.

Normal TSH???

- Normal TSH range
- Most common assays in U.S.A.
  - 0.4-5.5 uU/mL
  - 0.27-4.2 uU/mL
Normal TSH???

- Lower limit of the normal range is somewhat variable but relatively well established.
Normal TSH???

- Upper level of normal range is controversial.
Normal TSH???
NHANES III

N = 13,344
Healthy, antibody negative subjects
Normal TSH???

- Consensus conference (ATA, AACE, Endo Soc) accepted NHANES III derived normal range.
- National Academy of Clinical Biochemistry proposed 0.4-2.5 uU/mL for normal range.
- AACE proposed 0.3-3.0 uU/mL
Practical considerations

- Results of lowering upper limit of normal range from 5 to 2.5 uU/mL changes prevalence of sub-clinical hypothyroidism:
  - 4.6% to 20%

Fatourechi V. et al. JAMA 2003;290:3195-3196
Practical considerations

- TSH varies with time.
  - Mildly abnormal TSH should be rechecked in 3-4 months to confirm persistent elevation.
    - Transient elevations are not uncommon.
Practical considerations

- TSH elevations NOT associated with SC hypothyroidism:
  - Recovery from non-thyroidal illness.
  - Adrenal insufficiency.
  - Treatment with metoclopramide and domperidone
  - TSH secreting adenomas
  - Thyroid hormone resistance
  - Assay variability
  - Late evening pulse in TSH secretion
Practical considerations

- Decreased TSH also could be seen with conditions that are not associated with hyperthyroidism.
Practical considerations

- Decreased TSH NOT associated with SC hyperthyroidism:
  - Central hypothyroidism
  - Non-thyroidal Illness
  - Glucocorticoid and dopamine use
  - Recovery from hyperthyroidism
  - Early pregnancy
Practical considerations

- Even TSH over 20 uU/mL can be associated with normal TH levels.
Practical considerations

- Attempts to identify individuals with mild thyroid disorders based on search for thyroid specific symptoms have not been successful.
Sub-clinical hypothyroidism

- Should be diagnosed in patients who do NOT complain of symptoms associated with hypothyroidism.
- In patients who are screened for presence of thyroid disorder because of increased risk.
Elevated TSH normal TH

- If patient complains of symptoms and elevated TSH with normal TH is found, than disorder cannot be considered to be sub-clinical.
Mild hypothyroidism

- In my opinion, after rechecking to confirm TSH elevation, treatment should be seriously considered in such patients.
- TSH should be corrected to below 2.0 uU/mL and therapeutic effects assessed after 2-3 months.
- If benefit is derived treatment should be continued.
Sub-clinical hypothyroidism

- Individuals with TSH from upper limit of normal to 10 uU/mL
  - With normal TH levels
  - With no symptoms that could be explained by hypothyroidism

Have “Sub-clinical hypothyroidism”
Epidemiology

- Whickham survey
- Prevalence
  - Men 2.8%
  - Women 7.5%
  - Women >60 y 11.6%

Epidemiology

- NHANES III
- Prevalence in 16,533 individuals
  - Patients with known thyroid disease were excluded.
  - SCH found in 4.3%

Epidemiology

- Colorado Thyroid Disease Prevalence Study
- N – 25,862
- Prevalence
  - Overall 9.5%
  - 18-24 y 4.0%
  - Women >74 22%
  - Men >74 y 16%

Epidemiology

- Increased prevalence is reported in patients with:
  - Diabetes mellitus type 1 (1)
  - Schmidt’s syndrome (2)
  - Celiac disease (3)

- Due to presence of Hashimoto’s thyroiditis

Etiology–SC hypothyroidism

- Common causes
  - Iatrogenic
    - In patients with coexisting heart disease
    - In patients with malignant diseases
    - In patients with poor compliance
    - In patients taking medications inappropriately
Etiology–SC hypothyroidism

- **Common causes**
  - Iatrogenic
  - Hashimoto’s thyroiditis
    - Most common cause
    - 54% of SCH patients in U.S. are abs positive (1)
    - UK study found abs in 67% of women and 40% of men with SCH (2)

Etiology – SC hypothyroidism

- Common causes
  - Iatrogenic
  - Hashimoto’s thyroiditis
  - Postpartum thyroiditis
Etiology–SC hypothyroidism

- Common causes
  - Iatrogenic
  - Hashimoto’s thyroiditis
  - Postpartum thyroiditis
  - Medications
    - Amiodarone
    - Lithium
    - Interferon
    - Sunitinib
    - Sorafenib
Etiology–SC hypothyroidism

- Common causes
  - Iatrogenic
  - Hashimoto’s thyroiditis
  - Postpartum thyroiditis
  - Medications
  - Partial thyroidectomy
Etiology–SC hypothyroidism

- Common causes
  - Iatrogenic
  - Hashimoto’s thyroiditis
  - Postpartum thyroiditis
  - Medications
  - Partial thyroidectomy
  - Head and neck radiation
Etiology—SC hypothyroidism

- **Common causes**
  - Iatrogenic
  - Hashimoto’s thyroiditis
  - Postpartum thyroiditis
  - Medications
  - Partial thyroidectomy
  - Head and neck radiation
  - RAI ablation of Graves’ disease
Clinical consequences

- Progression to overt hypothyroidism
  - 2-5% yearly
  - 10% may eventually normalize
  - Higher initial TSH – higher the risk of progression
  - Positive AMA-s – higher risk of progression

Clinical consequences

- Development of hypothyroidism, 20 year follow up – Whickham survey
  - 27% if abs positive
  - 33% if TSH higher than normal
  - 55% if TSH higher and abs positive
  - 4% if TSH was normal and abs negative

Clinical consequences

Clinical consequences

- Risk of CV disease
  - Diastolic dysfunction
  - Diastolic hypertension
  - Increase in LDL-C
  - Increased hsCRP
- Alteration in coagulation parameters
- Endothelial dysfunction

Alber CP. et al. Am Heart J 1964
Clinical consequences

- Risk of CV disease
  - Whickham survey showed no association over 20 years with:
    - Coronary heart disease
    - Dyslipidemia
    - Mortality

Clinical consequences

- Risk of CV disease
  - Rotterdam study showed increased prevalence of atherosclerosis (odds ratio 1.7) and MI (odds ratio 2.3) in women with SCH.

Clinical consequences

- Risk of CV disease
  - Studies show mixed results but population studied are different and number of patients are usually small (total number of subjects is high but patients with SCH are not many).

  - Example – 4331 subjects but 281 with SCH (1)

Controversy

- McDermott MT, Ridgway EC 2001 Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 86:4585–4590.

Clinical Consequences

- **Fertility**
  - 17% of Tg and AM antibodies positive had spontaneous miscarriage, compared to 8.4% of antibody negative women (1)
  - 2.3% of 25,756 pregnant women had SCH, and their risk for placental abruption and preterm delivery was 2 times normal (2)

Clinical Consequences

- Fertility
  - The 16 and 11 recurrent aborters with positive TPO-abs were treated with T4 and IV immunoglobulins respectively.
  - T4 treated patients had 81.2% delivery rate and IV Immunoglobulin treated 54.5%.

Clinical Consequences

- Neuropsychiatric disorders
  - SCH patients with depression have poorer response to antidepressant medications (1)
  - SCH patient have increased lifetime prevalence of depression (2)
  - Women with SCH and goiter have increased rate of anxiety and depressive features (3)

Clinical Consequences

- Mortality
  - CV health study (N = 3,233) showed NO increase (1)
  - Meta-analysis showed increased risk in those older than 65 (2)
  - Several studies showed increase in CV and all-cause mortality (3-5)

Our experience

- We examined cohort of 6,408 patients at HIGH RISK for cardiovascular disease.
- Patients were enrolled in cardiovascular disease prevention program of Cleveland Clinic between January 16, 1995 and June 25, 2008.
- Data about patients were entered in the Preventive Cardiology Information System (PreCIS) database.

McQuade C, et al. ATA meeting, Chicago IL, 2008 abstract 311.
Methods

- Patients:
  - Secondary prevention ~ 50%
  - Primary prevention ~ 50%
    - Hypercholesterolemia
    - Strong family history of CVD

- The CVD risk factors are aggressively treated.
Methods (cont)

- Five TSH intervals predefined:
  - <0.4 µU/ml (hyperthyroid)
  - 0.4-3.0 µU/ml (normal)
  - 3.0-6.0 µU/ml (mild SCH)
  - 6.0-10.0 µU/ml (moderate SCH)
  - >10.0 µU/ml (hypothyroid)
### Methods (cont)

- **Number of patients:**

<table>
<thead>
<tr>
<th>Value Range</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4 µU/ml</td>
<td>168 patients</td>
</tr>
<tr>
<td>0.4-3.0 µU/ml</td>
<td>4,755 patients</td>
</tr>
<tr>
<td>3.0-6.0 µU/ml</td>
<td>1,214 patients</td>
</tr>
<tr>
<td>6.0-10.0 µU/ml</td>
<td>178 patients</td>
</tr>
<tr>
<td>&gt;10.0 µU/ml</td>
<td>79 patients</td>
</tr>
<tr>
<td>No TSH available</td>
<td>14 patients</td>
</tr>
</tbody>
</table>
Patients characteristics:

- There was no difference between groups:
  - Framingham risk score
  - Diabetes mellitus
  - LDL
  - Lp(a)
  - Microalbuminuria
  - Body mass index
  - Diastolic blood pressure
Results

- Adjustment was made for:
  - Age
  - Sex
  - Smoking
  - HDL
  - LDL
  - Systolic blood pressure
  - Diastolic blood pressure
  - Diabetes
Results

- After adjusting for common risk factors there were no increased risk for the group of patients with TSH less than 0.4.
All cause mortality - adjusted

All Patients (n = 6,394)

P < 0.001
All cause mortality - adjusted

All Patients (n = 6,394)

P=0.021
Limitations

- Thyroid status based only on elevated TSH values as L-T4 and T3 values are not consistently available.
- The PreCIS database consists of exclusively preventive cardiology patients at the Cleveland Clinic. The cohort is highly selected for patients with or at risk for CHD. Results may not be generalizable.
- Cause of death cannot be determined from the SS death index.
Effect of treatment

- Psychometric outcomes and hypothyroid symptoms scores in double blind randomized trials:
  - Improvement is seen consistently in those with TSH >10 uU/mL.

Effect of treatment

- Cholesterol
  - T4 treatment decreases:
    - Total Cholesterol in those with initial level over 240 mmol/L (meta-analysis)
    - LDL – C
    - Apolipoprotein B-100

Effect of treatment

- Cardiac function, blood pressure
  - Cardiac output increases (1)
  - Vascular resistance decreases (1)
  - Mean arterial pressure decreases (1)
  - Carotid intimal-media thickness decreases (2)
  - Diastolic and systolic function improve (3)

Bottom line:

- I treat individuals with SCH if there are associated clinical symptoms or positive thyroid autoantibodies.
  - A 2-6 months later clinical and laboratory response is assessed.
  - Decision to treat or not to treat further is made in discussion with patient.
SC hyperthyroidism

- Etiology
  - Iatrogenic
    - 25% of patients taking T4 may have low TSH.
      
      Some of these are intentional
      - Thyroid carcinoma
      - History of head and neck radiation
      - Presence of nodules and goiters

De Whalley P. Br J Gen Pract 1995;45:93.
SC hyperthyroidism

- **Etiology**
  - Iatrogenic
  - Autonomous nodules (solitary and in MNG)
    - A 22% of patient with MNG found to have SC hyperthyroidism (1)
    - In hyperthyroid patients over 55 years of age with MNG 57% were sub-clinical (2)

Diaz JJ. Gerontology 2003;49:316
SC hyperthyroidism

- Etiology
  - Iatrogenic
  - Autonomous nodules (solitary and in MNG)
  - Graves’ disease
    - About 6% of patients with Graves’ disease are sub-clinical.

SC hyperthyroidism

- **Etiology**
  - Iatrogenic
  - Autonomous nodules (solitary and in MNG)
  - Graves’ disease
  - Thyroiditis
  - Graves’ disease in remission
  - High hCG
SC hyperthyroidism

- **Epidemiology**
  - Reports vary from 0.7% to 12.4%
    - NHANES III showed 0.7% (1)
      - Smokers two times higher prevalence.
    - Another study found 1.8% with TSH <0.1 uU/mL in U.S. (2)
    - In England 6% had TSH <0.5 uU/mL (3)

SC hyperthyroidism

- Natural course
  - 40-60% normalize (1-3)
  - About 4% progresses to overt hyperthyroidism (4,5)

Clinical consequences

- Bone metabolism
  - No good data on fracture rates.
  - A meta-analysis found decreased BMD, but only in postmenopausal women (1).
  - In those taking T4 low BMD was found only if dose was higher than 1.6 mcg/kg/d (2).
  - Markers of bone turnover have been reported to be increased (3)

Faber J, Galloe AM. Eur J Endocrinol 1994;130:350
Loviselli A, et al. Thyroid 1997;7:561
Clinical consequences

- CV effects
  - Atrial fibrillation
    - Prospective study- 2,000 adults over 60 followed for 10 years
      - TSH <0.1 uU/mL - 28% cumulative incidence
      - TSH 0.1-0.4 uU/mL - 16% cumulative incidence
      - TSH >0.4 uU/mL - 11% cumulative incidence

Clinical consequences

- CV effects
  - Atrial fibrillation
    - A cross-sectional study, 24,000 hospitalized patients.
      - 14% prevalence if overtly hyperthyroid
      - 13% prevalence in SC hyperthyroidism
      - 2% prevalence in euthyroid controls

Clinical consequences

- CV effects
  - Other described effects
    - Increased heart rate and atrial premature beats
    - Reduced exercise tolerance
    - Increased cardiac contractility
    - Increase in LV mass index
    - Lower LDL-C and total cholesterol
    - Systolic hypertension
Clinical consequences

- **Mortality**
  - In 3,121 cardiac patients SC hyperthyroidism was associated with 2.32 increased risk for cardiac death (1)
  - Meta-analysis of 290 subjects over 60 found 41% increase in all cause mortality (2)
  - Cardiovascular Health Study (3,233 subjects over 65 y) found no increase in mortality (3)

SC Hyperthyroidism

- Most individuals with TSH of 0.1 um/mL or higher do not experience any symptoms.
Management

- **High risk patients**
  - TSH <0.1 uU/mL evaluate and treat.
  - TSH 0.1-0.4 uU/mL evaluate and treat if BMD low, a-fib or symptoms of hyperthyroidism are present.

- **Low risk patients**
  - TSH <0.1 uU/mL evaluate and treat if BMD low or symptoms present.
  - TSH 0.1-0.4 uU/mL observe.
Questions

- What is the appropriate normal range for TSH?
  - Answer will require more studies that will need to include antibody determination and more than one determination of TSH over period of time to avoid transient elevations to creep into the normal ranges.
Questions

Should we screen for SC thyroid dysfunction?

- Population screening is probably not cost effective.
- Testing patients with mild symptoms suggestive of hypothyroidism is NOT screening.
Questions

Who should we screen for SC thyroid dysfunction?

- High risk groups should be screened.
  - History of neck irradiation
  - Pituitary surgery or irradiation
  - Use of medications known to affect thyroid
  - Presence of thyroid nodule or MNG
Questions

Should we screen for SC thyroid dysfunction?

- Studies needed about
  - Patients with autoimmune disorders
  - Unexplained infertility
  - Previous postpartum thyroiditis
  - Refractory depression
  - Turner’s and Down’s syndrome
  - Obesity
Questions

- **Is there a treatment benefit?**
  - Studies are inconclusive.
  - Patients with mild laboratory abnormalities should not be treated automatically.
  - These should be followed in 3-6 months and reassessed.
  - If even mild symptoms are present treatment should be offered.
  - Long term outcomes need studies.