Subclinical Hypothyroidism
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Subclinical Hypothyroidism

- Objectives
  - Recognize and manage permanent and reversible causes of hypothyroidism
  - Recognize causes for persistently raised TSH in patients receiving replacement therapy
  - Diagnose and interpret subclinical hypothyroidism
  - Select patients with subclinical hypothyroidism who are more likely to benefit from therapy
  - Evaluate and interpret risks/benefits of levothyroxine treatment in patients with subclinical hypothyroidism with TSH between 4.5 and 10mIU/L
Subclinical Hypothyroidism

- Hypothyroidism
  - Iodine deficiency - Worldwide
  - Autoimmune thyroid disease - Developed World
    - Hashimoto’s Disease
  - Thyroid Ablation (radioactive iodine, surgery, drugs)
- Subclinical Hypothyroidism
Subclinical Hypothyroidism

- Hypothyroidism
  - Reversible causes
    - Hashimoto’s thyroiditis (about 5%)
    - Postpartum thyroiditis - 70% become euthyroid
    - Subacute thyroditis - nearly 100% become euthyroid
    - Iodine/drug induced
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- Incidence of Hypothyroidism
  - 4.1/1000 in women
  - .6/1000 in men
- Genetic (HLA-DR3, CTLA-4, thyroglobulin gene mutations) - unclear
- Environmental factors (infection, smoking, iodine status) - unclear.
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- Raised TSH activity in patients receiving therapy
  - Non-compliance
  - Inadequate dose
  - Interaction with drugs
    - reduced absorption - iron tablets, cholestyramine, calcium carbonate, soya
    - rapid clearance of LT4 - phenytoin, carbamazepine, rifampicin, valproate
  - Residual gland dysfunction
    - autoimmune, post-irradiation, surgery
  - Pregnancy/ Gluten sensitivity patients
  - Postmenopausal estrogen treatment (increase in TBG concentrations)
  - Systemic illness.
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- The most common cause of hypothyroidism in United States?
  - a. post ablation
  - b. surgery
  - c. autoimmune
  - d. environmental
  - e. iodine
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- All are causes of raised TSH in patients receiving LT4 except?
  - a. Non-compliance
  - b. Interactions with iron, cholestyramine, calcium
  - c. residual gland dysfunction
  - d. systemic illness
  - e. all the above
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- Serum thyroid-stimulating hormone level above the upper limit of normal despite normal levels of serum free thyroxine.
- 2-fold change in FT4 will produce a 100-fold change in TSH.
- Serum TSH is the necessary test for diagnosis of mild thyroid failure.
- Individual range for peripheral thyroid hormones is narrower than reference laboratory range.
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- Prevalence of 3% to 8% increases with age and is higher in women
- Antithyroid antibodies can be detected in 80% of pts
- Before diagnosis of SCH
  - Determine other causes of elevated TSH
  - Determine the clinical importance of therapy
  - What is the upper limit of normal for TSH level?
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- Clinical importance of therapy
  - 2007 meta analysis of 14 randomized clinical trials concluded that levothyroxine for SCH did not result in improved survival or decrease cardiovascular morbidity
- Progression to Overt Hypothyroidism
  - SCH with +TPOAb higher rate of progression
  - TSH >10 predicts higher rate of progression
  - TSH will normalize in over 50% pts with SCH (TSH<10)
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- **Systemic Symptoms of Hypothyroidism**
  - Patients with serum TSH 5-10 did not show any benefit. Am J Med 2002
  - Patients with serum TSH < 10 did not show any benefit. JAMA 2004
  - Some improved memory in appr. 25% patients (TSH up to 30)
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- Cardiac Risk Factors
  - meta-analysis of 13 studies concluded that the lipid profile improved with therapy
  - not categorized for serum TSH levels 5-10
  - homocysteine and lipoprotein(a) - no role in SCH
  - Metabolic syndrome patients with raised HsCRP are at a significant risk for subclinical hypothyroidism
  - SCH was not related to elevations in cholesterol, LDL level or Triglyceride level and low HDL level
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- **Adverse Cardiac End Points**
  - Conclusion of 6 recent meta-analyses suggest that a cardiovascular risk exists for persons younger than 70 y/o, no effect for those aged 70-80 y/o, possibly protective effect for those older than 80.

- **Cardiac Dysfunction**
  - Improved only in pts with TSH >10
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- **Adverse Fetal Effects**
  - Haddow et al showed a 7-point reduction in intelligence quotient in children aged 7-9 y/o whose mothers had SCH at pregnancy compared with children of euthyroid mothers.
  - Important to screen pregnant women and therapy for mild thyroid failure in women who are pregnant or planning on becoming pregnant.
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- Psychiatric and Cognitive Dysfunction
  - No association with anxiety, depression or cognitive dysfunction--low threshold!!
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- What is the upper limit of normal for the serum TSH?
  - Lowering the serum TSH level from 5 to 3mI/L - controversial
    - not indicated as a clinical important abnormality
    - Levothyroxine may not provide a benefit
    - No difference in cognitive and psychological function between control vs. levothyroxine  BMJ 2001
  - Follow up TSH in one year recommended (+TPOAb)
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- Serum TSH level between 5.1 and 10 mIU/L?
  - Reduction of cholesterol with therapy - inconclusive
  - Most studies are not stratified for individuals in this level
  - Improve cognition, neuropsychiatric, cardiac, and muscle abnormalities included a wide spectrum of TSH levels
  - Cardiovascular risk factor?
  - Treatment should be individualized
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- Factors favoring levothyroxine therapy in Patients with a TSH level of 5 to 10 mIU/L
  - Pregnancy or intention of pregnancy, infertility
  - Goiter
  - Bipolar disorder, depression
  - Presence of antithyroid antibodies
  - Progressive TSH increase
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- Factors favoring Levothyroxine therapy in patients with TSH level of 5 to 10 mIU/L
  - ovulatory dysfunction
  - childhood and adolescence and young age of patient
  - Hyperlipidemia?
  - 2 TSH levels >8 mIU/L
  - Elevated CPK
  - Therapeutic trial of possible hypothyroid symptoms
What about TSH level greater than 10 mIU/L?

- Authorities favor treatment
  - start with a daily dose of 25 to 75 ug
  - recheck TSH level in 6 weeks
  - Strive for a TSH level 0.3 to 3.0 mIU/L
  - Watch for overdosing of levothyroxine therapy resulting in suppressed TSH
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- Thyroxine replacement therapy
  - Start with 25-50 mcg/day in the elderly and cardiac patients
  - Start with 50-100 mcg/day in the young and healthy
  - Increase dose every 6 weeks to aim for TSH normalization (recommend 0.5 to 2.5 mU/l as target during replacement therapy) and symptom control
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- Screening For Subclinical Hypothyroidism
  - ATA recommends screening over 35 y/o with repeat tests every 5 years
  - RCP and USPSTF against population screening of nonpregnant asymptomatic adults
  - USPSTF - Risks for elevated TSH - Caucasian ethnic background, Type I DM, Down Syndrome, Radiation to H/N, family history of thyroid disease and previous Hyperthyroid.
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- Conclusions
  - SCH (mild thyroid failure) - peripheral thyroid hormone levels are within normal reference range but serum TSH levels are mildly elevated.
  - 3%-8% population, women>men, prevalence with Inc. age
  - Before diagnosis of SCH rule out other causes of elev. TSH
  - Cardiovascular risk factor is still up for debate
  - TSH > 10 treat, TSH <10 individualize therapy
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- Conclusions
  - TSH returns to normal in about 5% in the first year and repeating thyroid tests in 4-12 weeks is important
  - Pregnancy and anticipation of pregnancy are indications for LT4 treatment
  - Patients with TSH between 4.5 and 10 mIU/L if not treated should be monitored annually especially if they are +TPOab
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- Finally, very old patients (e.g. >85 years) may be biologically different from moderately older patients (e.g. >60-70 years)
  - Octogenarians with high blood pressure tend to live longer than those with lower levels
  - Wisdom of treating hypertension and other abnormalities (subclinical hypothyroidism) is being questioned
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- Administration of thyroid hormone could theoretically accelerate the aging process by increasing metabolic rate.
- Age-related hormone deficiencies (e.g. growth hormone) are not necessarily associated with bad outcomes.
- Could restoring hormone levels in older patients have adverse affects.
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- Which one of the following statements about mild thyroid failure (SCH) is true?
  - All cases of mild thyroid failure of autoimmune origin are associated with the presence of TPO antibodies.
  - Almost all patients with a serum TSH level greater than 10.0 mIU/L need levothyroxine therapy.
  - Women older than 60 years are 4 times more likely to have a serum TSH level than men in the same age group.
  - The best therapy for SCH is a combination of levothyroxine and T3.
  - Levothyroxine is indicated in a pt. with a serum TSH of 8 mIU/L and mildly elevated cholesterol.
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Which one of the following patients is most likely to benefit from levothyroxine therapy?

- An 86 y/o man with a serum TSH level of 5 mIU/L and cognitive changes
- A women in the first trimester of pregnancy with a serum TSH level of 4.5 mIU/L who tests positive for TPO abs
- A 55 y/o woman with a serum TSH level of 5 mIU/L and a serum cholesterol of 210
- A 40 y/o hospitalized man with pneumonia with sepsis with a TSH of 10 mIU/L and low serum T4
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Management principles are clear in most thyroid disorders and include which of the following?

a. start 25-50 mcg/day in the young and healthy pt.

b. there is no current evidence to support combination therapy of LT4 and T3

c. Increase dose every 1-2 weeks to aim for TSH normalization

d. Lower doses may be required in gluten sensitivity and pregnancy.
Hyperthyroidism

• Autoimmune Graves Disease and Toxic Multinodular Goiter - most common causes
• Prevalence in women between 0.5 to 2%
• 10X more common in women than in men
• Dx: elevated FT4 and FT3 and suppressed TSH
• Positive uptake in thyroid scan
• Tx: Antithyroid drugs and/or radio ablation
Subclinical Hyperthyroidism

- Suppressed TSH, Normal FT3 and FT4
- Persistent - Exogenous/iatrogenic, Endogenous - Graves/TMN/SNG
- Transient - Treatment of Thyrotoxic state with antithyroid drugs or radio ablation, thyroiditis, Amiodarone-induced thyrotoxicosis
- More common in women and Black subjects and iodine deficient areas with MNG
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- Other causes of Suppressed TSH include:
  - Hypothalamic/Pituitary disease
  - Non-thyroid illness
  - Steroids, Dopamine, Amiodarone
Amiodarone

- Contains 2 iodine atoms (3 mg/100mg amidarone)
- Daily diet 3 mg/day
- Lipophilic - T1/2 100 days
- Prevent T4 to T3
- Block T3 receptors and thus increase TSH
- Direct effect on Thyroid follicular cells - Destructive Thyroiditis.
Subclinical Hyperthyroidism

- Why treat SCHyper?
- Triiodothyronine Affects
  - Cardiac pacemaker - atrial fib, AV ectopic beats
  - Vascular Smooth Muscle - Atherosclerosis
  - Myocardial contractility
Subclinical Hyperthyroidism

- Beneficial effects on BMD in postmenopausal Women with osteopenia.
- Large Cohort of PMW >65
- 4x vertebral fracture and 3x hip fracture
Non-Thyroid illness

• Euthyroid Sick Syndrome - Suppressed TSH, decrease FT4 and FT3 (Transient Central Hypothyroidism)
• 2-3 % of hospital patients have suppressed or elevated TSH (<50% of patients have a thyroid problem)
• Acute psychotic disturbances and clinical depression may prompt inappropriate intervention
• Not recommended ordering thyroid function tests in seriously ill unless strong clinical suspicion for thyroid
Non-Thyroid illness

• Elevated TSH
  • recovery phase of non-thyroid illness and will normalize

• Suppressed TSH
  • Steroids, amiodarone, dopamine
Thyroid in Pregnancy

- Increased estrogen will increase TBG will increase T4
- Increase HCG - increase FT4 - Decrease TSH
- Need to check TSH and FT4 every 3 months
- Most common - Autoimmune Graves Disease
# Treatment of Thyroid Disease

<table>
<thead>
<tr>
<th>Serum TSH (mIU/l)</th>
<th>Risks</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Risk of progression to overt hyperthyroidism</td>
<td>Determine aetiology</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>Consider intervention with thionamides or radioiodine</td>
</tr>
<tr>
<td></td>
<td>Increased risk of osteoporosis</td>
<td>Annual check if decision to not intervention</td>
</tr>
<tr>
<td></td>
<td>Possible increased risk of cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>0.1–0.4</td>
<td>Probable non-thyroidal illness</td>
<td>Repeat thyroid function tests in 3 months to confirm resolution</td>
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<td></td>
<td></td>
<td>Reassure normal thyroid function</td>
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<tr>
<td>0.4–2.5</td>
<td>Euthyroid</td>
<td>L-T4 to achieve target serum TSH 0.5 mIU/l only if pre-conception or</td>
</tr>
<tr>
<td>2.5–4.0</td>
<td>Risk of progression to overt hypothyroidism</td>
<td>pregnant</td>
</tr>
<tr>
<td></td>
<td>Increased risk of adverse pregnancy outcome</td>
<td></td>
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<td></td>
<td>Impaired intellectual and psychomotor outcomes in children</td>
<td></td>
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<tr>
<td>4.0–10.0</td>
<td>Risk of progression to overt hypothyroidism</td>
<td>Repeat serum TSH and anti-TPO antibodies in 3 months</td>
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<tr>
<td></td>
<td>Symptoms of depression/impaired cognitive function</td>
<td>Consider trial of L-T4 if serum TSH persistently raised</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia</td>
<td>Annual check if decision to not intervene</td>
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<tr>
<td></td>
<td>Diastolic dysfunction and heart failure</td>
<td></td>
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<tr>
<td></td>
<td>Adverse cardiovascular outcomes if &lt;65 years</td>
<td></td>
</tr>
</tbody>
</table>
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References

- Fatourechi, MD. Subclinical Hypothyroidism: and Update for Primary Care Physicians. Mayo Clinic Proceedings. 2009 January;84(1) 65-71
- Surks MI, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; 291(2):228-238