

Case 1: 44y/F, perimenopausal patient has come with irregular menses, emotional lability, facial puffiness on getting up from sleep, weight gain of about 2-3 kg in last 12 months. She was found to have TSH of 7  $\mu$ IU/ml with normal T3 and T4. There is no family history of thyroid dysfunction and no goiter on examination. No history of significant co morbidities in her. She has been advised to start thyroxin for all these symptoms.

She has 'googled' about thyroxin therapy and found that it can be bad for her bones and is seeking second opinion for the same.

### Questions

1. Can these problems be attributed to hypothyroidism? Which symptoms would respond to Thyroxin therapy?
2. Adverse effects of Thyroxin replacement therapy?

Case 2: 32y/F, married since 2 years, trying to conceive since 1 year. She has regular monthly menses with normal bleeding pattern and amount. No co-morbidities in the patient. Husband's semen analysis has been reported as normal. Further work up revealed a TSH of 7.9  $\mu$ IU/ml and normal T4. There was a history of hypothyroidism in her mother for the last 20 years. She has a fairly large Goitre on examination. Her physician started her on daily dose of 50 mcg thyroxin. On follow up, her TSH reduced to 4  $\mu$ IU/ml.

### Questions

1. Indications for starting treatment in Subclinical hypothyroidism?
2. How to monitor the treatment?

## APPROACH TO SUBCLINICAL HYPOTHYROIDISM

### Definition

Subclinical hypothyroidism (SCH) is defined as a clinical scenario characterized by elevated TSH, with normal T4 and T3. Earlier it was also called as preclinical myxedema or early clinical hypothyroidism or compensated euthyroidism. These terms have been abandoned.

However, the upper limit of normal range for TSH is variable depending upon the lab as well as the assay. Large studies of healthy human volunteers without any underlying thyroid disease or significant risk factors have suggested much lower levels of TSH as normal, compared to traditional values of 4 or 5  $\mu$ IU/ml. Values of 2.5  $\mu$ IU/ml (NACB, 2003), 3  $\mu$ IU/ml (AACE) have been considered as the upper limit of normal range.

Use of age adjusted reference ranges for TSH has also been suggested as these studies reveal increase in normal values of TSH with increasing age. Values of TSH greater than 5  $\mu$ IU/ml are generally thought to be diagnostic of SCH.

In women seeking fertility, TSH level above the normal upper limit of range, which is appropriate for the 1<sup>st</sup> trimester should be considered as SCH in the presence of normal thyroid hormone levels.

### Epidemiology

Prevalence of SCH in general population ranges from 4-15%. Elderly age, women, white race and iodine deficiency are associated with increased prevalence.

### Etiology

The causes of subclinical and overt hypothyroidism are similar. Some conditions unrelated to thyroid dysfunction can also give rise to similar biochemical findings.

Chronic autoimmune thyroiditis, inadequately treated overt hypothyroidism and destructive therapy for prior thyrotoxicosis are few common causes. All the causes have been enlisted below in Table 1.

### Differential diagnosis

Apart from above mentioned causes, some clinical situations that are associated with similar biochemical picture need to be considered:

### Natural history

SCH can either remain stable or progress to overt hypothyroidism (OH). Spontaneous recovery has been noted in a fair number of patients (upto 30% at end of 1 year of follow up).

High TSH (> 10  $\mu$ IU/ml), anti TPO antibody positivity, high dose external neck radiation or radioactive iodine therapy are associated with progression to OH. Annual progression rates are about 3 to 10% and cumulative

**Table 1: Causes of Hypothyroidism**

Chronic autoimmune thyroiditis
Inadequately treated overt hypothyroidism
Destructive therapy for prior thyrotoxicosis
External neck irradiation
Drugs: lithium, iodine containing drugs/ contrast agents
Inactivating mutations in TSH receptor gene
Pseudohypoparathyroidism type 1a

**Table 2: Problems faced in treatment of Subclinical Hypothyroidism**

Thyroid related/ unrelated situations	Lab related issues
Following thyrotoxic phase in thyroiditis	Assay variability
TSH secreting pituitary adenoma (T3 and T4 high)	Heterophile antibodies
Resistance to Thyroid hormones (T3 and T4 may be normal or high)	Macro TSH: anti TSH autoantibodies (1.6% of SCH patients)
Pulsatile secretion, nocturnal surge of TSH	Rheumatoid factor interference
Recovery from non thyroid illness (transient)	
Morbid obesity related (High leptin mediated)	
Metoclopramide, Domperidone	
Untreated adrenal insufficiency	
Central hypothyroidism: 25% associated with normal or slightly high, upto 5 $\mu$ IU/ml	

progression rates over 10-20 years are 33 to 55%. SCH can remain stable in patients with thyroid surgeries for non thyrotoxic conditions, low dose neck radiation. Spontaneous recovery has been seen in patients without any anti TPO antibodies, in TSH <10 mIU/L and in first 2 years of follow up.

### Clinical presentation

No correlation has been observed between symptoms and TSH levels. Most patients get diagnosed based on biochemical findings and few patients complain about symptoms that are mild or non-specific like fatigue, weight gain, constipation, dry skin etc.

### Consequences of SCH

Various studies have associated SCH with CVD: CHD, stroke, heart failure, hyperlipidemia, weight gain, fertility problems, neuropsychiatric symptoms, Alzheimer's disease and increased mortality in general.

### Randomized trials

Many available randomized trials have not selected patient population and replacement doses carefully. Few recent trials failed to demonstrate any significant benefit of Thyroxin therapy in these patients. Factors that improve with treatment are total cholesterol and LDL cholesterol concentration and few parameters of myocardial and endothelial function.

## OBSERVATIONAL STUDIES

### SCH and lipid profile

- About 1700 people with TSH 5.1-10  $\mu$ IU/ml associated with high mean total cholesterol concentration (223 mg/dl vs 216 mg/dl) compared to people with normal TSH.
- Thyroxin replacement associated with reduction in total cholesterol (about 9 to 15 mg/dl) and LDL (mean 11 mg/dl).

### SCH and cardiovascular risk and mortality

Most studies show that TSH above 10 mIU/L is associated with increased incidence of coronary artery disease, ischemic heart events, heart failure and stroke.

Men tend to have higher cardiovascular risk if TSH is >10mU/L.

However, a contrasting study has shown that there was no increase in cardiovascular mortality or coronary artery disease and in fact, SCH was associated with reduced mortality in age group of 80-85 years!

### SCH and neuropsychiatric symptoms

SCH has been associated with increased risk of depression, poor verbal memory and executive functioning defects (reversible with treatment), senile and multiinfarct dementia, increased risk of Alzheimer's disease in men. However, most studies did not show any improvement in neuropsychological symptoms.

### SCH and reproductive dysfunction

In women, SCH is associated with ovulatory dysfunction and unexplained subfertility especially when associated with positive anti TPO antibody.

Increased chances of miscarriage are also seen in women with SCH and euthyroid women with positive anti TPO antibodies compared to normal.

Fertility improves and pregnancy outcomes are better on treatment of SCH. All associations recommend treatment of SCH in these situations.

### Miscellaneous effects of SCH

Modest weight gain

Increased risk of common bile duct stones

Non alcoholic fatty liver disease

Neuromuscular problems

### Diagnosis of SCH

As discussed earlier, SCH is diagnosed by the presence of elevated TSH level with normal serum levels of thyroid hormones T3 and T4. In addition to these tests, anti TPO antibodies could be checked to determine the etiology of SCH.

In the presence of nodular goiter, Ultrasound of thyroid could be done to look for any suspicious features.

### Management of SCH

Treatment of all cases of SCH with thyroxin replacement therapy is a controversial issue.

Points in favour of treatment are reduction in chances of progression to OH, size of goiter, spontaneous abortions and pre term deliveries. Few studies have supported beneficial effects on lipid profile and cardiac dysfunction, better treatment outcomes in iron deficiency anemia, moderate effects on weight loss and neuropsychiatric symptoms.

Points against treatment include lack of strong evidence for clinical benefits in these studies, additional cost, risk of overtreatment in elderly patients (iatrogenic thyrotoxicosis) in terms of cardiac arrhythmias and osteoporosis.

#### Whom to treat

- Presence of goiter (likely to progress to OH, 50% goiters reduce in size to some degree)
- Family history of thyroid disease
- Those with rising titre of TSH
- Anti TPO positivity (likely to progress to OH)
- In females trying to conceive (when normal upper limit of TSH is 2.5mIU/l in first trimester) and those who are pregnant
- When TSH is greater than 10  $\mu$ IU/ml (high chances of progression to OH)
- In patients with dyslipidemia (possible cardio protective effects on lipid profile)
- In newborn term infants with TSH elevation >10 mIU/l beyond 2 weeks of life (critical period for neurodevelopment)

#### Whom not to treat

- Morbidly obese patients with modest elevation of TSH (related to high Leptin levels)
- Very elderly patients with modest elevation of TSH (a normal age related variation in TSH level and it may be protective)

Treatment is with thyroxin. Starting dose of the same is generally slightly lower than full replacement dose

(1.6mcg/kg). Goal is to maintain TSH level in the lower half of normal range ( $\leq 2.5$   $\mu$ IU/ml). Subsequently, adjustments in dose by 12.5 to 25 mcg are every 6-8 weeks to keep the TSH in target range.

### MONITORING

After starting the treatment or after changing the dose of thyroxin, TSH levels can be evaluated after 6 weeks and as the TSH goal is achieved and the dose stabilizes, checking once in 6 months is enough.

When no treatment is advised for SCH, repeat testing can be done after 3 months and if the levels are similar, further checking can be done annually.

In pregnant patients, monthly evaluation is advised in first trimester till TSH reaches goal level. Thereafter they are monitored every 4-6 weeks throughout the pregnancy. In the post-partum period, thyroxin requirements return to pre pregnancy levels. About 6 weeks after delivery, due to restoration of immune function, which is suppressed throughout the pregnancy, there may be a resurgence of auto-immune thyroiditis. Thyroxin requirements may go up at this stage. Hence, monitoring TFTs is indicated even in post partum period till these variations settle down.

In elderly patients and patients with poor cardiac reserve, cautious dosing and monitoring is indicated as the risks of overtreatment in these populations may be serious.

### TRIAL OF THYROXIN

In some situations, when clear benefits of treatment are not evident, trial of thyroxin can be given for a period of 3-6 months. Subsequently, if there is no benefit, thyroxin treatment should be stopped and TFTs may be monitored annually. Examples include patients with negative anti TPO antibodies or those with goiter and no decrease in size of the same in spite of treatment.

### REFERENCES

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