THYROID HORMONE REPLACEMENT THERAPY IN SUBCLINICAL HYPOTHYROIDISM

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INTRODUCTION

- Subclinical hypothyroidism (SCH) is a purely biochemical diagnosis.
- TSH levels are raised and free T3 and T4 levels are within normal range (usually lower end).
- The term subclinincal hypothyroidism only applicable when
  - thyroid function has been stable for weeks or more,
  - the hypothalamic-pituitary-thyroid axis is normal, and
  - there is no recent or ongoing severe illness.

TSH Level

- The normal range for TSH values, with an upper limit of 4.12 mU/L is largely based on NHANES III data, but it has not been universally accepted. [1]

- Some have proposed that the upper normal should be either 2.5 or 3.0 mU/l.

- There are two categories of subclinical hypothyroidism

  Mildly increased level of TSH 4-10mU/l

  Severely increased level of TSH >10mU/l

1. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: Implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007;92:4575–82.

- The risk of progression to overt hypothyroidism is related to number of factors including
  - initial serum TSH concentration,
  - presence of auto antibodies,
  - family history and
  - presence goiter.

- The prevalence of SCH is 3-8%, which increases with age, more prevalent in females; but it approaches to males after 6th decade

Recommendations

An initial raised serum TSH with FT 4 within reference range should be

- investigated with a repeat measurement of both serum TSH and FT 4 ,
- along with thyroid per-oxidase antibodies,

preferably after a 2- to 3-month interval.

Who to Treat/Who to Observe: Younger Adults (<65–70 Years)

Treatment should be commenced if the following are present

- symptoms suggestive of hypothyroidism,
- positive thyroid antibodies, or
- evidence of heart disease or associated risk factors for these diseases.

- There is a concern that many patients who do not meet these criteria are being placed on long-term thyroid hormone replacement therapy.
- 14-22% of patients on thyroid hormone replacement therapy are overtreated.
- Too much circulating thyroid hormone can
  - increase the risk of abnormal heart rhythms such as atrial fibrillation and
  - can promote bone loss, contributing to osteoporosis.

MENTAL IMPROVEMENT

- There is limited evidence for improvement in mental function with L- thyroxine treatment of SCH in younger individuals [2]

2 Jorde R, Waterloo K, Storhaug H, et al: Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endo- crinol Metab 2006

Link to Thyroid Cancer

- Increasing TSH levels even within the normal range are associated with an increased risk of thyroid cancer [3]
- A large study of 27,914 patients showed that treatment with L -thyroxine was associated with a lower risk of cancer [4]

3. Boelaert K: The association between serum TSH concentration and thyroid cancer. En- docr Relat Cancer 2009; 16: 1065–1072. 4 1 Fiore E, Vitti P: Serum TSH and risk of papil- lary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab 2012; 97: 1134–1145.

4. Fiore E, Rago T, Provenzale MA, et al: L -Thy- roxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross- sectional study on 27,914 patients

Younger Adults (<65–70 Years) : Dyslipidaemia

L- Thyroxine therapy of SCH is able to reduce the levels of both total and LDL cholesterol, although normalisation of serum lipids is seldom achieved.

The effect of L -thyroxine replacement on serum lipid concentrations is more pronounced in patients with pre-treatment serum TSH value >10 mU/l.

Younger Adults (<65–70 Years) : Dyslipidaemia (Cont.d)

Even in the absence of symptoms, replacement therapy with L -thyroxine is recommended for younger patients (<65 years) with serum TSH >10 mU/l. [5]

5. Razvi S, Shakoor A, Weaver JU, et al: The influence of age on ischemic heart disease and mortality in subclinical hypothyroid- ism – a meta-analysis. J Clin Endocrinol Metab 2008;

Younger Adults (<65–70 Years): Coronary Heart Disease and Heart Failure

SCH may act as an independent risk factor for heart failure development and for progression to worsening heart failure. [6]

3 recent meta analyses showed a positive association between SCH and Coronary Heart Disease events and mortality. [7]

6. Biondi B: Mechanisms in endocrinology: heart failure and thyroid dysfunction. Eur J Endocrinol 2012; 167;609-618

7. Ochs N, Auer R, Bauer DC, et al: Meta-anal- ysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortal- ity. Ann Intern Med 2008; 148: 832–845

Outcomes in Older People- Heart Failure and Coronary Heart Disease

Age-specific reference ranges for serum TSH should be considered in order to establish a diagnosis of SCH in older people.

The oldest old subjects (>80–85 years) with elevated serum TSH ≤ 10 mU/l should be carefully followed with a wait and see strategy, generally avoiding hormonal treatment.

Although the deleterious effects of SCH on the CV system in younger patients (<65) has been documented, there hasn't been any evidence the moderately old i.e 70-75 and the oldest of the old patients 80 and above.

TREATMENT

If the decision is to treat SCH, then oral L -thyroxine, administered daily, is the treatment of choice. There is no evidence to support use of liothyronine (T 3) or combined L- thyroxine/liothyronine in the treatment of SCH.

TREATMENT (CONT.D)

For patients without cardiac disease, a weight related dose of L-thyroxine should be used, approximating to 1.5 µg/kg/day (e.g. 75 or 100 µg/day for a woman, 100 or 125 µg for a man).

For patients with cardiac disease and in the elderly, a small dose of L-thyroxine should be started, 25 or 50 µg daily. The dose of L -thyroxine should be increased by 25 µg/day every 14–21 days until a full replacement dose is reached

TREATMENT (CONT.D)

For patients with mild SCH (serum TSH <10 mU/l) who have been started on L -thyroxine for symptoms attributed to SCH, response to treatment should be reviewed 3 or 4 months after a serum TSH within the reference range is reached.

If there is no improvement in symptoms, L -thyroxine therapy should generally be stopped.

Follow-Up of Untreated Patients

If thyroid function has normalised following an initially abnormal serum TSH result, then no further testing is required in those who are

- asymptomatic,
- have negative thyroid autoantibodies or
- do not have goitre.

In those who have persistent SCH but in whom treatment is not commenced, thyroid function should be tested 6 monthly for the first 2 years and then yearly thereafter.

Follow-Up of Treated Patients

Once patients with SCH are commenced on L - thyroxine treatment, then serum TSH should be monitored at least annually thereafter.

SPECIAL SITUATION- PREGNANCY

The rate of pregnancy loss,

- including spontaneous miscarriage before 20 weeks gestation and
- stillbirth after 20 weeks,

is increased in anti-thyroid antibody-negative women with TSH values between 2.5 and 5.0 .

Treatment is warranted on these occasions.

CONCLUSION

With newer and more sensitive assays becoming available the detection of SCH is increasing.

At the end of the day, the decision to treat SCH should be tailored to the individual patient.

THANK YOU