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A REVIEW ON MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Subclinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed when thyroid hormone levels are within normal laboratory range but serum thyroid-stimulating hormone (TSH) levels are slightly elevated. This condition occurs in 3% to 8% of the general population. It is more seen in women than men, and its occurence increases with age. Of patients with SCH, 80% have a serum TSH of less than 10 mIU/. Subclinical hypothyroidism is high likelihood of progression to clinical hypothyroidism. Large-scale randomized studies are needed for evidence-based recommendations regarding screening for subclinical hypothyroidism and levothyroxine therapy for this condition. Currently, the practicable approach is routine levothyroxine therapy for persons with a persistent serum TSH of more than 10.0 mIU/L and individualized therapy for those with a TSH of less than 10.0 mIU/L.

KEYWORDS: Subclinical hypothyroidism, clinical conditions, levothyroxine, complications, management.

INTRODUCTION

Subclinical hypothyroidism is termed as an elevated serum TSH level associated with normal range of T_4 and T_3 values. The overall prevalence of SCH has been reported to range from 4-10% in large population screening surveys[1-5] and from 7-26% in studies of the elderly people.[1-11] One of the myths that surrounds SCH is that the laboratory profile of an elevated

serum Thyroid stimulating hormone and normal free thyroid hormones levels represents "compensated hypothyroidism." The reasoning behind this idea is that, since the circulating levels of thyroid hormones are with in reference range with only the serum TSH is being elevated, the affected subjects is really euthyroid because the increased TSH is stimulating the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a disease thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH levels remains elevated, the thyroid hormones levels are not truly normal for that individual the clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable. Because the half-life of T_4 is 7 days and that of T_3 is 1 day, the serum TSH which has a half-life of less than 1 hr. would certainly be expected to return to normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone are insufficient, with a few rare exceptions (TSH – secreting tumors, thyroid hormone resistance syndromes). We, indeed, believe that subclinical hypothyroidism represents mild thyroid failure and is a clinically important that has adverse clinical consequences and that should be treated in most, if not all, cases. We will support this position by reviewing the reported objective data regarding its natural history, its clinical, manifestation, and the benefits of treatment.[1-11]

Evaluation of Subclinical Hyperthyroidism

Epidemiology

Subclinical hypothyroidism is a common condition. Prevalence is 3-8%, increasing with age and being more common in women. After the sixth decade the combined prevalence in both men and women is around 10%. 80% of these patients have a serum TSH of less than 10 mIU/L, and 80% have antithyroid antibodies.[12]

Aetiology

Important causes of hypothyroidism

Autoimmune thyroiditis—Hashimoto's thyroiditis, atrophic autoimmune thyroiditis, this is by far the most common cause, accounting for 90% of cases.

Thyroiditis—subacute thyroiditis (also known as De Quatrain's thyroiditis), silent thyroiditis, postpartum thyroiditis

Iatrogenic— radioiodine therapy, thyroidectomy

Congenital hypothyroidism—thyroid aplasia or hypoplasia, defective biosynthesis of thyroid hormones.

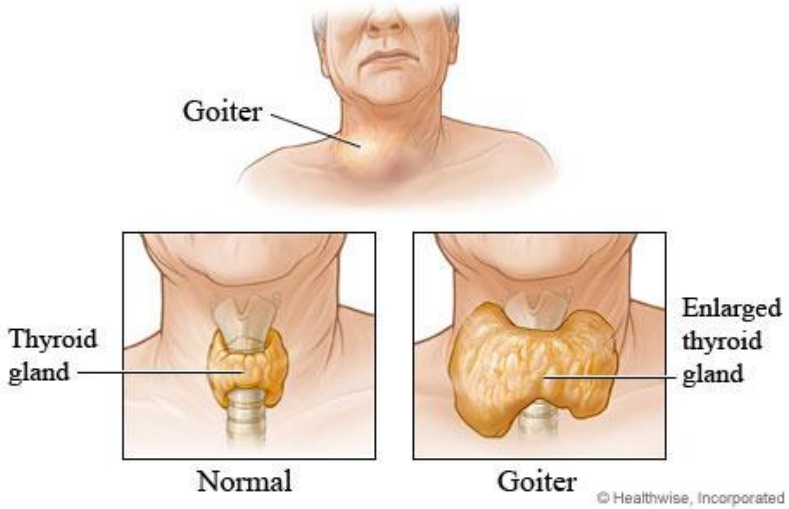
Iodine deficiency

Drugs—carbimazole, iodine, amiodarone, lithium, interferons, thalidomide, rifampicin methimazole, propylthiouracil, sunitinib.

Disorders of the hypothalamus or pitutary (secondary hypothyroidism).[13]

ASSOCIATED CLINICAL CONDITIONS

SCH appears to be associated with reduced bone mineral density, atrial fibrillation ,cardiac dysfunction, and progression to overt hyperthyroidism in patients with known thyroid disease.[14-17] In the Framingham study, investigators found that the person with subclinical hypothyroidism had a relative risk of three to one for developing atrial fibrillation when compared with control patients over 10 years. In another study, accelerated bone loss was documented in women who received excessive levothyroxine replacement therapy when compared with control patients over a period of more than eight years.[17]



DIAGNOSTIC APPROACH

Proper diagnosis of SCH, although challenging, is critical in the identification of individuals who may benefit from thyroid hormone replacement therapy. Detection of SCH depends on laboratory findings, given that the manifestations of the condition often are not clinically obvious. Differential diagnosis of SCH in elderly adults requires consideration of many factors that can influence TSH concentrations. In addition to the natural rise in TSH levels with aging, other underlying causes of thyroid dysfunction that can affect thyroid hormone

levels and may be more prevalent in older adults include Hashimoto's thyroiditis, ineffectual thyroxine replacement therapy (due to inadequate dosage or poor adherence), prior treatment of hyperthyroidism with radioiodine, and Graves' disease. Clinicians should also be mindful that medications for conditions as diverse as mood disorders (lithium), cardiac dysfunction (amiodarone), and malignancies (the tyrosine kinase inhibitor sunitinib) are associated with high TSH and thyroid dysfunction. Individuals recovering from various nonthyroidal illnesses or who have recently received iodine-containing contrast agents may also experience a transitory rise in TSH levels that is generally unrelated to underlying thyroid disease.[18-20]

Investigation of Raised Serum TSH The population prevalence of SCH amounts to approximately 5–10%, being more frequent in women and with increasing prevalence with advancing age.[21-22] Subclinical hypothyroidism is also more common in individuals of white Caucasian origin and in iodine-sufficient regions[23] SCH is generally classified in two categories according to serum TSH level: mildly increased TSH levels (4.0–10.0 mU/l) and more severely increased serum TSH concentrations (>10.0 mU/l) In particular, both healthy individuals and those with SCH have a circadian fluctuation in serum TSH concentration, with a nadir in the early afternoon and approximately 30% higher concentrations being present during the evening and night.[24-25] It has been demonstrated that the degree of variation in serum TSH was lower in SCH than in euthyroid controls, but rises as serum TSH concentrations increased.[26] Thus, several tests, ideally on blood drawn at the same time of day, are needed to establish a representative baseline for serum TSH.[26] In addition, measurement of serum FT 4 is necessary to rule out overt hypothyroidism. Although the reference range for serum TSH in the general adult population is between 0.4 and 4.0 mU/l, TSH concentrations in a healthy individual have a much smaller variation over time, approximating to a third of the reference interval.[27] This can be conceptualised as an individual's 'TSH setpoint'. Furthermore, follow-up of individuals using sequential TSH measurements over long periods of time shows a tendency for the TSH set point to increase a little with advancing age.[28]

Thyroid Antibody Testing

Since chronic AIT, which is the most common cause of SCH, is marked by the presence of circulating antithyroid peroxidase antibodies (TPOAb), and/or antithyroglobulin antibodies (TgAb), measurement of serum thyroid autoantibodies will allow a firm aetiological

diagnosis of AIT to be established. TPOAb are the most sensitive serological test for thyroid autoimmunity in SCH[29] and provide valuable information as to the rate of progression to overt hypothyroidism, which occurs most rapidly in patients with positive TPOAb (4.3% per year) as compared to those with negative TPOAb (2.6% per year).[30] Serum concentrations of TPO-Ab may wane over time, but repeated antibody measurements do not enhance the monitoring of individual SCH patient.[31] Serum TPOAb determination is useful in patients with goitre or with other autoimmune diseases to diagnose AIT, as well as in patients with elevated serum TSH to identify the cause.[32]

Imaging and Additional Testing Modalities

A significant proportion of otherwise healthy people have asymptomatic chronic AIT, and 8% of women (10% of women >55 years of age) and 3% of men have SCH. In about 20% of SCH patients, TPOAb and/or TgAb antibodies are not detected. However, a hypoechoic or an inhomogeneous thyroid echo pattern at ultrasound (US) may be present before circulating autoantibodies and provide early evidence for thyroid autoimmunity. While aspiration cytology is the most sensitive method for diagnosing AIT, a non-invasive examination by US also constitutes a reliable diagnostic tool. Nevertheless, unless there are additional clinical indications, such as goitre, US is not routinely required in the management of SCH.[33]

Recommendations

(1) There are two categories of SCH according to the elevation in serum TSH level: mildly increased TSH levels (4.0–10.0 mU/l), and more severely increased TSH value (>10 mU/l).

(2) 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 peroxidase antibodies, preferably after a 2- to 3-month interval.

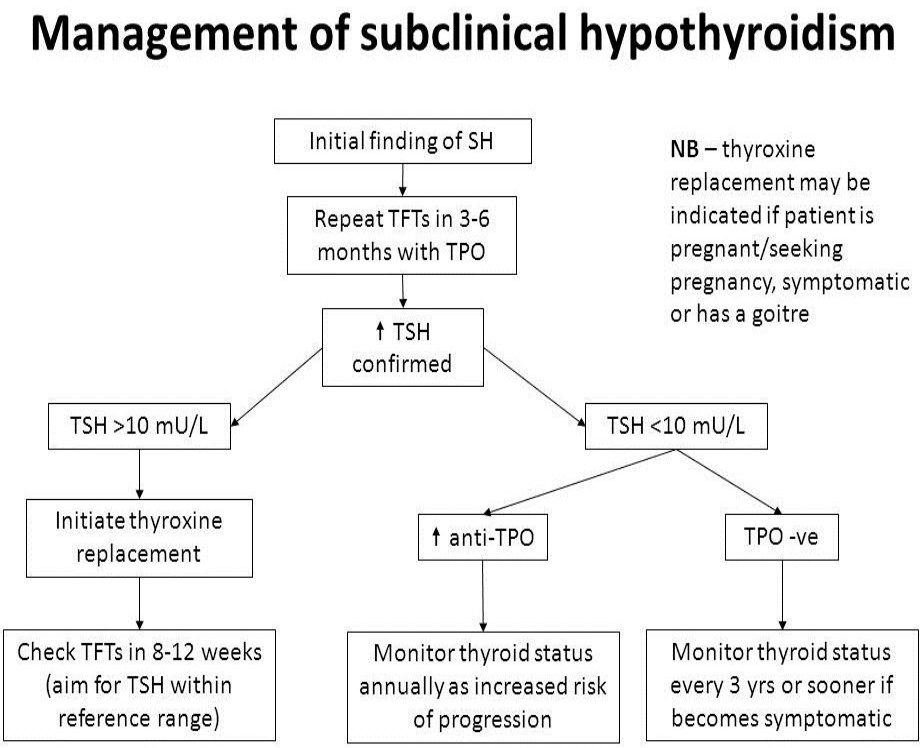
(3) Individuals found to have positive antithyroid peroxidase or thyroglobulin antibodies, and/or those with a hypoechoic or an inhomogeneous echo pattern on thyroid US should have serum TSH measured.[34]

THERAPEUTIC INTERVENTIONS

Management of SCH differs depending on whether the serum TSH concentration is 3 to 5 mIU/L, 5.1 to 10 mIU/L, or higher than 10 mIU/L.

Especially in elderly adults, preexisting CVD, other morbidities, and the risk of progression to overt hypothyroidism should all be considered in the clinician's decision to initiate treatment. Levothyroxine sodium, the drug used to treat SCH, has a narrow therapeutic index.

Therefore, it is critical to determine the optimal dose, especially in older adults. Current guidelines advise starting individuals aged 50 to 60 and older at a 50-lg dose of levothyroxine replacement therapy,



unless they have a history of CVD, in which case an initial dose of 12.5 to 25 lg should be given.[35] It has been suggested that targeted TSH levels with intervention be 3 to 4 mIU/L for individuals aged 60 to 75 and 4 to 6 mIU/L for those older than 75.[36]

SERUM TSH CONCENTRATION OF 3 TO 5 MIU/L

Lowering the upper limit of normal for the serum Thyroid stimulating hormone level from 5.0 to 3.0 mIU/L is still controversial. Levels between 3 and 5 mIU/L are unlikely to indicate a clinically important abnormality, and levothyroxine therapy at such levels may or may not give a benefit. Although persons with a serum TSH level of 3 to 5 mIU/L may be at higher risk of progression to hypothyroidism.[37] In fact, in a randomized, crossover, 12-week study of patients with symptoms that suggestive of hypothyroidism with serum TSH in the upper normal range, no difference in cognitive and psychological function was observed between levothyroxine-treated and control groups. With these findings, intervention cannot be recommended for this group, but follow-up by serum Thyroid stimulating hormone

measurement in 1 year would be a reasonable approach, particularly if antithyroid antibodies are detected.[38]

SERUM TSH CONCENTRATION OF 5.1 TO 10 MIU/L

Large-scale randomized studies to show reduction of cholesterol level with levothyroxine therapy in this subgroup are lacking. Most studies are not stratified for different categories of serum TSH levels, and although benefits for symptoms and lipid levels have been shown for mild thyroid failure as a group, results cannot be extended to most patients with SCH who are in this subgroup.[39] One study of TSH levels of 5.0 to 10.0 mIU/L did not show any benefit. Also, neuropsychiatric, cognitive, muscle, and cardic abnormalities described in studies including a wide spectrum of TSH levels in SCH should be confirmed by larger randomized studies. The possibility that an elevated serum TSH level is a cardiovascular risk factor is still highly controversial. Hence, decision for levothyroxine therapy for this group should be individualized and should depend on the age of the patient (favoring therapy for younger persons), associated medical conditions, degree of TSH elevation, persistence and gradual increase of TSH, presence of antithyroid antibodies, presence of goiter, and hypothyroid symptoms.[40]

Given both the findings of reduced intelligence quotient in the children of women who had SCH while pregnant and the adverse effects of mild thyroid failure on pregnancy outcome, levothyroxine therapy should be advised for pregnant women and women who anticipate becoming pregnant. Because of the effect of thyroxine on growth and development, levothyroxine therapy for children and adolescents is also reasonable. Therapy may be considered for patients with a persistent serum TSH level of more than 8 mIU/L because these levels are associated with a 70% progression to a TSH level of 10 mIU/L in 4 years (V.F. and colleagues, unpublished data, 2003).[41]

SERUM TSH CONCENTRATION GREATER THAN 10 MIU/L

Most thyroidologists agree that all patients with SCH and a serum TSH level above 10 mIU/L should be treated with levothyroxine.[42-43] Evidence is more compelling for the adverse effects of mild thyroid failure in this group. Studies have shown that levothyroxine therapy results in an 8-mg reduction in low-density lipoprotein levels.Among the factors that predict response of lipid levels to levothyroxine therapy are higher levels of TSH, insulin resistance, higher levels of pretherapy cholesterol, and type III hyperlipidemia. Some evidence suggests that mild thyroid failure can aggravate bipolar disorder and depression and that it is

associated with abnormalities of muscle function, nerve conduction, cardiac function,and cognitive and psychological function, with improvement after levothyroxine therapy.[44-46]

LEVOTHYROXINE THERAPY FOR SCH

For all patients with SCH and a serum TSH concentration above 10 mIU/L and for patients with serum TSH concentrations of 5.1 to 10.0 mIU/L in whom individualized decision for therapy is made, therapy should be started with levothyroxine. We do not currently recommend a combination of T4 plus T3 therapy. In my experience, the usual required daily levothyroxine dose is 50 to 75 µg. Anticipating future progression of thyroid failure, some endocrinologists recommend a full replacement dose. I prefer to start with a daily dose of 25 to 75 µg, depending on the age of the patient, the level of free thyroxine, and the serum TSH level. Serum TSH should be checked after 8 weeks, and the dose should be adjusted. Once a normal serum TSH level has been achieved, TSH should be measured again after 6 months and then annually. In younger persons, a reasonable goal for serum TSH is 0.3 to 3.0 mIU/L. For older age groups, the therapeutic goal can be higher. The benefits of fine-tuning levothyroxine therapy to achieve lower levels of serum TSH should be weighed against the possibility of adverse effects of overzealous levothyroxine therapy resulting in suppressed TSH and SCH.[47]

CONCLUSION

Subclinical hypothyroidism occurs in the clinical setting of a serum TSH level above the upper limit of normal despite a normal serum free thyroxine concentration. Initiating levothyroxine replacement therapy is recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. The strongest arguments for levothyroxine therapy are the high risk of progression to overt hypothyroidism, the possible improvement of quality of life, and the possibility that SCH is a cardiovascular risk factor. Recent evidence shows that any possible increased cardiovascular risk would be to persons younger than 70 years; those aged 70 and 80 years have no additional risk, and those older than 80 years may actually enjoy a protective benefit. Large-scale, government-sponsored, multicenter, randomized, placebo-controlled studies are urgently needed to assess the efficacy of levothyroxine therapy in the subgroup with TSH levels of less than 10 mIU/L. Meanwhile, therapy of this subgroup

should be individualized by taking into account patient preference, presence of symptoms, age, and associated medical conditions.

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