Review Article

Subclinical hypothyroidism: Controversies to consensus

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ABSTRACT

Diagnoses of subclinical hypothyroidism (SCH) is biochemically made, when serum thyroid stimulating hormone (TSH) levels is elevated while free thyroid hormone levels are within normal reference range. SCH is diagnosed after excluding all other causes of elevated TSH levels. Symptoms of SCH may vary from being asymptomatic to having mild nonspecific symptoms. 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. Various screening recommendations for thyroid function assessment are in practice. There are still controversies surrounding SCH and associated risk of various cardiovascular diseases (CVDs), pregnancy outcomes, neuropsychiatric issues, metabolic syndrome, and dyslipidemia. Consensus will require more large randomized clinical studies involving various age groups and medical condition, especially in developing countries. All these efforts will definitely improve our understanding of disease and ultimately patient outcomes.

Key words: Hypothyroidism, Sub Clinical Hypothyroidism, Early Thyroid failure, Risks associated with subclinical hypothyroidism

Introduction

Subclinical hypothyroidism (SCH) is biochemically diagnosed when there is a persistently high TSH level, while circulating free thyroid hormone levels are within range.[1,2] Other terms for this condition are mild hypothyroidism, early thyroid failure, preclinical hypothyroidism, and decreased thyroid reserve.[3] The prevalence of SCH is 3-8%, which increases with age, more prevalent in females; but it approaches to males after 6th decade.[4,5] Presence of thyroid antibody raises the risk of developing subclinical and then progressing to overt hypothyroidism. Role of iodine is somewhat controversial and iodine sufficient area have higher incidence of developing SCH than the iodine insufficient, especially studies done in Europe.[6]

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Medical condition which can lead to biochemical diagnoses of SCH[1] [Table 1] Include. Chronic autoimmune thyroiditis, persistently elevated TSH in subacute thyroiditis, postpartum thyroiditis and painless thyroiditis, injury to thyroid, partial thyroidectomy (other neck surgery), radioactive iodine/external radiotherapy exposure, drugs causing impairment of thyroid function (iodine and iodine-containing medications, e.g., amiodarone, radiographic, contrast agents, lithium carbonate, cytokines (especially interferon-α), aminoglutethimide, ethionamide, sulfonamides, and sulfonylureas), inadequate replacement therapy for overt hypothyroidism, (inadequate dosage, noncompliance, drug interactions (iron, calcium carbonate, cholestyramine, fiber, dietary soy, etc.), increased thyroxine (T4) clearance (phenobarbital, phenytoin, carbamazepine, etc.), malabsorption), infiltration of thyroid, (amyloidosis, sarcoidosis, hemochromatosis, Riedel's thyroiditis, cystinosis, acquired immunodeficiency syndrome (AIDS), primary thyroid lymphoma), central hypothyroidism, toxic substances, industrial and environmental agents, and mutations of TSH receptor gene like G α gene mutations. Transient rise in TSH levels can be seen in granulomatous, postpartum, and silent thyroiditis cases.[5]

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Table 1: Screening recommendations

American Thyroid Association	Women and men >35 years of age should be screened every 5 years
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened
American Academy of Family Physicians	Patients ≥60 years of age should be screened
American College of Physicians	Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

Adapted from Garber *et al.*, Clinical Practice Guidelines for hypothyroidism in adults. Endocr Pract 2012;18(No. 6).[7]

Diagnosis and Natural Progression of Disease

SCH is a biochemical diagnoses when there is persistently high TSH levels, while circulating free thyroid hormone levels are within range.[1,2] Single high reading of TSH should be repeated after 4-6 weeks, as there is transient fluctuation in TSH in different medical/physiological conditions. Controversies surround the upper normal limit of TSH level too, while traditionally most of the laboratories consider 4 mU/L as upper limit, there are some expert/organization that are advocating levels of 2.5-3 mU/L as true upper limits. There is also a physiological rise in TSH with age and levels of 6-8 mU/L could be considered in individuals >80 years of age.[8]

Certain conditions which do not qualify to be labeled as Subclinical Hypothyroidism based on the natural history include

When recovering from nonthyroidal illness, recovery phase of subacute/painless/postpartum thyroiditis, assay variability, heterophilic antibodies, and rheumatoid factor interfering with TSH measurements,[9] autoantibodies causing TSH-anti-TSH immunoglobulin (Ig)G complexes (Macro-TSH) lacks biologic activity but may be immunoreactive, and cause spuriously high TSH values (often >100 mU/L) in euthyroid individuals,[10-12] untreated adrenal insufficiency, rare mutations of TSH receptor, TSH producing pituitary adenomas, and resistance to thyroid hormone (commonly presenting as elevated TSH is associated with elevated serum free T4 and/or T3) and central hypothyroidism, in which up to 25% of patients have a mildly elevated serum TSH ≤10 mU/L and a low or low normal free T4.

Symptoms of thyroid disease are vague and different in various cultural backgrounds, so it is the biochemical evidence which makes/roles out the diagnoses of subclinical vs overt hypothyroidism. In one study done in Pakistan, most common symptoms for SCH were "weakness" and "lethargy".[13]

Overall, progression from subclinical to overt hypothyroidism is very high, the incidence range from 33 to 55% in prospective studies with nearly 10-20 years of follow-up.[4,14,15] This progression rate is considered to be around 2.6-4.3% each year.[4] Presence of thyroid autoantibodies,[14,16,17] goiter, underlying autoimmune diseases, and prior exposure to radioactive iodine/radiation are considered high risk for conversion into overt hypothyroidism.

While in few individual, TSH may normalize within 2 years, this is more commonly seen in individuals with negative antithyroid antibodies and serum TSH levels of <10 mU/L.[18]

Disease Burden in Region

Thyroid diseases are one of the most commonest endocrine disorders. Developing countries are equally affected as developed countries. According to one study, the prevalence of hypothyroidism and SCH in Pakistani population is 4.1 and 5.4%, respectively and female is predominant gender.[19] Data from few other countries reveal similar prevalence 4-8% in Brazil,[20] which are comparable to prevalence of 3-8% in USA.[21] However, in India there have been much higher reported cases in study by Hari Kumar *et al.*, where they published as high as 30%.[22] Study on school going children in Pakistan showed prevalence of 8.43%,[23] which is higher as compared to 1.7% in US children.[24] India has estimated 42 million people suffering from thyroid diseases,[25] with prevalence of SCH as high as 9.4% with female dominance of 11.4 vs 6.2% in men.[26]

Discussion: Controversies to Consensus

Due to lack of randomized prospective clinical trials, it is difficult to formulate the consensus on creating guidelines managing SCH. Below we discuss some of the data available in this regard.

Subclinical hypothyroidism and pregnancy

There is insufficient evidence to recommend the use of one intervention for clinical or SCH prepregnancy or during pregnancy over another, for improving maternal, fetal, neonatal, and childhood outcomes.

Thyroid hormone disturbances have known to have adverse effect in pregnancy outcomes. That is why thyroid function assessment is relevant in reproductive dysfunction.[27] Our

review of literature revealed that SCH increased the rate of miscarriage/fetal death and later it adversely affects the cognitive development of offspring. Though universal screening for thyroid hormone abnormalities in pregnancy is not routinely recommended at present, but thyroid function must be assessed in those having reproductive dysfunction and treated as appropriate.

Although it is evident from current literature that pregnancy outcomes are worse in women with overt hypothyroidism vs SCH. Studies done in individuals with SCH show an increased risk of preterm birth/pregnancy loss (almost two-fold),[28] association of impaired cognitive development in children,[29] and severe preeclampsia.[30]

Subclinical hypothyroid and mental dysfunction in young females

Though there is evidence of mental dysfunction related to working memory in SCH in young females, but this link is still under debate. Results of one study comparing young females with SCH and controls revealed that SCH females had greater susceptibility for unpleasant emotional stimulation, inward attention and increased anxiety for physical danger. Electroencephalogram (EEG) done in this study showed reduced alpha activity in resting state and increased beta-2 activity during stimulation, which means that SCH females had higher levels of arousal and greater susceptibility to negative emotions than controls.[31] These conclusions support the need for further studies.

Subclinical hypothyroidism and bone health

Thyroid hormone and TSH play an important role in bone mineral homeostasis and bone growth. Thyroid hormone has direct effect on stimulation of bone resorption through osteoclast function. Overt hyperthyroidism is associated with increased bone turnover and an increased risk of osteoporosis and fracture,[32] but SCH effects on bone are not well-established. Results of one study conducted to determine the impact of SCH on bone health in children demonstrated no significant impairment in bone health which is evaluated by lumbar spine dual-energy X-ray absorptiometry (DXA) and phalangeal quantitative ultrasound (QUS).[33]

Subclinical hypothyroidism and risk of heart failure

SCH and cardiovascular risk, which is well-recognized in young, is still debated in the elderly (>65 year).[34] Thyroid dysfunction, that is, both high and suppressed TSH, is one of the exacerbating condition in heart failure and American Heart Association (AHA) recommend its determination as a precipitating factor in heart failure patients. Results of six prospective cohorts in the United States and Europe revealed that risk of heart failure were increased in patients with high TSH particularly when it is above 10 mIU/L.[35]

Subclinical hypothyroidism and cardiovascular risk

Risk of cardiovascular disease in overt hypothyroidism is more established than in SCH. Although, there are observational studies[36-40] that suggest increased risk of coronary heart disease in SCH, but others unable to substantiate this relationship.[41,42] In one study when myocardial perfusion by contrast enhanced echocardiography and intima media thickness was compared between SCH and normal thyroid females, there was myocardial hypoperfusion and increased intima media thickness in SCH females which suggest it as cardiovascular disease (CVD) risk.[43]

In a meta-analysis involving 25,977 participants out of which 2,020 were with SCH (seven prospective cohort studies) revealed a significant trend of increased risk of coronary heart disease (CHD) events at higher serum TSH concentrations.[44] This increased risk was not affected based on gender, age, or presence of preexisting CVD. Participants with TSH ≥10 mU/L had a significant increase in CHD events (38.4 versus 20.3 events/1,000 person, heart rate (HR) 1.89, 95% CI 1.28-2.80) when compared with euthyroid subjects. Contrary to that patients having serum TSH ranging from 4.5 to 6.9 mU/L were not associated with an increased risk (HR 1.00, 95% CI 0.96-1.43).

There are other cardiovascular risk factors associated with SCH.[45-50] Cardiovascular defects such as diastolic dysfunction and increased peripheral vascular resistance are seen both in overt as well as SCH.[51] While association with left ventricular mass or function was no different in individuals with serum TSH ranging from 3.5 to 10 mU/L compared to those with normal TSH.[52]

Subclinical hypothyroidism and cholesterol metabolism

A cross-sectional study (25,862 participants, median age 56 years), revealed individuals with serum TSH between 5.1 and 10 mU/L had significantly higher mean total cholesterol concentrations compared with euthyroid individuals (5.6 versus 5.8 mmol/L).[53] There are studies revealing a link between elevated TSH and cholesterol concentrations (total and LDL cholesterol).[43] This risk has not been substantiated with CVD outcome risk.

But it is still an unresolved clinical challenge in even older population, that is, age >85 years, where due to lack of large randomized trial to determine cardiovascular end points and negative impact of possible overtreatment, this population still need to be carefully followed with wait and see policy.[34] Meta-analysis of one prospective study showed that elderly individuals (>85 years) in the Netherlands with untreated SCH actually had a lower rate of cardiovascular and all-cause mortality.[54]

Subclinical hypothyroidism in polycystic ovarian syndrome

Our review of literature revealed variable contribution of SCH in dyslipidemia and insulin resistance in females with PCOS. One of the trial conducted in Namik Kemal University Medical Faculty, Turkey, revealed that females with SCH and PCOS have higher triglyceride (TG) and insulin levels compared to PCOS females with normal thyroid function test (TFT), which are statistically significant and it concluded that patients with PCOS and SCH should be evaluated for dyslipidemia and insulin resistance.[55] Another trial revealed that PCOS females with SCH have higher levels of low density lipoprotein (LDL) cholesterol, while all other parameters of lipid profile and phenotypic manifestations are not altered by SCH.[56]

Subclinical hypothyroidism and metabolic syndrome

Weight gain or failure to lose weight is one of the most common features of overt and subclinical hypothyroidism. Role of thyroid hormone is vital in lipid synthesis, mobilization, and metabolism. A trial conducted in Ege University Medical School, Izmir, Turkey revealed that metabolic syndrome frequency is increased in overt and subclinical hypothyroidism patients.[57]

Subclinical hypothyroidism and mortality

One of the controversial areas in literature is relationship between all-cause mortality and SCH. You can find studies in support[38,39,58-60] as well as inconclusive evidence.[41,61] Meta-analysis of patient from 11 prospective cohort studies revealed risk of cardiovascular mortality increased with higher concentrations of TSH and was significantly increased in participants with TSH concentrations ≥10 mU/L, but not all cause mortality (HR 1.58, 95% CI 1.10-2.27).[44] In contrast, minimal elevations of TSH ranging from 4.5 to 6.9 mU/L were not associated with cardiovascular or all-cause mortality.

Subclinical hypothyroidism and neuropsychiatric issues

There are several reports linking SCH with neuropsychiatric diseases,[62-65] while there are many including a large study of primary care patients in England do not support this observation.[15,66-68] Link between SCH and some of the neuropsychiatric disorders are exhibited in these studies, higher frequency of neuromuscular symptoms (weakness, paresthesias, fatigue, and cramps),[69] defects in verbal memory and executive functioning,[70,71] and increased risk of Alzheimer disease (AD) in women but not in men (in population-based study).[72]

Defects in verbal memory and executive functioning were noted in individuals with SCH[70,71] and these defects were corrected with T4 therapy. This was possible linked to abnormal hippocampal function rather than general cognitive slowing.

In contrast to above findings, another study (>2,000 elderly individuals), it was found that in individuals with TFT in subclinical range (4.5 to <7.0 mU/L), gait speed and walking endurance was better than individuals with TSH values within the normal range (0.4 to <4.5 mU/L).[73]

Sub clinical and weight gain

Weight changes remain the one of the most important manifestation of thyroid diseases. Weight loss in hyperthyroidism as well as weight gain in overt hypothyroidism is well-established. But only few studies look into weight fluctuation in SCH. There are three studies which reveal increasing serum TSH level within the normal range resulting in modest increase in body weight.[74-76]

Other important association

Although our knowledge regarding SCH remains limited due to lack of randomized clinical trials, but there are some date to show association of higher risk of unprovoked deep venous thrombosis (pilot study)[77] and more likelihood of common bile duct stones, thought to be secondary to sphincter of Oddi dysfunction.[78]

Another interesting finding was noted regarding replacement of iron in subclinical hypothyroid patient with coexisting iron deficiency anemia. Rise in hemoglobin was noted to be greater in patient when given both iron and thyroid hormone compared with those given iron alone.[79]

Conclusion/Rationale for Treatment

There have been few guidelines, including one from Clinical Consensus group (comprised of representatives from the American Thyroid Association, Endocrine Society, and the American Association of Clinical Endocrinologists) to help physician choose right candidate for treatment of SCH. Following suggestions could be made based on these recommendations:

- Treatment should be initiated if TSH concentration is >10 mU/L, as there is enough evidence to support the beneficial effects
- Treatment of asymptomatic patient with serum TSH values between 4.5 and 10 mU/L is somewhat controversial. They need to be followed-up every 6-12 months with serum TSH and clinical evaluation. Risk of overtreatment, precipitation of angina pectoris/cardiac arrhythmia in high risk group, compliance of patients to daily medication, cost of therapy, and more so for its monitoring are major issues in treating patient who fall in this category
- Patients with serum TSH values of 4.5-10 mU/L and have symptoms suggesting hypothyroidism or have goiter, and/or high titers of antithyroid peroxidase antibodies,

can benefit from treatment. Treatment can be offered and their TSH should ideally be kept < 2.5 mU/L, provided risk factors mentioned above are evaluated

- Treatment should be given to pregnant women with SCH or who wish to become pregnant and patients who have ovulatory dysfunction. In pregnancy trimester-specific reference ranges for TSH should be used[80]
- Elderly patient experience a physiological rise in TSH. Elderly patient with SCH should be closely followed and the decision when to start treatment is still a challenge due to negative impacts of overtreatment and lack of well-organized randomized trials in this age group[34]
- Treatment will help in preventing progression to overt hypothyroidism especially in patients with TSH above 10, resolving symptoms with lesser TSH levels, and decreasing goiter size if it is present.

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