

REVIEW ARTICLE

SUBCLINICAL HYPOTHYROIDISM CURRENT CONCEPTS & MANAGEMENT STRATEGIES

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ABSTRACT: Subclinical hypothyroidism is a biochemical diagnosis characterized by raised thyroid stimulating hormone (TSH) and normal free T3 & T4, without clinical features of hypothyroidism. Clinical significance of SCH remains uncertain and controversial. Symptoms of SCH may vary from being asymptomatic to having mild nonspecific symptoms. There are still controversies surrounding SCH and associated risk of various cardiovascular diseases (CVDs), pregnancy outcomes, neuropsychiatric issues, metabolic syndrome, and dyslipidemia. This review will summarize the current data related to the effects of SCH on cardiovascular risk, SCH in pregnancy, in dyslipidemia and clinical guidelines on management of this condition. The evidence has been updated by a Pub med search on the risks and treatment of subclinical hypothyroidism of most recent articles published until March 2015.

KEYWORDS: Sub Clinical Hypothyroidism, cardiovascular risk, associated risks with pregnancy.

INTRODUCTION: Subclinical hypothyroidism is often asymptomatic and is defined as elevated thyroid stimulating hormone (TSH) levels with free thyroxine concentrations within the normal reference range. (TSH) level exceeding the upper threshold of a specified laboratory reference interval (commonly but arbitrarily defined as 4.5 mIU/L) but a normal thyroxine (T4) level.⁽¹⁾ Patients with subclinical hypothyroidism are often further classified as having TSH levels between 4.5 and 10.0 mIU/L or greater than 10.0 mIU/L. Other causes of a raised TSH, a past history of thyroid disease and patients on T4 hormone treatment need to be excluded. The TSH method used should have a high functional sensitivity (at least 0.02m U/L). 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 of goiter. The consequences of Subclinical hypothyroidism are variable at several levels and depend on the duration and the degree of elevation of the serum TSH which include increased cardiovascular risk or mortality, negative influences on metabolic parameters with varied effects.⁽²⁾ Replacement therapy for subclinical hypothyroidism remains controversial. Early detection and treatment of asymptomatic persons with abnormal serum TSH levels with or without abnormal T4 levels may be beneficial because it may prevent longer-term morbidity and mortality from fractures, cancer, or cardiovascular disease. However, widespread screening and treatment of subclinical thyroid dysfunction can also result in harms due to labeling, false-positive results, and over diagnosis and overtreatment.⁽³⁾ There are no updated guidelines on SCH and due to lack of randomized clinical trials, it is difficult to formulate the consensus on creating of SCH guidelines managing SCH. This review focusses on consequences of SCH and the current available recommendations on clinical management.

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EPIDEMIOLOGY: In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 to 15 percent.^[4,5,6,7,8] In the United States National Health and Examination Survey III (NHANES III), which excluded subjects with known thyroid disease, 4.3 percent of 16,533 people had subclinical hypothyroidism.^[9] The prevalence rises with age, is higher in females than males, and is lower in blacks than in whites.^[7,8,9,10] However, the prevalence is determined by the upper limit of normal for serum thyroid-stimulating hormone (TSH). If the upper limit of normal rises with age, as appears to be the case, then the prevalence may not be as high as has been previously thought. In Europe, where iodine intake is variable, subclinical hypothyroidism is more prevalent in areas of iodine sufficiency. In one study, the prevalence of subclinical hypothyroidism ranged from 4.2 percent in iodine-deficient areas to 23.9 percent in an area of abundant iodine intake, despite a similar prevalence of patients with high serum concentrations of antithyroid peroxidase (anti-TPO) antibodies.^[11] Screening studies to assess thyroid disorder prevalence have provided valuable insights in understanding the epidemiology of all thyroid disorders in the population worldwide. There is a rise in the prevalence of all the thyroid disorders including SCH in India post iodization era However, screening studies have been a rarity in India and there is scanty literature on prevalence of these disorders in all regions of India. Various other epidemiological studies in India mentioned in the] have shown a prevalence rate varying between 9 and 11.4%.^(12,13,14,15,16,17)

There are varied thoughts on screening and present screening criteria are illustrated in table1 In most patients, the cause of subclinical hypothyroidism is autoimmune (Hashimoto's) thyroiditis, although many other causes have been identified (e.g., external radiation, Obesity, postpartum thyroiditis drugs causing impairment of thyroid function like lithium therapy cytokines (especially interferon- α), aminoglutethimide, ethionamide, sulfonamides, and sulfonylureas etc.). While subclinical hypothyroidism is extremely common, occurring in 4-20% of adults depending on age, sex, race, dietary iodine intake, and other factors, recent data on the statistical distribution of serum TSH levels in normal healthy individuals has added to the controversy of how to define a "normal" serum TSH level. Re-analysis of data from the United States National Health and Nutrition Epidemiologic Survey (NHANES) has shown that serum TSH levels rise with age in normal healthy people who are free of thyroid disease.^[18]

So the decision for screening and treatment is to be to be individualized considering risk factors also. Most patients who have subclinical hypothyroidism are asymptomatic. On the other hand, there are patients who have typical symptoms of hypothyroidism, but in fact, the number and type of symptoms (e. g cold intolerance, constipation, difficulty losing weight, etc.) are similar in frequency and severity to euthyroid age matched controls with the very low specificity of typical "hypothyroid symptoms". In the elderly. Several large studies have shown that subclinical hypothyroidism is not associated with physical function, cognitive dysfunction, depression, or anxiety.^[19]

Organization	Screening Recommendation
American Thyroid Association, American Association of Clinical Endocrinologists and The Endocrine Society	Routine examination in all adults, including pregnant women or women wishing to become pregnant, especially if symptoms/signs compatible with thyroid dysfunction

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College of American Pathologists	Women ≥ 50 years consulting a physician, all geriatric patients admitted to a hospital and at least every five years
American Academy of Family Physicians	Patients ≥ 60 years
American College of Obstetrics and Gynecology	High risk patients (autoimmune disorder, family history for thyroid disease)
American College of Physicians	Women > 50 years with recent occurrence of symptoms compatible with thyroid disorder
Royal College of Physicians	No screening indicated
U. S. Preventive Services Task Force	Insufficient evidence for or against screening

Table 1: Recommendations for screening of subclinical hypothyroidism in asymptomatic adults

Sub Clinical Hypothyroidism and CARDIOVASCULAR RISK: Potential cardiovascular risk is the major morbidity associated with subclinical hypothyroidism. Thyroid hormones action on cardiovascular system and cardiac function is an important consideration in therapeutic and morbid implications of SCH.

Some prospective studies have shown an increase risk of cardiovascular disease and cardiovascular mortality in sub clinically hypothyroid patients, whereas other studies have not demonstrated this finding. A recent meta-analysis of the 11 prospective cohort studies did show an increased risk of coronary heart disease, but this increase was only seen in persons with serum TSH levels > 10 mU/l.^[20] Another retrospective study has shown that treating subclinical hypothyroidism seems to have beneficial effects to lower cardiovascular morbidity in persons between age 40 and 70 years, but not in persons aged 70 years or more.^[21] SCH impairs ventricular function. LV diastolic dysfunction was found in SCH many studies, and abnormalities may be reversed by a short term substitutive L-thyroxine therapy.^[22] Finally, heart failure is more common in elderly people with serum TSH levels $> 8-10$ mU/l. On the other hand, patients with serum TSH levels between 5 and 9 mU/l should be treated depending on the clinical situation (treatment more likely to be of benefit in young and middle-aged persons and persons with possible symptoms of hypothyroidism, depression, goiter, or cardiovascular risk factors). Elderly patients with a mildly elevated serum TSH might not be truly hypothyroid, and even if they are, they are less likely to benefit from treatment; indeed, they might even be harmed, since treatment is associated with often associated with inadvertent iatrogenic hyperthyroidism.^[23]

Thus, only with prospective randomized controlled trials, looking at clinically relevant outcomes such as cardiovascular morbidity or mortality, will the question of treatment be answered satisfactorily and convincingly.

Dyslipidemia and Sub Clinical Hypothyroidism: Hypothyroidism is a well-known cause of hyperlipidemia. Some studies have also shown that patients with subclinical hypothyroidism may have dyslipidemia, especially in those patients who also are smokers or who had insulin resistance.^[24] There are studies with beneficial effects of thyroxine treatment, with significant reduction of total cholesterol levels whereas HDL-cholesterol and triglycerides remained unchanged. Thyroid hormone replacement in hypothyroidism has been observed to result in

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increased LDL clearance due to increased LDL receptor activity in the liver. Thyroid hormones enhance intravascular catabolism of VLDL, triglycerides and lower plasma total cholesterol and LDL cholesterol. It is clear that thyroid hormone replacement therapy has beneficial effects on the serum lipid profile and on the risk of CAD in overt hypothyroid cases.^[25] There is also impairment in vascular smooth muscle relaxation and arterial stiffness that has been observed, but the clinical significance of these observations is uncertain. Treatment of subclinical hypothyroidism has been shown to decrease arterial stiffness and systolic blood pressure.^[26] In patients with concomitant subclinical hypothyroidism and iron deficiency anemia, iron supplementation may be ineffective if LT4 is not given.^[27]

Subclinical Hypothyroidism and Pregnancy: Subclinical hypothyroidism (SCH) in pregnancy is defined by a serum thyroid-stimulating hormone (TSH) concentration higher than the upper limit of the pregnancy related reference range associated with a normal serum thyroxine [T4; either total (TT4) or free (FT4)] concentration. The serum tri-iodothyronine (T3) level is normal. The prevalence of subclinical hypothyroidism in women of reproductive age ranges from 0.5-5%. In pregnant women, the prevalence of hypothyroidism, mostly subclinical hypothyroidism is around 2.5%.^[28] Evidence for screening for SCH in pregnancy is equivocal. Despite the beneficial effects of levothyroxine treatment on obstetric outcome and the fact that the previously recommended targeted approach to screening thyroid function will miss a large percentage of women with thyroid dysfunction, universal screening for SCH is not recommended, because of the lack of grade 1 evidence.

Although there are still no well-controlled studies to justify universal screening, the majority of clinicians recommend universal screening because of the beneficial effects of levothyroxine treatment on unknown overt hypothyroidism, on obstetric outcome and the fact that the targeted approach will miss a large percentage of women with SCH, especially in mildly iodine-deficient women. Various studies have shown an increase in risk of miscarriage, preterm delivery, and gestational hypertension in women with subclinical hypothyroidism. Pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption. Current data indicate an increase in pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia and preterm delivery in women with SCH in pregnancy although the frequency of these adverse outcomes is lower than is seen in women who have overt hypothyroidism.^[28] Thyroid hormone is also important for normal fetal brain development, and some have suggested that untreated maternal SCH is associated with a decrease in the intellectual potential of the offspring,^[29] but not proven in various randomised control trials.

The recommended screening of 2014 European Thyroid Association Guidelines,⁽³⁰⁾ reference range upper limits of TSH in first trimester is 2.5 mU/l; in second trimester, 3.0 mU/l and third trimester are 3.5 mU/l. TSH should be measured at the beginning of pregnancy if screening is performed. If TSH is elevated, FT4 and Thyroid peroxidase antibodies (TPO Ab) should be determined. This will enable SCH or overt hypothyroidism to be diagnosed, in addition to identifying patients with isolated hypo-thyroxinaemia as well as central hypothyroidism. In the case of elevated TSH and negative TPOAb, Thyroglobulin antibodies (TgAb) should be measured. The Endocrine Society recommends T4 replacement in pregnant women with subclinical

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hypothyroidism.^[31] The American College of Obstetricians and Gynecologists does not recommend it as a routine measure.^[32] A recent Randomized prospective study also did not show a higher rate of adverse pregnancy outcomes in women with subclinical hypothyroidism untreated.^[33]

Due to the current lack of evidence regarding the optimal treatment strategy in individuals with subclinical hypothyroidism, to date the best management of such persons is the inclusion in randomized Control trials (RCT). Initiating treatment in individuals with TSH levels <10mIU/l is not recommended, but follow up of serum TSH values,^[34] is necessary. If TSH levels exceed 10mIU/l, levothyroxine substitution might be considered, but even in these persons, there is no direct evidence from RCTs justifying treatment.^[35]

CONCLUSIONS: Subclinical hypothyroidism is often a benign problem which requires expectant management with periodic monitoring of thyroid function tests and natural progression to overt hypothyroidism occur less frequently than expected. There is a paucity of studies on prevalence screening and interventions and studies focusing on clinical outcomes. Initiating levothyroxine replacement therapy remains controversial when serum TSH level is between 5 and 10 mIU/L but recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range. The strongest arguments for levothyroxine therapy are the high risk of progression to overt hypothyroidism, the possible improvement of quality of life, and reducing cardiovascular risk. Treatment should be individualized considering patient preference, presence of symptoms, age, and associated medical conditions.

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