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Review Article

Subclinical hypothyroidism in community perspective: Treat or not to treat?

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ABSTRACT

Subclinical hypothyroidism is a common clinical entity prevalent in the community setting, thyroid hormone testing is one of the most frequently asked investigations, and it also is placed in most health panel tests. It is defined as the value of thyroid-stimulating hormone between 4.5-10mIU/L and normal fT4 and fT3. In community-based studies, the prevalence of subclinical hypothyroidism was observed by nearly 4.4% in males and 7.5–8.5% in females. Prevalence of sub clinical hypothyroidism increases in females with advancing age. There is a gray zone for treating the clinical condition with a TSH value between 4.5-10 mIU/ml. Treatment for subclinical hypothyroidism is also under debate for more than two decades with varying opinions. The main focus of treatment is aimed at one of the following criteria: correction of lipid abnormality, progression to overt hypothyroidism, pregnancy, and other medical conditions. There are different schools of thought for deciding to treat such persons. This review highlights the importance, risk, and benefits of treating such conditions with thyroxin replacement from a community perspective.

Key message: insufficient data on subclinical hypothyroidism forced medical professionals to screen identified cases and initiate treatment of such conditions in the primary health care setting.

Methods for searching: We retrieved the relevant literature from PubMed, Medline, and Embase using keywords adult, pregnancy, female, children, adolescent, thyroxine, thyrotropin, TSH, thyroid function test, prevalence, risk factors, hypothyroidism, cardiovascular system, lipids, sub-clinical, primary health care, community.

1. Introduction

Subclinical hypothyroidism (SCH)is defined as the value of thyroid-stimulating hormone between 4.5-10mIU/L in the setting of normal fT4 and fT3. There is much controversy regarding the treatment of this condition. Physiological conditions affect the thyroid function test, and hence it is crucial to interpret the test results in light of a particular physiological state.Aging is associated with an increase in TSH concentration, and it has been sometimes considered as a harbinger of long life, at least in Ashkenazi Jew.[1,2] This increase is accounted for by multiple factors such as higher TSH set point, reduced bioactivity, TSH resistance, etc. rather than representing an occult thyroid disorder.[3] The cardiovascular system is mostly affected by rising TSH concentration; sub clinical hypothyroidism is an established risk factor in adults and older people, especially less than 65 years of age, as evidenced by a meta-analysis of 15 studies. All these studies included a TSH value of less than 10mIU/L.[4] The prevalence of subclinical hypothyroidism varies between 5-15% and shows higher prevalence as the age advances.[5] In community-based studies, the prevalence of subclinical hypothyroidism was also observed nearly 4.4% in males and 7.5–8.5 in females.[5,6] Prevalence of subclinical hypothyroidism increases in females with advancing age, and it is more commonly associatedwith elderly females as 7–18% compared to males as 2–15%[7,8]

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In a community study in Riyadh, the prevalence of subclinical hypothyroidism was also found to be 10% in visiting patients at primary health centers.[9] Primary health care focuses on a comprehensive approach to individuals, families, and communities' physical, mental, and social health needs. A majority of a person's health needs can be covered through primary health care, including prevention, treatment, rehabilitation, and palliative care.[10] Thyroid function test is the most commonly requested laboratory investigation in a community setting.[3] Treatment for subclinical hypothyroidism is under debate for more than two decades with varying opinions. The main focus of treatment, of course, is aimed at one of the following criteria:

1. Correction of lipid abnormality
2. Progression to overt hypothyroidism
3. Pregnancy and other medical conditions

1.1. Correction of lipid abnormality

There exists a plethora of evidence both in favor and against lipid abnormality in subclinical hypothyroidism. The notion of correcting lipid abnormality by treatment with levothyroxine supplementation and thereby reducing cardiovascular morbidity and mortality has strong proponents and opponents. Observational studies by Canaris et al. have shown a mean elevation in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and mean triglyceride level (TG) by approximately 8 and 6 mg% for HDL-C and LDL-C that was significant as against TG, which was not significantly elevated in patients with SCH,[11] these findings are not supported by other researchers like Vierhapper et al.[12] and Bell et al.[13] who observed no difference in lipid concentrations of SCH and euthyroid patients. NHANES III database also did not find any change in lipid values when adjusted for age, sex, lipid-lowering agents, and SCH.[14] However, a population-based survey in 2799 caucasian subjects had conflicting observations and showed total cholesterol elevation by approximately 9 mg/dl.[15] The concentration of apolipoprotein B (Apo B), a significant constituent of LDL-C and VLDL-C, has been seen to be elevated in SCH substantially.[16]

Treatment with levothyroxine (LT4) is as variable as lipid abnormality in SCH Apo B, which is found in atherogenic lipids is significantly lowered after treatment with LT4.[17,18] Study by Razvi et al. In a randomized placebo-controlled trial demonstrated a significant reduction in TC, LDL-C in 100 SCH patients without having much effect of other lipid molecules including Apo B.[19] A recent Cochrane review has however refuted the claim of the beneficial impact of LT4 replacement on lipid parameters except for TC.[20]

1.2. Progression to overt hypothyroidism

Subclinical hypothyroidism can progress to overt hypothyroidism (OH); the estimated rate at which SCH moves to OH is dependent on various factors like age and antithyroid peroxidase antibody status. Approximately 33-55%of patients with SCH will develop OH over ten years, with an average rate of 2-6% per year.[20,21] Females who are anti-TPO antibody positive have a higher chance of developing it against those who are negative for anti-TPO. The initial level of TSH is also an essential determinant of progression to OH.[22]*2. Coronary Heart Disease* Subclinical hypothyroidism has association with a higher risk of coronary heart disease and heart failure.[23] Patients in whom TSH is below 7 mIU/l has almost the same risk as euthyroid subjects.[24] Patients with TSH higher than 10 have had higher odds of developing heart failure.[25] Coronary heart disease, heart failure, and atrial fibrillation are more common in patients younger than 65 as opposed to more than 65 years of age, it portends that SCH has a protective role in preventing elderly from this group of diseases. All causes of mortality and deaths due to CHD were higher in both prospective[26] and retrospective studies in patients younger than 65years of age.[27] Razvi et al., in a retrospective cohort study, reported that the treatment of SCH in the age group 40-70years was associated with reduced all caused mortality and CHD; there was, however, no difference when age was more than 70 years.[27] In a Cochrane review, SCH was found to be associated with surrogate markers of CHD like hypertension, echocardiographic findings, lipid abnormality,endothelial dysfunction; these findings improved with treatment.[20]

2. Pregnancy and Other Medical Conditions

2.1. Pregnancy and SCH

The diagnostic criteria for SCH in pregnancy are different from the non-pregnant status as the features of non-pregnancy. That of SCH is often challenging to differentiate on clinical grounds. American thyroid association and endocrine society have given a trimester-specific range of TSH. The first, second, and third trimester values are 0.1-2.5 mIU/l, 0.2-3mIU/l, and 0.3-3.5mIU/l, respectively.[28] SCH in pregnancy has an impact on maternal and fetal outcomes. Casey et al. observed that the prevalence of preterm delivery and abruptio placentae was higher with SCH in 2500 pregnant subjects.[29] In a prospective study by Negro et al., miscarriage was also more in the SCH group than euthyroid subjects.[30] Fetal outcomes were also affected by maternal thyroid status; children born to SCH females more frequently required intensive care unit admissions.[31] Negro et al. in an RCT showed beneficial effects on the maternal and fetal outcomes when SCH was treated both in assisted reproductive technique and non-assisted reproductive pregnancies.[30]Currently, treatment is

advocated in those who are anti-TPO antibody positive. The data is highly inconclusive so far as infertility is concerned. Some studies have, however, found a positive correlation between the higher prevalence of infertility and SCH. This association was mainly found in ovulatory disorders and not in other disorders like tubal factors, etc.[32]

2.2. Neuropsychiatric symptoms

Subclinical hypothyroidism is associated with reduced quality of life, mood, and treatment failure in depressed patients.[33] This association was seen at a higher TSH level of more than 10 mIU/l. ACochrane review has convincingly proven that there is hardly any benefit of treating subclinical hypothyroidism as mood and quality of life is concerned in patients' SCH patients with lower TSH values.

3. Children and Adolescents

It is found that children with SCH do not usually progress to overt hypothyroidism. Lazer et al., in a retrospective study, found that only those children whose initial TSH was higher than 7.5mI U/l had a higher propensity for OH. It was more common in females, especially around the pubertal age group.[34] American thyroid association does not recommend treatment for children with TSH between 5-10 mI U/l.[35]

3.1. Risks with treatment

Treatment of SCH is associated with risk of thyrotoxicosis; some patients felt worse with levothyroxine supplementation in a placebo control study by Cooper et al.[36] Nystrom et al.[37] and Flynn RW et al.[38] also reported tachyarrhythmia's and angina pectoris and supplementation is also associated with low bone mass.

4. Conclusion

Treatment for subclinical hypothyroidism is under debate for more than two decades with varying opinions. Of course, treatment's primary focus is aimed at one of the criteria as correction of lipid abnormality, progression to overt hypothyroidism and pregnancy, and other medical conditions.A plethora of evidence exists both in favor and against lipid abnormality in subclinical hypothyroidism. Subclinical hypothyroidism can advance to overt hypothyroidism, and also it is associated with a higher risk of coronary heart disease and heart failure. The diagnostic criteria for SCH in pregnancy are challenging from the non-pregnant status. Even in depressed patients, subclinical hypothyroidism is also associated with reduced quality of life, mood, and treatment failure.As thyroid function test is the most commonly requested laboratory investigations in primary health care settings. However, insufficient data on subclinical hypothyroidism forced medical professionals to screen identified cases and initiate treatment of such conditions in the primary health care setting.

5. Source of Funding

None.

6. Conflict of Interest

None

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