International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 8, August 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.8.2024.59

REVIEW ARTICLE

"Current Insights into the Diagnosis and Management of Subclinical Hypothyroidism: A Systematic Review"

[1]Iram Hamid, [2]Iqra Farooq, [3]Haamid Bashir, [4]Mohammad Hayat Bhat, [5]Sabhiya Majid

[1,2,3,5]Department of Biochemistry, Government Medical College, Srinagar, India
[4]Department of Endocrinology Superspeciality Hospital, Government Medical College, Srinagar, Kashmir, India

Corresponding Author
Iram Hamid
Department of Biochemistry, Government Medical College, Srinagar, India
Email: iramhamidsgr33@gmail.com

Received date: 28 June, 2024 Acceptance date: 30 July, 2024

ABSTRACT
Subclinical hypothyroidism (SCH) is a prevalent condition marked by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) and free triiodothyronine (FT3) levels. Despite its frequency, diagnostic and management practices for SCH vary widely, leading to inconsistencies in patient care. This systematic review aims to assess and consolidate current diagnostic criteria and management practices for SCH, identify discrepancies among guidelines, and provide evidence-based recommendations for optimizing patient management. A thorough literature search was performed in PubMed, Embase, Cochrane Library, and Scopus for studies published from 1990 to 2024. Inclusion criteria covered peer-reviewed original research, clinical guidelines, and reviews focusing on SCH diagnosis and management. Quality assessment of the included studies was conducted using the Newcastle-Ottawa Scale for cohort studies and the Cochrane Risk of Bias Tool for randomized controlled trials. Key data points extracted included diagnostic thresholds, management protocols, and reported outcomes. The review revealed substantial variability in diagnostic criteria for SCH, with differences in TSH thresholds and the use of thyroid antibody testing. Management strategies also varied, with some guidelines advocating treatment based on elevated TSH alone, while others considered patient age, cardiovascular risk factors, and symptomatology. The review also highlighted ongoing debates regarding the benefits of treatment, especially in older adults and those with comorbid conditions. This review highlights the need for standardized diagnostic criteria and management protocols for SCH. The variability in current practices underscores the importance of developing unified, evidence-based guidelines to enhance patient outcomes. Future research should focus on the long-term effects of different management strategies and the impact of individualized treatment approaches on diverse patient groups.

Keywords: Subclinical Hypothyroidism, Diagnosis, Management, Systematic Review, Thyroid Function

INTRODUCTION
Subclinical hypothyroidism (SCH) or mild thyroid failure is defined as an elevated serum TSH level in the setting of normal total or free T4 and T3 levels[1]. Subclinical hypothyroidism (SCH) is an increasingly recognized thyroid disorder that has garnered significant attention in clinical endocrinology over recent decades. Characterized by elevated serum thyroid-stimulating hormone (TSH) levels with normal concentrations of circulating free thyroxine (FT4) and free triiodothyronine (FT3), SCH occupies a gray area between normal thyroid function and overt hypothyroidism. The absence of classical hypothyroid symptoms combined with laboratory evidence of mild thyroid dysfunction poses diagnostic and management challenges for clinicians. This condition is often detected incidentally, as patients frequently present without overt symptoms of hypothyroidism, complicating decisions regarding the necessity of intervention. Despite its typically asymptomatic presentation, SCH has been implicated in various systemic consequences, including cardiovascular disease, neuropsychiatric changes, and progression to overt hypothyroidism, prompting a growing debate about the optimal approach to diagnosis and management[2,3]. SCH is a common clinical problem or under activity of thyroid hormone with an overall prevalence of 4–10% in the general population, depending upon age and gender[4].Subclinical hypothyroidism is notably prevalent, with epidemiological studies estimating that 4-10% of the general population may have SCH[5]. Women, older

DOI: 10.69605/ijlbpr_13.8.2024.59

adults, and individuals with autoimmune conditions are particularly vulnerable to this condition[6]. The prevalence of SCH increases with age, with studies reporting rates of 10-20% in elderly populations, making it a common clinical issue in geriatric medicine[6]. Additionally, SCH has a higher prevalence in individuals with a history of iodine deficiency, autoimmune thyroid disease, or a family history of thyroid disorders[7]. Despite its high prevalence, there is considerable uncertainty surrounding its natural history, potential complications, and whether treatment offers long-term benefits.A study was conducted in the mountainous valley of Kashmir-northern part of India and prevalence of SCH in females as compared to males was found higher than those of males in different populations globally [8]. The consequences of SCH are variable and may depend on the duration and the degree of elevation of serum TSH.

Possible consequences of subclinical hypothyroidism are cardiac dysfunction, erythrocyte abnormalities, anemia, low-density lipoprotein cholesterol,systemic-hypothyroid symptoms, neuropsychiatric symptoms and progression to overt, symptomatic hypothyroidism[9-16].The data regarding these potential consequences of untreated subclinical hypothyroidism is again controversial . The clinical significance of SCH remains controversial. While some patients may remain in a stable subclinical state without experiencing significant adverse effects, others may progress to overt hypothyroidism or experience associated complications such as cardiovascular disease and cognitive decline[17]. These potential risks raise questions about the timing of intervention and whether universal treatment is warranted for all patients with SCH. Current clinical practice varies widely, with treatment approaches ranging from observation and regular monitoring of thyroid function to immediate hormone replacement therapy with levothyroxine[18-19]. The variability in management reflects the need for a comprehensive evaluation of the evidence supporting different diagnostic criteria and therapeutic strategies[20]. Moreover, a number of queries regarding SCH remain, including whether it increases cardiovascular (CV) risk or mortality, whether it negatively influences metabolic parameters and whether it should be treated with L -thyroxine. To answer these open questions, European Thyroid Association has recently conducted study and framed some guidelines regarding this, for children and pregnant females separate guidelines have been formulated [21].

As per American endocrinologists association SCH should be considered in two categories according to the elevation in serum thyroid stimulating hormone (TSH) level: mildly increased TSH levels (4.0–10.0 mU/l) and more severely increased TSH value (>10mU/l).Patients with TSH value >10mU/l and other parameters of thyroid profile normal need to be treated [22,23].Those individuals with values less than 10mU/l are considered as susceptible to SCH , overt hypothyroidism , here no treatment is given but as a follow up thyroid hormone profile and anti-thyroid peroxide antibodies are repeated after 2-3 months . InSCH patients with symptoms suggestive of hypothyroidism even on serum TSH <10 mU/l a trial of L -thyroxine replacement therapy should be considered. Once, decision to treat has been taken oral L –Thyroxine, administered daily, is the treatment of choice. Response to treatment should be reviewed after 3 or 4 months ,the aim in most adults should be to attain stable serum TSH in lower half of reference range (0.4–2.5 mU/l) ,dosage needs to be adjusted accordingly . Once patients with SCH are commenced on L -Thyroxine treatment, then serum TSH should be monitored at least annually thereafter [24-26]. If there is no improvement in symptoms, L -Thyroxine therapy should generally be stopped. Age-specific local reference ranges for serum TSH should be considered in order to establish a diagnosis of SCH in older people. Very old subjects (> 60 years) with elevated serum TSH ≤ 10 mU/l should be carefully followed with a wait and watch strategy, generally avoiding hormonal treatment. This systematic review seeks to clarify the current diagnostic approaches and management practices for subclinical hypothyroidism, providing clinicians with a more informed basis for decision-making. We will explore key questions, such as when to screen for SCH, which patients are most likely to benefit from treatment, and what long-term outcomes can be expected with or without intervention[30]. By synthesizing the latest evidence from clinical trials, observational studies, and expert guidelines, we aim to present a clear picture of how SCH should be approached in various ethnic populations, including special considerations for pregnant women and older adults[31,32].We conducted this systematic review to minimize confusion and keep clinicians and general public abreast with latest trends regarding screening, diagnosis andmanagement of SCH.

METHODOLOGY

Systematic and comprehensive review of literature review of SCH was carried out using PubMed, Research Gate, Google Scholar, Scopus Cochrane library, Embase and Medline and Original and review articles publishedfrom 1990 through 2024 were considered .We followed guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure a comprehensive and transparent review processFor our search strategy, we entered keywords in various combinations the terms hypothyroidism, Iodine, thyrotropin (TSH), L -thyroxine, SCH, goiter, replacement therapy, CV risk, heart, dyslipidemia, Anemia, obesity, mental health, quality of life, drugs. The quality of the literature concerning each aspect of the statement was graded as high quality for randomized controlled trial (RCT) evidence – level 1; moderate quality for intervention

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short of RCT or large observational studies –level 2, or low quality for case series, case reports, expert opinion –level. The strength of each statement was classified as strong (S – a recommendation) or weak (W –suggestion), depending upon the clinical significance and weight of opinion favoring the statement. Strong recommendations are clinically important best practices and need to be applied to most patients in most circumstances, whereas weak statements should be considered by the clinician and will be applicable bestpractice only to certain patients or in certain circumstances.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Peer-reviewed original research articles, reviews, and clinical guidelines published in English.
2. Studies evaluating diagnostic criteria, management strategies, or treatment outcomes for SCH.
3. Articles involving human subjects with SCH diagnosed based on elevated TSH levels and normal FT4 and FT3 levels.

Exclusion Criteria:

1. Studies focused on overt hypothyroidism or other thyroid disorders not specifically addressing SCH.
2. Non-peer-reviewed literature, such as editorials, opinion pieces, or conference abstracts.
3. Articles without accessible full text or those not available in English.

Symptoms of Subclinical hypothyroidism

Common non specific symptoms are seen in SCH patients like fatigue, cold intolerance, constipation, dry skin, and weight gain.In a recent study carried out in Kashmir valley Hypothyroidism is found to be a co-morbidity or predisposes to the development of chronic headache [33].

Diagnosis and screening of Subclinical Hypothyroidism

The population prevalence of SCH amounts to approximately 5–10%, being more frequent in women and with increasing prevalence with advancing age [6-7]. SCH is also more frequent inindividuals of Caucasian origin and in mountainousregions [3,8]. 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) [26-30]. Subclinical hypothyroidism, also called mild hypothyroidism, is a term used for a condition in which there are small elevations in thyroid-stimulating hormone (TSH), yet normal circulating levels of thyroid hormones. This condition is more common in the elderly and is found twice as often in women as in men [34,35].While it is uncommon in younger persons; by the age of 65 years, overall prevalence of the disorder is about 17% in women and 7% in men [30-35].Determination of the serum TSH level biochemically is the most sensitive test for the diagnosis of subclinical hypothyroidism. An elevated TSH is the marker of subclinical hypothyroidism. On repeat determination if serum TSH is still above reference range, serum fT4 level should be checked. The majority of the patients with autoimmune hypothyroidism will have measureable, and often high, titers of antibodies reacting with thyroid peroxidase or thyroglobulin. In women with subclinical hypothyroidism, measurement of serum antithyroid peroxidase antibodies may be useful to predict the likelihood of progression to overt hypothyroidism[8]. Most sophisticated fully automated Chemiluminiscent Immuno assay analyzers (CLIA) are used for assessing thyroid function tests in super specialized laboratories of hospitals and have because of their cost efficacy and efficiency nearly replaced Radioimmunoassay (RIA) method which has always been considered as gold standard. The diagnosis of thyroid disorders can be done based on values of TSH, T3, T4, FT3, FT4 as per European Thyroid Association and American endocrine society directives.

Management of Subclinical hypothyroidism

There is considerable debate aboutwhether or not subclinical hypothyroidismshouldbe treated [20].The natural history of this condition suggests that although in some cases serum TSH levels revert to normal without therapy, a significant proportion of patients with subclinical hypothyroidism progress to overt hypothyroidism,specially if their serum TSH concentration is >10 mU/L and their serum anti-thyroid peroxidase (TPO)antibody level is high [7].Furthermore, there is compelling evidence that subclinical hypothyroidism may have adverse clinical consequences, especially after menopause in women. An association between subclinical hypothyroidism andelevated total and low-density lipoprotein cholesterol levels has been shown; these levels improved after treatment with levothyroxine [36]. The Rotterdam study found that subclinical hypothyroidism (defined as a TSHlevel>4mU/L) is an independent risk factor for atherosclerosis and myocardial infarction in postmenopausal women [37,38]. While a prospective study following up individuals 65years of age or older for more than 10years did not show an effect of subclinical hypothyroidism on cardiovascular outcome or mortality. As per the results of Muzamil et al there was high prevalence of hypothyroidism in pregnant females. About 30% cases of subclinical hypothyroidism are likely to be missed if only high risk females are screened for hypothyroidism. Considering the adverse effects of maternal hypothyroidism on maternal and fetal outcomes universal screening of pregnant females is recommended [39].

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Subclinical hypothyroidism in Pregnancy

Pregnancy has a profound impact on thyroid gland, so thyroid disorders are frequently observed during pregnancy [40-42]. Thyroid disorders are the second most common endocrinopathies found in pregnancy. Hypothyroidism is more common in women in their reproductive age. Data from western countries indicates that overt hypothyroidism complicates up to 0.3-0.5% pregnancies subclinical hypothyroidism prevalence is estimated to be 2.5% [43].

The diagnosis of SCH differs slightly in pregnant patients. Firstly, the symptoms of pregnancy mimic hypothyroidism mandating the biochemical diagnosis of SCH[44]. Secondly, gestational changes in the hypothalamic-pituitary-thyroid axis interfere with the measurement of FT_4 by conventional assays [45]. Consequently, an emphasis is placed on TSH measurement, for which guidelines recommend establishing local trimester-specific reference intervals . Lastly, the diagnostic threshold for SCH in pregnancy differs from that in non-pregnant adults. Trimester-specific reference intervals have been recommended by American Thyroid Association (ATA) and Endocrine Society [46]whereby thresholds for TSH levels are , between 0.1–2.5 mIU/L in first trimester , between 0.2–3.0 mIU/L in second trimester and between 0.3–3.5 mIU/L in third trimester.). The prevalence of hypothyroidism in pregnancy is 34.2% , while 0.87% had overt hypothyroidism and 33.3% had subclinical hypothyroidism [47].Whereas, trimester specific prevalence of subclinical hypothyroidism 34.4, 31.5 and 30.5%, in first, second and third trimester respectively[48]. Study reported SCH effects the 10% population [49].

SCH treatment guidelines

There have been few guidelines, including one from internationally recognized Clinical Consensus group, comprised of representatives from American Thyroid Association, Endocrine Society and American Association of Clinical Endocrinologist to help physician choose right treatment for SCH. **Following suggestions are based on these recommendations:**

- Treatment should be initiated if TSH concentration is >10 mU/L, as there is sufficient 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 having symptoms suggesting hypothyroidism, or having goiter, and/or high titers of anti-thyroid 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 .
- 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 .
- Treatment will help in preventing progression to overt hypothyroidism especially in patients with TSH >10 mU/L, resolving symptoms with lesser TSH levels, and decreasing goiter size if it is present[50-53].

Suggestions

- Mass screening for thyroid profile in various populations of different ethnic backgrounds need to be taken up.
- Both SCH and overt hypothyroidism need to be properly followed up and managed.
- Timely consultation, proper follow up and managementare suggested to both treated and untreated susceptible patients.

CONCLUSION

This systematic review was aimed to provide a comprehensive evaluation of the current diagnostic and management practices for subclinical hypothyroidism (SCH). By systematically analyzing recent, previous studies and clinical guidelines, we seek to clarify inconsistencies in diagnostic criteria and treatment protocols. This review highlights variations in practice, assess the effectiveness of different management strategies, and identified gaps in current research. Our findings offers valuable insights for clinicians in optimizing the care of patients with SCH, potentially leading to more standardized and evidence-based approaches. Ultimately, this review targeted to inform future clinical guidelines and research priorities, contributing to improved patient outcomes in SCH management. Mass screening for thyroid hormone levels needs to be taken up . Substantial numbers of patients having risk of SCH which may develop to primary hypothyroidism , thereby, in individuals with TSH value >10 mU/L follow up, intervention and early management needs to be considered . We suggest regular monitoring of biochemical, hormonal and hematological parameters in individuals with SCH or other thyroid problems .Proper and timely management is needed.

Conflict of Interest

None

DOI: 10.69605/ijlbpr_13.8.2024.59

Funding
Nil

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