ISSN: 3065-5145
Review Article

World Journal of Medicine and Health Care

Pathophysiological and Clinical Implications of Elevated Thyroid- Stimulating Hormone (TSH): Consequences and Management Strategies

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Submitted: 12 February 2026 **Accepted:** 20 February 2026 **Published:** 26 February 2026

Citation: *Jamil, K., Asimuddin, M., Reddy, P. P., & Gade, S. (2026). Pathophysiological and Clinical Implications of Elevated Thyroid-Stimulating Hormone (TSH): Consequences and Management Strategies. Wor Jour of Medic and Heal Care, 4(1), 01-08.*

Abstract

Treatment of hypothyroidism with thyroid hormone replacement therapy (HRT) has been in use for more than a century and has demonstrated sustained clinical efficacy. Thyroid-stimulating hormone (TSH) is a central regulator of thyroid hormone synthesis and secretion through the hypothalamic–pituitary–thyroid axis. Elevated serum TSH reflects impaired thyroidal hormone output and increased pituitary feedback stimulation, most commonly due to early autoimmune thyroid dysfunction. Subclinical hypothyroidism (SCH), characterized by raised TSH with preserved circulating free thyroxine levels, represents a frequent biochemical finding in clinical endocrinology. Although often clinically silent, mild thyroid failure may exert measurable effects on lipid metabolism, vascular endothelial function, insulin sensitivity, and neurocognitive performance. In women of reproductive age, altered TSH homeostasis has important implications for fertility and pregnancy outcomes. Diagnostic evaluation requires confirmation with repeat testing and interpretation of thyroid autoimmunity to determine progression risk. Therapeutic decision-making remains individualized, balancing symptomatology, cardiovascular and metabolic risk, antibody status, and pregnancy considerations. This review integrates mechanistic insights with contemporary clinical evidence to guide rational evaluation and management of elevated TSH in routine practice.

Keywords: Thyroid-Stimulating Hormone (tsh); Clinical Endocrinology; Lipid Metabolism; Mechanistic Insights; Subclinical Hypothyroidism (sch).

Introduction

Thyroid disease is the most frequently arguably among the commonest endocrine disorder in the world. India is hardly an exception where it is estimated that about 42 million people in India is suffering from thyroid diseases [1]. Thyroid disorders are diagnosed 5–10 times more frequently in females than males, and the rate of their incidence increase with age. However, enlargement of the thyroid and abnormalities in the thyroid gland's normal functioning is referred to as thyroid diseases/disorders. Rapid thyreologic assessments along with confirmation of the effectiveness of the therapy undertaken is of the prime significance importance for the healthy society.

Physiological of Hypothyroidism

The thyroid is among the largest endocrine glands within the body, located in the neck, anterior to the trachea and larynx, at the levels of the 5th, 6th, and 7th cervical vertebrae, as well as the 1st thoracic vertebra. This gland, which is rich in blood vessels, weighs approximately 25g and is encased in a fibrous capsule.

Hormonal Regulation and Feedback Mechanism

The release of thyroid hormones from the thyroid gland is under the control of the Thyrotropin-Releasing Hormone (TRH) hormone released from the hypothalamus. The thyroid gland gener-

ates the thyroid hormones thyroxine (T4) and triiodo-thyronine (T3) in response to pituitary production of thyrotrophin or Thyroid stimulating hormone (TSH) [2, 3]. The primary target of thyroid stimulating hormone is to produce more/fewer thyroid hormones. The thyroid produces more T3 and T4 when blood TSH levels are higher, while the thyroid produces fewer of these hormones when blood TSH levels are lower. The pituitary receives feedback from both T3 and T4, which helps it determine how much TSH needs to be released into the blood [4]. Approximately 80% of the thyroid hormone is released as T4. T4 is converted to T3, a stronger thyroid hormone, by deiodination. Eighty percent of T3 comes from peripheral conversion via a deiodinase, even though only about twenty percent comes from the thyroid gland. Thyroid-binding globulin, prealbumin, and albumin bind to over 99% of thyroid hormones, while only 1 percent are free to circulate in the blood.

TSH is an important stimulating hormone which stimulates the production of thyroid hormone by effecting the T3 and T4 level which is mainly influence with digestion, mental health, breathing heart and nerves, internal heat level muscle strength, skin dryness, menstrual cycle weight and cholesterol level (Figure-1). Whereas the abnormal TSH levels are implicated in disorder such as hypothyroidism, hyperthyroidism, thyroiditis, dyslipidaemia thyroid, metabolic syndrome and cancer [5, 6].

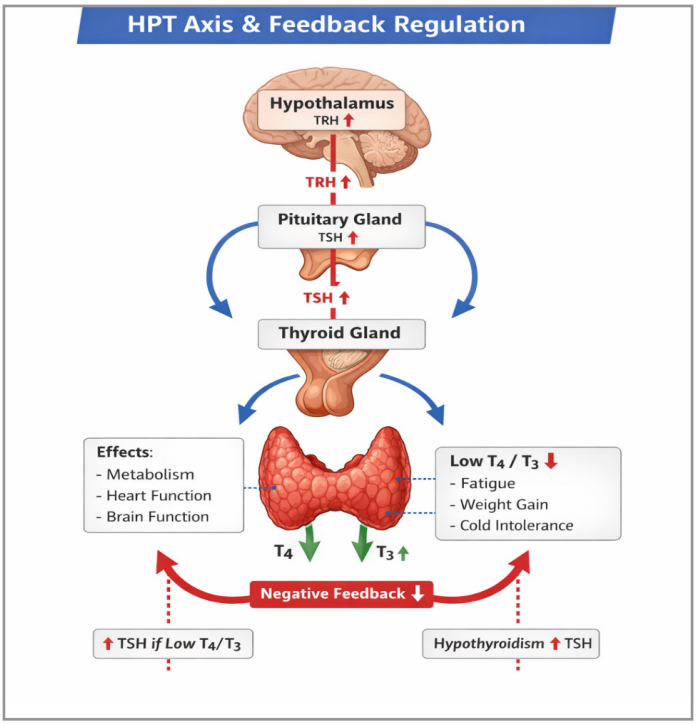

Figure- 1: Control of synthesis of thyroid hormones. Adopted from [7]

The relationship between the magnitude of differences in serum TSH and the resulting magnitude of differences in circulating thyroid hormones is the main characteristic feature of the regulation of thyroid function with respect to diagnosis of thyroid disorders [8]. Elevation of serum TSH reflects reduced thyroid hormone bioavailability at the tissue level, leading to enhanced pituitary feedback stimulation. Additionally, the relationship between these thyroid hormones and TSH is log-linear rather than linear, meaning that very slight variations in free T3 and/or free T4 will cause very significant variations in TSH [9]. Therefore, a small variation in TSH level reflect the extremely minute changes in free T3 and free T4. For instance, a small variation in free T4 will result in a 100-fold changes in TSH. Additionally, the relationship between TSH and T4 varies from person to person and can be influenced by several other factors, including age, smoking, levothyroxine treatment, and the presence of antibodies [10, 11] The use of TSH measurements as the gold standard for the diagnosis of thyroid disorders in current guidelines for the management of hypothyroidism is undoubtedly due to the fact that these large variations in TSH are more likely to be identified by routine measurements in diagnostic laboratories than small variations in T4 [12].

Interpretation of Thyroid Function Tests

As TSH and thyroid hormone assays are not uniform, there will be slight differences in the reference intervals between methods, particularly for FT4 and FT3. In overt primary hyperthyroidism TSH is almost always below 0.10 mIU/l and the FT4 is above the reference range. Plasma TSH is always elevated in overt primary hypothyroidism with a suppressed FT4 [13]. However, it can be more difficult to interpret thyroid function tests when there is a discrepancy in the results. Some causes of inconsistent results are listed in Table 1, and the more prevalent ones are covered below.

Subclinical Thyroid Disease

The term "subclinical thyroid disease" refers to patients who have abnormal laboratory results but no or very few thyroid-related symptoms. This condition is now more commonly diagnosed thanks to the screening test TSH. Low serum TSH levels with normal serum FT4 and FT3 levels are indicative of subclinical hyperthyroidism. This biochemical pattern may indicate a slight overabundance of thyroid hormone, but it may also indicate hypothalamic or pituitary disorders, non-thyroidal illness (NTI), or the use of medications that prevent TSH secretion [14,

15]. In the general population, the prevalence is between 1% and 2%, but it is higher in those over 60-year-old individual. In patients with subclinical hyperthyroidism that cannot be explained by NTI or medication therapy should undergo another thyroid function test within 3 to 6 months. If the subject is elderly or has underlying vascular disease, more frequent testing might be necessary. To determine the likelihood of developing overt hypothyroidism thyroid antibody measurement is recommended. Whereas the subclinical disease management is controversial and covered in other places.

Non-Thyroidal Illness (NTI)

The term "NTI syndrome" refers to a condition in which patients with acute or chronic systemic illnesses have abnormal or low thyroid hormone (TH) levels, usually without intrinsic thyroid gland dysfunction [16]. This condition can occur in both organic and psychiatric diseases and may affect 60–70% of critically ill patients. Although these patients are typically considered as euthyroid, it has been questioned whether these changes during illness are indicative of a related pathology that calls for thyroid hormone replacement therapy or if they are an adaptive response to stress that lowers metabolic rate, which may be advantageous for the sick patient. The most frequent finding in these patients, even in the mildest forms of NTI, is a decrease in T3. Similarly, the sick patients may also have a high, normal, or low T4 [17]. A TSH <0.10mIU/l is at least twice as likely to be caused by NTI as hyperthyroidism in hospitalized patients, while an elevated TSH is as likely to be the result of recovery from NTI as primary hypothyroidism. For this reason, unless otherwise indicated, it is not recommended to perform thyroid function tests on sick patients.

Inappropriate TSH

This is a biochemical diagnosis where an abnormally normal or elevated serum TSH concentration is linked to an increase in circulating FT4 and/or FT3 [18]. In this regard the common explanations are binding protein abnormalities leading to apparent elevation of FT4 or antibody interference with measurements of FT4, FT3 or TSH. Whereas the TSH-secreting pituitary tumors (TSHomas) and thyroid hormone resistance syndromes are additional causes of inappropriate TSH [19]. The thyroid disorder testing of family members and family history can frequently confirm thyroid hormone resistance syndromes. It is important to note that abnormal TSH isoforms are frequently secreted in central hypo or hyperthyroidism. These isoforms may have increased or decreased biological activity but may react randomly with TSH assays. Thus, the TSH result will not give an accurate prediction of TSH activity.

Antibody Interference

Intrinsic antibodies also known as interfering antibodies that can cause unpredictable results on thyroid testing [20, 21. They may be nonspecific antibodies, human anti-animal antibodies, or autoantibodies to TSH, T4, or T3. Even though assays are made to reduce these kinds of interferences, issues still arise in between 0.03 % and 0.3% percent of all samples. However, if the antibody interference is suspected, then the first step is to remeasure both TSH and FT4 using a different manufacturer's antibodies.

Table-1: Interpretation of common patterns of thyroid function tests

Raised TSH with a normal or raised FT4	**Low TSH with a normal or low FT4**
Subclinical hyperthyroidism	Subclinical hyperthyroidism
Recent treatment of hypothyroidism	Recent treatment of hypothyroidism
NTI (recovery phase)	T3 toxicosis
Drugs	Drugs (steroids, dopamine)
Interfering antibody	NTI
Resistance to thyroid hormone	Pituitary disease
Central hyperthyroidism	
Normal TSH with a raised FT4	**Normal TSH with a low FT4**
Intermittent T4 therapy	NTI
Interfering antibodies	Recent treatment of hyperthyroidism
Familial dysalbuminaemic hyperthyroxinaemia	Interfering antibodies
Central hyperthyroidism	Pituitary disease

Aetiology of Hypothyroidism

About 95% of cases have a primary elevated TSH level, which is caused by thyroid gland failure. The most prevalent form of hypothyroidism is primary hypothyroidism, which results from intrinsic thyroid gland dysfunction. Its major causes include autoimmune thyroiditis, iodine deficiency, and iatrogenic factors such as thyroidectomy or radioiodine therapy.

Autoimmune Thyroiditis

Hashimoto's thyroiditis is an autoimmune disorder characterized by lymphocytic and plasma cell infiltration of the thyroid gland, leading to the production of antibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg). These antibodies progressively destroy thyroid follicular cells, resulting in impaired thyroid hormone synthesis [22]. Furthermore, the major genetic susceptibility specifically HLA-DR3 and HLA-DR5 alleles, along with environmental causes such as viral infections, contributes to development of various autoimmune diseases, particularly autoimmune thyroid disease (AITDs) for instance Hashimoto's thyroiditis and Graves' disease [23, 24].

Iodine Deficiency and Excess

Iodine deficiency disrupts thyroid hormone production because iodine is essential for the iodination of tyrosine residues within thyroglobulin. Prolonged deficiency leads to chronic TSH stimulation and compensatory goiter formation [25]. Conversely, ex-

cessive iodine intake may paradoxically inhibit thyroid hormone synthesis through the Wolff–Chaikoff effect, especially in individuals with underlying thyroid autoimmunity [26].

Iatrogenic and Drug-Induced Causes

Iatrogenic hypothyroidism occurs following medical interventions such as treatment for hyperthyroidism, thyroid surgery, or radiation exposure, all which damage thyroid tissue and reduce hormone production [27]. Some pharmacologic drives agents, such as lithium, interferon-α, amiodarone and tyrosine kinase inhibitors, can intervene with thyroid hormone synthesis resulting in permanent hypothyroidism. These drug-induced forms require careful monitoring and dose adjustment of levothyroxine replacement therapy [28].

Clinical Manifestations of Hypothyroidism

The clinical manifestations of hypothyroidism range from minimal to life-threatening conditions such as myxoedema coma. Myxoedema coma is a rare but severe complication of long-standing, untreated hypothyroidism and was first recognized in the late 1900s. Early identification is essential due to its dramatic clinical course and high mortality rate, with approximately 40% of patients dying despite treatment [29]. Clinical features include hypothermia, increasing fatigue, bradycardia, and altered mental status, which may ultimately lead to multiple organ failure and death. Rapid initiation of thyroid hormone therapy and other supportive measure must be taken [30]. Appropriate and supportive care can reduce the complications and improve patient outcomes.

The correct mechanisms underlying the development of a hypothyroidism are poorly understood. The common symptoms include increased capillary fragility, lethargy, sensitivity to cold, dry, rough skin, weight gain, constipation, weakness, Anaemia, constipation, muscle weakness, deafness, brittle, and coarse hair, increased tongue size, slurred, hoarse speech, and slowed physical and mental activity. Whereas, in children, growth delay may occur. Physical findings may include periorbital puffiness, coarse skin and hair, bradycardia, and slurred or hoarse speech. Patients with secondary hypothyroidism due to pituitary failure often exhibit signs of an underlying pituitary disorder, such as visual field defects, galactorrhea, acromegaloid features, or manifestations of generalized hypopituitarism [31, 32].

Clinical and Metabolic Consequences

Systemic and Neurocognitive Effects

In brain metabolism thyroid hormones play an important role. Although subclinical hypothyroidism is frequently asymptomatic, patients may experience subtle manifestations such as fatigue, cold intolerance, weight gain, cognitive slowing, and depressive symptoms. These features are often nonspecific, contributing to underdiagnosis. Metabolic and Neuropsychiatric effects are observed through weight gain and fatigue, though subtle, patients may report symptoms like overt hypothyroidism. Cognitive effects were associated with impaired memory, slower processing speed, and depressive symptoms have been noted. Moreover, recent studies demonstrated that an animal models confirm the negative effect of hypothyroidism on the functioning of the central nervous system [33]. Whereas other recent reviews and meta-analyses focusing on odds ratios and risk ratios have indicated no association between Neurocognitive impairment and hypothyroidism [34].

Cardiometabolic Implications

Thyroid hormones play an important role in regulating basal metabolic rate, thermogenesis, and cardiovascular function, including heart rate and cardiac output [35, 36]. The secretion of thyroid-stimulating hormone is significantly sensitive to thyroid hormone concentrations and is frequently used clinically as a marker of their secretion [37].

TSH has also been increasingly recognized as an independent factor influencing cardiometabolic health, with elevated levels which is associated with dyslipidemia, insulin resistance, obesity, and increased cardiovascular risk, even within the reference range. TSH is also influence in lipid metabolism by comprising stimulating thyroid hormones, lipid synthesis and lipid breakdown which result in effecting lipoproteins. Furthermore, several studies suggested that elevated TSH has been associated with adverse lipid profiles, particularly increased low-density lipoprotein (LDL) cholesterol, thereby contributing to endothelial dysfunction and atherosclerosis [38]. Whereas thyroid deficiency may lead to change the synthesis and degradation of lipids as well as the function of various enzymes in the lipid metabolism pathway.

Various studies are also suggested that Insufficient production of TSH causes changes in the lipid profile, including levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG) [39-40]. However, these effects are dependent on the efficiency of thyroid function and/ or the degree of thyroid dysfunction. It is commonly known that thyroid hormones, in addition to TSH, can control lipid metabolism [41, 42]. Levothyroxine (LT4) medication may have improved blood cholesterol levels and other surrogate indicators of cardiovascular risk, according to some research [43].

However, there is conflicting evidence on levothyroxine (LT4) therapy's ability to lower total and LDL cholesterol levels and improve cardiovascular health in SCH patients. Although, Radetti et al. reported that higher TSH concentrations were associated with increased total cholesterol levels and elevated blood pressure, supporting a link between thyroid function and cardiometabolic risk [44].

More recently study from Ramouzi et al. suggested that in children and adolescents with overweight and obesity, the changes in T4, T3 and TSH concentrations are associated with changes in key cardiometabolic parameters, such as cholesterol, glucose, and triglyceride concentrations [45]. Patients with untreated subclinical hypothyroidism may be at increased risk of adverse cardiovascular outcomes. On the other hand, Various studies have indicated the incidence of subclinical hypothyroidism to be approximated at 3% to 10% and increasing to 18% to 20% in older people, depending on the population [46, 47].

Because of the increased risk of cardiovascular disease and the development of overt hypothyroidism, most guidelines for subclinical hypothyroidism (elevated TSH combined with FT4 within the reference range) need treatment when TSH ≥10 mIU/L [48-50]. However, TSH concentrations lower than currently used treatment thresholds are already associated with a higher

risk of fatal coronary heart disease [49]. Various studies have indicated the incidence of subclinical hypothyroidism to be approximated at 3% to 10% and increasing to 18% to 20% in older people, depending on the population investigated.

Reproductive and Pregnancy-Related Outcomes

Epidemiological data have shown that a high incidence of thyroid dysfunction in women of reproductive age [51]. The incidence of hypothyroidism ranges between 2% and 4% and is largely attributed to thyroid auto immune disorders [52]. The association between TSH and fertility remains unclear due to limited data in the literature. Nonetheless, inadequately treated hyperthyroidism is generally linked to an increased risk of early pregnancy loss [53].

However, Subclinical hypothyroidism has significant implications in maintaining homeostasis across several physiological systems particularly in female reproductive health, including menstrual irregularities, infertility, and adverse pregnancy outcomes. During pregnancy, even modest TSH elevation is linked to miscarriage, preterm delivery, and impaired neurocognitive development in offspring.

Regarding reproductive health issues in women SCH may contribute to menstrual irregularities, infertility, and adverse pregnancy outcomes (miscarriage, preterm birth). More recent data showed a significant lower prevalence of menstrual abnormalities of about 22% compared to 8% in healthy individuals [54]. Another, study suggested that menstrual abnormalities in up to 65% compared to 17% in healthy controls [55, 56]. These differences are likely attributable to secular trends in the diagnosis and treatment of subclinical hyperthyroidism.

Risk of Progression to Overt Hypothyroidism

Longitudinal studies suggest an annual progression rate of 2–5% from subclinical to overt hypothyroidism. The risk is significantly higher in individuals with elevated anti-thyroid peroxidase (anti-TPO) antibodies, female sex, and higher baseline TSH concentrations.

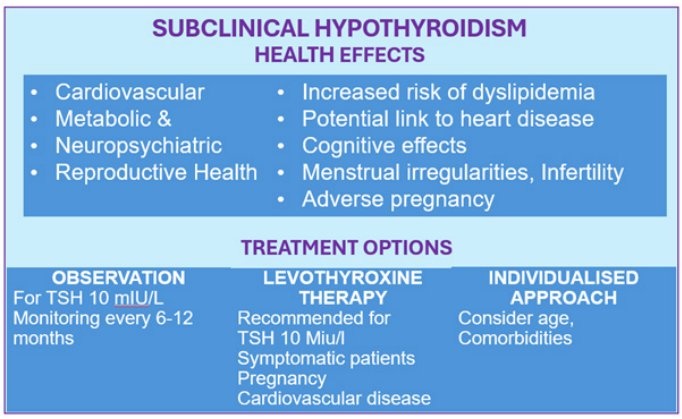

Figure-2: A visual info graph summarizing SCH's health effects and treatment pathways

Diagnostic Evaluation of TSH

Comprehensive evaluation of elevated TSH should include serum FT4 and FT3, Anti-TPO antibodies to assess autoimmune etiology [28]. However, testing for the thyroid peroxidase (TPO) antibody does not help in diagnose hypothyroidism. Further, Lipid profile and glycemic indices in patients with metabolic risk factors. Serial TSH measurements are recommended to confirm persistence before initiating therapy. For asymptomatic individuals with TSH levels between 4.5 and 10 mIU/L and negative thyroid antibodies, a conservative approach with periodic monitoring (every 6–8 weeks initially) is appropriate and needed. According to Pearce et al. subclinical hypothyroidism (SCH) is typically divided into two categories: mild-SCH, which has TSH levels between 4.0 and 10.0 mIU/l, and severe-SCH, which has TSH levels greater than 10.0 mIU/l. It's also important to keep in mind that TSH levels in both healthy people and SCH patients fluctuate throughout the day, peaking in the evening and at night. For a definitive diagnosis, it is advised to repeat the thyroid function tests at least three months apart [57].

Levothyroxine Replacement Therapy

Levothyroxine therapy is generally recommended in patients with a serum TSH concentration > 10 mIU/L, in those with symptomatic subclinical hypothyroidism, and in individuals with positive anti–thyroid peroxidase (anti-TPO) antibodies. However, there is still disagreement over the clinical significance of adverse events and the advantages of thyroxine treatment in patients with TSH <10.0 mIU/l (mild-SCH), and the available data on the risks and benefits of treatment for these patients is still debatable [58]. Treatment is also suggested in women who are pregnant or planning conception, as well as in patients with coexisting dyslipidemia or established cardiovascular disease. Endocrinologists have guided SCH through levothyroxine doses which generally range from 25 to 50 µg/day, with regular and subsequent titration guided by patient age, cardiovascular status, and serial biochemical assessment of thyroid function tests some values and stats are presented in -Table-2.

Table-2: TSH Ranges and Clinical Action

TSH Range (mIU/L)	Interpretation	Recommended Clinical Action
< 0.4	Suppressed TSH (possible hyperthyroid state)	Evaluate for hyperthyroidism or exogenous over-replacement; adjust therapy if on levothyroxine.
0.4 – 4.5 / 5.0 (Lab dependent)	Normal euthyroid range	No therapy; routine monitoring; assess symptoms/clinical context.
4.5 – 6.8 / 7.0	Mild subclinical hypothyroidism	Confirm with repeat TSH + free T4; generally, observe if asymptomatic; consider treatment if symptomatic, pregnant, or high risk (anti-TPO+, CV risk).
≈ 6.8 – 10 (per KTA)	Moderate SCH	Observation vs therapy guided by symptoms, age, risk profile (e.g., cardiovascular disease, dyslipidemia).
≥ 10	Severe SCH	Initiate levothyroxine therapy, especially in adults <70–75 years or with risk factors; confirmed on repeated testing.
Pregnancy specific (Trimester-specific)	Evidence suggests tighter targets in pregnancy	Treat any elevation above pregnancy-specific reference range (often ~4 mIU/L or lower) due to fetal neurodevelopment concerns.

Prognosis and Long-Term Outcomes

Early identification and appropriate management of elevated TSH can prevent progression to overt hypothyroidism and reduce associated cardiometabolic and reproductive complications [59]. In autoimmune cases, long-term or lifelong therapy is often required. There is limited evidence supporting the benefit of thyroxine replacement on lipid parameters in patients with TSH < 10 mIU/L. However, patients with subclinical hypothyroidism exhibit higher systolic and diastolic blood pressure and elevated cholesterol levels. A TSH value > 10 mIU/L is therefore considered an age-independent risk factor for future heart failure. As there is lack of evidence of the benefits of thyroxine replacements on lipid parameters in patients with TSH < 10 mIU/L. The goal of therapy is to keep the TSH in the normal range. A TSH of 3–5 mIU/mL is desirable for the elderly. In the elderly, any treatment for SCH should be individualized, gradual and closely monitored. For older patients (>70–75 years), a higher treatment target for serum TSH (around 1–5 mIU/L) is desirable [60]. This article particularly insists on the clinical dosage of the hormone replacement therapies such as Levothyroxine.

Although often subtle in presentation, its systemic implications warrant careful evaluation and individualized management, particularly in high-risk populations such as women of reproductive age and patients with above 65 years of age, and those suffering with cardiometabolic symptoms and comorbidities. A TSH value of ±7.01 mIU/L represents a clinically relevant biochemical abnormality consistent with subclinical hypothyroidism. In the elderly, any treatment for SCH should be individualized, gradual and closely monitored.

Conclusion

In conclusion, Subclinical hypothyroidism represents a biologically relevant endocrine state with heterogeneous cardiometabolic consequences. While current evidence does not consistently support lipid-lowering benefits of thyroxine replacement in individuals with TSH < 10 mIU/L, accumulating data indicate an association with elevated blood pressure and adverse lipid profiles. Importantly, a TSH threshold > 10 mIU/L emerges as an age-independent marker of increased cardiovascular risk, particularly heart failure. These findings emphasize the importance for individualized, risk-stratified therapeutic decisions rather than uniform treatment. Future prospective studies integrating thyroid function, metabolic markers, and cardiovascular outcomes are essential to refine treatment thresholds and optimize endocrine care.

Declarations

Acknowledgement

We Thank the Chairman of MHRC for his Encouragement

Funding

There was no Funding for this Work.

Ethics approval

As This is a Commentary no Ethics or Consent is Required.

Conflict of Interest

Authors Declare None.

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