REVIEW ARTICLE

Thyrotropin Controversy in Subclinical Thyroid Disorders

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Abstract

Aim: The thyrotropin controversy in subclinical thyroid disorders (STDs) is among the most common endocrine disorders globally. In India, approximately 42 million people suffer from thyroid disorders, with subclinical hypothyroidism (SCH) affecting about 9.4% of the population. SCH is more prevalent in females (11.4%) compared to males (6.2%).

Discussion: The diagnosis and treatment of SCH and subclinical hyperthyroidism (SHT) are controversial. SCH is often diagnosed based on biochemical markers, as patients may be asymptomatic or exhibit vague symptoms. Thyrotropin (TSH) levels may be elevated or decreased, while triiodothyronine (T3) and thyroxine (T4) remain within the normal reference range or near the lower or upper limits. STDs refers to an abnormal TSH with normal thyroxine (FT4) and free triiodothyronine (FT3) levels. It includes STDs and individuals at high risk for disease progression or adverse outcomes, with unclear prognosis. Progression of SCH to overt hypothyroidism depends on initial serum TSH levels, thyroid peroxidase antibodies (TPO), family history of thyroid disorders, previous radiation, and smoking. Controversies surround SCH and its association with cardiovascular diseases (CVD), pregnancy outcomes, neuropsychiatric issues, metabolic syndrome, dyslipidemia, and diabetes. Assay interference is a problem in interpreting thyroid function tests (TFTs), occurring in 1% of cases. The health package investigation systems often overlooks the impact of drug intake and assay interference. Various methods for measuring TFTs, such as radioimmunoassay, immunometric assay, and ELISA, differ in sensitivity, specificity, and standardization, leading to methodological variability. Common causes of assay interference include human antimurine antibodies (HAMA), thyroid hormone autoantibodies (THAAbs), rheumatoid factor, antistreptavidin, and antiruthenium antibodies. When diagnosing SCH, it is crucial to rule out other causes of elevated TSH, such as autoantibodies, goiter, and rare conditions such as thyroid hormone resistance (THR), diagnosed by serum glycoprotein alpha subunit (α-GSU) and family history. Biotin, a common supplement, can affect TFT assays, leading to spurious results. It can cause falsely high T4 and T3 levels and low TSH, leading to misdiagnosis of SCH.

Conclusion and recommendations: The timing of TFTs, whether fasting, postprandial, or random, remains a debated issue. Assay interference and biotin intake should be considered when analyzing TFTs. The role of iodine and iodine supplementation during pregnancy and its impact on STDs are not yet fully conceptualized. Large randomized clinical and epidemiological studies are needed to establish a consensus on the diagnostic threshold for TSH. These studies should include diverse populations and medical conditions to improve our understanding of the disease and patient outcomes. In practice, avoid rushing to treat elevated TSH levels between 4 and 10 mIU/L or low TSH between 0.5 and 0.1 mIU/L without confirming the diagnosis with additional tests (T3, T4, FT4, FT3, and TPO). TSH alone should not be the sole decision-maker; consider other TFTs and sequential testing from the same laboratory and time to make more informed decisions. While TSH levels can be affected by time and prandial state, FT3 and FT4 levels remain stable, suggesting all three TFTs may aid in accurate diagnosis and treatment decisions.

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Introduction

Thyroid disorders (TD) are one of the most common endocrine disorders globally. In India, about 42 million people suffering from TD and subclinical hypothyroidism (SCH) are about 9.4% with female preponderance; 11.4% compared to 6.2% in men.[1,2] Incidence and prevalence vary in sample population as environmental and regional differences are there regarding iodine content of the water, salt iodination, and we know that hilly areas have higher incidence of iodine deficiency disorders (IDD) compared to non-hilly areas. Hypothyroidism and hyperthyroidism prevalence is between 1–2% and 0.5–2% and 10 times more prevalent in women than in men. Studies suggest that 1% of males and 5% females have thyroid nodules, and the frequency increases with age and iodine-deficient populations. Developing countries are equally affected as developed ones, and globally, TD is common, and hypothyroidism and SCH in the Pakistani population are 4.1 and 5.4% with female preponderance,[3] 4–8% in Brazil,[4] 3–8% in the USA.[5,6] Kumar et al. reported SCH about 30% in India. Prevalence in school-going children of Pakistan is 8.43%[7] higher compared to 1.7% children in USA[8].

Discussion

There are few most controversial issues in the endocrine world such as diagnostic cut offs of plasma glucose in gestational diabetes mellitus (GDM), metformin in pregnancy; prediabetes to be treated or not and diagnosis of SCH and treatment decision of SCH because diagnosis of subclinical thyroid disorders (STDs) are more of a biochemical nature as most often but not patients with STDs are asymptomatic or have vague symptomatology and thyrotropin or thyroid stimulating hormone (TSH) is elevated or decreased and thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4) and free triiodothyronine (FT3) are within normal reference range or at lower or upper border of normal.[9,10]

A slightly raised TSH is the most common thyroid function (TF) abnormality worldwide. SCH is also known as mild hypothyroidism, early thyroid failure, preclinical hypothyroidism, or decreased thyroid reserve.[11] SCH prevalence is 3–8% and increases with age have female dominance, and lately around the sixth decade in males.[12,13] Presence of thyroid peroxidase antibody (TPO) increases the risk of developing SCH and progression of SCH to overt hypothyroidism. The role of Iodine supplementation is controversial, and iodine-sufficient areas have a higher incidence of SCH than iodine-insufficient regions, according to European studies.[14]

Subclinical thyroid dysfunction or disorder (STDs) is defined as an abnormal TSH with normal T3, T4, FT4, and FT3. Persons who are at high risk of disease progression and or adverse clinical outcomes and whose prognosis is not well understood are included in STDs. Initial serum TSH, TPO positivity, family history of TD, history of radiation, pollution, and smoking are the risk factors for SCH progressing to overt hypothyroidism. SCH has various outcome issues, such as cardiovascular disease risk (CVD), pregnancy

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outcomes, neuropsychiatric problems, metabolic syndrome, dyslipidemia, and diabetes. Type 2 diabetes mellitus (T2DM) patients are more likely to develop STDs, specifically SCT.[1516]

There is minimal data to support routine thyroxine replacement of STDs (serum TSH 0.1–0.45 mIU/L or 4.5–10.0 mIU/L), and recommendations are against routine treatment of such patients.[17]

Why STD are Important?

Poor understanding of STDs may lead to over or under treatment of people with these biochemical abnormalities. Cohort review of 500 patients with SCH at Mayo Clinic in 1995–1996 revealed 38.7% of patients with TSH between 5.1 and 10.0 mIU/L received treatment.[18] There is a difference of opinion regarding treating asymptomatic SCH or subclinical hyperthyroidism (SCHY).

Vary important fact to be remembered is that TSH varies with the time of sample collection and relation to food. Study of 57 patients with three groups: group I with normal T4 and TSH; group II with SCH with increased TSH and normal FT4, and group III with overt hypothyroid with low FT4 and high TSH; thyroid function tests (TFT), FT4, and TSH were done in fasting and 2-hour postmeal samples. TSH was found to be low in all three groups in postmeal samples irrespective of the fasting levels while FT4 values did not change significantly. This has led to reclassification of 15 out of 20 (75%) subjects as SCH based on fasting values, otherwise normal TSH in the postprandial sample.[19–22] Possible explanation for low TSH in postmeal sample may be foods causing an increase in serum somatostatin levels, which suppresses TSH secretion from the pituitary.[21–24] Another big controversy is about consensus on the timings of TFT and assay methodology, and is really confusing everyone, patients, biochemist and clinicians.[19] We all know TSH levels are highest in the early morning but decrease with prandial state, and one may argue that random testing may leave some SCH undiagnosed; quite right! And at the same time opponent may use this fact in their favor that fasting sample may overdiagnose SCH, which is also correct and scientific.

Hypothyroidism is mostly caused by autoimmune chronic lymphocytic thyroiditis, and TPO antibodies are the test required to confirm the diagnosis after TSH in the Western World. Elevated TSH with normal T4 is a controversial issue to treat or not, and levothyroxine replacement may be beneficial in some cases. Iodine supplementation is recommended routinely to women planning a pregnancy unless contraindicated,[20] though the routine iodine supplementation is also a controversial issue requiring large-scale studies and more data.

Thyroid disorders are usually benign and present with varied manifestations. About one-third of the global population lives in iodine-deficient areas despite a whole lot of efforts to increase iodine intake by way of iodizing salt or iodine fortification of oil, and at the same time, TD are common in iodine-repleted areas. Another important factor is that TDs are usually autoimmune in nature, such as primary atrophic hypothyroidism, Hashimoto's thyroiditis, and Graves' disease. In iodine-repleted areas, congenital hypothyroidism affects one in 3,500–4,000 births, and the routine screening is recommended universally with a heel-prick blood sample. Controversy also persists about healthy adults' screening for TD as the prevalence of overt TD is low, but STDs are significant, 10% SCH, and 1% with subclinical hyperthyroidism SCHY.[25]

Assay Interference

Assay interference is another issue in TFT interpretation. About 1% of all TFTs have assay interference. Health package investigation system by various corporate organizations, hospitals, and laboratories does not pay enough attention to the possible intake of drugs, timing of sample, which may cause assay interference.

Assay interference is an important consideration because of several methods to assess TFT, such as radioimmunoassay, immunometric assay, tandem mass spectrometry, and ELISA. Differences in their sensitivity, specificity, and standardization can result in significant methodological variability.

Other causes of assay interference leading to high TSH are human antimurine antibodies (HAMA), thyroid hormone autoantibodies (THAAbs), rheumatoid arthritis (RA) factor, antistreptavidin and antiruthenium antibodies[4]; and rare incidences of thyroid hormone resistance (THR) having serum glycoprotein alpha subunit (α-GSU) along with a family history of the disorder**.**

Biotin is another element interfering with TFT assays, a common health supplement for skin ailments, *per se,* that does not affect thyroid function, but certain TFT assays for TSH, T3, T4, and thyroglobulin. Biotin causes spuriously high T4 and T3 and low TSH, leading to misdiagnosis of SCHY.[3]

As per Helfand's review, TSH is a widely available, reliable, and acceptable test to detect the STDs with a sensitivity of more than 98% and specificity of more than 92%. However, it remained unclear whether treating patients with STDs would reduce morbidity or not.[26]

Thyroid disorders are an important cause of adverse pregnancy outcomes; hence trimester-specific reference range was laid down by various guidelines with controversies, but consensus is on lower cut-offs for TSH throughout pregnancy. American Thyroid Association (ATA), Endocrine Society clinical practice guideline[5,6] gave TSH cutoffs as 0.1–2.5 Miu/L in the first, 0.2–3.0 mIU/L in the second, and 0.3–3 mIU/L in the third trimester. ATA 2017 recommended the upper cutoff 0.5 mIU/L less than the preconception TSH value or 4.0 mIU/L when local population-specific reference range is not available.[27,28]

Conclusion

- STDs and overt thyroid disorders are common with varied presentations.
- No universally accepted guideline for the diagnosis and treatment of STDs and SCH.
- Assay interference and biotin intake should always be at the back of mind while analyzing TFT.
- The role of iodine supplementation during pregnancy and otherwise in STDs has not yet been conceptualized.
- Pregnancy cutoffs and trimester-specific ranges are still a debatable issue, but consensus is on lower cutoffs for TSH and no controversy on TSH < 2.0 mIU/L for SCH and 0.1 mIU/L for SCHY.
- Controversy regarding the timing of TFT persists, whether fasting, postprandial, or a random sample is still a debatable issue.
- Routine healthy adult population screening for TD is controversial, as the prevalence of STDs is significant, 10% SCH, and 1% with subclinical hyperthyroidism SCHY.
- Another controversial issue is the population-specific reference range recommended by some of the guidelines.

Recommendations

- Large randomized clinical and epidemiological studies are required to solve the various controversial issues discussed above.
- TSH alone is a double-edged sword as it is highest in the early morning but decreases with meals, and one may argue that random testing may leave some SCH undiagnosed; quite right! And at the same time opponent may use this fact in their favor that a fasting sample may overdiagnose SCH, which is also scientifically correct.
- What we can understand with the review of literature and infer and recommend is not rush to treat raised TSH in the range of

4.0–10 mIU/L or TSH below 0.5 mIU/L without confirming the diagnosis and taking into consideration the clinical presentation and T3, T4, FT4, FT3, and TPO testing.

- TSH alone should not be a decision maker but the other TFTs and sequential TFTs from the same laboratory and time may help you decide better as we have seen that TSH level is affected by prandial state but not the FT3 and FT4 so TFT including other parameters such as TSH and T3, T4, FT3, FT4 and TPO can be useful to correctly diagnose or exclude thyroid dysfunction.
- In person, I also recommend writing thyrotoxic in place of hyperthyroidism in clinical practice as there are minor differences in spelling of hypothyroidism and hyperthyroidism, which may confuse the patient if handwriting is not clear, which most of the time is…! Here, I would like to clarify that while recommending this narrative, I know the difference between hyperthyroidism and thyrotoxicosis.

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