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Research Article

Clinical Perspective on Thyroid Hormones and Autoantibodies in Subclinical Hypothyroidism

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ABSTRACT

This study examines biochemical and immunological markers in individuals with subclinical hypothyroidism (SCH), particularly focusing on thyroid autoantibodies' role in disease progression. We recruited 200 patients from Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Salem, Tamil Nadu, India Vinayaka Mission's Research Foundation (Deemed to be University) having normal levels of triiodothyronine (T3) and tetraiodothyronine (T4) and excessive levels of thyroid stimulating hormone (TSH) (>4.0 mIU/L). Overt hypothyroidism, pregnancy, thyroid medication, and other illnesses that affect thyroid function were among the exclusion criteria. Chemiluminescent immunoassay and the enzyme-linked immunosorbent assay were used to test fasting blood samples for serum TSH, T3, T4, anti-thyroglobulin antibodies (AB-TG), and anti-thyroid peroxidase antibodies (AB-TPO). Thyroid compensation was indicated by aberrant T3 and T4 levels and markedly raised TSH levels (6.3 ± 0.16 mIU/L) in SCH patients. A strong association between TSH and AB-TPO levels ($r = 0.45$, $p < 0.01$) suggests an autoimmune involvement, as do elevated levels of AB-TG (170.97 ± 3.617 IU/mL) and AB-TPO (11.77 ± 0.313 IU/mL). These results emphasize the autoimmune aspect of SCH and imply that tracking thyroid autoantibodies may help with the course and treatment of the condition. Future research should explore gender-specific strategies in SCH diagnosis and clinical care.

Introduction

Thyroid-stimulating hormone (TSH) levels in the blood are high in subclinical hypothyroidism (SCH), but thyroid hormones T3 and T4 are within normal ranges.[1-3] Despite often being asymptomatic, SCH is a condition of clinical importance due to its potential to progress into overt hypothyroidism and its association with metabolic and cardiovascular risks.[4] Routine health checkups frequently identify SCH, emphasizing its role in preventive healthcare.

The progression of SCH to overt hypothyroidism brings more noticeable symptoms and requires more intensive treatment. Moreover, SCH has been linked to health issues such as high cholesterol, hypertension, and cardiovascular disease. Effectively recognizing and managing SCH is crucial for reducing these risks over the long term.[5,6]

The underlying cause of SCH often involves a combination of genetic, environmental, and hormonal factors. A primary factor is autoimmune thyroiditis, a condition associated with the presence of thyroid-specific autoantibodies like anti-thyroglobulin antibodies (AB-TG) and anti-thyroid peroxidase antibodies (AB-TPO).[7,8] These autoantibodies gradually damage thyroid tissue, impairing hormone production and causing TSH levels to rise in an attempt to stimulate thyroid function.[9] The generation of hormones is further hindered by inflammation and damage to thyroid follicles in Hashimoto's thyroiditis, a prevalent type of autoimmune thyroiditis.[10] Over time, overt hypothyroidism may result from ongoing autoimmune damage.

The presence of autoantibodies like AB-TG and AB-TPO significantly influences the development and progression

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of SCH. These autoantibodies attack thyroid proteins, leading to chronic inflammation and the gradual destruction of thyroid follicles. This process reduces the thyroid's ability to produce hormones, causing TSH levels to rise as the body attempts to compensate.[8] While the thyroid gland may temporarily increase T3 production to maintain normal metabolic activity, this compensation often falls short, leading to the characteristic pattern of elevated TSH with normal T3 and T4 levels seen in SCH.[7] As autoimmune damage continues, the thyroid may struggle to compensate, resulting in overt hypothyroidism, marked by high TSH and low T3 and T4 levels.[9]

The presence of elevated autoantibodies in individuals with SCH highlights the need for careful monitoring and timely intervention. High levels of AB-TG and AB-TPO suggest a greater likelihood of progression to overt hypothyroidism, which may warrant closer follow-up and earlier treatment. Understanding the role of these autoantibodies is vital for creating effective management plans and assessing the risk of disease progression.

From a pharmaceutical perspective, studying SCH is increasingly relevant as awareness grows about its potential complications. SCH's association with conditions such as dyslipidemia and cardiovascular disease underscores the importance of early intervention strategies. Medications aimed at maintaining thyroid function and addressing associated risks are critical. Additionally, exploring the autoimmune mechanisms underlying SCH can guide the development of targeted therapies to slow or prevent disease progression. By advancing research in this area, pharmaceutical interventions can be better tailored to reduce the long-term health risks associated with SCH.

Materials And Methods

Study Population

The study involved 200 patients randomly (Healthy individuals and subclinical hypothyroidism patients), recruited from Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Salem, Tamil Nadu, India Vinayaka Mission's Research Foundation (Deemed to be University)

Inclusion Criteria

- Elevated TSH levels (>4.0 mIU/L) with the usual level of T3 and T4 levels.

Exclusion Criteria

- Individuals with overt hypothyroidism.
- Pregnant women.
- Participants are currently on thyroid medications.
- Individuals with significant medical conditions that could affect thyroid function.
- Relevant approvals were obtained from the Institutional Ethics Committee VMKVMCH, Salem and informed Consent was secured from all participants.

Biochemical Analysis

Fasting in order to prevent hormone level fluctuations throughout the day, blood samples were taken between 8:00 and 10:00 in the morning. A very sensitive chemiluminescent immunoassay was used to assess serum levels of TSH, T3, T4, AB-TG, and AB-TPO.[1] As directed by the manufacturer, AB-TG and AB-TPO levels were measured using enzyme-linked immunosorbent assay (ELISA) kits from Thermo Fisher Scientific. The reference ranges were TSH (0.4–4.0 µIUm/L), T3 (100–200 ng/dL), T4 (5–12 µg/dL), AB-TG (116 IU/mL), and AB-TPO (<35 IU/mL).[11-13]

Statistical Analysis

Microsoft Excel 2019 and the Statistical Package for Social Sciences (SPSS) version 22.0 were used for analysis. For every variable, descriptive statistics were computed. When comparing regularly distributed variables between healthy and SCH patients, independent t-tests were utilized; for non-normally distributed data, non-parametric tests (Mann-Whitney U) were utilized. Statistical significance was defined as a p-value of less than 0.01.

Descriptive Statistics

Calculated for all variables, including means, standard deviations, and medians.

Comparative Analysis

When comparing normally distributed data between SCH patients and healthy individuals, independent t-tests were used. For variables that were not normally distributed, Mann-Whitney U tests were used.

Significance Threshold

For every analysis, a *p-value* of less than 0.01 was deemed statistically significant. Meaningful interpretations of biochemical and immunological changes in SCH patients were made possible by the analytical technique, which guaranteed strong comparisons across groups.

Results

TSH Levels

TSH levels were measured and compared between the two groups in order to determine whether statistically significant differences existed. The study examined TSH levels in two different cohorts: those with normal thyroid function (Healthy) and those with SCH. The mean TSH level in the healthy cohort was within the physiological reference range, which is consistent with normal thyroid function. On the other hand, the TSH levels in the SCH cohort were noticeably higher, with a mean ± standard deviation (SD) of 6.3 ± 0.16 mIU/L

(Fig. 1 & Table 1), which is higher than the top limit of the normal range and suggests thyroid dysfunction. A *p-value* > 0.01 indicated that the mean TSH levels in the SCH and healthy groups differed statistically significantly (Table 1). The pathogenic rise in TSH that takes place as a compensatory strategy in response to decreased thyroid hormone synthesis is highlighted by this statistically significant increase in TSH levels among people with SCH. These results are consistent with previous research showing a greater frequency of SCH, especially in groups at risk for autoimmune thyroiditis and other endocrine disorders. The elevated TSH levels seen in SCH patients might be caused by a number of factors, including genetic predispositions and hormonal fluctuations.

T3 and T4 Levels

The study assessed the levels of T3 and T4 in individuals categorized as having normal thyroid function (Healthy) and those diagnosed with subclinical hypothyroidism (SCH) to elucidate the differences between these two cohorts. In the healthy population, T3 and T4 levels remained within the normal physiological range, consistent with optimal thyroid function. Conversely, in the SCH population, a distinctive hormonal profile was observed. T3 levels were elevated beyond the normal range, while T4 levels were reduced compared to the healthy group. This dichotomy in hormone levels is indicative of early thyroid dysfunction in SCH, where the thyroid gland compensates for declining T4 levels by increasing T3 production. The statistical analysis revealed a significant difference in both T3 and T4 levels between the SCH and healthy populations ($p < 0.01$) (Table 1). The observed elevation in T3 (104.18 ± 2.29 µg/mL) and reduction in T4 (5.215 ± 0.139 µg/mL) (Fig. 1 & Table 1) among SCH individuals reflect an adaptive response by the thyroid gland, as it attempts to maintain metabolic homeostasis under conditions of impaired function. Thyroid autoantibodies like anti-thyroid peroxidase antibodies (ATPOA) are commonly linked to this hormonal imbalance in SCH. The existence of these antibodies points to an autoimmune cause, such as Hashimoto's thyroiditis, which can gradually harm thyroid tissue and reduce the production of T4. In order to maintain thyroid hormone function, the body makes up for it by producing more T3. These findings are consistent with the clinical characterization of SCH, wherein thyroid hormone levels may remain within or near the normal range, but elevated TSH levels reflect underlying thyroid dysfunction. The association of thyroid autoantibodies with this altered hormone profile further supports the autoimmune origin of SCH, emphasizing the progressive nature of thyroid impairment in affected individuals.

AB-TG and AB-TPO Levels

The study evaluated anti-thyroglobulin (AB-TG) and anti-thyroid peroxidase (AB-TPO) antibody levels in individuals with normal thyroid function (Healthy) and those diagnosed with subclinical hypothyroidism (SCH) to elucidate immunological differences between these groups. In the healthy cohort, AB-TG and AB-TPO levels were maintained within normal physiological ranges, indicating a minimal likelihood of autoimmune thyroid pathology and the preservation of normal thyroid function. Conversely, the SCH cohort exhibited a pronounced elevation in AB-TG levels, with values significantly surpassing those in the healthy population (170.97 ± 3.617 IU/mL) (Fig. 1 & Table 1), indicative of a heightened autoimmune response targeting the thyroid gland. Similarly, AB-TPO levels were elevated in the SCH group (11.77 ± 0.313 IU/mL) (Fig. 1 & Table 1) relative to the healthy population, though this increase was less substantial compared to the rise in AB-TG. The statistical analysis confirmed that the differences in AB-TG and AB-TPO levels between the SCH and healthy populations were highly significant ($p < 0.01$) (Table 1). The marked elevation in AB-TG within the SCH group points to a robust autoimmune component, likely contributing to the subclinical thyroid dysfunction observed in this cohort. The existence of an autoimmune condition that gradually damages thyroid function, such Hashimoto's thyroiditis, is further supported by elevated AB-TPO levels. The pathogenic significance of autoimmunity in the onset and progression of SCH is highlighted by the association between higher antibody levels and thyroid dysfunction, which results in changes to thyroid hormone production and metabolism. These findings are consistent with the autoimmune etiology of SCH, where elevated thyroid-specific antibodies, particularly AB-TG and AB-TPO, are instrumental in the gradual decline of thyroid function. The significant disparities in antibody levels between the SCH and healthy populations highlight the central role of autoimmunity in the pathogenesis of subclinical hypothyroidism.

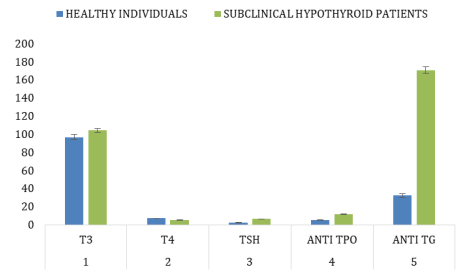

Fig. 1: Comparison of thyroid profiles between healthy individuals and subclinical hypothyroid patients

Correlation Analysis

TSH levels and AB-TPO antibody levels were shown to be positively correlated in the subclinical hypothyroidism (SCH) population. This association was statistically significant, with a correlation coefficient (r) of 0.45 and a *p-value* > 0.01. This discovery implies that the high TSH in SCH patients may be directly caused by autoimmune

Table 1: Comparison of thyroid profiles between healthy individuals and subclinical hypothyroid patients

Test variables	*Healthy individuals (Mean ± SD)*	*Subclinical hypothyroid patients mean ± SD)*	*p-value*
T3	96.78 ± 2.761	104.18 ± 2.291	<0.01
T4	7.027 ± 0.169	5.215 ± 0.139	<0.01
TSH	2.308 ± 0.131	6.3 ± 0.165	<0.01
Anti TPO	5.097 ± 0.103	11.77 ± 0.313	<0.01
Anti TG	32.192 ± 2.344	170.97 ± 3.617	<0.01

(n = 100)

processes, as seen by elevated AB-TPO levels. TSH and AB-TPO levels, however, did not significantly correlate in a subgroup of the sample (r = 0.20, p = 0.10). This lack of correlation suggests potential differences in the underlying pathophysiology of SCH within different groups, indicating that factors other than autoimmunity may influence TSH levels in certain individuals. These results highlight the complex interplay between thyroid autoimmunity and thyroid function, underscoring the significant role of AB-TPO in driving TSH elevation in some individuals with SCH, while also pointing to the variability in SCH pathogenesis across different populations.

Discussion

There is a complex interaction between endocrine control and immunological response in subclinical hypothyroidism (SCH), which is characterized by elevated blood thyroid-stimulating hormone (TSH) with normal T3 and T4 levels.[14] The results of the study highlight how important thyroid autoantibodies—more especially, anti-thyroid peroxidase (AB-TPO) and anti-thyroglobulin (AB-TG)—are to the pathogenesis of SCH. According to earlier research, people with SCH had high levels of AB-TPO and AB-TG antibodies, which suggests a significant autoimmune component frequently linked to Hashimoto's thyroiditis, a common cause of SCH.[15]

The observed elevation in TSH levels among SCH patients can be interpreted as a compensatory mechanism initiated by the pituitary gland in response to the decreased thyroid hormone synthesis, likely due to autoimmune-mediated thyroid damage (Biondi and Cooper 2008). This feedback loop is a protective response to maintain euthyroid conditions despite an ongoing autoimmune process that affects thyroid function over time.[7,8] Elevated AB-TPO antibodies are particularly significant, as they target thyroid peroxidase, an enzyme essential for iodine organification and thyroid hormone synthesis, thus impairing hormone production.[9] The idea that autoimmune processes play a key role in SCH and that AB-TPO may be a useful indicator for assessing the risk of illness development is supported by the positive connection between TSH and AB-TPO levels (r = 0.45, p < 0.01).[3,16] Additionally, while AB-TG antibodies provide supplementary evidence for autoimmune thyroiditis, they are less specific than AB-TPO. Nevertheless, their presence supports an autoimmune diagnosis and further suggests that antibody profiling could be essential in identifying individuals at increased risk for advancing thyroid dysfunction.[16,17] The accumulation of these antibodies reflects ongoing thyroid tissue destruction, which can eventually diminish thyroid hormone reserves and progress to overt hypothyroidism if left unmanaged.[7,8]

This study's data aligns with earlier research, underscoring the importance of monitoring thyroid autoantibodies in clinical settings for SCH management. Identifying elevated AB-TPO and AB-TG levels in SCH patients may offer predictive value for early intervention, potentially delaying or preventing progression to overt hypothyroidism.[18] Furthermore, the autoimmune genesis of SCH lends support to a treatment strategy that involves routine antibody testing to determine the risk of future thyroid failure, particularly in patients with substantial increases in TSH.[9]

Beyond endocrinological implications, thyroid dysfunction, even in subclinical forms, appears to influence neuropsychiatric health, as evidenced by associations with mood disturbances and anxiety.[19] Thyroid hormones modulate central nervous system function, including neurotransmitter pathways, myelination, and neurogenesis.[20] SCH has been linked to mood disorders through effects on serotonin and norepinephrine pathways, suggesting that subtle declines in thyroid function can have broader effects on brain health.[21,22] The observed correlation between elevated AB-TPO levels and anxiety points toward the possibility that thyroid autoimmunity may intensify neuroinflammatory processes, exacerbating mental health symptoms in SCH patients.[7,18] This highlights the importance of holistic management that includes mental health assessments in SCH patients, particularly for those exhibiting elevated autoantibody levels.

These findings underscore that thyroid autoimmunity is a substantial factor in SCH pathogenesis, impacting both thyroid function and, potentially mental health. Monitoring AB-TPO and AB-TG antibodies in SCH can guide clinicians in identifying patients at higher risk for disease progression, facilitating timely interventions. In order to further enhance clinical management techniques

and patient outcomes, future research should examine gender-specific variations in the course of SCH and the effect of autoimmunity on mental health.[9,16]

Conclusion

The study provides important insights into the biochemical markers associated with SCH, particularly the role of thyroid autoantibodies in the condition's pathophysiology. Elevated TSH levels in SCH are indicative of compensatory mechanisms in response to autoimmune thyroiditis, as evidenced by increased AB-TPO and AB-TG antibody levels. The correlation between thyroid antibodies and thyroid dysfunction emphasizes the need for thorough monitoring and management of individuals with SCH to prevent progression to overt hypothyroidism. Furthermore, the effect of thyroid dysfunction on mental health emphasizes how crucial it is to manage SCH holistically, taking into account both the psychological and physical components of the illness. The involvement of thyroid autoantibodies in SCH has been better understood according to recent studies. Research has improved our understanding of the disease processes by identifying environmental variables and genetic predispositions that contribute to autoimmune thyroiditis. Furthermore, new imaging and biomarker technologies are being investigated to enhance SCH monitoring and diagnosis, which might lead to more individualized and successful treatment plans. Future studies should keep looking at the intricate relationships that exist between genetic predisposition, thyroid function, and autoimmune processes. To find preventative measures and get a better understanding of the transition from SCH to overt hypothyroidism, longitudinal studies are required. Investigating how lifestyle choices like nutrition and stress affect thyroid autoimmunity and SCH may yield important information for treatment and prevention plans.

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