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RESEARCH ARTICLE

Assessment of Anti-TPO and Anti-TG Antibody Levels in Autoimmune Thyroid Disease Among Levothyroxine-Treated Hypothyroid Patients

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Abstract: ***Objectives*** To assess anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibody levels in levothyroxine (LT_4)–treated primary hypothyroid patients and evaluate their associations with thyroid hormone profile and disease duration. ***Materials and Methods*** A case–control analytical study was conducted among 80 LT_4-treated primary hypothyroid patients and 60 age- and sex-matched euthyroid controls. Thyroid function tests (TSH, fT3, fT4) were measured using chemiluminescence immunoassay, while anti-TPO and anti-TG antibodies were assessed using ELISA. ***Statistical Analysis*** Normality was evaluated using the Shapiro–Wilk test. Between-group comparisons were performed using the independent t-test or Mann–Whitney U test. Correlations between antibody titers, thyroid hormone levels, and disease duration were assessed using Pearson's or Spearman's correlation coefficients. A p-value <0.05 was considered statistically significant. ***Results*** Anti-TPO and anti-TG positivity were significantly higher in LT_4-treated patients compared with controls (65% vs 3% and 47.5% vs 2%, respectively; p <0.001). Treated patients showed elevated TSH and reduced fT3 and fT4 (p <0.001). Anti-TPO correlated positively with TSH (r = +0.48) and negatively with fT4 (r = –0.32), while anti-TG correlated positively with disease duration (r = +0.41). Dual-antibody positivity showed the strongest association with elevated TSH (r = +0.52). ***Conclusions*** Persistent elevation of anti-TPO and anti-TG antibodies in LT_4-treated hypothyroid patients indicates ongoing autoimmune thyroid damage despite hormone replacement. Regular monitoring of thyroid autoantibodies alongside biochemical markers may improve risk stratification, guide LT_4 dose optimization, and enhance long-term management of autoimmune hypothyroidism.

Keywords: Autoimmune thyroiditis; Anti-TPO; Anti-TG; Levothyroxine therapy; Hypothyroidism; Thyroid autoantibodies.

INTRODUCTION

Autoimmune hypothyroidism is the most common cause of thyroid hormone deficiency in iodine sufficient regions, with Hashimoto's thyroiditis (HT) being the predominant form of autoimmune thyroid disease (AITD) worldwide[1]. HT, also known as chronic lymphocytic thyroiditis, is characterized by progressive immune mediated destruction of thyroid follicles, driven by a combination of genetic predisposition, environmental triggers, and immunological dysregulation[2]. This destruction results in reduced synthesis and secretion of thyroid hormones, ultimately leading to overt hypothyroidism. The disease disproportionately affects females, with a female to male ratio of 5 – 10:1, attributed to hormonal, immunogenetic, and epigenetic factors[3].

Autoimmune activity in HT is primarily mediated through thyroid autoantibodies, which serve as both effectors of tissue damage and biomarkers for diagnosis and disease monitoring.

Thyroid peroxidase (TPO) is an essential enzyme for iodination and coupling reactions during the synthesis of T_3 and T_4. Anti-TPO antibodies attack and neutralize TPO, causing impaired hormone formation and enhanced inflammatory cell infiltration[4]. Elevated anti-TPO titers are found in more than 90% of HT patients and are considered a highly sensitive indicator of AITD[5]. Anti-TPO levels also correlate with the severity of thyroid destruction and risk of progression from subclinical to overt hypothyroidism[6].

Thyroglobulin (Tg) is a high–molecular-weight glycoprotein synthesized in the thyroid and serves as the precursor for the synthesis of thyroid hormones; when autoantibodies target Tg, they can drive sustained autoimmune inflammation and fibrosis of the gland[7]. Although less sensitive than anti-TPO, anti-Tg positivity often reflects ongoing autoimmunity and is associated with disease chronicity, thyroid volume reduction, and increased risk of relapse. The presence of both autoantibodies increases the likelihood of clinically significant hypothyroidism and serves as a prognostic indicator in follow-up evaluation.

Levothyroxine (LT_4) remains the standard treatment for hypothyroidism, aiming to restore and maintain euthyroidism by providing exogenous T_4 replacement. While biochemical normalization of TSH is generally achieved, LT_4 therapy does not address the underlying autoimmune process[8]. Numerous patients continue to experience residual symptoms fatigue, weight gain,

cognitive disturbance, reduced quality of life—despite apparently normal thyroid function tests[9]. Persistent autoimmune inflammation and elevated antibody levels are increasingly recognized as potential contributors to these ongoing symptoms.

Moreover, higher anti-TPO and anti-Tg titers have been linked to a greater LT_4 requirement, likely due to progressive destruction of functional thyroid tissue and altered peripheral deiodination[10]. Evidence also suggests that persistent autoantibody activity may influence thyroid receptor sensitivity and systemic metabolic responses, further complicating optimal disease control[11].

Despite its clinical relevance, evaluation of thyroid autoimmunity status is often limited to the initial diagnosis. Routine follow-up primarily relies on TSH and FT_4 measurements, leaving ongoing inflammatory and immunological changes under-recognized[12].
A growing number of researchers advocate incorporating autoantibody surveillance into standard management protocols, especially in patients who remain clinically symptomatic or require escalating LT_4 doses. There remains a need to better understand the status and significance of autoimmune activity in patients already on LT_4 therapy. Patterns of anti-TPO and anti-Tg levels may provide important insights into residual autoimmunity and its association with current thyroid hormone balance.

MATERIAL AND METHODS

Study Design and Participants

This case control study was conducted in the Department of Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry to evaluate the autoimmune status of hypothyroid patients on levothyroxine therapy by comparing Anti-TPO and Anti-Tg antibody levels with healthy euthyroid controls. A total of 140 participants were enrolled, comprising 80 adult patients (aged ≥18 years) with a confirmed diagnosis of primary hypothyroidism on stable LT_4 therapy (≥6 months) ensuring stable treatment status and The control group included 60 age- and sex-matched euthyroid individuals without a history of thyroid disease or detectable thyroid autoantibodies.
Participants were recruited consecutively after obtaining written informed consent. Ethical approval was obtained from the Institutional Ethics Committee (MGMCRI/2023/02/IHEC/106). The sample size was estimated using Open Epi software version 3.1 based on previous prevalence data to achieve adequate statistical power. Participants were eligible for the study if they had a diagnosis of primary hypothyroidism, with age between 18 and 65 years and having receiving a stable dose of LT_4 for ≥6 months.
Subjects were excluded if they had coexisting autoimmune disorders (e.g., type 1 diabetes, celiac disease), Hepatic or renal dysfunction, Pregnancy or lactation, Thyroid surgery or radioiodine therapy, Recent use of steroids, immunomodulators, or high-dose iodine supplements, which may alter immune or thyroid function status. These criteria ensured accurate assessment of thyroid autoantibodies without confounding influences.

Data Collection and

Venous blood samples were obtained from all participants in the morning following an overnight fast. Serum was separated by centrifugation and stored at –20 °C until analysis.

Laboratory Measurements

Following clinical evaluation, 5 mL of venous blood was collected in the morning after an overnight fast. All laboratory analyses were performed using standardized, validated commercial kits. Thyroid Function Tests (TFTs) include Serum TSH, free T3 (fT3), and free T4 (fT4) that were measured using a chemiluminescence immunoassay (CLIA, Roche Cobas E411, Germany). Autoimmune Marker Evaluation were carried out using Thyroid-specific autoantibodies including Anti-thyroid peroxidase antibody (Anti-TPOAb) and Anti-thyroglobulin antibody (Anti-TgAb) using a quantitative ELISA technique (M/s Calbiotech, USA).

Statistical Analysis

All data were compiled and analyzed using standard statistical software. Normality of continuous variables was assessed using the Shapiro–Wilk test. Comparisons between hypothyroid and control groups were made using the Independent sample t-test for normally distributed variables and the Mann–Whitney U test for skewed data. Correlation between thyroid antibody titers and biochemical parameters (TSH, fT3, fT4) as well as disease duration was evaluated using Pearson's or Spearman's correlation coefficients as appropriate. Results were expressed as mean ± standard deviation or median with interquartile range. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of **140 subjects** were included in the study, of which **80 were LT_4-treated hypothyroid patients** and **60 were euthyroid controls** (Table 2). There was **no significant difference** in age or sex distribution between the groups (p > 0.05), indicating comparability in demographic characteristics. However, BMI was significantly higher in the hypothyroid group (p = 0.02), suggesting an increased risk of weight gain in treated patients (Table 2). Evaluation of thyroid function showed that LT_4-treated hypothyroid patients continued to exhibit **biochemically higher TSH** levels

compared to controls (median **6.9 vs 2.1 µIU/mL,** $p < 0.001$), along with **significantly lower fT3 and fT4 levels** ($p < 0.001$) (Table 2).

Autoimmune marker assessment revealed **high prevalence of autoimmune thyroiditis** in treated patients, with **65% Anti-TPO positivity** and **47.5% Anti-Tg positivity** compared to negligible levels in controls (Table 4). Furthermore, **dual positivity** was observed in **40%** of treated patients, reinforcing active immune-mediated thyroid destruction. Quantitative antibody levels were markedly higher in treated patients compared to controls (**Anti-TPO: 126.8 ± 84.5 vs 11.4 ± 6.2 IU/mL; Anti-Tg: 63.1 ± 51.7 vs 9.6 ± 4.8 IU/mL,** both $p < 0.001$) (Table 2). Correlation analysis demonstrated a **moderate positive association** between Anti-TPO titers and serum TSH (r = +0.48), and a **negative correlation** with fT4 levels (r = –0.32). Anti-Tg levels showed a positive correlation with disease duration (r = +0.41). Additionally, dual antibody positivity displayed the strongest correlation with elevated TSH (r = +0.52) (Table 2).

Table 1. Baseline Characteristics and thyroid hormone profile in levothyroxine treated Hypothyroidism compared to control

Parameter	Controls (n=60)	LT_4-treated Hypothyroid (n=80)	*p* value
Age (years)	41.2 ± 9.3	42.7 ± 10.1	0.38 (NS)
Sex (M/F)	18/42	22/58	0.84 (NS)
BMI (kg/m²)	24.8 ± 3.9	**27.1 ± 4.5**	**0.02***
TSH (µIU/mL)	2.1 (1.5–3.0)	**6.9 (4.8–10.2)**	**<0.001***
fT3 (pg/mL)	3.22 ± 0.41	**2.71 ± 0.39**	**<0.001***
fT4 (ng/dL)	1.25 ± 0.18	**1.02 ± 0.20**	**<0.001***
Anti-TPO Positive ≥35 IU/mL	2 (3%)	**52 (65%)**	
Anti-Tg Positive ≥40 IU/mL	1 (2%)	**38 (47.5%)**	
Dual Positivity	0	**32 (40%)**	
Anti-TPOAb (IU/mL)	11.4 ± 6.2	**126.8 ± 84.5**	**<0.001***
Anti-TgAb (IU/mL)	9.6 ± 4.8	**63.1 ± 51.7**	**<0.001***

*NS: Not Significant; $p<0.05$ significant. Statistics- Student t test.

Table 2. Correlation Between Autoantibodies & Disease Severity

Correlated Variables	r-value
Anti-TPO vs TSH	+0.48
Anti-TPO vs fT4	–0.32
Anti-Tg vs Disease Duration	+0.41
Dual Positivity vs TSH	+0.52

All correlations significant at $p < 0.01$ correlation by pearson's correlation where r is pearson's correlation coefficient. P value <0.05 were considered statistically significant.

DISCUSSION

Autoimmune hypothyroidism represents a spectrum of thyroid gland destruction mediated by autoreactive immune responses[13]. In the present study, despite patients receiving levothyroxine (LT_4) replacement therapy, a considerable proportion continued to exhibit elevated anti-thyroid antibodies, particularly anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg)[14]. These findings indicate incomplete restoration of euthyroidism despite ongoing LT_4 therapy which could possibly due to immunological aggression against the thyroid gland, aligning with the established pathophysiology of Hashimoto's thyroiditis as a chronic autoimmune disease rather than a reversible endocrine dysfunction[15]. Persistent elevation of autoantibodies in treated patients suggests ongoing, subclinical thyroid damage even when biochemical euthyroidism is achieved. Anti-TPO antibodies correlated strongly with thyroid hormone imbalance, consistent with previous evidence showing their role in blocking thyroid peroxidase enzyme required for iodination and hormone synthesis[16]. Anti-Tg antibodies—which often reflect long-standing inflammatory infiltration and fibrosis—were higher in patients with longer disease duration, highlighting their value as a biomarker of chronicity. These findings collectively indicate that LT_4 restores circulating hormone levels but does not attenuate the underlying autoimmune aggression, a fact supported by multiple longitudinal studies.[17]. Thus, some patients may appear clinically stable while the thyroid continues to deteriorate anatomically and functionally, as autoantibody titers do not normalize with LT_4 therapy. Higher antibody titers found in more severe hormone imbalance groups strengthen the immuno-hormonal association where greater autoimmune aggression leads to greater impairment of hormone synthesis, as

supported by population studies[18]. Existing literature consistently reports anti-TPO positivity in 85–95% of Hashimoto's thyroiditis cases, making it the most sensitive diagnostic biomarker for autoimmune thyroid disease[19]. Anti-Tg positivity is relatively lower (~60–80%) but correlates strongly with relapse risk and treatment-resistant hypothyroidism[20]. This is especially relevant for levothyroxine-treated patients, as persistent autoantibodies predict future thyroid atrophy and need for dose adjustment over time [21]. Studies also show that patients with combined anti-TPO and anti-Tg elevation have higher long-term risk of overt hypothyroidism, illustrating the importance of dual-antibody evaluation rather than relying on anti-TPO alone[22]. The findings of this study highlight the importance of incorporating regular autoantibody testing into the clinical management of autoimmune hypothyroidism, particularly in patients who continue to experience symptoms despite achieving normalized TSH levels on LT_4 therapy. Persistent elevation of thyroid autoantibodies provides valuable prognostic information beyond standard biochemical assessment. High anti-TPO titers indicate a greater likelihood of ongoing autoimmune destruction and an increased need for future LT_4 dose escalation as thyroid reserve declines. Meanwhile, elevated anti-Tg antibodies serve as a marker of chronic inflammation and fibrosis, suggesting a higher risk of relapse and further glandular deterioration over time. When both anti-TPO and anti-Tg antibodies remain elevated, the probability of progression to permanent and more severe hypothyroidism significantly increases, often associated with poorer functional recovery of the thyroid gland. Therefore, integrating antibody monitoring into routine follow-up can support better prediction of disease trajectory, guide timely dose optimization, and improve long-term patient outcomes. Thus, antibody monitoring should complement routine biochemical follow-up rather than being limited to initial diagnosis. Additionally, patients with prolonged elevation may require closer follow-up for associated conditions such as thyroid eye disease or other organ-specific autoimmunity. The prevalence of anti TPO positivity (65%) and anti Tg positivity (47.5%) observed in our study is lower than, but broadly consistent with, published data. According to review sources, anti TPO antibodies are present in over 90% of Hashimoto's thyroiditis patients, while anti Tg antibodies are found in 50–80%.[23] Persistent antibody elevation has been strongly associated with future thyroid atrophy, higher LT_4 dose requirements, progression to overt hypothyroidism, and poorer recovery of thyroid reserve.[24] In particular, dual antibody positivity has been highlighted as a more robust predictor of disease severity than single-antibody elevation, reinforcing the importance of evaluating both antibodies in clinical follow-up. While levothyroxine (LT_4) effectively restores hormonal balance, it has no direct impact on the immunological mechanisms driving autoimmune thyroiditis. Therefore, adjunct therapeutic strategies have gained attention for their role in modulating autoimmunity. Selenium supplementation is among the most studied interventions, owing to its antioxidant and immunoregulatory effects on thyroid tissue. Randomized clinical trials demonstrate that selenium intake, particularly in selenium-deficient individuals, can lead to a 20–30% reduction in anti-TPO antibody titers within 6 months, indicating a meaningful reduction in autoimmune activity[25]. In addition, Vitamin D optimization has been shown to play a critical role in immune tolerance. Vitamin D deficiency is highly prevalent in patients with autoimmune hypothyroidism, and supplementation has been associated with lower anti-thyroid antibody levels and improved inflammatory markers, suggesting suppression of Th1-mediated responses[26]. Dietary modulation is another area of interest, where anti-inflammatory dietary patterns, including omega-3 rich foods, polyphenols, and in some cases, reduced gluten intake, have demonstrated beneficial effects on systemic immune regulation, although the evidence is still evolving. Furthermore, early and adequate LT_4 dose optimization may indirectly contribute to immune control by preventing fluctuations in thyroid hormone levels, as persistently elevated TSH can amplify autoimmune infiltration and inflammation within the thyroid gland[27]. Collectively, these supportive therapies do not eliminate the need for LT_4 replacement but highlight opportunities for a comprehensive management approach targeting both endocrine and immune aspects of the disease. However, these findings should be interpreted cautiously because of several methodological limitations. The cross-sectional design restricts the ability to establish causal relationships, making it unclear whether elevated antibody levels directly contribute to thyroid dysfunction or merely indicate the underlying severity of autoimmune destruction. The relatively modest sample size also limited detailed subgroup analyses between Hashimoto's and non-Hashimoto hypothyroid cases.

Moreover, the study primarily focused on biochemical markers without evaluating clinical symptom burden, thyroid ultrasound characteristics, or patient quality-of-life outcomes, which are essential for comprehensive disease assessment. Variations in the duration and dosage of levothyroxine therapy were not uniformly controlled, reducing the ability to determine how treatment influences the persistence of autoantibodies. These limitations underscore the need for longitudinal studies incorporating imaging modalities such as thyroid ultrasonography and exploring immune-modulating or nutritional interventions to better assess long-term progression or remission. Nevertheless, the persistent elevation of anti-TPO and anti-Tg antibodies in LT_4-treated hypothyroid patients supports the concept of ongoing autoimmune activity in Hashimoto's thyroiditis. Continued antibody monitoring remains clinically relevant, offering insights into disease severity, potential future decline in thyroid function, and the need for tailored therapeutic strategies

aimed at improving both hormonal regulation and immune recovery.

CONCLUSION

In this study, LT_4-treated hypothyroid patients demonstrated a high prevalence of persistent autoimmune activity, reflected by significantly elevated Anti-TPO and Anti-Tg antibody levels compared to euthyroid controls. Despite ongoing hormone replacement therapy, many individuals continued to show biochemical hypothyroidism, indicating incomplete thyroid functional recovery and ongoing immune-mediated glandular destruction. The strong correlation between antibody titers and disease severity highlights their importance in assessing the progression and prognosis of autoimmune thyroid disease. Routine monitoring of thyroid autoantibodies, in conjunction with thyroid hormone profile, may support early identification of patients at risk of persistent or worsening dysfunction and guide timely dose optimization or adjunct therapeutic strategies. Therefore, autoantibody testing should be an integral component of long-term management in autoimmune hypothyroidism to improve clinical outcomes and prevent future complications.

Conflict of interest:

The authors do not have any conflict of interest

Acknowledgement / Declaration of Interest:

We thank the host institute for providing facility to carry out this project.

Authors contribution:

Author contributions Conceptualization: all authors; Data curation: IV, VV; Formal analysis: VV; Methodology, Project administration: VV; Investigation: IV; Software: VV Supervision: VV, SRG; Writing-original draft: VV, IV; Writing-review & editing: VV

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