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# The role of Anti-TPO and IL-10 in progression of Autoimmune Thyroid disorders

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## Abstract

**Background.** Thyroid disorders are prevalent health issues that origin from impaired thyroid hormone production due to factors including inflammation, autoimmune conditions, tumors, or medical interventions. **Aim.** This study aimed to investigate the role of Interleukin-10 (IL-10) and anti-thyroid peroxidase antibodies (Anti-TPO) in the prediction and prognosis of autoimmune thyroid disorders (AITD). **Methods.** In this research, One hundred patients with thyroid disease and fifty healthy controls were included. Thyroid function hormones (TSH, T3, and T4) were assessed using Cobas analyzer. Serum levels of IL-10 and Anti-TPO were measured using the ELISA technique. **Results.** The results of current study demonstrated significantly higher Anti-TPO levels in patients compared to controls ($p<0.001$), suggesting its efficiency may act as indicator for the prognosis of AITD. Although no significant difference in IL-10 levels was observed among groups ($p>0.05$). **Conclusion.** Elevated Anti-TPO serves as a reliable prognostic biomarker for autoimmune thyroid conditions due to their strong association with disease pathophysiology, as confirmed by ROC analysis. Conversely, IL-10 levels lack diagnostic significance for these disorders, potentially because of complex interactions within the inflammatory signaling pathway. The study highlights that further research is warranted to elucidate the potential role of IL-10 in the pathophysiology of thyroid disorders, particularly in the context of chronic inflammation.

**Keywords:** Thyroid Disorders, Anti-TPO, IL-10, autoimmune thyroid disease.

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## Introduction

The fundamental endocrine glands that collectively make up the well-established endocrine system are the pituitary, adrenal, parathyroid, thyroid, pancreas, and gonads (1). Thyroid-stimulating hormone (TSH) is produced by the thyroid and is regulated by the pituitary gland. The thyroid gland receives instructions from TSH to produce and release a suitable quantity of hormone (2). The thyroid produces three hormones that are important for regulating body temperature, energy production, weight, hair and nail growth, and menstrual cycle maintenance. The feedback mechanism controls the manufacturing of these hormones (3). Thyroid dysfunction ranks among the most prevalent endocrine conditions in the globe. Patients' sexual health and function as well as quality of life, are known to be affected by thyroid diseases (4). Thyroid dysfunction can show up as either hypothyroidism or hyperthyroidism which can have a significant impact on a person's general

health (5). Thyroid dysfunction is caused by both genetic and environmental factors (6).

Thyroid hormones (T3 and T4) are produced with the help of iodine. As a result, a lack of iodine causes a decrease in T3 and T4 synthesis, resulting in hypothyroidism. High iodine intakes cause an increase in the rate of T3 and T4 production leading to hyperthyroidism (7). Thyroid dysfunction is prevalent in females more than in males and can range from inflammatory lesions to neoplastic tumors (8). About 40% of people worldwide have a thyroid problem (9). While2-5% of people have autoimmune thyroid disease (AID) (8).

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are prevalent autoimmune thyroid gland illnesses that cause hypothyroidism and hyperthyroidism, respectively (10). The autoantibodies against thyroid peroxidase and thyroglobulin that are present in Hashimoto's thyroiditis set it apart, while Graves' disease has been linked to autoantibodies against the TSH receptor. The environment, epigenetic modifications, and a multitude of susceptibility genes all play a role in the two diseases' pathogenesis (11). The presence of antibodies (anti-TPO, anti-Tg, and anti-TSHR) that target the thyroid self-antigens as well as autoreactive T and B lymphocyte infiltrates within the thyroid can directly establish that autoimmune reactions occur in both GD and HT (12). Immune system-produced antibodies are similar to antibodies that are produced against viruses and bacteria, but instead of attacking outside invaders, autoantibodies attack the body itself, Anti-TPO antibodies are a type of autoantibody (13). Autoimmune antibodies prevent TPO from using iodine which causes hypothyroidism, a disorder in which the thyroid does not produce enough hormones, as well as inflammation, which can ultimately lead to the destruction of all or part of the thyroid gland. It may also develop nodules or become enlarged as a result of the inflammation (14).

A cytokine with potent anti-inflammatory activity and immunosuppressive properties. The IL-10, played a main role in the immunomodulatory actions that suppress the development of autoimmune hyperthyroidism disease (15). The pleiotropic cytokine IL-10 is essential for controlling inflammation and preserving cell homeostasis. Its main function is that of an anti-inflammatory cytokine, protecting the body from an unchecked immunological response, primarily via the signaling pathways of Jak1/Tyk2 and STAT3 (16). This study intended to quantify the levels of anti-thyroid peroxidase antibodies (Anti-TPO) and the anti-inflammatory cytokine interleukin-10 (IL-10), as well as the thyroid hormones triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH), in a representative sample of patients with thyroid disorders in the Iraqi population.

**Ethical Approval**

Before enrollment, all participants provided written informed consent, and the study protocol was approved by the Congress of the Institute of Genetic Engineering and Biotechnology at the University of Baghdad (Ref no. 4011 on 21/11/2023). Additionally, necessary approvals were obtained from the collaborating centers, hospitals, and laboratories.

**Subjects**

A case-control study included two groups: 50 healthy individuals (Control Group) randomly selected from hospital visitors, and 100 individuals (Patient Group) diagnosed with AITD based on standard laboratory tests (TSH, T3, and T4 levels) including both hypothyroidism (Hashimoto's Thyroiditis) with high TSH level along with low level of both T3 and T4 or hyperthyroidism (Graves' Disease) with low TSH and high level of T3 and T4. Patients were recruited from the National Diabetes Center, Mustansiriyah University, and Al-Yarmouk Teaching Hospital in Baghdad. The duration of the study was extended from November, 2023 until March, 2024. Pregnant women, women using hormonal contraceptives, individuals with a history of thyroidectomy, those with liver or kidney disease, and individuals currently using biotin were excluded from the study.

**Methods**

**Biochemical examination**

The Cobas E411 system employs automated technology for accurate thyroid hormone (TSH, T3, and T4) analysis. The TSH hormone measured according to the sandwich principle is utilized, where a biotinylated antibody and a ruthenium-labeled antibody bind to different sites on the TSH antigen. The captured complex emits light upon electrical stimulation, and the light intensity directly correlates with the TSH concentration in the sample. While competitive principle is applied to evaluate T3 and T4 where a ruthenium-labeled antibody competes with the target hormone (T3 or T4) for binding sites. The remaining unbound antibody is captured, and its emitted light intensity inversely reflects the hormone concentration in the sample.

**IL-10 Serum Level Measurement**

Serum IL-10 levels were measured using a sandwich ELISA kit (Innova Biotech, China; cat no.In-Hu2131). This technique involves capturing IL-10 in the sample with specific antibodies, followed by the addition of HRP-conjugated antibodies. After incubation and washing, a colorimetric reaction is catalyzed by HRP, and the resulting absorbance at 450 nm is directly proportional to the IL-10 concentration in the sample.IL-10 level was finally measured in pg/ml.

**Anti-thyroid peroxidase antibodies (Anti-TPO)**

Anti-TPO antibody levels were assessed using an indirect ELISA (Demeditec company, Germany. Cat no.DE7580). The assay utilized TPO-coated microplates to capture patient antibodies. Following incubation and washing steps, enzyme-conjugated secondary antibodies were added to bind to the captured patient antibodies. A subsequent enzymatic reaction generated a colored product, the intensity of which, measured at 450 nm, was proportional to the concentration of anti-TPO antibodies. The TPO-Ab serum level was measured in IU/ml.

**Statistical Analysis**

Data were analyzed using SPSS version 26. Descriptive statistics (mean ± SD) were calculated. Normality was assessed with the Shapiro-Wilk test. Independent t-tests were used to compare groups. Receiver Operating Characteristic (ROC) Curves were employed for Study parameters. Pearson correlation used that evaluate the strength and direction of the linear relationship between two continuous

variables. Statistical significance was determined at $p < 0.05$.

## Results

### 1. Demographic Characterized

Table (1) presents the age distribution of participants in a study, comparing a group of patients with a control group. There's a slight difference in the proportion of patients (17%) and controls (28%) in (20-30) age group, but it's not statistically significant (NS). The age group category (31-41) has the highest proportion of patients (37%) compared to controls (30%). Furthermore, 26% and 17% among age group 42-52 were enrolled.

The higher proportion of patients (29%) compared to controls (16%) among the (54-60) age group. This observation suggests a potential association between older age and thyroid disorders. The mean age of patients (43.54) is slightly higher than that of controls (39.02) but without significant difference (P-value =0.07). Table (1) shows the result.

**Table (1): Comparison between patients and control groups in Age.**

| Age groups | Groups | | P- value |
|---|---|---|---|
| | Patients (100) % | Control (50) % | |
| **20-30** | 17 (17%) | 14 (28%) | 0.07 NS |
| **31-41** | 37 (37%) | 15 (30%) | |
| **42-52** | 17 (17%) | 13 (26%) | |
| **54-60** | 29 (29%) | 8 (16%) | |
| **Mean ± SD** | 43.54 ± 13.69 | 39.02 ± 10.89 | |

*NS: Non-significant, SD: Standard deviation

Table (2) presents data on the distribution of Body Mass Index (BMI) categories among patients and the control group. The categories of BMI are as follows: A BMI of 18.5 to 24.9 is in the healthy weight range, a BMI of 25 to 29.9 is in the overweight range and a BMI of 30 or more is in the obese range. The P-value was (0.1) this indicates that the observed differences in BMI distribution between the Patients and Control groups are not statistically significant.

**Table (2): Comparison between patients and control groups in BMI.**

| BMI | Groups | | P-value |
|---|---|---|---|
| | Patients (100) | Control (50) | |
| **18.5 – 24.9** | 30 (30%) | 12 (24%) | 0.1 NS |
| **25 -29.9** | 28 (28%) | 26 (52%) | |
| **> 30** | 42 (42%) | 12 (24%) | |
| **Mean ± SD** | 28.86 ± **6.97** | 27.08 ± **4.49** | |

### 2. Thyroid function test

Biochemical analysis of thyroid hormones (Table3) indicated no significant differences in T4 ($p = 0.1$) and T3 ($p = 0.3$) levels between patients and healthy individuals. In contrast, TSH levels were significantly elevated in patients compared to healthy controls ($p = 0.001$). The mean TSH level was 5.66 ± 0.66 in patients and 2.08 ± 0.17 in healthy individuals.

**Table (3): Serum T3, T4, and TSH among studied groups.**

| Groups | Mean ± SE | | P-value |
|---|---|---|---|
| | Patients | Control | |
| T4 | 73.55 ± 5.82 | 61.63 ± 5.36 | 0.1 NS |
| T3 | 1.85 ± 0.20 | 1.68 ± 0.05 | 0.3 NS |
| TSH | 5.66 ± 0.66 | 2.08 ± 0.17 | 0.001** |

## 3. Anti- TPO serum Level

The analysis revealed a significant elevation in mean levels of anti-thyroid peroxidase (Anti-TPO) antibodies among patients with thyroid disorders compared to the healthy control group. The mean Anti-TPO level in the patient group was 1608.58 ± 1292.83 IU/mL, while in the control group, it was 587.73 ± 540.42 IU/mL (p-value = 0.0001). This substantial and statistically significant difference indicates a robust autoimmune response against the thyroid gland in patients, supporting a diagnosis of autoimmune thyroid diseases such as Hashimoto's thyroiditis. (Table 4 and Figure 1) display the result.

**Table (4): Serum Anti-TPO levels among studied groups.**

| Parameters | Group | Mean | Std. Deviation | Std. Error Mean | P-value |
|---|---|---|---|---|---|
| Anti-TPO (IU/mL) | patients | 1608.585 | 1292.83 | 184.69 | < 0.001** |
| | control | 587.733 | 540.42 | 108.08 | |

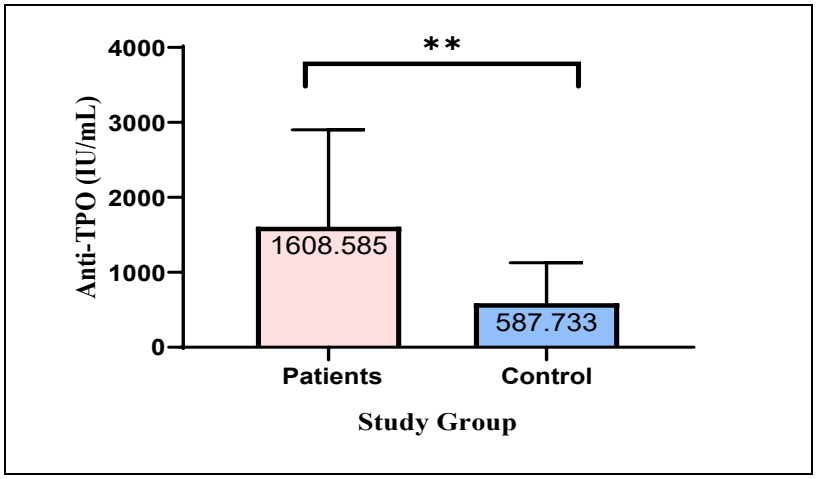


**Figure (1): Difference in Mean and SD among study groups in Anti-TPO level.**

The marked elevation of Anti-TPO antibody levels strongly supports the presence of an active autoimmune response directed against thyroid tissue in individuals with autoimmune thyroid disorders. These findings underscore the diagnostic significance of anti-TPO levels in identifying these conditions including inflammation, damage and cytokine production that increased immune response against thyroid gland.

## 4. IL-10 Serum Level

The study results demonstrated no statistically significant difference in mean levels of the anti-inflammatory

cytokine IL-10 between the group of patients with thyroid disorders and the healthy control group. The mean IL-10 level in the patient group was 34.85 ± 14.78, while in the control group, it was 36.78 ± 17.28 (p-value = 0.5) as shown in (Table 5 and Figure 2).

**Table (5): Serum IL-10 levels among studied groups.**

| Parameters | Group | Mean | Std. Deviation | Std. Error Mean | P-value |
|---|---|---|---|---|---|
| IL-10 (pg/ml) | Patients | 34.848 | 14.78 | 2.09 | 0.5 N.S |
| | Control | 36.777 | 17.28 | 2.44 | |

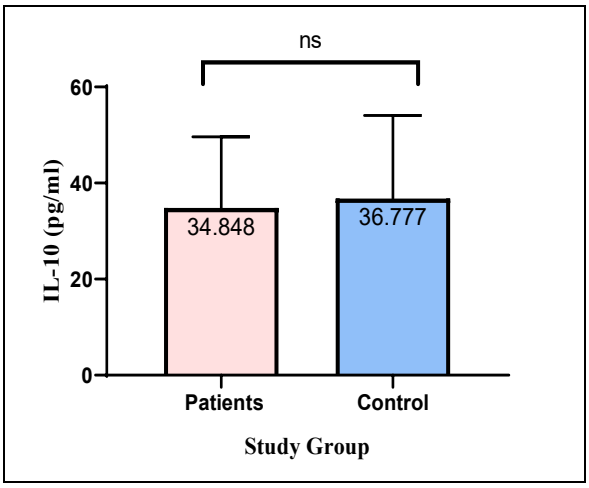


**Figure (2): Difference in Mean and SD among study groups in IL-10 level.**

The high standard deviation (SD) in both groups indicates substantial variability in IL-10 levels among individuals within each group, suggesting that factors other than thyroid disorders may influence the production of this cytokine. Although the p-value greater than 0.05 indicates that the observed difference between the groups is not large enough to be attributed to chance, we cannot reject the null hypothesis that there is no true difference between the groups. These findings suggest that there is no strong evidence of a direct relationship between thyroid disorders and increased or decreased IL-10 production. Other factors, such as disease severity, treatment type, or genetic factors, may influence IL-10 levels in patients with thyroid disorders. Further studies are needed to confirm these findings and to investigate the potential influence of additional variables on IL-10 levels.

## 5. ROC Curve of Anti-TPO

A receiver operating characteristics curve analysis (17) of anti-TPO demonstrated that area under the curve (0.766) with a high significant p-value (<0.001**). The best cut-off value was (450.67) with 78% sensitivity and 72% specificity which may indicate the used anti-TPO as a biomarker for prognosis, diagnosis, and target thyroid disorder. (Table 6 and Figure 3) illustrate the result.

**Table (6): Receiver operating characteristics curve of anti-TPO.**

| Area | Explanation | P- value | Cut off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| 0.766 | Good | <0.001** | 450.67 | 78% | 72% |

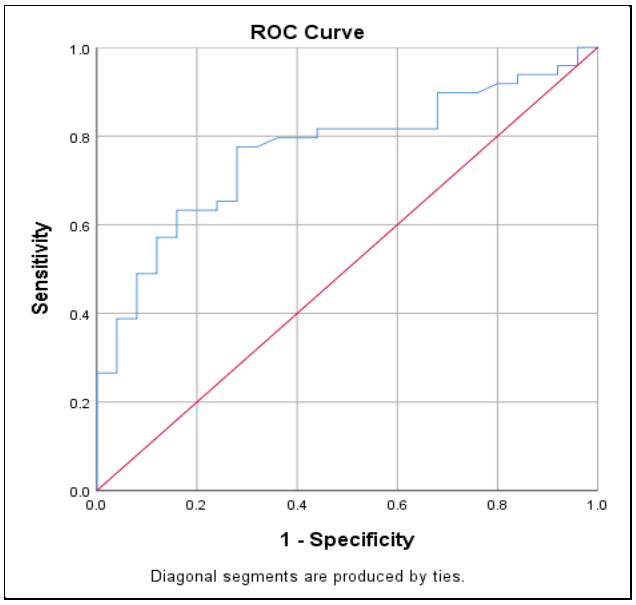


**Figure (3): Receiver operating characteristics curve of anti-TPO.**

## Discussion

Antibodies such as anti-thyroid peroxidase (TPO) are commonly detected in patients with autoimmune thyroid disorders, the current study detected a high level of anti-TPO in patients group level compared to healthy one. This result consisted of a previous retrospective study that involved 141 Graves' disease (GD) patients in Basrah and found that 58.9% of patients tested positive for anti-TPO antibodies. Additionally, a "giraffe appearance" on thyroid ultrasonography was more prevalent in the anti-TPO positive group (87.0% vs. 13.0%; p=0.005) (18). Another study similar to the result of the current investigation done by (19) revealed highly significant differences in these markers between the hypothyroid patient group and the control group furthermore, demonstrated that immunological markers, particularly anti-TPO protein levels, in hypothyroid individuals have been found to assist in diagnosis and predict clinical outcomes, indicating an increased risk of overt hypothyroidism in adults.

A previous study, which was not directly comparable to this study, aimed to assess thyroid hormone levels and the prevalence of anti-TPO antibodies in Iranian female breast cancer patients compared to a control group. The results showed no statistically significant difference in serum anti-TPO levels between the breast cancer patients and the control group (p-value: 0.184). While no significant difference was found in T3 levels (p-value: 0.177), significant differences were observed in T4 and TSH levels between the two groups (p-value: 0.034 and <0.001, respectively) (20). Another study in Gorgan, Iran, evaluated the prevalence of anti-TPO antibodies among women with polycystic ovary syndrome (PCOS), celiac disease (CD), men with hepatitis C, and matched controls. Results showed significantly higher anti-TPO positivity in PCOS patients compared to controls (18.4% vs. 0%; p = 0.000). No significant difference was found between CD patients and controls (26.9% vs. 21.1%; p = 0.413). The control group had a higher incidence of anti-TPO positivity compared to hepatitis C patients (25% vs. 10%; p =

0.031). Overall, high anti-TPO antibody levels were observed in both patients and healthy individuals, highlighting the need for autoimmune disorder screening in the region (21). Previous studies have reported findings consistent with this research. For example, Zha *et al.* investigated immune dysregulation in patients with Graves' disease. Using the ELISA technique to measure TPO antibodies, they observed elevated TPO antibody levels. Their results indicated an association between elevated TPO antibody production and compromised regulatory function of (CD19+CD24hiCD27+ B cells), highlighting the role of compromised immune regulation in provoking thyroid autoimmunity (22).

This study provides evidence for autoimmune-mediated thyroid disorders, characterized by the disruption of thyroid hormone production. Significantly elevated TPO antibody levels were observed in patients with thyroid disease, establishing their clinical effectiveness as a diagnostic biomarker. The diagnostic accuracy of the anti-TPO assay was validated through ROC curve analysis, demonstrating high sensitivity and specificity. These findings underscore the importance of anti-TPO testing in clinical studies for the early detection and management of thyroid diseases.

The association between anti-TPO and cytokine production is complex and indicates a significant role for anti-TPO in the inflammatory processes associated with AITD (23). The observed correlation between elevated anti-TPO titers and increased pro-inflammatory cytokine levels highlights the clinical significance of monitoring anti-TPO in Hashimoto's thyroiditis, as this relationship is pivotal for developing effective management strategies aimed at mitigating the inflammatory process and preventing progressive thyroid damage (24).

The research elucidates a statistically significant positive correlation between elevated ATPO titers, exceeding 1000 U/ml, and a concomitant increase in the frequency of T lymphocytes expressing Th1/Tc1 cytokines, notably interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), within a cohort of individuals diagnosed with Hashimoto's thyroiditis. These observed elevations in cytokine expression, indicative of a pronounced pro-inflammatory milieu, are posited to contribute to the pathophysiological mechanisms underlying thyroid follicular cell damage and subsequent cellular demise (25).

A multifunctional cytokine with immunosuppressive and antiangiogenic properties is IL-10, singing assorted functions in the etiology and progression of cancer (26).

Considering the cells that express IL-10 are distributed differently throughout tissue compartments and under different stimulation conditions, it is still unknown which mechanisms underlie its receptor- and cell-type-specific production. Furthermore, it suggests that inherited determinants affect the patterns of human IL-10 expression, leading to variations in its expression and increased susceptibility to disease (27).

The current study found no significant difference in IL-10 levels between thyroid disorder patients and healthy controls. This may be attributed to the complex factors influencing regulatory B cell function. These factors can potentially inhibit cytokine activity or suppress cytokine production. Previous research has demonstrated that other cytokines, such as (IFN-γ), produced by T lymphocytes and natural

killer cells, can suppress IL-10 release from regulatory B cells. Additionally, regulatory B cells may develop resistance to IL-10 by increasing IFN-γ excretion; thereby reducing the efficiency of IL-10 (28).

According to the current investigation, the lack of statistically significant differences in IL-10 serum levels between patients and healthy controls among the Iraqi population suggests a limited role for this cytokine in the pathogenesis of autoimmune-related thyroid disorders. Even though the impact of treatment-related medications on IL-10 levels cannot be completely controlled and the inflammatory response that may interact with the IL-10 signaling pathway, further research is needed to investigate this possibility and explore the correlation between this cytokine and specific medications used in thyroid disease management. Moreover, larger studies are required to validate these findings and examine the molecular mechanisms underlying the function of IL-10 in thyroid disorders.

## Conclusion

This study highlights autoimmune-related thyroid disorders and the important role of the immune system in compromising thyroid function. Elevated TPO antibody levels in patients, confirmed by ROC analysis and revealed to be used as a reliable prognostic biomarker, were strongly associated with the pathophysiology of autoimmune thyroid conditions. In contrast, IL-10 levels did not significantly differ between the study groups, suggesting a limited role in the diagnosis and pathophysiology of these disorders and may be due to the inflammatory response that interacts with the IL-10 signaling pathway. These findings emphasize the importance of anti-TPO antibody testing for the early detection of thyroid diseases and improved patient outcomes. Future studies with larger sample sizes are recommended to investigate the potential role of IL-10 in refining diagnostic and therapeutic approaches for thyroid disorders.

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