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# Pathogenesis of Autoimmune Thyroid Disease (AITD) in Type 1 Diabetes: The Role of Autoantibodies (anti-TPO and anti-TG) and Cytokines (IL-10, IL-6, and TNF-α)

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**Abstract**:

Objectives: Diabetes mellitus type 1 (T1DM), which is also an autoimmune disorder, can coexist alongside other types of autoimmune diseases. This study aimed to investigate the possibility of a subclinical association between diabetes disease and autoimmune thyroid dysfunction. The clinical condition of the patient and their approach to managing their diabetes were specifically considered when deciding whether or not the patient had autoantibodies.

Methods: This study included sixty individuals who were diagnosed with diabetes type 1. (thirty males and thirty women, with a mean age of 21.04 years) and 30 healthy controls (12 males and 18 females).

Results: Diabetics had considerably greater serum IL-10, IL-6, and TNF-α levels than healthy controls. Stepwise regression indicated significant positive correlations between IL-10, IL-6, and TNF-α with these antibodies and strong inversed relationships between IL-6 and Anti-TPO, Anti-TG, antibodies.

. No matter if the antibodies were present or how severe they were, this held true. The study's findings lend credence to the idea that people with type 1 diabetes should have their thyroid antibodies and function checked.

Conclusions: Thyroid antibodies were most common among type 1 diabetics aged 21–35, according to our study (Anti-TPO and Anti-TG). IL-10, IL-6, and TNF-α levels in diabetic patients and controls were significantly different (P<0.01). IL-10, TNF-α, HbA1C, and body mass index positively correlated with thyroid antibodies, except for IL-6. Thyroid antibodies and functional abnormalities should be tested often in type 1 diabetics due to the high occurrence of thyroid autoimmune illnesses.

## INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune illness that has been recognized for over 30 years(1). Autoantibodies targeting beta-cell components and endogenous insulin are hallmarks of this condition, which also involves the self-destruction of pancreatic beta cells (2). Both insulin and thyroid hormones play a role in the metabolism of cells, and changes in either can perturb or impair the other's operation (3). It is estimated that between 8.2% and 9.8% of people in the general population have thyroid disorders (4). Furthermore, autoimmune conditions including autoimmune thyroiditis and autoimmune adrenal insufficiency are more common in people with type 1 diabetes, and the emergence of any of these conditions can have a significant impact on how diabetic patients are treated (5). According to information from the National Institute of gastrointestinal, diabetes, and kidney disorders, one out of every 400 to 600 kids and teenagers would be given a diabetes diagnosis in 2005. By 2025, there will be 300 million diabetic patients globally, up from the anticipated 124 million in 1997, according to the World Health Organization (6, 7).

The thyroid gland is a prominent site of damage caused by autoimmune disorders (8). The two most prevalent types of autoimmune thyroid disease (AITD), which is an immunological reaction to the thyroid brought on by an immune system dysfunction, are Graves disease (9) and Hashimoto thyroiditis (HT)(10). Some studies have suggested that thyroid dysfunction increases the severity

of diabetes in T1DM when it coexists with ATD; however, other investigations have not confirmed this association (11).

Two of the most frequent thyroid autoantibodies, thyroglobulin antibody (TG-Ab) and thyroid peroxidase antibody (TPO-Ab), have been linked to the development of allergic rhinitis, chronic spontaneous urticarial, atopic dermatitis, as well as Grave's disease and Hashimoto thyroiditis (HT)(12, 13). This study investigated how proinflammatory cytokines (IL-6, IL-10, and TNF-α) and thyroid autoimmune disease antibodies affect Type-1 DM in Iraqi patients.

## METHODS

### *Patients and Sampling*

A case-control study data collecting taking place between May 1 and October 15, 2022, a case-control study involving 60 patients with type 1 diabetes (30 males and 30 females) and 30 healthy controls (12 males and 18 females) was performed.

A vein puncture was used to obtain five millilitres of blood, which was divided into two tubes for the HbA1C test and the gel tube centrifugation. The sera were then kept at -80 degrees Celsius for biochemical and immunological analysis.

### *Exclusion Criteria*

Patients with other autoimmune diseases, severe systemic illnesses, malignancies, and other autoimmune problems such as psoriasis, Behçet's disease, and bullous diseases that significantly reduce the quality of life were eliminated. Patients who had received immunological preparations during the preceding three months and were pregnant or were nursing were also excluded.

### *Ethics*

Each patient signed an informed consent form before the trial. Age, sex, medical and pharmaceutical histories, and other demographic information about the patients were recorded.

### *Measurement of target factors*

*Measurement of Blood glucose*

The enzymatic colorimetric method, which was used to assess the glucose level in the venous blood, made use of Randox diagnostic tools (14). In the presence of glucose oxidase, glucose is measured after it has undergone an enzymatic oxidation reaction. A red-violet quinone imine dye is created when the peroxidase-catalyzed hydrogen peroxide produced is combined with the phenol and 4-aminophenazone. The test tube was then filled with ten microliters of serum and 1000µl of the working solution. After being incubated for ten minutes at 37oc, the absorbance was measured at 500 nm.

*Measurement of Hemoglobin A1c test (HbA1C)*

The Cobbas C411 in vitro diagnostic test device quantified total and mmol/mol hemoglobin A1c by a photometric transmission measurement. Diluted blood was mixed with TRIS buffer to extract hemoglobin from erythrocytes. Materials were mixed with sodium lauryl sulfate in a reaction chamber (SLS). SLS created SLShemoglobin. SLS hemoglobin complex measurements at 525 nm were used to determine total hemoglobin concentration. HbA1C from another sample was denatured using potassium ferricyanide and sucrose laurate. The latex particle's HbA1C antibody binds to denatured HbA1C. Synthetic antigen and HbA1C antibody react to suppress latex agglutination. HbA1C concentration was measured by latex agglutination inhibition response at 625 nm. The HbA1C percentage was calculated by dividing the concentration by the total amount.

*Measurement of IL-10, IL-6 and TNF-α by ELISA*

40µl of sample dilution buffer and 10µl of the sample (dilution factor is 5) were added to the sample wells. Samples were loaded onto the microplate's bottom without touching the side walls. The membrane of the closure plate was sealed, well mixed, and lightly shaken followed by a 30-minute incubation period at 37ºc.

The extremely concentrated washing buffer was diluted with distilled water to get the desired consistency (30 times for 96T and 20 times for 48T). The plate was completed after the closure of the plate membrane was carefully peeled off, the membrane was aspirated, and the plate was then refilled with wash solution. The washing solution was diluted after it had been allowed to sit for a thirty-second interval. The washing procedure was repeated five times before adding 50µl of HRP-conjugate reagent to each well (except for the well that served as a blank control). This was followed by incubation as described in Step 3 and washing as described in Step 5. In the course of the coloring procedure, each well was supplied with an additional 50µl of chromogen solution A and another 50µl of chromogen solution B. After gently shaking the wells, the solutions were incubated for 15 minutes at 37°c. Avoiding light while coloring solutions. Each well-received 50µl of stop solution to terminate the reaction. The process ended. The well water suddenly changed from blue to yellow. After 15 minutes, the experiment was terminated by the stop solution, and the absorbance density was determined at 450nm.

*Measurement of Anti-TPO and TG-Antibodies by ELISA*

After adding biotin in the same volume, all wells received 50µl of the patient's diluted serum and the

standards. After 30 minutes of incubation at 20–32ºc, the wells were washed three times with 300 millilitres of washing buffer (diluted 1:50). The plates were incubated at 20-32ºc for 30 minutes and 100µl of the conjugate added to each well before being washed: Then, 100µl of TMB was added to each well, and they were all incubated for 30 minutes at 20-90ºc. The final step was adding 100µl of stop solution to each well and measuring its absorbance at 450 nm.

## STATISTICAL ANALYSIS

An analysis using a t-test was carried out on the data (15). To investigate the connections between the variables, non-parametric Spearman correlation coefficients were utilized. We decided to use a significance level of $P<0.05$ as our cutoff for statistical significance. The mean and standard deviation of the numbers are displayed here.

## RESULTS

*Characteristics of T1DM patients on a general and laboratory level*

Table 1 presents the characteristics of patients with type 1 diabetes. According to the data, there were 30 patients with type 1 diabetes mellitus for each gender. Even though men's average age was 10.83 and women's average age was 9.82, the average age of the entire patient group was 10.35 and 10.34 years, respectively. Table 1 also reveals that all of the patients had an average body mass index (BMI) of 21.0 kg/m2, with males having a BMI of 20.49 kg/m2, women having a BMI of 21.55 kg/m2, and kids having a BMI of 2.89 kg/m2.

*The measure of HbA1C, BMI and random blood sugar in T1DM patients*

In Table 2, type 1 diabetes patients with anti-TPO antibodies differ significantly from the control group in HbA1C, BMI, and random blood sugar levels. Different HbA1c and irrational blood sugar levels were seen among patients with type 1 diabetes who had anti-TPO antibodies (see Table 2).

*Anti-TPO antibody prevalence in T1DM patients*

Based on the data in Table 3, only 2 (3.3%) of persons with type 1 diabetes had anti-TPO positive antibodies, while 58 (96.6%) had anti-TPO negative antibodies. The absence of the antibody in the control group was statistically distinct from the presence of the antibody in the patients group ($P<0.001$).

*Assessment of IL-10 in control and T1DM patients*

The control group had higher serum IL-10 levels than the T1DM patients ($P<0.0001$). Although both groups had IL-10 levels in the normal range (4.8-9.8 pg/Ml), the T1DM group had considerably higher levels (Mean SD: 5.082.81±1.9050.77)(Figure 1A).

*Assessment of IL-6 in control and T1DM patients*

The control and T1DM patient groups had

**Table 1.** Characteristics of type 1 diabetics participated in the studyy

| variable | Age years ( mean ± SD ) | BMI (kg.m$^{-2}$) |
|---|---|---|
| **Female (30)** | 9.82±12.62 | 21.55±2.72 |
| **Male (30)** | 10.83±7.81 | 20.49±2.89 |
| **Total (60)** | 10.35±10.34 | 21.0±2.84 |

**Table 2.** Comparison of diabetic individuals› HbA1C, BMI, and blood glucose levels based on whether or not they had positive or negative levels of anti-TPO antibody.

| Parameter | Patients with positive anti-TPO Ab | Patients with negative anti-TPO Ab | Control group |
|---|---|---|---|
| **HbA$_1$C (%) (mean±SD)** | 8.4±0.7 | 1.44±6.43 | 5.02±0.09 |
| **BMI( kg/m2) (mean±SD)** | 18.55±0.77 | 21.09±2.82 | 22.67±2.80 |
| **Random blood sugar (g/dl) (mean±SD)** | 319±57.98 | 324.9±90.72 | 100±0.0 |

**Table 3.** Percentage and number of diabetes patients having a positive and negative level of Anti-TPO Antibody.

| Case | Anti TPO Ab positive Number (%) | Anti TPO Ab negative Number (%) | Statistical significance (*P*-value) |
|---|---|---|---|
| **Type1 diabetic patient (n=60)** | 2 (3.3%) | 58 (96.6%) | < 0.001 |
| **Healthy Control (n=25)** | 0 (0%) | 30 (100%) | |

significantly different serum IL-6 concentrations (P<0.0001). Compared to the healthy control group, the T1DM group exhibited considerably higher serum IL-6 levels (Figure 1B).

*Assessment of TNF-α in control and T1DM patients*

Statistical analysis showed a highly significant difference in TNF-α levels (P<0.0001) between the control group and the group of patients with type 1 diabetes. In contrast to the healthy individuals who served as the control group, those with type 1 diabetes had serum TNF-α much higher levels (Figure 1C).

*Assessment of Anti-TPO Antibody in control and T1DM patients*

Figure 2A demonstrates a substantial difference in serum anti-TPO antibody concentrations (P<0.0001) between the Control group and the T1DM patient group. Patients with type 1 diabetes had significantly more serum anti-TPO antibodies than the healthy control group.

*Assessment of Anti-TG Antibody in control and T1DM patients*

The levels of anti-TG antibodies in the serum of the control group and T1DM group were noticeably different (P<0.0001) from one another. Anti-TG antibodies were found in higher concentrations in type 1 diabetic patients than in healthy controls (Figure 2B).

Figure 2. A. Anti-TPO antibody levels in the sera of type 1 diabetic patients compared to healthy controls. B. Anti-TG antibody concentrations in the sera of type 1 diabetic patients compared with those of healthy controls.

*Correlation of anti-TPO Ab with IL-10, IL-6 and TNF-α*

According to the obtained results, there was a positive correlation between anti-TPO Ab and (IL-6, IL-10 and TNF-α) in T1DM patients (Figures 3A, B and C).

*Correlation of anti-TPO Ab with IL-10, IL-6 and TNF-α*

According to the obtained results, there was a positive correlation between anti-TPO Ab and (IL-6, IL-10 and TNF-α) in T1DM patients.

## DISCUSSION

It is estimated that the number of people diagnosed with type 1 diabetes mellitus has increased by between

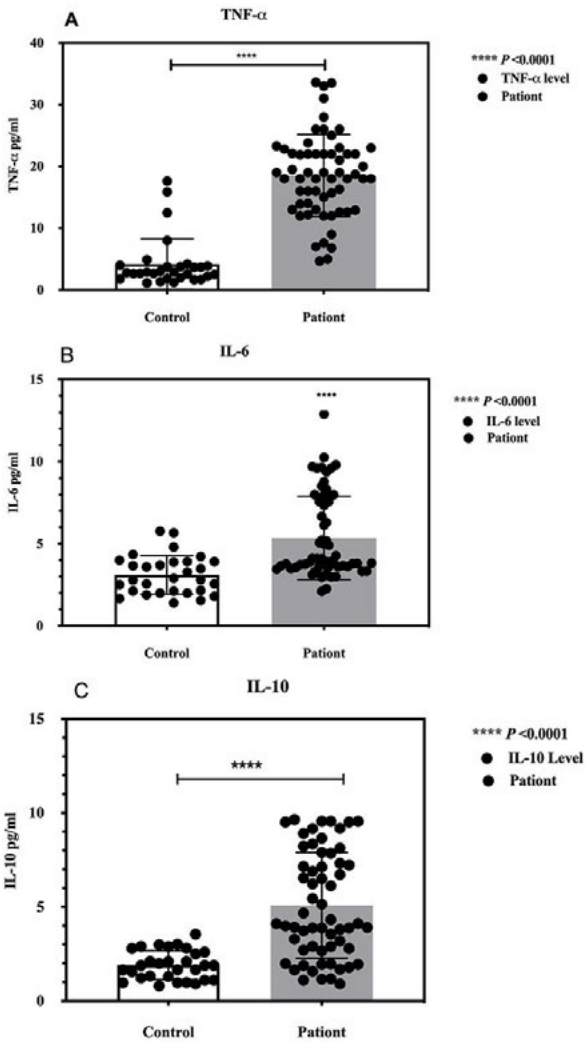


**Fig1.** A. Serum IL-6 levels in type 1 diabetics versus healthy controls. B. Serum IL-10 levels in type 1 diabetics and healthy controls. C. Serum TNF-a levels in type 1 diabetic patients and healthy controls.

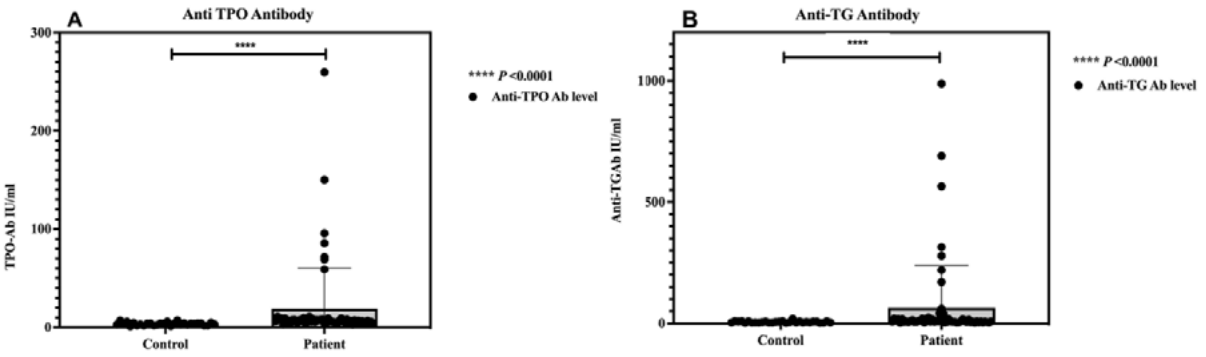


**Fig 2.** A. Anti-TPO antibody levels in the sera of type 1 diabetic patients compared to healthy controls. B. Anti-TG antibody concentrations in the sera of type 1 diabetic patients compared with those of healthy controls.

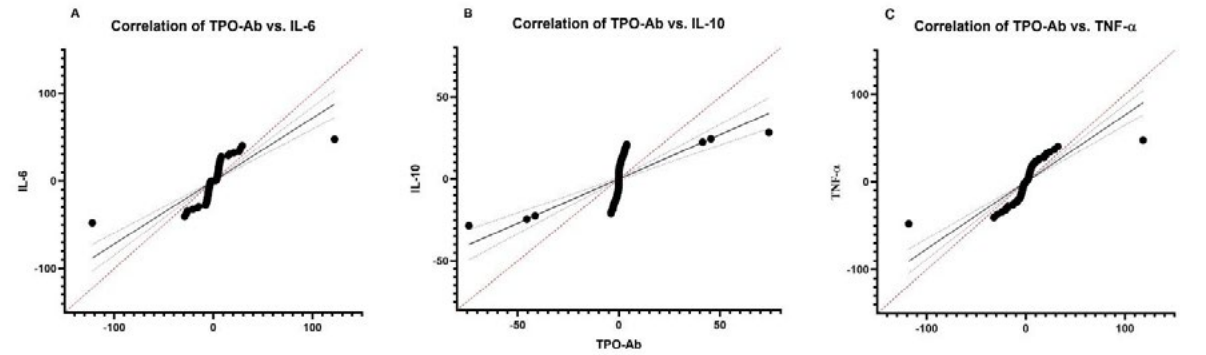


**Fig3.** A. Scatter plot depicting the participants› levels of anti-TPO Ab and IL-6 illustrates the link between the two. There is a close relationship between anti-TPO Ab and IL-6 (r = 1.00, P< 0.0001, positive association). B. Scatter plot showing the association between the levels of TG-Ab and IL-10 in the subjects. There is a positive association between anti-TPO Ab and IL-10 (r = 1.00, P< 0.0001, significant positive correlation). C. Scatter Plot showing the Correlation between anti-TPO Ab and TNF-α among the Subjects. anti-TPO Ab positively correlates with TNF-α (P<0.0001, r=1.00). (TPO-Ab: IU/mL, IL-6: pg/mLand TNF-α: pg/mL).

3% and 5% every year over the previous few decades. Predictions indicate that this pattern will be maintained (16). T1DM is assumed to be predominantly brought on by the autoimmune death of beta cells in the vast majority of individuals (17).

Changes in thyroid hormone levels are another potential complication of diabetes(18). Diabetic individuals who also suffer from thyroid issues sometimes struggle to maintain stable blood sugar levels (19). Both hypothyroidism and hyperthyroidism have negative effects on glucose tolerance and glucose management in diabetic individuals, however, hypothyroidism can reduce insulin requirements (20). Due to decreased gluconeogenesis and liver glucose excretion, hidden hypothyroidism causes recurrent hypoglycemia crises. Hyperglycemia occurs in hyperthyroidism due to increased glucose absorption and glycogenolysis (21).

There is a higher risk for autoimmune hypothyroidism and hyperthyroidism, and 17% to 30% of people with type 1 diabetes also have AITD (22).anti-TPO and anti-TG antibody levels are considered to be indicators of autoimmune thyroiditis(23). Evaluating these antibodies in distinct populations of adult patients with type 1 diabetes was the aim of our research(24).

Sixty type 1 diabetics without thyroid issues were enrolled in this trial. The study included 30 men and 30 women. Blood samples were collected from all subjects to check for the presence of pro and anti-inflammatory markers including TPO-antibody, TG-antibody, IL-10, IL-6, and TNF-α. Children and adolescents with type 1 diabetes had higher levels of thyroid antibodies compared to the healthy controls. Antibody positivity and autoimmune thyroiditis were investigated in this study of type 1 diabetic children and adolescents in Iraq.

TPO Ab and Tg Ab were shown to have the highest incidence among individuals with type 1 diabetes in a study that analyzed the prevalence of various autoantibodies in a sample of 814 people with type 1 diabetes.

Although no statistically significant difference was detected, the current investigation revealed that, with a ratio of 5/1, females were more likely than males to have positive serum anti-TPO antibodies. Similarly, even though there were more female patients with these antibodies than male patients, Hansen et al (25), Prazny et al (15), and Sharifi et al. (26) reported that

there was no statistically significant difference in the prevalence of positive serum anti-TPO antibodies between the sexes. In our investigation 5 (8.3%) of 60 antibody-positive patients showed antibodies against both TG and TPO. Moreover, one in sixty patients had anti-TPO antibodies and, one person had only anti-TG antibodies.

There is a lack of consensus among the published studies concerning the part that IL-10 plays in the beginning stages of type 1 diabetes. It has been demonstrated that prolonged exposure to IL-10 during an early stage in the evolution of a disease can speed up the development of that disease (27), but IL-10 exposure during the later stages of prediabetes can stop disease progression (28). Our results showed that serum IL-10 levels were considerably greater in diabetes patients than in controls. The production of IL-10 in T1DM patients may be a response to the rise in pro-inflammatory cytokines, according to He et al. (29) and Reis et al. (30) studies, which both support these findings.

Diabetes patients' blood levels of IL-6 are either higher or equivalent to those of normal people when compared to those levels (31). As a multifunctional cytokine, IL-6 is secreted by a wide variety of cell types such as T cells, macrophages and endothelial cells (32). Several studies found that low amounts of IL-6 increase insulin synthesis, while large levels block it (33, 34). Type 1 diabetics have higher serum IL-6 levels than controls in a comprehensive study. IL-6 can also damage pancreatic b cells over time by encouraging B lymphocyte growth and killer T cell activity (33). Changing blood IL-6 levels have not been linked to type 1 diabetes development. IL-6 may be a biomarker for type 1 diabetes, according to recent studies(35).

When IL-6 levels were compared between young people with type 1 diabetes and healthy controls, it was revealed that they were similar in both groups (36). However, another study involving young volunteers found that those with type 1 diabetes had much greater levels of IL-6 (37). Additionally, Bradshaw and colleagues (38) discovered that Type 1 Diabetes patients had considerably higher amounts of IL-6 release in their isolated monocytes from blood cells than did individuals in a healthy state.

Type 1 diabetes mellitus, whether it's complicated or not, is profoundly impacted by TNF-α. TNF-α levels were discovered to be lower in the blood of children with newly diagnosed type 1 diabetes mellitus compared to those without the disease; nonetheless, issues remain about its function and the validity of the presented data (39). The researchers found TNF-α serum levels comparable to healthy children. Newly diagnosed type 1 diabetic children have higher TNF-α and IL-6 levels than those with severe diabetes for a longer time(40). Our results demonstrated that type 1 diabetic patients' TNF-α levels were significantly greater than those of healthy controls and that these patients also developed antibodies against TPO and TG ($r = 1$, $P<0.0001$).

## CONCLUSIONS

Patients with type 1 diabetes may be screened for autoantibodies to identify subclinical cases of AITD, however, the test's ability to predict the emergence of clinical symptoms is limited. Patients who have been found to have positive autoantibodies need to be monitored closely since there is a possibility that their diabetes control could worsen further and that their organs will become dysfunctional.

## FUNDING

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