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Autoimmune thyroid disease in patients with type 1 diabetes mellites

A cross-sectional study from Syria

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Abstract

The present study aimed to investigate the occurrence of autoimmune thyroid disease (AITD) in patients with type 1 diabetes mellitus (T1DM) by the presence of antithyroid peroxidase (anti-TPO Ab). Furthermore, we studied the relationship of clinical and thyroid ultrasound (US) characteristics with anti-TPO Ab. This cross-sectional study was performed in Al- Mowasat and Al-Assad University Hospitals from 2021 to 2023. Clinical, laboratories, and US features were collected and analyzed between positive compared to negative anti-TPO Ab. Of 76 patients, anti-TPO Ab was positive in 12 patients (15.7%) with female predominance [n = 10 (83.3%)]. Gender showed a difference between anti-TPO Ab groups (P = .026). DM duration showed a difference (P = .034), which was dominant for a group of positive anti-TPO Ab (median = 9). The age at DM diagnosis also showed a difference (P = .048), where most patients were under 10- years old at diagnosis [n = 39 (51.3%)] and the highest number of anti-TPO Ab positive patients [n = 7 (58.3%)] were in this age category. US findings showed a significant difference (P = .001). Regarding positive anti-TPO Ab patients, the most frequent US finding was immune pattern [7 (58.3%)], which was more common than in the negative group (12.5%). Age, hemoglobin A1c (HBA1c), and body mass index (BMI) did not present differences (P = .391, 0.692, and 0.453, respectively), however, all anti-TPO Ab positive patients were older than ten years and had HBA1c more than 8. Thyroid-stimulating hormone (TSH) was abnormal in 2 patients (16.6%) and both in anti-TPO Ab positive group. This study suggests that anti-TPO Ab appears in older patients and with longer MD duration. Also, data support using US and anti-TPO Ab as earlier markers for AITDs, and further recommending regular annual monitoring by US and anti-TPO Ab in all patients with T1DM for AITDs diagnosis, especially in females.

Abbreviations: AITD = autoimmune thyroid disease, anti-TG Ab = antithyroglobulin, anti-TPO Ab = antithyroid peroxidase, BMI = body mass index, HbA1c = hemoglobin A1c, T1DM = type 1 diabetes mellitus, TSH = thyroid-stimulating hormone, US = thyroid ultrasound.

Keywords: antithyroid peroxidase (anti-TPO Ab), autoimmune thyroid disease (AITD), thyroid ultrasound (US), type 1 diabetes mellitus (T1DM)

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the destruction of beta islet cells in the pancreas, in which T cells play a key role.[1] In addition, patients with T1DM have a higher risk of other autoimmune disorders such as celiac disease, vitiligo, alopecia, Hashimoto thyroiditis, and Graves' disease.[2,3] The pathogenetic mechanism underlying this concomitant occurrence has not been clearly understood.[4] Studies have suggested genetic predisposition and environmental factors, which might be involved in the pathogenesis of these diseases.[3–5] Some conditions have consequences and can affect diabetes control if its concomitant with T1DM.[2]

Autoimmune thyroid disease (AITD) is characterized by the presence of thyroid antibodies such as antithyroid peroxidase (anti-TPO Ab), antithyroglobulin (anti-TG Ab), and thyroid-stimulating hormone (TSH) autoantibodies.[6,7] Increasing

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The study was approved in accordance with the Declaration of Helsinki and in line with the STROBE criteria.

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evidence suggests that AITD is a common autoimmune disorder associated with T1DM and is often clinically silent but it may appear as hypothyroidism or hyperthyroidism.[8]

Glucose metabolism is affected via several mechanisms in diabetes patients with hyperthyroidism and hypothyroidism. When hyperthyroidism occurs with DM, the insulin half-life is reduced, which promotes hyperglycemia. On the contrary, DM patients can present with hypoglycemic episodes if concomitant hypothyroidism occurs because the production of liver glucose is reduced which accounts for a decrease in the insulin requirements.[9]

Up till now, there is no consensus or guidelines for screening or therapeutic intervention for AITDs in patients with T1DM due to differences in the prevalence of thyroid dysfunction.[4,10] Also, AITD associated with T1DM is often clinically silent but may develop into overt thyroid dysfunction that affects glycemic control.[8]

The present study aimed to investigate the occurrence of AITD in patients with T1DM through the presence of anti-TPO Ab. Furthermore, we studied the clinical and thyroid ultrasound (US) characteristics in patients with positive compared to negative anti-TPO Ab.

2. Material and methods

This cross-sectional study was prospectively performed at Al-Mowasat and Al-Assad University Hospitals from February/ 2021 to March/ 2023. The participants were collected after admission to Endocrinology Departments or when referred to the endocrinology clinic. The study protocol was approved by the Research Ethics Committee of Damascus University and by the Declaration of Helsinki.

The inclusion criteria were patients with known T1DM. The exclusion criteria included patients with severe systemic diseases such as infections, who were treated with steroids, pregnant females, and patients who refused to participate. Of a total of (130) T1DM patients, (54) patients were excluded. Of them, 32 patients were due to severe systemic disease (n = 15 with infection, n = 17 with diabetic ketoacidosis), 6 patients with steroids treatment, 5 patients were pregnant, 4 patients refused drawing tests, and 7 patients refused participation in the study.

Data from 76 patients were collected, where clinical data included age, gender, weight, height, body mass index (BMI), age at diagnosis of DM, DM duration, and number of ketoacidosis episodes. Laboratories" tests included; TSH, anti-TPO Ab, and hemoglobin A1c (HbA1c). If the patient had low TSH or symptoms of hyperthyroidism, further free T4 (FT4) was assessed. If the patient had elevated TSH or symptoms of hypothyroidism, further FT4, total T3, and thyroid-stimulating immunoglobulin (TSI) were assessed.

Also, the thyroid US was collected and classified as; normal, low-density, presence of nodules, and immune pattern.

The immune pattern included the presence of heterogeneous and hypoechoic parenchymal patterns aligned with the presence of multiple fine echogenic fibrous septe.[11] The low-density pattern was determined by the intermediate appearance between the immune and normal appearance. Also, this pattern was determined by the degree of low echogenicity area within the thyroid gland compared to the adjacent anterior strap muscle.[11,12]

Weight and height were measured in light clothing and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Participants were divided into 4 groups based on BMI: under-weight (<18.5 kg/m^2), normal weight (BMI: ≥ 18.5 to < 25 kg/m^2), overweight (BMI: ≥ 25 to < 30 kg/m^2), obesity (BMI: ≥ 30 kg/m^2).

Measurement of serum anti-TPO Ab was by Mindray and normal levels have been defined as <9 IU/ml. TSH was measured by Simens and the normal TSH level was determined by levels between 0.4 and 4.5 mIU/ml.[13]

2.1. Statistical analysis

The data obtained has been inserted into Microsoft Excel worksheet. SPSS software version 23.0 (IBM, Armonk, New York) was used. The categorical data has been expressed as rates, ratios and proportions has been used to compare the data. The continuous data have been expressed as mean ± standard deviation (SD) and the comparison has been done using unpaired "t" test. We used nonparametric statistics such as Chi square test. Mann-Whitney U-Test was used to assess deference between medians of more than 2 independent samples those distributions are not equal. One Way ANOVA test to assess deference between the median of more than 2 independent samples. A probability value ("P" value) of less than or equal to 0.05 has been considered as statistically significant.

3. Results

3.1. Patient characteristics (Tables 1 and 2)

The mean age was (15.58 ± 5.28 years; range 7–41 years), whereas the mean age at DM diagnosis was (9.8 ± 4.78 years) and the mean duration of DM was (5.77 ± 4.85 years). The mean number of ketoacidosis episodes was (2.46 ± 2.53) ranging from 1 to 12 episodes, aligning with mean HBA1c (9.6 ± 1.27; range 7–13). The mean TSH level was (2.2 ± 2.55; range 0–23) and anti TPO (29.84 ± 105.33; range 0.2–742).

The US findings were as follows (Table 2); the normal thyroid US was reported in 19 patients (25%), immune patterns were reported in 15 patients (19.7%), and low-density thyroid US was reported in 42 patients (55.3%).

Table 1

Patient characteristics.

	Mean	Median	SD	Range	Min	Max
Age (yr)	15.58	15	5.28	34	7	41
Weight (kg)	49.43	50	16.23	83	17	100
Height (cm)	153.79	155.5	14.01	62	118	180
BMI (kg/m^2)	20.42	19.45	4.39	19.4	11.4	30.8
ketoacidosis episodes	2.46	1	2.53	11	1	12
Age at diagnosis (yr)	9.8	9	4.78	30.5	1.5	32
Anti-TPO Ab (IU/mL)	29.84	1	105.33	741.8	0.2	742
TSH (mIU/mL)	2.2	1.8	2.55	23	0	23
HBA1c	9.6	9.5	1.27	6	7	13
DM duration (yr)	5.77	5	4.58	20.9	0.1	21

anti-TPO Ab = antithyroid peroxidase, BMI = body mass index, HbA1c = hemoglobin A1c, TSH = thyroid-stimulating hormone.

3.2. Comparison of the study variables depending on anti-TPO Ab (Table 3)

The total sample was 76 patients, consisting of 35 males (46.1%) and 41 females (53.9%). Anti-TPO Ab was positive in 12 patients (15.7%) compared to negative anti-TPO Ab in 64 patients (84.2%). Female predominance was noted in the cases with positive anti-TPO Ab patients [n = 10 (83.3%)].

Gender represents a significant difference between positive and negative anti-TPO Ab groups (P = .026). Age did not present a significant difference (P = .391); however, most patients were between 10- to 20-year-old [n = 60 (78.9%)] and most anti -TPO Ab positive patients [n = 9 (75%)] were present in this age category.

HBA1c and BMI did not present a significant difference (P = .692 and 0.453; respectively). Most patients [n = 52 (68.4%)] had HBA1c between 8 and 10. All anti-TPO Ab positive patients had HBA1c more than 8, where 8 patients [n = 8 (66.6%)] had HBA1c (from 8 to 10) and 4 patients [n = 4 (33.3%)] had HBA1c more than 10.

DM duration categories (by Chi-Square test) did not present a significant difference (P = .175) and patients with positive anti-TPO showed similar distribution in age categories. However; the analysis of the mean DM durations (Mann–Whitney U test) between anti-TPO Ab groups showed a significant difference (P = .034). This difference was dominant for anti-TPO Ab positive patients (median = 9) compared to anti-TPO Ab negative patients (median = 4).

The age at DM diagnosis showed a significant difference (P = .048). Most patients were under 10- years old at diagnosis [n = 39 (51.3%)] and the highest number of anti-TPO Ab positive patients [n = 7 (58.3%)] were in this age category.

US findings showed a significant difference (P = .001). Low-density US was the most frequent pattern [n = 42 (55.3%)]. In positive anti-TPO Ab patients, the most frequent US finding was immune pattern [7 (58.3%)], 3 patients (25%) had normal US, and low-density US was reported in 2 patients (16.6%). The normal US was equally presented between positive and negative anti-TPO Ab groups (25%). Low-density US was more common in the negative anti-TPO Ab group (62.5%) compared to the positive group (16.6%). The immune pattern was more common in the anti-TPO positive group (58.3%) compared to the negative group (12.5%). Thyroid nodules were presented in 8 (10.5%) of the total sample. Patients with positive anti-TPO Ab reported a higher prevalence of nodules (2 patients; 16.6%) compared with negative anti-TPO Ab group (6 patients; 9.3%).

Of note, TSH was abnormal in 2 patients (16.6%) and both in anti-TPO Ab positive group. One patient had hypothyroidism and the other patient had hyperthyroidism. Also, TSI was positive in 1 patient who had hyperthyroidism. So TSH and TSI did not include in further analysis tests.

Table 2

Thyroid ultrasound.

		N	%
US	Immune pattern	15	19.7
	Normal	19	25.0
	Low density	42	55.3
Total		76	100

US = thyroid ultrasound.

4. Discussion

Different prevalence of AITDs has been reported in patients with T1DM in the literature. Omar et al found 12% positive serum

Table 3

Comparison of the study variables with anti TPO.

			Anti-TPO Ab N = 76			
Variables		Statistical tests	Neg * N = 64; 84.2% N (%)	Pos £ N = 12; 15.7% N (%)	Total € N = 76 N (%)	*P* value
Gender	M	Chi-Square	33 (51.5%)	2 (16.6%)	35 (46.1%)	.026
	F		31 (48.4%)	10 (83.3%)	41 (53.9%)	
HBA1c	<8	Chi-Square	3 (4.6%)	0 (0%)	3 (3.9%)	.692
	8–10		44 (68.7%)	8 (66.6%)	52 (68.4%)	
	>10		17 (22.4%)	4 (33.3%)	21 (27.6%)	
		Mann-Whitney T test N (mean ± SD)	64 (9.56 ± 1.2)	12 (9.79 ± 1.6)		.568
DM duration	<5	Chi-Square	33 (51.5%)	4 (33.3%)	37 (48.7%)	.175
	5–10		23 (35.9%)	4 (33.3%)	27 (35.5%)	
	> 10		8 (12.5%)	4 (33.3%)	12 (15.8%)	
		Mann–Whitney U test median (range)	4 (0.1–21)	9 (0.4–15)		.034
BMI	<18.5	Chi-Square	25 (39%)	4 (33.3%)	29 (38.2%)	.453
	18.5–24.9		28 (43.7%)	4 (33.3%)	32 (42.1%)	
	25–29.9		10 (15.6%)	3 (25%)	13 (17.1%)	
	>30		1 (1.5%)	1 (8.3%)	2 (2.6%)	
Age	<10	Chi-Square	5 (7.8%)	0 (0%)	5 (6.6%)	.391
	10–20		51 (79.6%)	9 (75%)	60 (78.9%)	
	20–30		7 (10.9%)	2 (16.6%)	9 (11.8%)	
	>30		1 (1.5%)	1 (8.3%)	2 (2.6%)	
Age at diagnosis	<10	Chi-Square	32 (50%)	7 (58.3%)	39 (51.3%)	.048
	10–20		32 (50%)	4 (33.3%)	36 (47.4%)	
	20–30		0 (0%)	1 (8.3%)	1 (1.3%)	
US	Normal	Chi-Square	16 (25%)	3 (25%)	19 (25.0%)	.001
	Low- density		40 (62.5%)	2 (16.6%)	42 (55.3%)	
	Immune pattern		8 (12.5%)	7 (58.3%)	15 (19.7%)	
	Nodules		6 (9.3%)	2 (16.6%)	8 (10.5%)	

anti-TPO Ab = antithyroid peroxidase, BMI = body mass index, HbA1c = hemoglobin A1c, US = thyroid ultrasound.

anti-TPO Ab in fifty diabetic children.[10] Another Iranian study among one hundred patients with T1DM reported positive anti-TPO Ab and anti-TG Ab in 19.3% and 11.1%; respectively.[14] on the other hand, a high prevalence of anti-TPO Ab positivity was reported in a Brazilian study, where the overall prevalence of anti-TPO positive was 25.2% (54 out of the 214 T1DM patients).[4]

In our study, anti-TPO was positive in 12 patients (15.8%) out of 76 patients. However, in Arab studies, the prevalence of positive anti-TPO Ab was lower than in other studies, a Sudanese study showed a prevalence of 6%.[15]

A recent meta-analysis of 180 articles including a total of 293 889 T1DM patients was performed to estimate pooled prevalence of the association between T1DM and other autoimmune diseases. Similar to our study, this study reported that the prevalence of thyroid antibodies (concluded from 35 studies) was 18.9% for anti-TPO Ab, anti-TG Ab, or both.[2]

These differences in the prevalence of thyroid autoantibodies in T1DM are depending on the different methods for measurement of antibodies, the number of patients, genetic factors, and ethnicity of patients.[2,8,10]

It is well known that endocrine autoimmunity and AITDs develop more frequently in females.[16,17] In our study, gender showed a significant difference between positive and negative anti-TPO Ab groups ($P = .026$) in addition to female predominance in cases with positive anti-TPO Ab; 10 patients (83.3%) out of 12 patients. Corresponding with the previous studies, female predominance was the main finding in cases of positive thyroid antibodies.[4,10,18,19] However, the gender significance was controversial.[4,10,18,19]

These differences in gender distribution of AITDs in T1DM patients might suggest different etiologic factors for developing antibodies related to AITD rather than T1DM, which represented solely a reflection of the predominant prevalence of thyroid diseases in females.[4,16,17] Also, recent meta-analysis findings have determined that human leukocyte antigen, the autoimmune regulator transcriptional factors, cytotoxic T lymphocyte-associated antigen-4, infection, vitamin D deficiency, and other factors could confer to the development and prognosis of both AITDs and T1DM.[3]

Albeit, there were only 2 patients (16.6%) with abnormal TSH levels in our study, previous studies found an association between positive anti-TPO Ab in T1DM and abnormal TSH level.[4,10,14] In a meta-analysis, the prevalence of hypothyroidism among T1DM patients was twice as high as in the general population.[2] Also, Araujo et al[4] and Omar et al[10] found that patients with positive anti-TPO Ab had a higher proportion (approximately 50% of patients) of abnormal TSH.

On the contrary, other studies found a lower proportion of abnormal TSH levels in patients with positive anti-TPO Ab.[18,19] Kordonouri et al[18] found that 16% of patients with AITDs had abnormal TSH levels compared with 8% in the group without thyroid antibodies, however, the mean TSH levels were still in normal ranges in both groups. Shiva et al[19] also found only 2 patients with abnormal TSH levels. Albeit, TSH is usually the first screening test for thyroid disease, these differences in the proportion of abnormal TSH levels in patients with positive anti-TPO Ab suggest low suitability of TSH as an initial screening tool for patients with AITDs concomitant to T1DM.

We found that HBA1c did not present a significant difference ($P = .692$) between positive and negative anti-TPO Ab groups. Similar findings were reported by Omar et al,[10] Prazny et al,[20] and Kakleas et al[21] However, patients with positive anti-TPO Ab tend to have higher levels of HBA1c, where all anti-TPO Ab positive patients in our study had HBA1c more than 8; 8 patients (66.6%) had HBA1c between 8 and 10, and 4 patients (33.3%) had HBA1c more than 10.

Data were more controversial in the association of anti-TPO Ab with age, DM duration, and age at DM diagnosis.[4,10,14,18] Omar et al,[10] Ardestani, et al,[14] and Araujo et al[4] did not find a significant association between anti-TPO Ab and age, DM duration, and age at DM diagnosis. On the other hand, Araujo et al[4] found a tendency for increased prevalence of AITDs in older patients, although this finding was not statistically significant. Moreover, Kordonouri et al[18] found that patients with at least one positive thyroid antibodies were significantly older and had a longer duration of T1DM than those without antibodies. Another Meta-regression analysis found that the prevalence of anti-TPO Ab increased by 3.5% for every 10-year increase in age.[2] Furthermore, every 10-year increase in DM duration is associated with an increased prevalence of anti-TPO Ab by 7%.[2]

In the current study, however, age did not show a significant difference ($P = .391$) between positive and negative anti-TPO Ab groups; all anti-TPO Ab-positive patients were older than ten years. Also, the age at DM diagnosis showed a significant difference ($P = .048$), where most patients with anti-TPO Ab positive (7 patients; 58.3%) were under 10- years at DM diagnosis. When DM duration was classified as categories, there was a similar distribution between positive and negative anti-TPO Ab groups ($P = .175$). on the other hand, the analysis of the means of DM durations between anti-TPO Ab groups showed a significant difference ($P = .034$), with predominant for anti-TPO Ab positive patients (median = 9). These findings align with previous studies might support that anti-TPO Ab appeared in older patients and with longer MD duration.

Some limitations should be pointed out in this study such as being a cross-sectional study and small sample size. Also, this study did not screen for other autoimmune disorders in T1DM patients or their families, so future studies could apply in this context. Since the loss of follow-up could mask the outcome of anti-TPO Ab positive patients; i.e. future development of abnormal thyroid function, future studies should focus on the recommendations for follow-up and treat those patients. When there was no continuous glucose monitoring, we could not specify the frequency of hypoglycemic or hyperglycemic episodes in the positive anti-TPO group compared with a negative anti-TPO control group.

When AITDs could manifest in various thyroid function statuses, the US could be of valuable contribution to patients with normal thyroid function status. Moreover, as mentioned previously in regard differences in the prevalence of abnormal TSH levels in patients with positive anti-TPO Ab and low suitability of TSH as an initial screening tool.

Interestingly, Hwang et al[12] investigated the US images in patients with goiter and normal thyroid function with positive or negative thyroid Antibodies. Thirty-three AITD patients were compared to 52 non-AITD patients. The author focused on thyroid parenchymal hypoechogenicity and heterogeneity patterns, that were divided into two grades. AITD patients showed more severe hypoechogenicity and heterogeneity patterns compared with non-AITD patients with statistically significant results.

Another study of 40 Hashimoto's thyroiditis patients with euthyroid function and elevated anti-TPO Ab were examined compared with 46 healthy individuals. Morphological gray-scale imaging, including echogenicity, nodularity, septations, and undulation of the margins, showed significant differences between the groups, meanwhile, the distribution of these echogenic patterns was predominant in Hashimoto's thyroiditis patients.[22]

In our study, US findings showed a significant difference ($P = 0.001$) between anti-TPO groups. The immune pattern and thyroid nodules were more common in the anti-TPO positive group (58.3% and 16.6%, respectively) compared to the negative group (12.5% and 9.3%, respectively).

In conclusion, this study suggests that anti-TPO Ab appears in older patients and with longer MD duration, which mandates

regular monitoring. Also, data support using US and anti-TPO Ab as earlier markers for AITDs, and further recommending regular annual monitoring by US and anti-TPO Ab in all patients with T1DM for AITDs diagnosis, especially in females.

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