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Screening for thyroid disease among children and adolescents with type 1 diabetes mellitus

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KEYWORDS

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Abstract Altered thyroid hormones have been described in patients with diabetes especially those with poor glycemic control. The aim of this work was to evaluate; the presence of serum anti-thyroid peroxidase (serum anti-TPO) autoantibodies and the prevalence of autoimmune thyroid disease in children with type 1 diabetes mellitus.

Patients and methods: Fifty diabetic children coming for regular follow-up in the diabetes clinic of El-Shatby University Children's Hospital were enrolled in the study and 20 healthy children matching in age and sex were taken as control. History taking, clinical examination, measurement of HbA1c, serum anti-TPO autoantibodies and serum TSH levels were carried out. Serum T4 and T3 were measured in samples with abnormal serum TSH level.

Results: Serum anti-TPO was positive in 12% of cases, and was negative in 100% of controls. Serum TSH level was abnormal in 50.0% of positive serum anti-TPO cases, in cases where serum anti-TPO was negative, 97.7% had normal serum TSH level, this difference was statistically significant $P = 0.004$. Good metabolic control was found in 42% of all diabetic children, 19% of them had positive serum anti-TPO, fair control was seen in 36%, only 5% of them were positive for serum anti-TPO, 22% had poor control and 9.1% were positive for serum anti-TPO, these differences had no statistical significance $P = 0.550$.

Conclusion: Although serum TSH screening is more sensitive for detecting thyroid abnormalities in children and adolescents with type1 diabetes, the presence of positive serum anti-TPO antibodies may be an earlier marker for thyroid disease, therefore, patients with positive antibodies should be monitored for serum TSH elevation at yearly intervals.

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1. Introduction

Children with type 1 diabetes mellitus (T1DM) are more prone to develop organ-specific autoimmune diseases, among which autoimmune thyroiditis (AIT) is more frequently encountered, is characterized by the production of autoantibodies against the thyroid gland, T-lymphocytic infiltration of the gland, and subsequent development of various degrees of thyroid

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dysfunction. These autoantibodies are directed toward specific thyroid gland proteins, which are thyroglobulin (Tg), a fundamental component of thyroid colloid, and thyroid peroxidase (anti-TPO), an enzyme participating in the production of thyroid hormones.[1] Reduced serum T3 levels have been observed in uncontrolled diabetic patients; this "low serum T3 state" could be explained by impairment in peripheral conversion of serum T4 to serum T3 that normalizes with improvement in glycemic control.[2]

Hyperthyroidism has long been recognized to promote hyperglycemia; the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors, as for hypothyroidism, glucose metabolism is affected as well via several mechanisms. A reduced rate of liver glucose production is observed in hypothyroidism and accounts for the decrease in insulin requirement in hypothyroid diabetic patients. Recurrent hypoglycemic episodes may be the presenting signs for the development of hypothyroidism in patients with type 1 diabetes.[2]

American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend that thyroid antibody tests and thyroid function should be considered close to the time of diagnosis and repeated if clinical circumstances suggest the possibility of thyroid disease, if normal consider rechecking every 1 to 2 years. Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia and with reduced linear growth.[3,4] Furthermore, thyroxine replacement therapy started early in patients with subclinical hypothyroidism reduces the risk of hyperlipidemia and atherosclerotic heart disease.[5] Hyperthyroidism alters glucose metabolism, potentially resulting in the deterioration of metabolic control.[3]

Up till now, there is no consensus about the best policy for screening for thyroid dysfunction in diabetic children and the time point of therapeutic intervention.[6]

The aim of this work was to evaluate; the presence of serum anti-thyroid peroxidase (serum anti-TPO) autoantibodies and the prevalence of autoimmune thyroid disease in children with type 1 diabetes mellitus (DM) attending in Alexandria University children's hospital diabetes clinic.

2. Patients and methods

A cross sectional hospital based study was used to evaluate the presence of serum anti-TPO antibodies in children and adolescents with type 1 DM. Fifty diabetic children coming for follow-up in the diabetes clinic were enrolled in the study and 20 healthy children matching in age and sex were taken as control, during the period from October 2011 till May 2012. The inclusion criteria for the diabetic group were: Type 1 DM, age: 1–18 years. The exclusion criteria included: Subjects with a positive history of previous thyroid disorders, patient with evident organ system disease e.g. Thalassemia, congenital heart disease and patients receiving corticosteroids. All children in the study will be subjected to:

- Detailed history and clinical examination.
- Assessment of anthropometric measures (weight and height). Anthropometric measurements were expressed as age and sex specific standard deviation (SDs) from the mean (z scores) on the basis of WHO Child Growth Standards.[7]
- Measurement of serum anti-TPO Ab: solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay. Normal levels have been defined as less than 35 IU/ml.
- Serum TSH level: solid-phase, chemiluminescent immunometric assay. Reference range: age 1–6 years: 0.85–6.5, 7–12 years: 0.28–4.3, 13–16 years: 0.36–4.7 (uIU/ml/ml).
- Serum T4 and T3 on samples with abnormal serum TSH level.
- HbA1c was measured by Nyco Card, the mean of the last four readings for HbA1c was calculated. Reference range: in diabetic children, values of 6–8.5% represent good metabolic control, values of 9–10%, fair control, and values of >10% or higher represent poor control.[8]
- Follow-up of serum anti-TPO positive cases was done for 6 months.
- Data were analyzed using the Statistical Package for the Social Sciences (SPSS 14.0). Differences between the groups were calculated by the chi-square test for categorical

Table 1 Distribution of children with T1DM and healthy controls according to age, sex, and family history of DM.

	Cases		Controls		Total		X^2	P
	No	%	No	%	No	%		
Age								
2–4	3	6.0	3	15.0	6	8.6	4.515	0.105
5–10	17	34.0	10	50.0	27	38.6		
>10	30	60.0	7	35.0	37	52.8		
Mean (SD)	10.7 (3.3)		4.8 (3.3)		8.9 (4.2)		t = 1.93	0.057
Sex								
Male	19	38.0	10	50.0	29	41.4	0.89	0.357
Female	31	62.0	10	50.0	41	58.6		
Family history of DM								
Yes	15	30.0	2	10.0	17	24.3		FEp = 0.122
No	35	70.0	18	90.0	53	75.7		

^ P value based on Mont Carlo exact probability. FEp: p value for Fisher Exact test.

Table 2 Serum anti-TPO level in children with T1DM and healthy controls.

Anti-TPO	Cases		Controls		Total		*P*
	No	%	No	%	No	%	
Negative	44	88.0	20	100.0	64	91.4	0.173[a]
Positive	6	12.0	0	0.0	6	8.6	
Total	50	100.0	20	100.0	70	100.0	

[a] *P* value based on Fisher exact probability.

Table 4 Level of serum anti-TPO and TSH in children with T1DM.

Anti-TPO	Positive		Negative		Total		*P*
	No	%	No	%	No	%	
Normal	3	50.0	43	97.7	46	92.0	0.004
Abnormal	3	50.0	1	2.3	4	8.0	
Total	6	100.0	44	100	50	100	

[!] *P* value based on Fisher exact probability.

variables, ANOVA test for two or more continuous variables, the study protocol was approved by the institutional review board of the college of medicine in Alexandria University (Egypt), and a written parental consent and child assent were obtained.

3. Results

Table 1 shows that both cases and controls were comparable as regards age, sex and family history of DM.

Table 2 shows that 12% of cases have positive serum anti-TPO, and 100% of controls have negative serum anti-TPO, but this difference was not statistically significant $P = 0.173$.

Table 3 shows that a female predominance was noted in the cases with positive serum anti-TPO (83.3%). In negative cases, females were 59.1% but this difference was not statistically significant $P = 0.387$. As regards the duration of DM, height for age and weight for age, there was no statistical difference between positive and negative cases $P = 0.160$, 0.650, 1.000 and 1.000, respectively.

Table 4 and Fig. 1 illustrate that 50.0% of positive serum anti-TPO cases had abnormal serum TSH level, in cases where serum anti-TPO was negative, 97.7% had normal serum TSH level, this difference was statistically significant $P = 0.004$.

Table 5 and Fig. 2 show that 21 cases (42%) of all diabetic children had good metabolic control, 19% of them had positive serum anti-TPO. Fair control was seen in 36%, only 5% of them were positive for serum anti-TPO. 22% had poor control, 9.1% were positive for serum anti TPO, these differences had no statistical significance $P = 0.550$.

Table 6 shows that six cases were serum anti-TPO positive at initial assessment. Five were females and one was male. Their age range was 7 to 11 years with a mean of 8.73 ± 2.04. Abnormal serum TSH values were observed in three cases "case number 7, 25 and 30". Case no 25 had clinical hypothyroidism evidenced by raised TSH, low serum T4 and goiter, after 6 months follow-up, case no 7 had subclinical hypothyroidism evidenced by high serum TSH and normal serum T4, however this case started treatment because of further rise in serum TSH. Case no 30 had hyperthyroidism evidenced by low serum TSH and raised serum T4 level.

Table 3 Serum anti-TPO level, age, sex, duration of DM, and anthropometric measurements in children with T1DM.

	TPO				Total		*P*
	Negative		Positive				
	No	%	No	%	No	%	
Sex							
Male	18	40.9	1	16.7	19	38.0	FEp = 0.387
Female	26	59.1	5	83.3	31	62.0	
Age							
2–4	3	6.8	0	0.0	3	6.0	FEp = 0.242
5–10	13	29.5	4	66.7	17	34.0	
> 10	28	63.6	2	33.3	30	60.0	
Duration of DM							
< 5 years	29	65.9	6	100.0	35	70.0	FEp = 0.160
> 5	15	34.1	0	0.0	15	30.0	
Height for age							
Normal	40	90.9	6	100.0	46	92.0	FEp = 1.000[a]
Stunted	4	9.1	0	0.0	4	8.0	
Weight for age							
Normal	38	86.4	6	100.0	44	88.0	MCp = 1.000^
Underweight	5	11.4	0	0.0	5	10.0	
Overweight	1	2.3	0	0.0	1	2.0	

MCP: *P* value based on Mont Carlo exact probability.
[a] *P* value based on Fisher exact probability [*] $P < 0.05$ (significant).

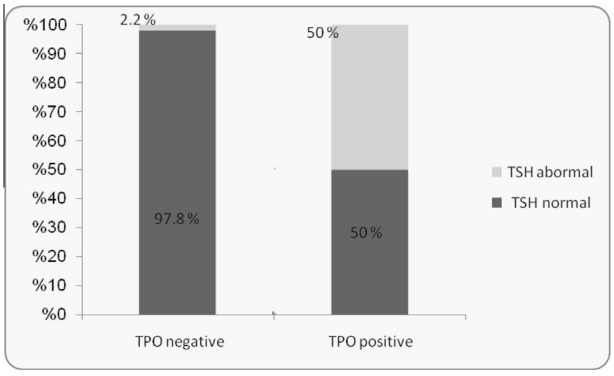

Figure 1 Serum anti-TPO and TSH in children with T1DM.

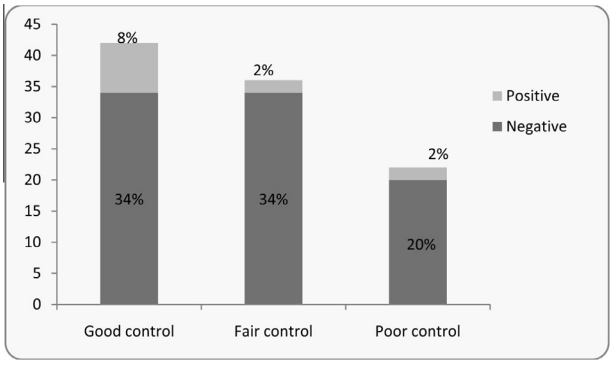

Figure 2 Serum anti TPO and control of diabetes.

4. Discussion

Autoimmune diseases affect a substantial percentage of the population, providing a strong drive for research into ways whereby such diseases can be detected, prevented and even cured. It is well known that certain autoimmune diseases occur in association with each other, such as autoimmune thyroid disease (ATD), pernicious anemia, celiac disease and idiopathic adrenal insufficiency, but the most common combination is type 1 DM and ATD.[9]

The aim of the present study was directed to evaluate the presence of serum anti-TPO autoantibodies and the prevalence of autoimmune thyroid disease in children with type 1 DM.

The prevalence of positive serum anti-TPO antibodies reported among children with T1DM in the present study was 12.0%. Studies done on antimicrosomal antibodies in Brazilian children with type 1 DM reported an average prevalence of 16.7% as reported by Mantovani et al.,[10] meanwhile European whites had a prevalence of 11.1%.[11] On the other hand, a figure as high as 35% was quoted among American Hispanic patients[12] and 39.6% among Iranian children as reported by Sharifi et al.[13] A higher incidence was reported in India (54.3%). Similarly, the large scale cohort performed by Kordonouri et al.[14] on type 1 DM patients aged 0.1–20 years showed an overall prevalence of positive serum anti-TPO antibodies, as 10%, such figure is comparable to the prevalence reported in the present study, however, studies done on Arab children with type 1 DM showed different prevalence figures than the current study, Mohamed et al.[15] in their study on Sudanese children, reported a lower overall incidence of 6%. A similar figure was reported by Abdullah et al.[16] in Saudi Arabia which was 8%.

In this study the cut-off value for anti -TPO antibody was 35 IU/ml, Sharifi et al.[13] using RIA; serum anti-TPO antibodies was set at 16 IU/ml. Moayeri et al.[9] and Sarah et al.[17] used ELISA while Kordounori et al.[14] used RIA, and the normal reference range was up to 100 IU/ml. It may be apparent that the previous studies on the prevalence of thyroid auto-immunity and autoantibodies in children and adolescents with type 1 DM have shown various results depending on the difference in cut off points, patients' age, the number of cases, the duration of diabetes and may be ethnicity of patients studied.

It is well known that organ-specific endocrine autoimmunity develops more frequently in females, including type 1 DM with thyroid auto-immunity as the production of serum anti-TPO is inheritable in an autosomal fashion in females but not in males,[15,18] the present study showed that the presence of positive serum anti-TPO antibodies was more common among females, with a ratio of 5/1 but no statistical difference was found. Similarly, Hansen et al.[19], Prazny et al.[20] and Sharifi et al.[13] reported; although female patients with positive

Table 5 Serum anti-TPO level in children with T1DM and degree of diabetes control.

Serum anti-TPO	Good control HbA1c 6–8.5%		Fair control HbA1c 9–10%		Poor control HbA1c > 10%		Total		MCp
	No	%	No	%	No	%	No	%	
Negative	17	34.0	17	34.0	10	20.0	44	88.0	0.550
Positive	4	8.0	1	2.0	1	2.0	6	12.0	
Total	21	42.0	18	36.0	11	22.0	50	100.0	

Table 6 Clinical and hormonal characteristics of serum anti-TPO positive cases.

Case No.	Age	Sex	Anti TOP titer	TSH	TSH follow up	T4	Hb A1c
7	11.0	F	72.30	7.70	9.1	3.50 → 4.9	7.80
25	7.0	F	1001.0 → 2050	776.0	1.38	0.10	13.3
30	11.0	F	1047.0	2.23	0.031	135	9.00
33	10.0	F	333.0	2.79	3.23	8.9	7.70
44	7.0	F	37.7	2.13	1.7	8.5	6.6
50	7.0	M	83.0	1.74	1.57	7.0	7.20

serum anti-TPO antibodies were more than males, there was no significant difference between both sexes as regards the frequency of positive serum anti-TPO antibodies, on the other hand, Holl et al.,[21] Kordonouri et al.,[14] reported that girls were significantly more affected than boys.

The present study reported a significant association between the positivity of serum anti-TPO antibodies and abnormal serum TSH levels, cases with positive serum anti-TPO antibodies were more likely to have abnormal serum TSH. Ghoraishian et al.[22] reported strong statistical significant differences between those with normal and raised serum anti-TPO antibody titers regarding the levels of serum TSH, Kordonouri et al.[14] reported similar findings where serum TSH levels were higher in patients with thyroid autoimmunity than in control subjects and even higher serum TSH levels were observed in patients with both serum anti-TPO and anti-TG antibodies. In accordance, Kakleas et al.[23] also reported that the presence of serum anti-thyroid antibodies, including serum anti-TPO antibodies, was positively associated with serum TSH levels, along with other factors. The authors reported that the increase in serum TSH levels was directly proportional to the degree of anti-thyroid antibody positivity, with the lowest values occurring in the group without thyroid autoimmunity and the highest ones in the group with double thyroid antibody positivity.

The elevated serum TSH levels associated with the degree of anti-thyroid antibody positivity may be due to the direct involvement of autoantibodies in the pathophysiologic mechanism of thyroid gland destruction or may be due to the association of these autoantibodies with tissue destruction by thyroid-infiltrating T cells.[23]

At initial assessment in the present study we reported different types of thyroid dysfunction; 16% of serum anti-TPO positive cases with clinical hypothyroidism (defined as both a raised serum TSH and a low free serum T4 level) and 16% with subclinical hypothyroidism (defined as elevated serum TSH concentrations with serum free thyroxin (T4) levels within the reference range), furthermore we found, after 6 months follow-up, one case out of 6 (16% of positive serum anti-TPO cases) developed hyperthyroidism (defined as a raised free serum T4 with a low serum TSH level). Moayeri et al.[9] reported that serum anti-TPO antibodies were found in 34 (23.4%), Subclinical hypothyroidism, hypothyroidism and thyrotoxicosis occurred in 1, 9, 1 patients, respectively, on the other hand Mohamed et al.[15] found among 6% of anti-TPO positive cases, 16% of them had biochemical evidence of hypothyroidism, although clinically looked euthyroid, and there was no evidence of subclinical hypothyroidism or hyperthyroidism.

The present study showed that there was no relationship between the level of control of diabetes (HbA1c level) and serum anti-TPO antibody positivity ($p = 0.550$). The same finding was reported by Prazny et al.[20] Kakleas et al.[23] and Hansen et al.[19]

It could be concluded that, although serum TSH screening is more sensitive for detecting thyroid abnormalities in children and adolescents with type1 diabetes,[24] the presence of positive serum anti TPO antibodies may be an earlier marker for thyroid disease, as it is specific and sensitive; therefore, patients with positive antibodies should be monitored for serum TSH elevation at yearly intervals.

Conflict of interest

None declared.

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