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Autoimmune Thyroid Disorder in Children and Adolescents with Type I Diabetes Mellitus

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Abstract

Background

Type one diabetes mellitus (Type 1 DM) is the most common type of diabetes in children and adolescents, arising through a complex interaction of immune, genetic and environmental factors. Autoimmune thyroid disease is the most frequent disorder associated with Type one diabetes mellitus. This study aimed to evaluate incidence of autoimmune thyroid disease in children and adolescents with type I diabetes mellitus.

Materials and Methods

Cross sectional case control study was made on forty diabetic children with regular attending to the Endocrinology clinic and patients from pediatric ward in Al-Imamain Al-Kadhimain Medical City, Eraq, and forty healthy children matching in aged (1-15 years) and gender were taken as control. History taking, clinical examination, measurement of hemoglobin A1C, serum thyroid peroxidase autoantibodies and serum thyroid stimulating hormone levels were carried out. Serum thyroxine and triiodothyronine were measured.

Results

Serum thyroid peroxidase antibodies was positive in 15 % of diabetic patients, while it was negative in controls. In those with positive thyroid peroxidase antibodies 100% had subclinical hypothyroidism, 50% had hyperthyroidism. Risk of autoimmune thyroid disease was more in patients older than 5 years and it was neither related to the degree of control of diabetes nor to the duration, but it was more common in females.

Conclusion

There is higher incidence of autoimmune thyroid disease in children and adolescents with type one diabetes compared with normal children and this risk is not related to duration of diabetes, but it is more common in those older than 5 years. The risk of hypothyroidism is double the risk of hyperthyroidism in these patients.

Key Words: Autoimmune thyroid disease, Children, Type I diabetes mellitus.

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1- INTRODUCTION

Type one diabetes mellitus (Type 1 DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents. This disorder results from immune and non-immune destruction of β- cell islets of the pancreas. Therefore, children and adolescents with type 1 DM are at increased risk for developing other autoimmune diseases (1). Type1 DM accounts for approximately 10% of all cases of diabetes, affecting up to 3 million people in the United States and more than 15 million people in the world. Data from European diabetes centers suggest that the annual rate of increase in type1 DM incidence is 2-5% up to 9%, the overall prevalence of diabetes among school-age children is approximately 1.9 in 1,000.

Girls and boys are almost equally affected (2). Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported. Thyroid disorders remain the most frequent autoimmune disorders associated with type 1 DM. This was shown in a cross sectional study involving 1,419 children with type 1 DM, where 3.5% had Hashimoto's thyroiditis (3). Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with type 1 diabetes (4).

There was a wide variability in the prevalence reported in different studies varying between 4.8% and 31.4%, partly explained by the different definitions used for the diagnosis of DM and thyroid disorders. Particularly when antibody testing for type1 DM and thyroid disease (AITD) was included in the analysis, prevalence rates were much higher. This was confirmed in a study evaluating the prevalence of various autoantibodies in a population of 814 individuals with type1 DM in which anti-thyroid peroxidase antibodies (antiTPO) and or anti-thyroglobulin antibodies (anti-TG) were the most commonly expressed autoantibodies, reaching a proportion of 29% (5). The autoimmune thyroid disorders are the most prevalent endocrinopathy among patients with type 1 diabetes. The similar pathogenesis of the two disorders and their frequent clustering within families and individuals, suggest that they may have a shared genetic etiology (6). Identification of common genes is currently restricted almost exclusively to autoimmune causes. Among human autoimmune conditions, the strongest association is seen between type1 DM and AITD (7).

Hashimoto's thyroiditis, first described in 1912, is the most prevalent autoimmune disease associated with type1 DM. Although many subjects with Hashimoto's thyroiditis are hypothyroid, there is a subgroup of thyroid autoantibody-positive cases who are euthyroid. It may take years for those subjects to develop thyroid disease (8). The diagnosis is made by clinical features, elevated Thyroid-stimulating hormone (TSH), low thyroid hormones and the presence of anti-thyroid peroxidase antibodies. TPO antibody is more specific and sensitive than TG antibody in the diagnosis of autoimmune hypothyroidism (9).

Importantly, compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH (10). Subclinical hyperthyroidism can be diagnosed in 6 to 10% of type1 DM patients. The incidence of overt hyperthyroidism in persons with a suppressed serum TSH is calculated at 2% to 4% per year (8). Thyroid hormones are positively associated with insulin resistance not only in clinically diagnosed diabetes mellitus, but also in subjects with a normal glucose tolerance (11). Thyroid

hormones in excess promote hyperglycemia by several mechanisms, increased glucose absorption in the bowel, impaired insulin secretion, accelerated insulin degradation, elevation of glucagon levels, increased hepatic glucose production, insulin resistance and, possibly, hypercatecholaminemia. In other words, in hyperthyroidism there is a high glucose output from the liver and a diminished action of insulin (12). The development of thyrotoxicosis may further induce diabetic ketoacidosis, a life-threatening condition (13).

Currently, several guidelines suggest not only baseline testing for thyroid dysfunction in newly diagnosed DM: the British Thyroid Association supports, in addition, anti-TPO testing at baseline and TSH monitoring at yearly intervals (14). The American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) to screen type1 DM patients for thyroid dysfunction using TSH at onset of diabetes, or in case of symptoms of hypothyroidism or hyperthyroidism, and one to two years thereafter. Since patients who are TPO-antibody positive have an 18-fold increased risk of developing thyroid disease compared with patients who are TPO-antibody negative, they suggest screening type 1 DM patients using TPO autoantibodies, TSH and thyroxine (T4) levels at onset of type1 DM and yearly thereafter (8).

It is also well known that the prevalence of postpartum autoimmune thyroiditis in patients with type 1 DM is three times that observed in the general population (15). High anti-TPO titers have been reported in pregnant women at risk for gestational DM (16). Transient thyroid dysfunction is common in the postpartum period and warrants routine screening with serum thyroid-stimulating hormone 68 weeks after delivery. Glucose control may fluctuate during the transient hyperthyroidism followed by hypothyroidism typical of the postpartum thyroiditis. It is important to monitor thyroid function tests in these women since approximately 30% will not recover from the hypothyroid phase and will require thyroxine replacement. Recurrent thyroiditis with subsequent pregnancies is common (17).

2- MATERIALS AND METHODS

2-1. Study design and setting

A cross sectional case control study was performed at Al-Imamain Al-Kadhimain Medical City, Eraq, to evaluate the presence of serum anti-TPO antibodies in children and adolescents with type 1 DM. Forty diabetic children with regular visits to the Endocrinology clinic and patients from pediatrics ward, all of them were enrolled in this study as cases and forty healthy children matching in age and sex were taken as control, during the period from 1st of March 2016 till 31th of December 2016.

2-2. Participants

The inclusion criteria for the diabetic group were: Type 1 DM and aged between 1-15 years. The exclusion criteria included subjects with a positive history of previous thyroid disorders, patient with evident organ system disease and patients receiving corticosteroids or drugs affecting thyroid function or size.

2-3. Data Collection

A questionnaire was filled out for diabetic patients and control group which included information on age, sex, duration of diabetes, history of thyroid disease, symptoms and signs of AITD (bradycardia or tachycardia, constipation or diarrhea, weight gain, growth retardation), drug history, other associated autoimmune diseases (celiac disease, vitiligo, adrenal deficiency). All children in the study were subjected to detailed history and clinical

examination in form of measurements (weight and height) and thyroid gland examination.

2-4. Clinical and laboratory parameters

Assessment of anthropometric measures (weight and height, which expressed as age and sex specific percentile) based on World Health Organization (WHO) Child Growth Standards. Thyroid gland examination was done in all patients and control group and it was normal. Blood samples were taken for determination of serum level of thyroid stimulating hormone (TSH), total thyroxin (T4) and triiodothyronine (T3). All samples were measured at the reference laboratory of Al-Imamain Al-Kadhimain Medical City by the same person using the same method and the reference range defined according to the range used in the same lab. Measurement of serum anti-TPO: measured by Rapid ELISA Kit, solid-phase assay for quantitative determination of Immunoglobulin G (IgG) autoantibodies to Thyroid Peroxidase antigen (Ag) in Al-Nahrain University Research Center Lab. Levels have been defined according to the Kit used:

Negative: < 50 IU/ml,
Borderline: 50-75IU/ml,
Positive: 75 IU/ml (considered as AITD).

Serum TSH level: solid-phase, Immunoradiometric assay (IRMA). Reference range: (0.25-5.0) MIU/ml. Overt hypothyroidism was defined as elevated TSH and low T4, subclinical hypothyroidism as elevated TSH and normal T4, overt hyperthyroidism as low TSH and elevated T4 and subclinical hyperthyroidism as low TSH and normal T4. Serum T4 and T3 on samples with abnormal serum TSH level using radioimmune assay. Reference range for T4 (60-120) nmol/L and for T3 (0.95-2.5) nmol/L. Hemoglobin A1c (HbA1c) was measured by NycoCard® test. Patients were divided into three groups: in diabetic children, values of 6-7.5% represent good metabolic control, values of 7.6-9.9% fair control and values of 10% or higher represent poor control (6).

2-5. Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 23.0). Differences between the groups were calculated by the chi-square test for categorical variables, Correlation between quantitative variables was calculated by Spearman's rank correlation coefficient. P-value less than 0.05 was considered statistically significant. ANOVA test for two or more continuous variables. Agreements were obtained from all children's parents enrolled in this study.

3- RESULTS

Th result showed that 6 (15%) of diabetic patients have positive serum anti-TPO antibodies, while no one of the control group have these antibodies and this difference was statistically significant (P= 0.013) (**Table.1**).

Table-1: Serum anti-TPO level in children with Type1 DM and healthy controls.

Variables		Controls		Diabetic patients		Total		P-value
		NO.	%	NO.	%	NO.	%	
Anti-TPO	Negative	40	100.0	34	85	74	92.5	0.013
	Positive	0	0.0	6	15	6	7.5	
Total		40	100.0	40	100.0	80	100.0	
Chi-Square Value Calculated =6.486, df = 1, Tabular value =3.841								

Anti- TPO: Anti-thyroid peroxidase; df: degrees of freedom; Type1 DM: type 1 diabetes mellitus.

All diabetic patients with positive anti-TPO antibodies are more than 5 years of age and the difference was not significant P-value 0. 076. Females were more affected than males 4(66.7%) versus 2(33.3%) with no statistical significance. All the patients with positive anti-TPO antibodies have less than 5 years' duration of diabetes which is not significant. Underweight was present in 2 (33.3%) with positive anti-TPO and 10 (29.4%) in those with negative group P-value not significant. All patients with positive anti-TPO antibodies have normal height, while 12(35.3%) in negative cases have stunted height (**Table.2**).

Table-2: Serum anti-TPO level with age, gender, duration of DM and anthropometric measurements in children with Type 1 DM.

		Anti TPO				Total		P-value
		Negative		Positive				
		NO.	%	NO.	%	NO.	%	
Age	Less than 5 years	10	29.4	0	0.0	10	25.0	0.076
	5-10 years	8	23.5	4	66.7	12	30.0	
	More than 10 years	16	47.1	2	33.3	18	45.0	
Total		34	100.0	6	100.0	40	100.0	
Chi-Square Value Calculated = 5.142, df = 2, Tabular value =5.991								
		Anti TPO				Total		P-value
		Negative		Positive				
		NO.	%	NO.	%	NO.	%	
Gender	Male	20	58.8	2	33.3	22	55.0	0.247
	Female	14	41.2	4	66.7	18	45.0	
Total		34	100.0	6	100.0	40	100.0	
Chi-Square Value Calculated = 1.339, df = 1, Tabular value =3.841								
		Anti TPO				Total		P-value
		Negative		Positive				
		NO.	%	NO.	%	NO.	%	
Duration of DM	Less than 5 years	26	76.5	6	100.0	32	80.0	0.184
	More than 5 years	8	23.5	0	0.0	8	20.0	
Total		34	100.0	6	100.0	40	100.0	
Chi-Square Value Calculated = 1.765, df = 1, Tabular value =3.841								
		Anti TPO				Total		P-value
		Negative		Positive				
		NO.	%	NO.	%	NO.	%	
Weight-for-age	Normal	22	64.7	4	66.7	26	65.0	0.826
	Underweight	10	29.4	2	33.3	12	30.0	
	Overweight	2	5.9	0	0.0	2	5.0	
Total		34	100.0	6	100.0	40	100.0	
Chi-Square Value Calculated = 0.382, df = 2, Tabular value =5.991								
		Anti TPO				Total		P-value
		Negative		Positive				
		NO.	%	NO.	%	NO.	%	
Height-for-age	Normal	22	64.7	6	100.0	28	70.0	0.082
	Stunted	12	35.3	0	0.0	12	30.0	
Total		34	100.0	6	100.0	40	100.0	
Chi-Square Value Calculated = 3.025, df = 2, Tabular value =5.991								

Anti- TPO: Anti-thyroid peroxidase; df: degrees of freedom; Type 1 DM: type 1 diabetes mellitus.

The 2 (100%) of diabetic patients with positive anti-TPO antibodies have Subclinical Hypothyroidism, 2 (50%) have Hyperthyroidism and the remaining have normal thyroid function test (TFT), while 94.1% of patients with negative antibodies have normal TFT. This difference considered highly significant (P= 0.00) (**Table.3**).

Table-3: The association between serum anti-TPO antibodies and TFT level in diabetic patients.

Variables		Normal		Subclinical Hypothyroidism		Hyperthyroidism		Total		P-value
		NO.	%	NO.	%	No.	%	NO.	%	
Anti-TPO	Negative	32	94.1	0	0.0	2	50.0	34	85.0	0.000
	Positive	2	5.9	2	100.0	2	50.0	6	15.0	
Total		34	100.0	2	100.0	4	100.0	40	100.0	
Chi-Square Value Calculated =17.393, df = 2, Tabular value =5.991										

Anti- TPO: Anti-thyroid peroxidase; df: degrees of freedom; TFT: thyroid function test.

Six cases were serum anti-TPO positive; four were females and two were males. Their age range was 6 to 13 years. Abnormal serum TSH values were observed in four cases. Two cases have subclinical hypothyroidism evident by raised TSH, normal serum T3 and T4 level and both have good control of blood sugar as $HbA1_C$ (6.5, 6.6) respectively. Two cases have hyperthyroidism evident by low serum TSH and raised serum T4 with normal T3 (in the upper limit) and showed poor control of their blood sugar as $HbA1_C$ (12, 11.5), respectively (**Table.4**).

Table-4: The characters of patients with positive anti-TPO antibodies.

Case No.	Age, year	Gender	TSH, mU/L	T4, mU/L	T3, mU/L	$HbA1_{C,\ \%}$
43	13	F	3.1	75	2	6.8
52	6	F	6	108	1.5	6.5
53	8	M	0.07	135	2.3	12
63	13	F	3.3	88	1.7	6.8
72	6	F	5.8	85	1.22	6.6
73	8	M	0.06	127	1.94	11.5

Anti- TPO: Anti-thyroid peroxidase; TSH: Thyroid-stimulating hormone; T4: thyroxine; T3: Triiodothyronine.

The 14.3% of diabetic patients with positive anti-TPO antibodies have poor diabetic control in contrast to 85.7% in negative cases, while 25% with good control in patients with positive anti-TPO antibodies in contrast to 75.0% in negative cases and this difference was statistically not significant (P= 0.220) (**Table.5**).

Table-5: Serum anti-TPO antibodies level in children with Type1 DM according to the level of HbA1c.

Variables		HbA1c						Total		P-value
		Good control (6-7.5%)		Fair control (7.6-9.9%)		Poor control (> 10%)				
		NO.	%	NO.	%	No.	%	NO.	%	
Anti-TPO	Negative	12	75.0	10	100.0	12	85.7	34	85.0	0.220
	Positive	4	25.0	0	0.0	2	14.3	6	15.0	
Total		16	100.0	10	100.0	14	100.0	40	100.0	
Chi-Square Value Calculated =3.025, df = 2, Tabular value =5.991										

Anti- TPO: Anti-thyroid peroxidase; df: degrees of freedom; Type 1 DM: type 1 diabetes mellitus.

4- DISCUSSION

It has been shown that type 1 DM has strong relationship with other autoimmune disorders such as pernicious anemia, celiac disease, idiopathic adrenal insufficiency and autoimmune thyroiditis which is the most prevalent autoimmune disease associated with type 1 DM. The reason for the high prevalence of some autoimmune disorders in these patients remains undetermined (18). The incidence of positive serum anti-TPO antibodies reported among children with type 1 DM in the current study was 15%. This study was comparable to many studies (19-27). 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 values for anti-TPO antibodies, genetic factors, patients' age, sample size, the duration of diabetes and may be ethnicity of patients studied (28).

In this study, all diabetic patients with positive anti-TPO antibodies were above 5 years old but with no statistically significant difference between them and the negative group, this result agreed with other studies (29, 30). Other studies described an age dependent increase of AIT incidence which is in concordance with the current study (22, 23, 25, 30). In the present study 66.7% of diabetic patients with positive anti-TPO antibodies were females, while only 41.2% of negative group were females, but no statistical difference was found. Many studies agreed with the current study including studies with statistical significance like (29, 31-33). It is well known that organ-specific endocrine autoimmunity develops more frequently in females, including type 1 DM with thyroid auto-immunity because the production of serum anti-TPO is inheritable in an autosomal fashion in females (28), also sex hormones have been reported to affect the development of antibodies. In this study, there was no relationship between duration of diabetes and the development of autoimmune thyroiditis (AIT) because all patients with anti-TPO positivity had less than 5 years duration of diabetes, similar results revealed by Omar et al. (28), but other studies described a tendency to increase thyroid autoimmunity with increasing diabetes duration which is against the current study (22, 23, 28, 30).

The highest prevalence of thyroid antibodies observed with increasing diabetes duration suggests that autoimmune disease is the final phase of a process starting with auto-recognition, passing through immunity with the appearance of autoantibodies and finally leading to cell destruction and autoimmune disease, also apart from diabetes duration, the presence of sex hormones may significantly contribute to the development of thyroid autoimmunity in adolescence (30).

The present study revealed no statistical difference between positive versus negative anti-TPO diabetic patients regarding their growth inform of height for age and weight for age, but we found 35.3% of negative anti-TPO diabetic patients were stunted which might be explained by poor control of their blood sugar as in (28-30). The present study showed highly significant association between the positivity of serum anti-TPO antibodies and abnormal thyroid function test (P= 0.00). There were reported different types of thyroid dysfunction; 100% of positive serum anti-TPO antibodies patients have subclinical hypothyroidism and 50% with clinical hyperthyroidism compared with the negative group.

Normal TFT was found in 5.9% of positive cases which explained by fluctuation in the concentration of positive autoantibodies, so need more frequent measurements of anti-TPO antibodies, which is in line with other studies (18, 23, 30, 34, 35). The abnormal serum TSH levels associated with anti-thyroid antibody positivity may be due to involvement of autoantibodies in the pathophysiologic mechanism of thyroid gland destruction or may be due to direct tissue destruction by thyroid-infiltrating T cells (28). The present study showed that there was no relationship between the level of control of diabetes (HbA_{1c} level) and serum anti-TPO antibody positivity (p = 0.220). The same finding was reported by Iddah MA and Macharia (18) and Omar et al. (28).

4-1. RECOMMENDATION

Screening of thyroid antibodies, particularly anti-TPO antibodies, in all children and adolescents with Type 1DM is recommended. 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 at more frequent intervals.

5- CONCLUSION

The present study confirmed higher incidence rate of AITD in children and adolescents suffering from type 1 DM. The risk of developing AITD was not related to duration of diabetes, but all the patients were more than 5 years of age, indicating increased risk of AITD with increasing age. Girls were predominantly more predisposed to AITD. There were no differences in growth parameters and metabolic control between patients with or without AITD. The percentage of subclinical hypothyroidism was double the percentage of hyperthyroidism in diabetic patients with AITD, all patients with hypothyroidism were females in contrast to hyperthyroidism who were males.

6- CONFLICT OF INTEREST: None.

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