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Correlation between auto-immune diseases and type 1 diabetes mellitus in the pediatric age group in Erbil city

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Abstract

Background and objective: Type-1 diabetes mellitus is the most common chronic endocrine disorder of childhood and adolescence and is characterized by immune-mediated destruction of pancreatic cells, which has been proven to be correlated with and increase the risk of developing autoimmune thyroid disease, celiac disease, Addison's disease, and further autoimmune diseases. The aim of this study is to evaluate the prevalence of autoimmune disease-related markers in type 1 diabetes mellitus in children and adolescents in Erbil city.

Methods: One hundred children and adolescents with type 1 diabetes mellitus were enrolled in this cross-sectional study. Patients <1 year old were excluded from the study. Autoimmune thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) along with tissue transglutaminase (IgA and IgG) antibodies were measured with further evaluation by thyroid function test and endoscopy with biopsy (for positive serological autoantibodies level).

Results: Elevated anti-thyroglobulin, anti-thyroid peroxidase, and tissue transglutaminase IgA and IgG antibodies were determined in 24.0%, 26%, 10%, and 8%, respectively. 50.0% of cases with positive anti-thyroid peroxidase antibodies had overt hypothyroidism; on the flip side, 3.8% had subclinical hypothyroidism. As well, the high level of thyroid autoantibodies was significantly correlated to the prevalence of overt hypothyroidism (P <0.001). Nine of the patients with positive tissue transglutaminase antibodies were verified to have biopsy-proven celiac disease.

Conclusion: Children and adolescents with type 1 diabetes mellitus are at risk of developing positive antithyroid and celiac-related autoantibodies, so they are at risk of progressing to autoimmune thyroid and celiac diseases.

Keywords: Diabetes mellitus; Autoimmune diseases; Overt hypothyroidism.

Introduction

Type-1 diabetes mellitus is the most common endocrine-metabolic disorder of childhood and adolescence that is caused by abnormal metabolism of carbohydrates, fat, and protein, with hyperglycemia as a cardinal feature due to a deficiency of insulin secretion caused by non-reversible pancreatic cell destruction by an autoimmune process.[1] The universal rise in the prevalence of diabetes mellitus in children all around the world is a highly esteemed fact, reflecting an annual increase in the incidence of about 3–5%.[2,3] Pathogenesis is predominantly complex and multifactorial; it is caused by an incompletely understood multiplex interplay between risk-conferring genes and environmental factors evolving in immune-mediated, selective destruction of islet β-cell mass.[4,5,6] As a matter of fact, type-1 diabetes increases the susceptibility to developing other autoimmune diseases, such as autoimmune thyroid diseases,

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which are the most frequent autoimmunity (15–30%), celiac disease (4–9%), autoimmune gastritis (5–10%), Addison's disease (0.5%), and vitiligo (2–10%).[7,8,9,10] Moreover, the incidence of these diseases is higher in children and adolescents with type 1 diabetes mellitus as opposed to well-healthy children. Thoroughly, these autoimmune diseases are discovered by the detection of specific autoantibodies in blood serum prior to the development of clinically overt disease.[2,11] In regard to clinical forms, autoimmune thyroiditis exhibits usually as hypothyroidism (Hashimoto's thyroiditis) in 14–28%, subclinical hypothyroidism, and less frequently as hyperthyroidism (Graves' disease) in 0.5–7% of cases.[12,13,14]

It is noteworthy that the development of thyroid autoimmunity in type 1 diabetes mellitus enhances with age, duration of the disease, puberty, female gender, and long-term persistence of anti-GAD (anti-glutamic acid decarboxylase) antibodies.[15,16] Celiac disease is a chronic autoimmune gluten-sensitive enteropathy; the diagnosis of celiac disease is based on the determination of specific autoantibodies and verification of the disease by biopsy of the small intestine.[2,17] Approximately 2% of children and adolescents with type 1 diabetes are announced to have anti-adrenal antibodies, and <0.5% are diagnosed as having clinical adrenal insufficiency. [18] Vitiligo may precede the development of type 1 diabetes mellitus. Diabetes can develop in about 16–20% of vitiligo patients.[19]

The main objectives of this study are to detect the levels of anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) and anti-tissue transglutaminase antibodies (IgA and IgG) in type-1-diabetic children and adolescents. To further investigate the development of thyroid dysfunction and celiac disease in autoantibody-positive cases. To correlate the level of autoantibodies and glycemic control with the duration of diabetes.

Methods

In this cross-sectional study, a sample of one hundred cases of children and adolescents with type 1 diabetes mellitus was selected. The study was conducted at Raparine Teaching Hospital by gathering information from diabetic patients in inpatient wards and emergency units from May 2021 to May 2022. The inclusion criteria for involving the participants in this study include diabetic children > 1 year and adolescents <18- years, newly diagnosed cases, and known cases of diabetes mellitus. Infants less than 1 year old (as the type of diabetes is neonatal) were excluded from the study. The data were obtained from the parents or the participant, if the age is feasible, through a designed questionnaire including the following information:age, sex, duration of diabetes, presentation at diagnosis, insulin therapy type, family history of diabetes, both types 1 and 2, thyroid disease, and celiac disease.

The anthropometric measures (height and weight) and body mass index were assessed for each participant. Consequently, the procedure for withdrawing the blood samples was explained to the parents and participants. A venous blood sample was drawn out for anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies, thyroid function tests including thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3), IgA and IgG tissue transglutaminase antibodies, and hemoglobin A1c levels (HbA1c).

The results of serum levels of autoantibodies were assessed as follows: anti-thyroglobulin levels less than 115 IU/ml were considered negative, and more than 115 IU/ml were labeled as positive.[20] anti-thyroid peroxidase level less than 34 IU/ml was classified as negative, and more than 34 was considered positive,[21] and both IgA and IgG tissue transglutaminase levels less than 10 U/ml were identified as negative, and more than 10 U/ml was marked as positive.[22]

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The thyroid antibodies were conducted by ECL (ElectroChemiLuminescence) technology for immunoassay analysis (Cobas 6000) and tissue transglutaminase antibodies by ELISA technology (Algeria). The normal ranges for thyroid function tests were as follows: TSH 0.270–4.20 uIU/ml, FT3 1.30–3.10 nmol/L, FT4 66–181.00 nmol/L,[20] and HbA1c (4.2–6.5%).[23]

Endoscopy with a small intestinal biopsy was performed for participants whose serum levels of IgA and IgG tissue transglutaminase were higher than the normal range. The endoscopy was done in the operations room of the Raparine Teaching Hospital for Pediatrics by a pediatric gastroenterologist under general anesthesia. The blood samples, in conjunction with the biopsy sample, have been sent to a private laboratory in Raparine Teaching Hospital; those investigations are missing.

Ethical Considerations:

This study was approved by the ethical committee of the College of Medicine, Hawler Medical University, and followed the Helsinki Declaration of Medical Ethics in Human Research Conduction. Written informed consent was obtained from the participants. The personal information was stored for at least 2 years from the date of completion of the study.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). The Chi-square test of association was used to compare the proportions of two or more groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells in the table. A *P* value of ≤0.05 was considered statistically significant.

Results

The mean age (SD) was 10.2 (4.1) years. The median age was 10.8 years, and the age range was 1.3–17.5 years. Additionally, around half of cases (47%) were aged 10–14 years, and 65% were females (Table 1).

Table 1 Basic demographics characteristics of patients with type-1-diabetes

	No.	(%)
Age (years)		
< 5	15	(15.0)
5-9	25	(25.0)
10-14	47	(47.0)
≥ 15	13	(13.0)
Mean (SD)	10.2	(4.1)
Gender		
Male	35	(35.0)
Female	65	(65.0)
Total	100	(100.0)

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The duration of diabetes was less than one year for 38% of the patients. Most of the patients (83%) were on insulin injections. The majority (78%) of the patients had usual symptoms of diabetes at diagnosis, while 22% had diabetic ketoacidosis. More than one-third (35%) of the patients had no family history of diabetes, and another 32% had a family history of type-2 diabetes mellitus. Inversely, more than one-third (34%) of patients had a family history of thyroid disease, and only 3% had a history of celiac disease (Table 2).

Table 2 Crucial clinical historical points.

	No.	(%)
Duration of diabetes (years)		
< 1	38	(38.0)
1-4	36	(36.0)
≥ 5	26	(26.0)
Mean (SD)	2.6	(2.8)
Insulin therapy		
Insulin injection	83	(83.0)
Insulin pump	2	(2.0)
Insulin pen	15	(15.0)
Symptoms at diagnosis		
Usual symptoms of diabetes	78	(78.0)
Diabetic keto-acidosis	22	(22.0)
Family history of diabetes		
None	35	(35.0)
Type 1 DM	22	(22.0)
Type 2 DM	32	(32.0)
Both	11	(11.0)
Family history of thyroid disease		
Yes	34	(34.0)
No	66	(66.0)
Family history of celiac disease		
Yes	3	(3.0)
No	97	(97.0)
Total	100	(100.0)

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The prevalence rates of positive anti-thyroglobulin and anti-thyroid peroxidase antibodies were 24% and 26%, respectively, although the rates of positive tissue transglutaminase IgG and IgA antibodies were 8% and 10%, respectively (Table 3).

Around half (45.8%) of patients with positive anti-thyroglobulin antibodies had overt hypothyroidism, compared with 2.6% of those with normal anti-thyroglobulin antibodies (*P* <0.001). The same pattern was observed regarding antithyroid peroxidase antibodies, where it is evident in Table 4 that 50% of patients with positive antibodies had overt hypothyroidism, while none of those with normal antibodies had overt hypothyroidism (*P* <0.001). On top of that, subclinical hypothyroidism was perceived in 4.2% of cases with positive anti-thyroglobulin antibodies and in 3.8% of cases with positive anti-thyroid peroxidase antibodies. 3.9% of people with normal anti -thyroglobulin levels and 4.1% of people with normal anti-thyroid peroxidase antibody levels were found to have subclinical hypothyroidism (Table 4).

Table 3 Prevalence of autoimmune markers in patients with type-1-diabetes mellitus.

	No.	(%)
Anti-thyroglobulin antibodies		
Normal (< 115 IU/ml)	76	(76.0)
Positive (≥115 IU/ml)	24	(24.0)
Mean (SD)	74.0	(111.1)
Anti-thyroid peroxidase antibodies		
Normal (< 34 IU/ml)	74	(74.0)
Positive (≥ 34 IU/ml)	26	(26.0)
Mean (SD)	101.9	(185.4)
Tissue transglutaminase IgG antibodies		
Normal (< 10 (U/ml)	92	(92.0)
Positive (≥ 10 U/ml)	8	(8.0)
Mean (SD)	12.8	(45.2)
Tissue transglutaminase IgA antibodies		
Normal (< 10 U/ml)	90	(90.0)
Positive (≥ 10 U/ml)	10	(10.0)
Mean (SD)	15.9	(51.1)
Total	100	(100.0)

Table 4 Correlation between thyroid autoimmunity and thyroid function test.

		Thyroid function tests **				
		Normal	Overt hypothyroidism	Sub-clinical hypothyroidism	Other abnormalities	
	N	No. (%)	No. (%)	No. (%)	No. (%)	*P*
Anti-thyroglobulin antibodies						
Normal	76	68 (89.5)	2 (2.6)	3 (3.9)	3 (3.9)	
Positive	24	12 (50.0)	11 (45.8)	1 (4.2)	0 (0.0)	< 0.001*
Anti-thyroid peroxidase antibodies						
Normal	74	68 (91.9)	0 (0.0)	3 (4.1)	3 (4.1)	
Positive	26	12 (46.2)	13 (50.0)	1 (3.8)	0 (0.0)	< 0.001*
Total	100	80 (80.0)	13 (13.0)	4 (4.0)	3 (3.0)	

*By Fisher's exact test. **Normal: Both T4 and TSH are normal. Overt hypothyroidism: Low T4 and high TSH. Sub-clinical hypothyroidism: Normal T4 and high TSH. Other abnormalities: Normal TSH with either low or high T4.

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It is clearly evident in Table 5 that older age groups (≥ 10 years) were associated with higher rates of positive anti-thyroid peroxidase antibodies (*P* = 0.021) and positive anti-thyroglobulin antibodies (*P* = 0.007). No significant association was detected between gender and the above-mentioned antibodies (*P* = 0.364 and *P* = 0.432, respectively). It is quite apparent in this table that there is no significant association between family history of thyroid disease and the prevalence of positive anti-thyroid peroxidase antibodies (*P* = 0.577) and positive anti-thyroglobulin antibodies (*P* = 0.678). Over and above that, table 5 stated that the longer the duration of diabetes, the higher the prevalence of positive thyroid autoantibodies, but the differences were not significant.

Furthermore, the prevalence of positive anti-thyroid peroxidase antibodies was 27.1% among patients with uncontrolled diabetes, compared with 0% among patients with controlled diabetes (*P* = 0.570). The prevalence of positive anti-thyroglobulin antibodies was 25% among patients with uncontrolled diabetes, while none of the children with controlled diabetes had a high level of anti-thyroglobulin antibodies (*P* = 0.570), as revealed in Table 5.

Table 5 Prevalence of positive thyroid autoantibodies by the studied factors.

		Positive anti-thyroid peroxidase Ab		Positive anti-thyroglobulin Ab	
	N	**No. (%)**	***P***	**No. (%)**	***P***
Age (years)					
< 5	15	0 (0.0)		0 (0.0)	
5-9	25	5 (20.0)		3 (12.0)	
10-14	47	17 (36.2)		17 (36.2)	
≥ 15	13	4 (30.8)	0.021*	4 (30.8)	0.007*
Gender					
Male	35	11 (31.4)		10 (28.6)	
Female	65	15 (23.1)	0.364†	14 (21.5)	0.432†
Family history of thyroid disease					
Yes	34	10 (29.4)		9 (26.5)	
No	66	16 (24.2)	0.577†	15 (22.7)	0.678†
Duration of diabetes (years)					
< 1	38	7 (18.4)		5 (13.2)	
1-4	36	10 (27.8)		10 (27.8)	
≥ 5	26	9 (34.6)	0.333†	9 (34.6)	0.114†
HbA1c					
Controlled	4	0 (0.0)		0 (0.0)	
Uncontrolled	96	26 (27.1)	0.570*	24 (25.0)	0.570*
Total	100	26 (26.0)		24 (24.0)	

*By Fisher's exact test. †By Chi square test.

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Celiac disease has been proven by endoscopy and biopsy in nine patients with positive tissue transglutaminase antibodies (*P* <0.001). Beyond that, no significant association was identified between glycemic control and biopsy-proven celiac disease (Table 6).

Discussion

Our current study delineated the interrelationship between type-1 diabetes in children and adolescents and other autoimmune diseases by determining autoimmune markers as a tool for early identification of such diseases. It is remarkable to mention the coexistence of autoimmune antibodies in individuals with type-1 diabetes mellitus in different countries and ethnic groups.[24] This study revealed an increased prevalence of positive anti-thyroid peroxidase and anti-thyroglobulin antibodies that entirely matched the South Korean study,[25] showing a prevalence of positive anti-thyroglobulin antibodies close by (22.5%) but higher than the results of Jonsdottire et al.[26] and Ardestani et al.[27] As mentioned above, this variation in data can be clarified by the fact that there is a geographical distribution of autoimmune diseases, dissimilarity in genetic factors, age, and sex of the studied population, together with methods used for the measurement of anti-bodies. [27] The prevalence of positive tissue transglutaminase IgA and IgG antibodies throughout our study was high, which is halfway the findings of Italian (12,8%, *P* = 0.005)[28] and Brazilian (7%) studies.[14] The diagnosis of biopsy-proven celiac disease was confirmed in nine cases of type 1 diabetes in our study; all were asymptomatic with no clinical manifestations of celiac disease (silent celiac disease). Regarding thyroid status in relation to thyroid autoimmunity, our study evidenced that around half of the cases of positive anti-thyroglobulin and anti-thyroid peroxidase antibodies had overt hypothyroidism, which is within reach of the findings of Ardestani et al.[27]

It is worth mentioning that three cases with normal anti-thyroid antibody levels had subclinical hypothyroidism. This highlights the importance of performing both the antibody level and the thyroid function test as screening tools. This study proved the

Table 6 Intestinal biopsy findings in relation to tissue transglutaminase antibodies level and glycemic control.

	Intestinal biopsy and endoscopic findings			
	Celiac	No celiac	Total	
	No. (%)	No. (%)	No. (%)	*P*
Tissue transglutaminase Ig G				
High	8 (88.9)	0 (0.0)	8 (8.0)	
Normal	1 (11.1)	91 (100.0)	92 (92.0)	< 0.001*
Tissue transglutaminase IgA				
High	9 (100.0)	1 (1.1)	10 (10.0)	
Normal	0 (0.0)	90 (98.9)	90 (90.0)	< 0.001*
HbA1c				
4.2-6.5	0 (0.0)	4 (4.4)	4 (4.0)	
> 6.5	9 (100.0)	87 (95.6)	96 (96.0)	1.000*
Total	9 (100.0)	91 (100.0)	100 (100.0)	

*By Fisher's exact test.

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fact of increased autoimmunity prevalence with increasing age, ensuring that the maximum autoimmune activity is observed during puberty[16], as the most affected age group with positive anti-thyroid antibodies was≥10- years and no patient was affected less than 5 years, totally agreeing with the Iraqi study[20] showing the same result. As it is known, there is a well-established relationship between thyroid autoantibodies and female sex. This is explained by the reality that female sex steroid hormones, such as estradiol, hasten the progression of autoimmune diseases by strengthening the pathway of T-helper lymphocyte type 2.

On the other hand, androgens have a defensive effect.[2,16] In spite of this fact, our study exhibits consequential gender-thyroid autoantibody dissociation. This was agreed upon by Ardestani et al.[27] and contradicted by Jonsdottir et al.[26]

Our contemporary study put on view that there is no remarkable association between duration of diabetes and positivity of thyroid antibodies, making certain the findings of Alves et al. (P = 0.809).[14]

This study demonstrated no notable association between a family history of thyroid diseases and positive thyroid autoimmunity. No cardinal relation was found in this study between glycemic control and thyroid antibodies, inconsistent with the results of the Iraqi study.[20] One patient in this study had type-1 diabetes mellitus with both overt hypothyroidism and celiac disease. As we know, vitiligo is an autoimmune disease that induces white-colored patches on the skin, but oculocutaneous albinism is a genetic disorder that causes the skin to appear exceptionally light.[30,31] Interestingly, our study revealed only one female patient who has both oculocutaneous albinism and type 1 diabetes. To our knowledge, it is not yet clear if there is any association between oculocutaneous albinism and type 1 diabetes mellitus.

Conclusion

This study ratified the increased prevalence of thyroid and celiac-related autoantibodies among children and adolescents with type 1 diabetes mellitus. It was concluded in this study that the emergence of autoimmune thyroid disease and celiac disease in positive anti-thyroglobulin, anti-thyroid peroxidase, and tissue transglutaminase (IgA and IgG) antibodies with no symptoms of both illnesses, as the onset of an autoimmune response and the appearance of autoantibodies emerge many years before the manifestations of the disease. Because of the concomitance of type 1 diabetes with these two autoimmune diseases, it is critical and essential to investigate at diagnosis and year by year the existence of the related autoantibodies to reduce the impact on the course of the disease.

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Competing interests

The authors declare that they have no competing interests.

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