ORIGINAL ARTICLE

CELIAC AND AUTOIMMUNE THYROID DISEASE IN PATIENTS WITH ANTI-GAD POSITIVE TYPE-1 DIABETES MELLITUS

Versha Rani Rai, Zubair Khoso, Maira Riaz, Roshia Parveen, Shazia Mahar, Mohsina Noor

National Institute of Child Health Karachi-Pakistan

Background: Type-1 diabetes mellitus (T1DM) and autoimmune thyroid disease can occur concomitantly and patients with TIDM have a high risk of other autoimmune conditions like thyroid disease and celiac disease. This study aimed to analyze the association of anti-GAD positive T1DM with anti-thyroid antibodies and celiac disease. **Methods:** This cross-sectional study was conducted at the Department of Paediatric Endocrinology & Diabetes, National Institute of Child Health, Karachi Pakistan from July 2022 to December 2022. A total of 115 children of both genders aged between 1–18 years having known T1DM were analyzed. Children with chronic kidney disease or chronic liver disease were excluded. Those children were also not included whose parents/caregivers did not wish their children to be part of this research. The blood sample of each child was taken in a sterilized container and sent to an institutional laboratory for biochemical investigations. **Results:** In a total of 115 patients, 67 (58.3%) were female and 48 (41.7%) males. The mean age was 8.87±3.43 (ranging between 1.5–17 years). The mean HbA1c was 11.86±7.31%. It was found that anti-GAD IgG was having signification association with celiac disease (p<0.001). Significant correlation of anti-GAD positive antibodies with Ttg-IgG antibodies (correlation coefficient=0.303, p=0.001), thyroid peroxidase antibodies (correlation coefficient=0.228, p=0.001). **Conclusion:** High proportions of children with anti-GAD positive T1DM patients were found to have thyroid disorders and celiac disease. A significant correlation was found between anti-GAD positive antibodies, celiac disease and anti-thyroglobulin antibodies.

Keywords: Anti-GAD antibodies; Anti-thyroid antibodies; Celiac disease; HbA1c; Type-1 diabetes mellitus

Citation: Rai VR, Khoso Z, Riaz M, Parveen R, Mahar S, Noor M. Celiac and autoimmune thyroid disease in patients with anti-GAD positive type-1 diabetes mellitus. J Ayub Med Coll Abbottabad 2023;35(3):452–6.

DOI: 10.55519/JAMC-03-12011

INTRODUCTION

Recently International Diabetes Federation (IDF) published facts and figures reports on diabetes mellitus and reported that type-1 diabetes mellitus (T1DM) is affecting more than one million children throughout the world.[1] Type-1 diabetes mellitus and autoimmune thyroid disease can occur concomitantly.[2] Patients with TIDM have a high risk of other autoimmune conditions like thyroid disease and celiac disease.[3] Patients with long-standing TIDM have a 27–44% chance of positive antithyroid antibodies and a 23–25% chance of developing hypothyroidism which can be overt or subclinical.[4] Anti-Gad antibody is the most prevalent positive antibody found in more than 70% of children diagnosed with T1DM although its titre is highest in 1st year of the diagnosis and declines after that period due to a decline in residual beta cells.[4]

Autoimmune thyroid diseases are described as dysfunction in the monitoring of self-antigen and the presence of autoantibodies like thyroid peroxidase antibodies (anti-TPO), antithyroglobulin antibody and thyroid stimulating hormone autoantibodies.[5] Graves' disease and Hashimoto thyroiditis are the two commonest types of autoimmune thyroid diseases. The prevalence of Hashimoto thyroiditis is more than Graves' disease in type I diabetes mellitus (T1DM).[6] T1DM and autoimmune thyroid disease have similar immunogenetic susceptibility. Antibodies like anti-TPO and antithyroglobulin can be determined long before dysfunction of the thyroid.[6] Few studies have shown an association of Anti-Gad positive antibodies in T1DM with antithyroid and celiac antibodies but no study has been conducted so far in Pakistan to explore this association.[5]

Many factors are related to thyroid autoimmunity in the general population like heredity, increased age, female gender, use of contraceptives and puberty whereas in T1DM, female gender, increased age and positive anti-GAD are major contributors.[7,8] T1DM is associated with anti-insulin antibodies and these antibodies precede long before the onset of T1DM. The most commonly associated antibodies are Anti GAD

(80%), IA2 (60%) followed by IA and Znt8.[9] People with celiac disease (CD) are unable to consume gluten-containing meals because gluten triggers the autoimmune reaction in these patients, resulting in the loss of tiny intestinal villi & malabsorption.[10] Celiac disease, during which antibodies to dietary gluten & autoantibodies to endomysium (EMA) are present, is reported to affect about 5% T1DM patients.[11]

Though there is a lot of data available on T1DM association of anti-GAD antibodies with anti-thyroid antibodies and celiac antibodies have been scarcely researched. The study was planned to see the association of anti-Gad antibodies with celiac and thyroid disorders. Moreover, it is a worldwide public health problem and puts a substantial burden on health care so, it is important to conduct research on this topic. This study aimed to determine the association of anti-GAD antibodies type-1 diabetes mellitus with anti-thyroid antibodies and celiac disease

MATERIAL AND METHODS

This cross-sectional study was conducted at The Department of Paediatric Endocrinology & Diabetes, National Institute of Child Health, Karachi Pakistan from July to December 2022. Approval from "Institutional Ethical Review Board (IERB)" was acquired (reference: IERB-52/2021, dated: 24-1-2022). Written and informed consent were obtained from parents/caregivers. The sample size of 115 was calculated by taking the prevalence of celiac disease as 5%,[11] considering the confidential level as 95% and the margin of error as 4%. Non-probability consecutive sampling technique was adopted. Inclusion criteria were children of both genders aged between 1–18 years having known T1DM. Children with chronic kidney disease or chronic liver disease were excluded. Those children were also not included whose parents/caregivers did not wish their children to be part of this research.

All children of T1DM with raised insulin autoantibodies IAA were included. Patients with diabetic ketoacidosis defined as venous ph<7.3 or serum bicarbonate concentration <15 mmol/L, serum glucose concentration >200 mg/dL together with ketonemia, glucosuria, and ketonuria confirmed through the blood and urine test" or those having evidence of pancreatic calcifications (confirmed through the abdominal x-ray; hyperdense foci in front of T2 and L1 vertebral body) were excluded. Patients with other known causes of malabsorption as per the medical record of the patient or those whose parents/caregivers did not wish their children to be a part of this study were excluded. T1DM was labelled if the child taking anti-diabetic therapy (insulin) or had fasting blood glucose ≥126 mg/dL on more than one separate occasion. Insulin autoantibodies (IAA) test was done by radioimmunoassay (RIA) and confirmed on the presence of one of the following tests: positive anti-insulin antibodies IgG if >2.4 U/ml; positive insulinoma-associated antigen 2 (IA2) if >10 IU/ml; positive anti-GAD IgG if >5 IU/ml; positive antithyroglobulin if >40 IU/ml; positive thyroid peroxidase antibody if >35 IU/ml; positive TTG IgA if >20U/ml; positive TTG IgG if >20u/ml. Celiac disease was labelled if the tissue transglutaminase IgA antibody >20 times the upper normal limit or biopsy-proven in IgA sufficient individual. (>100 U/ml).

The blood sample of each child was taken in a sterilized container and sent to an institutional laboratory for IAA test including anti-insulin IgG, IA2, and anti-GAD IgG for T1DM and thyroid profile, and TTG IgG and IgA evaluation. Hypothyroidism was defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. Mild or subclinical hypothyroidism was defined by TSH concentrations above the reference range and free thyroxine concentrations within the normal range. Hyperthyroidism referred to increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis was labelled by the clinical manifestations of inappropriately high thyroid hormone action in tissues. Normal values of T3 free T4 and TSH were taken as T3 0.92–2.76 nmol/ml, 0.7–1.9 ng/dl and 0.5–5 uIU/ml respectively. A special proforma was plotted to record study data.

After the collection of the data, data was entered into SPSS-26.0. Mean and standard deviation were calculated for quantitative variables like age (years), duration of T1DM (months), fasting glucose (mg/dL), anti-insulin IgG (U/ml), IA2 (IU/ml), anti-GAD IgG (IU/ml), levels of TSH (μU/ml), T3 (ng/ml), T4 (μg/dl), antithyroglobulin antibody (IU/ml), and thyroid peroxidase antibody (IU/ml) TTG ig A and TTG IgG. Frequency and percentages were calculated for gender, duration of T1DM, and thyroid disorder. Effect modifiers like gender, age, and duration of T1DM, were controlled by stratification with a thyroid disorder by applying a chi-square test and taking a p-value ≤0.05 as significant.

RESULTS

Of a total of 115 patients, 67 (58.3%) were female and 48 (41.7%) males. The mean age was 8.87±3.43 (ranging between 1.5–17 years). The mean HbA1c

was 11.86±4.31%. Anti-GAD IgG antibodies were positive in 40 (34.8%) children. None of the patients were islet cell antibodies IgG positive. Table-1 is showing clinical and biochemical findings.

It was found that positive anti-GAD IgG is having significant association with celiac disease (p<0.001). Positive thyroid peroxidase antibodies were found to have a significant relationship with positive anti-GAD antibodies (p<0.001). The distribution of demographic, clinical and biochemical variables with regard to anti-GAD IgG is shown in table-2.

A weak but significant correlation between the Tissue Transglutaminase IgG antibody and anti-GAD antibodies was found (according to Spearman's rank correlation coefficient as 0.303 with p=0.001) as shown in figure-1. Figure-2 is showing the correlation between the Tissue Transglutaminase IgA antibody and anti-GAD antibodies and a weak but strong correlation was found according to Spearman's rank correlation coefficient as 0.314 (p=0.003). The correlation between the thyroid peroxidase antibodies and anti-GAD antibodies was weak but significant (according to Spearman's rank correlation coefficient as 0.228 with p=0.014) as shown in figure-3. Figure-4 is showing a correlation between anti-GAD antibodies and antithyroglobulin antibodies (according to Spearman's rank, the correlation coefficient was 0.054 with p=0.570).

Table-1: Clinical and Biochemical Parameters (n=115)

Parameters		**Number (%) / Mean±SD**
Gender	Male	48 (41.7)
	Female	67 (58.3)
Age (years)	1-5	23 (20.0)
	6-10	50 (43.5)
	11-18	42 (36.5)
HbA1c (%)	≤7	10 (8.7)
	>7	105 (91.3)
T1DM antibodies	Insulinoma-associated antigen 2, positive	14 (12.2)
	Anti-GAD IgG, positive	40 (34.8)
	Anti-Insulin antibodies IgG, positive	8 (7.0)
Celiac Disease Antibodies	TTG IgA, positive	17 (14.8)
	TTG IgG, positive	22 (19.1)
Autoimmune thyroid disease antibodies	TPO antibodies	40 (34.8)
	Anti-thyroglobulin	40 (34.8)
Thyroid Dysfunction	Normal	94 (81.7)
	Overt Hypothyroidism	2 (1.7)
	Subclinical Hypothyroidism	6 (5.2)
	Overt Hyperthyroidism	3 (2.6)
	Subclinical Hyperthyroidism	8 (7.0)
	Thyrotoxicosis	2 (1.7)

Table-2: Distribution of demographic, clinical and biochemical variables with regard to IAA2 and anti-GAD IgG

Parameters		**Anti-GAD IgG**		***p*-value**
		Positive (n=40)	**Negative (n=75)**	
Gender	Male	15 (37.5%)	33 (44.0%)	0.501
	Female	25 (62.5%)	42 (56.0%)	
Age (years)	1-5	6 (15.0%)	17 (22.7%)	0.603
	6-10	19 (47.5%)	31 (41.3%)	
	11-18	15 (37.5%)	27 (36.0%)	
HbA1c (%)	≤7	2 (5.0%)	8 (10.7%)	0.304
	>7	38 (95.0%)	67 (89.3%)	
Thyroid Dysfunction	Normal	32 (80.0%)	62 (82.7%)	0.215
	Overt Hypothyroidism	2 (5.0%)	-	
	Subclinical Hypothyroidism	1 (2.5%)	5 (6.7%)	
	Overt Hyperthyroidism	2 (5.0%)	1 (1.3%)	
	Subclinical Hyperthyroidism	3 (7.5%)	5 (6.7%)	
	Thyrotoxicosis	-	2 (2.7%)	
Celiac Disease		20 (50.0%)	7 (9.3%)	<0.001
Thyroid Perxodidase antibody, positive		24 (60.0%)	16 (21.3%)	<0.001
Antithyroglobulin, positive		18 (45.0%)	22 (29.3%)	0.093

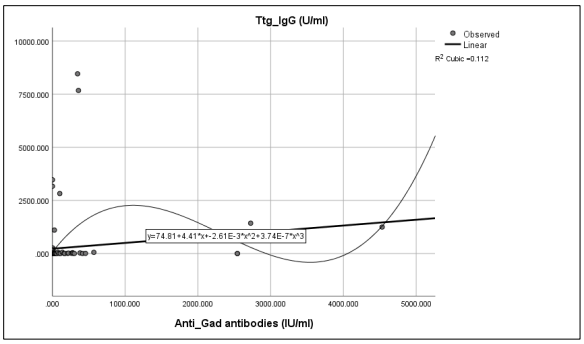

Figure-1: Correlation between the Tissue Transglutaminase IgG antibody and anti-GAD antibodies.

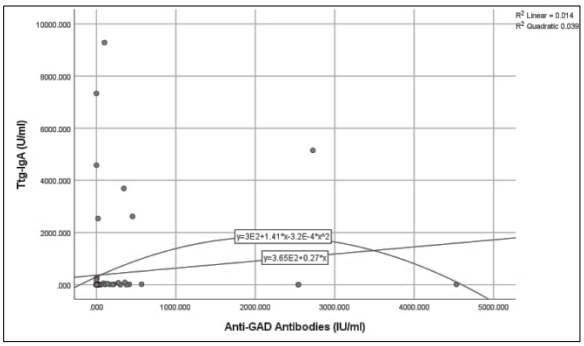

Figure-2: Correlation between the Tissue Transglutaminase IgA antibody and anti-GAD antibodies.

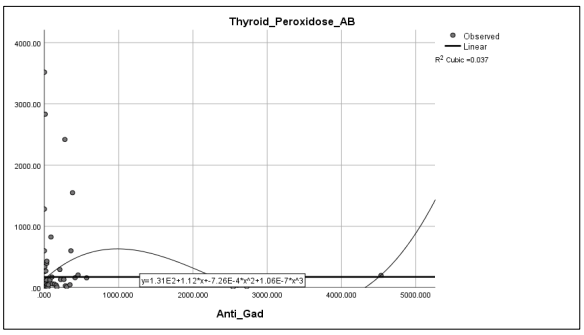

Figure-3: Correlation between the Thyroid peroxidase antibodies and anti-GAD antibodies.

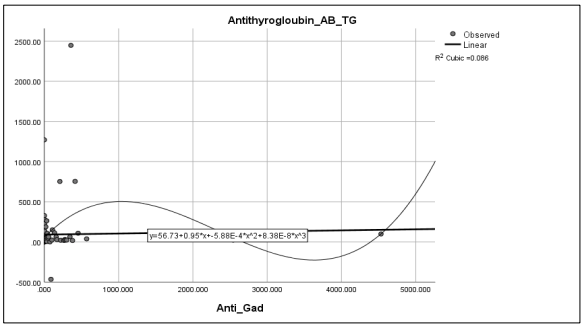

Figure-4: Correlation between the anti-thyroglobulin and anti-GAD antibodies.

DISCUSSION

The present study seems to be the first one from Pakistan to evaluate details about the relationship T1DM with autoimmune thyroid disease and celiac disease. In this study, celiac disease was noted among 23.5% of patients. The literature reveals that 10–15% of individuals with T1D express the exact serological indicators of celiac CD.[12,13] The relationship between CD and T1DM was initially documented by Smith-Walker and Grigor in the 1960s.[14] These days, this association is rather well established and our findings are quite consistent with what is described in the literature.[12,13,15–20]

We noted that large proportions of T1DM patients were having thyroid-related abnormalities. Autoimmune thyroid disease antibodies like TPO antibodies and anti-thyroglobulin were found among 34.8% of patient's Abnormal thyroid functions were revealed by 18.3% of patients. Thyroid diseases represent a significant burden of endocrine disorders among children and are tatted as the 2nd commonest abnormality after diabetes mellitus globally.[8] Thyroid hormones are vital for children's early neurocognitive development and overall growth and development.[9] Hypothyroidism is common in children having T1DM and the literature highlights the proportion of hypothyroidism as 0.1–2% in the general population whereas the occurrence of hypothyroidism in T1DM is described in the ranges between 3–30%.[10,11] Hyperthyroidism is a relatively rare condition in children but frequent with other autoimmune conditions. The incidence is thought to be rising and is about 0.1/100000 person-years in young children to 3/100000 person-years in adolescents.[16] The prevalence of hypothyroidism in children having T1DM was reported by different researchers; such as Fatourechi *et al* reported the 9.6% prevalence of hypothyroidism in T1DM children.[10] Sharma *et al*. reported the prevalence of hypothyroidism as 14.1%, and hyperthyroidism in 3.3% among T1DM children and adolescents respectively.[16] Hypothyroidism and hyperthyroidism were noted among 6.9% and 9.6% T1DM patients respectively. In this study, no association of HbA1c with thyroid antibodies, T1DM antibodies or TtG antibodies were found and these findings are quite consistent with what others described in the past.[21–23]

Study Limitations: As this was a single-center study conducted on a relatively small sample size, multi-center trials involving a large sample of T1DM patients should be planned to further verify and add what is known about the spectrum and relationship of autoimmune thyroid diseases and celiac disease. As this was a cross-sectional study, the affected patients should be prospectively followed up to review the

impact of these abnormalities on short-term as well as long-term outcomes.

CONCLUSION

High proportions of children with anti-GAD positive T1DM patients were found to have thyroid disorders and celiac disease. A significant correlation was found between anti-GAD positive antibodies, celiac disease and anti-thyroglobulin antibodies.

Conflict of interest: Nill

AUTHORS' CONTRIBUTION

VRR: Data collection, drafting. ZK: Study concept, supervision. MR: Critical revisions, proofreading. RP: Literature review, Discussion. SM: Data analysis, discussion. MN: Data interpretations, Literature review

REFERENCES

1. Orzan A, Novac C, Mihaiela MI, Tirgoviste CI, Balgradean M. Type 1 diabetes and thyroid autoimmunity in children. Maedica 2016;11(4):308.
2. Gul K, Ustun I, Aydin Y, Berker D, Erol HK, Unal M, *et al*. Autoimmune thyroid disease in patients with anti-GAD positive type 1 diabetes mellitus. Cent Eur J Med 2009;4(4):415–22.
3. Kakleas K, Paschali E, Kefalas N, Fotinou A, Kanariou M, Karayianni C, *et al*. Factors for thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Ups J Med Sci 2009;114(4):214–20.
4. Li L, Liu S, Yu J. Autoimmune thyroid disease and type 1 diabetes mellitus: same pathogenesis; new perspective? Ther Adv Endocrinol Metab 2020;11:2042018820958329.
5. Kawasaki E. Type 1 diabetes and autoimmunity. Clin Pediatr Endocrinol 2014;23(4):99–105.
6. Karuranga S, Fernandes JDR, Huang Y, Malanda B. IDF Diabetes Atlas. 8th ed. International Diabetes Federation; 2018.
7. Oyenusi EE, Ajayi EO, Akeredolu FD, Oduwole AO. Pattern of thyroid disorders in children and adolescents seen at the Lagos university teaching hospital, Nigeria, over a 10-year period. Niger Med J 2017;58(3):101–6.
8. Leung AKC, Leung AAC. Evaluation and management of the child with hypothyroidism. World J Pediatr 2019;15(2):124–34.
9. Krzewska A, Ben-Skowronek I. Effect of associated autoimmune diseases on type 1 diabetes mellitus incidence and metabolic control in children and adolescents. BioMed Res Int 2016;2016:6219730.
10. Fatourechi A, Ardakani HM, Sayarifard F, Sheikh M. Hypothyroidism among pediatric patients with type 1 diabetes mellitus, from patients' characteristics to disease severity. Clin Pediatr Endocrinol 2017;26(2):73–80.
11. Léger J, Carel JC. Hyperthyroidism in childhood: causes, when and how to treat. J Clin Res Pediatr Endocrinol 2013;5(Suppl 1):50–6.
12. Bhadada SK, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, *et al*. Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India. J Gastroenterol Hepatol 2011;26(2):378–81.
13. Agrawal RP, Rathore A, Joshi A, Changal H, Kochar DK. Prevalence of celiac disease in type 1 diabetes mellitus in North West Rajasthan, India. Diabetes Res Clin Pract 2008;79(1):e15–6.
14. Walker-Smith JA, Grigor W. Cœliac disease in a diabetic child. Lancet 1969;293(7603):1021.
15. Pulikkal AA, Kolly A, Kumar KP, Shivaprasad C. The seroprevalence of immunoglobulin A transglutaminase in type 1 diabetic patients of South Indian origin. Ind J Endocrinol Metabol 2016;20(2):233–7.
16. Sharma B, Nehara HR, Saran S, Bhavi VK, Singh AK, Mathur SK. Coexistence of autoimmune disorders and type 1 diabetes mellitus in children: an observation from western part of India. Indian J Endocrinol Metab 2019;23(1):22–6.
17. Marwaha RK, Garg MK, Tandon N, Kanwar R, Narang A, Sastry A, *et al*. Glutamic acid decarboxylase (anti-GAD) & tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity. Indian J Med Res 2013;137(1):82.
18. Basu M, Pandit K, Banerjee M, Mondal SA, Mukhopadhyay P, Ghosh S. Profile of auto-antibodies (Disease related and other) in children with type 1 diabetes. Indian J Endocrinol Metab 2020;24(3):256–9.
19. Riseh SH, Farhang MA, Mobasseri M, Jafarabadi MA. The Relationship between Thyroid Hormones, Antithyroid Antibodies, Anti-Tissue Transglutaminase and Anti-Gliadin Antibodies in Patients with Hashimoto's Thyroiditis. Acta Endocrinol (Buchar) 2017;13(2):174–9.
20. Oujamaa I, Sebbani M, Elmoumou L, Bourrahouate A, El Qadiry R, El Moussaoui S, *et al*. The Prevalence of Celiac Disease-Specific Auto-Antibodies in Type 1 Diabetes in a Moroccan Population. Int J Endocrinol 2019;2019:7895207.
21. Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A, *et al*. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care 2003;26(4):1181–5.
22. Hansen D, Bennedbaek FN, Høier-Madsen M, Hegedüs L, Jacobsen BB. A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes. Eur J Endocrinol 2003;148(2):245–51.
23. Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Effect of age, gender and HLA type. Horm Res 1999;52(3):113–8.

Submitted: April 18, 2023	*Revised: July 7, 2023*	*Accepted: July 12, 2023*

Address for Correspondence:

Versha Rani Rai, Assistant Professor, Paediatrics, National Institute of Child Health Karachi-Pakistan
Cell: +92 333 363 6460
Email: versharai.sg@gmail.com