Open Access

Pak J Med Res
Vol. 62, No. 1, 2023

Original Article

Thyroid Disorder and Association of Insulin Antibodies with Thyroid Antibodies in Children with Type 1 Diabetes Mellitus

Muniba Jalil[1], Mohsina Noor Ibrahim[2], Sajid Ali[3], Sidra Saleem[1], Shahzadi Dilawar[1], Arit Parkash[4]

Department of Pediatric Medicine[1], Department of Paediatric Endocrinology[2], Department of Paediatric Surgery[3], Department of Pediatric Gastroenterology[4], National Institute of Child Health, Karachi.

Abstract

Background: During past decade, type 1 diabetes (T1DM) disease burden has increased among all ages, but the rapid growth was seen in young children. It is quite common to have coexistence of other autoimmune disorders among children having T1DM.
Objective: To evaluate the frequency of thyroid dysfunction in children having T1DM and association of insulin antibodies with thyroid antibodies in TIDM.
Study type, settings & duration: This cross-sectional study was performed at Department of Endocrinology, National Institute of Child Health, Karachi from June to December 2021.
Methodology: Children of age 2-17 years with T1DM were enrolled for this the study. Patients' socio-demographic and clinical profile was documented in a pre-designed proforma. SPSS version 21 was used for statistical analysis.
Results: Mean age of patients was 10.49±4.24 years. Out of 133 children, 59.4% were females. 18.79% were positive for Insulin autoantibody, while 16.5% were positive for IA-2 and 33.1% for generalized anxiety disorder (GAD). 22.6% of patients were positive for thyroid peroxidase (TPO) and 39.09% were positive for Tg-AB. A total of 84.2% of subjects had euthyroidism, 13.53% of subjects had hypothyroidism (subclinical or clinical) while 2.3% had hyperthyroidism. A significant association among the subjects with positive insulin autoantibodies and those with thyroglobulin antibodies was observed.
Conclusion: A positive association between Insulin and Thyroglobulin antibodies suggests that patients with positive insulin antibodies are more likely to have thyroglobulin antibodies. Therefore, it is imperative to test and manage these markers on a frequent and regular basis to avoid the aggravation of the health of the patients suffering from type 1 diabetes mellitus.
Key words: Type 1 diabetes mellitus, hypothyroidism, hyperthyroidism, autoinsuline antibodies, antithyroid antibodies.

Introduction

Autoimune destruction of beta cells in pancreas leads to Type 1 diabetes mellitus (T1DM), as a consequence insulin deficiency occurs.[1] Globally, T1DM prevalence is rising and has almost doubled during previous 40 years with a prevalence of 9.5 per 10,000 persons. Incidence is higher among girls of age group 5-9 years and boys of age 10-14 years. Contrasting to majority of autoimmune disorders, T1DM is more frequent in male gender.[2]

During previous years, burden of T1DM disease burden has increased among all ages including both the gender and different ethnicities but the rapid growth has been seen in young children.[3] Recently international diabetes federation (IDF) published the facts and figures reports on diabetes mellitus and reported that T1DM is

Corresponding Author:
Muniba Jalil
Department of Pediatric Medicine
National Institute of Child Health
Karachi.
Email: muniba927@gmail.com
Received: 26 May 2022, **Accepted:** 15 February 2023,
Published: 05 May 2023

Authors Contribution

MJ conceptualized the project. SS & SD did the data collection. MJ, MNI & AP did the literature search. SA, SS & AP performed the statistical analysis. Drafting, revision & writing of manuscript were done by MJ, MNI & SS.

affecting more than one million children throughout the world, as well as approximately 21 million children suffering from diabetes at the time of birth.[4] In pediatric endocrinology, thyroid disorders contribute in higher proportion, being ranked second disorders after diabetes across the world.[5] Thyroid disorders are more frequently associated with T1DM due to a mutual genetic disposition. The immune-mediated damage is considered to be activated by ecological factors in inherently vulnerable individuals. Autoimmune thyroid disease is divided into hypothyroidism and hyperthyroidism, among which hypothyroidism is more common.[6,7]

Comparatively, hyperthyroidism is an infrequent condition in children but is frequent with other autoimmune conditions. The incidence is growing and is nearly 0.1 per 100000 person-years in young children to 3 per 100000 person-years in adolescents.[8] Different prevalence of hypothyroidism in children having T1DM was reported by the different researchers; such as Fatourechi A, et al. reported the 9.6% prevalence of hypothyroidism in T1DM children.[9] Another study by Sharma B, et al. reported the prevalence of hypothyroidism 14.1% and hyperthyroidism in 3.3% of T1DM children.[10]

Studies on thyroid disorders in T1DM children have been performed throughout the world,[9,10] but local data regarding association of antibodies of insulin and thyroid is not available in the population of Sindh. Even though timely recognition of autoimmune thyroid disease is very important and of utmost because clinical symptoms of thyroid disorder are vague and most of the children remain undiagnosed. The aim of the study was to ascertain the frequency of thyroid disorder in children having T1DM and association of insulin antibodies with thyroid disorders. Therefore, this study was designed to generate evidence based data that would be helpful in the early detection of thyroid disorder in children suffering from T1DM.

Methodology

This cross-sectional study was performed at the Pediatric Endocrinology Department of National Institute of Child Health (NICH), Karachi from June to December, 2021. A written consent was obtained from parents of children. All children of either gender suffering from T1DM of age 2-17 years were included as study subjects while children whose parents/ guardian did not give consent were excluded. The sample size was calculated based on findings of a previous study reporting a 9.6% prevalence of hypothyroidism in T1DM children[9]. Taking confidence interval of 95% and 5%margin of error, a sample size of 133 patients was required. Sample size estimation was performed on Open-Epi online sample size calculator. A non-probability sampling technique, consecutive sampling was used to recruit the subjects.

A blood sample of 2 ml was collected in a sterilized container and sent to a laboratory for detection of insulin autoantibodies including anti-insulin IgG, Insulinoma associated antigen 2 (IA2), and Anti-glumatic acid decarboxylase (anti-GAD) for T1DM.Similarly, thyroid antibodies including Anti-thyroid peroxidase, (Anti-TPO) and Anti-thyroglobulin (ATG). Thyroid Stimulating Hormone (TSH), thyroxin (T4), and triiodothyronine (T3) levels were estimated for the confirmation of thyroid disorder. Insulin autoantibodies (IAA) test was done by radioimmunoassay (RIA) and a sample was declared positive for Insulin antibodies if it contained >2.4 U/ml anti-insulin antibodies IgGs, >10 IU/ml IA2, and >5 IU/ml Anti-GAD IgGs. Similarly, thyroid antibodies including antithyroglobulin, and thyroid peroxidase antibody >4 IU/ml were declared positive.

Data was entered in SPSS version 21 for statistical analysis. Frequency and percentages were computed for categorical variables. Mean and standard deviation was reported to present numerical variable. Chi-square or Fisher-exact test was applied to determine association of insulin antibodies and thyroid antibodies. P-values of ≤ 0.05 were taken as significant.

The ethical approval was obtained from Institutional Ethical Review Board (IRB) of National Institute of Child Health, Karachi vide IRB # 41/2019.

Results

Total 133 patients were enrolled into the study. Mean age of the subjects was 10.49±4.24 years and majority of them were females 79 (59.4%). Total 25 (18.8%) patients were positive for Insulin autoantibody, while 22 (16.5%) were positive for IA-2 and 44 (33.1%) for generalized anxiety disorder (GAD). Similarly, 30 (22.6%) of patients were positive for TPO and 52 (39.1%) were positive for Tg-AB. Out of 18 (13.5%) hypothyroidism cases, only 5 (3.7%) had subclinical hypothyroidism (Table-1).

Table-2 shows the association of age and gender with thyroid disorders. Age of the study population did not show any significant association with thyroid disorders (p=0.224). Gender distribution was significantly different among thyroid disorders with higher frequency of hypothyroid and hyperthyroid among females (p=0.047).

Table-3 depicts association insulin antibodies and thyroid antibodies. Insulin antibodies was associated with anti-ATG whereas IA-2 was found to be associated with anti-TPO and anti-ATG.

Table 1: Demographic and clinical feature of the subjects.

Variable	*Frequency*	*Percentage*
Age (in years)#	10.49±4.4	-
Gender		
Male	54	40.6
Female	79	59.4
Anti-Insulin IgG		
Positive	25	18.8
Negative	108	81.2
IA2		
Positive	22	16.5
Negative	111	83.5
Anti-GAD IgG		
Positive	44	33.1
Negative	89	66.9
Anti-thyroglobulin		
Positive	52	39.1
Negative	81	60.9
Thyroid peroxidase		
Positive	30	22.6
Negative	103	77.4
Thyroid disorder		
Hypothyroidism (subclinical or clinical)	18	13.5
Euthyroidism	112	84.2
Hyperthyroidism	3	2.3

#: Age is expressed as mean±standard deviation

Table 2: Association of age and gender with thyroid disorders.

Variables	*Euthyroid N (%)*	*Hypothyroid n(%)*	*Hyperthyroid n(%)*	*p-value*
Age groups				
<5 years	37 (94.9)	2 (5.1)	0 (0)	
5-10 years	31 (79.5)	7 (17.9)	1 (2.6)	0.224
>10 years	44 (80.0)	9 (16.4)	2 (3.6)	
Gender				
Male	50 (92.6)	3 (5.6)	1 (1.9)	*0.047
Female	62 (78.5)	15 (19)	2 (2.5)	

*Statistically significant at $p<0.05$

Discussion

It is quite common to find coexistence of other autoimmune disorders among children having T1DM. Pathogenesis of TIDM makes to comprehend its rapid incidence with other autoimmune disorders. Many researchers who attempted to give explanation related to its molecular mechanism and genetic background bring focus towards HLA proteins which are highly important genes involved in concomitant existence of T1DM and thyroid autoimmunity.[11] Coexsistence of autoimmune disorders in T1DM not only may cause complications in diabetes management but may also lead to other clinical symptoms ranging from minor to life-threatening conditions, particularly in adrenal insufficiency. Thus, knowing the disease burden autoimmune disorders following the T1DM is crucial for appropriate screening and management strategies for better glucose regulation and quality of life.[12]

It has been evident in literature that thyroid diseases develop in early age among T1DM than general population and quarter of children with T1DM suffers with autoimmune hypothyroidism.[13] In the present study, 84.2% children had euthyroidism whereas prevalence of hypothyroidism and hyperthyroidism was 13.5% and 2.3% respectively. Another similar study from Pakistan reported 11.1% frequency of hypothyroidism (subclinical or clinical) and 3.9% were hyperthyroid.[14] Our findings are consistent with another similar study from India, investigating coexistence of other autoimmune diseases in TIDM among children reported a higher prevalence of hypothryroidism (14.1%) than Grave's disease (3.3%).[10] Fatourechi et al conducted a study in Iranian children to investigate hypothyroidism among pediatric patients having TIDM. Fatourechi et al detected hypothyroidism in 9.6% of TIDM children.[9] A Chinese study explored factors prevalence and factors of thyroid disorders in children with TIDM and found that 14.9% with TIDM had thyroid disorders with higher frequency of

Table 3: Association of thyroid and insulin antibodies.

Insulin Antibodies	*Thyroid peroxidase+ve n(%)*	*Thyroid peroxidase-ve n(%)*	*p-value*	*Antithyroroglobulin+ve n(%)*	*Antithyroglobulin-ve n(%)*	*p-value*
AntiInsulinIgG+ve	8 (32)	17 (68)	0.440	8 (32)	17 (68)	**<0.001
AntiInsulinIgG-ve	22 (20.4)	86 (79.6)		44 (40.7)	64 (59.3)	
IA2+ve	14 (63.6)	8 (36.4)	**<0.001	7 (31.8)	15 (68.2)	**<0.001
IA2-ve	42 (37.8)	69 (62.2)		47 (42.3)	64 (57.7)	
Anti-GAD IgG+ve	25 (56.8)	19 (43.2)	0.077	22 (50)	22 (50)	0.162
Anti-GAD IgG-ve	33 (37.1)	56 (62.9)		33 (37.1)	56 (62.9)	

**Statistically significant at $p<0.01$

subclinical hypothyroidism and clinical hypothyroidism was 10.3% and 3.4% respectively while hyperthyroidism was present in 1.2% children.[15] Another study from Saudi Arabia studied 305 children and adolescents having T1DM and demonstrated a substantial increased risk for development of thyroid dysfunction with a 21.35% prevalence.[16] Jurayyan et al reported 8.5% of patients had evidence of overt hypothyroidism and 12.8% had subclinical hypothyroidism whereas none of these patients had hyperthyroidism.[16] A study conducted in US on children for autoimmune thyroiditis reported a quite lower prevalence of Grave's disease (1.3%) and hypothyroidism (1.3%), 97% of these children had euthyroid.[17] The variable findings could be due to different population features such as their age and ethnicity. The difference in findings could also be possible because of different methodology like different thresholds and disease detection with different criteria for autoimmune, subclinical and clinical hypothyroidism.

In pediatric population, incidence of autoimmune is commonly seen in puberty period, however it may emerge at any age, even in infants. Usually, female gender is more likely to develop thyroid problems than males. Hence, a concern related to gender distribution exists when evaluating this kind of data in pediatric endocrinology. In this study, thyroid disorders prevalence including both hypothyroidism and hyperthyroidism was predominately presented in females. The findings are consistent with previously reported literature.[10,18,19] Various factors may cause this remarkable gender dissimilarity which may be hereditary effects, gender discrepancy in sex hormones, immune response and organ susceptibility.

T1DM contributes to 5-10% of diabetes cases which occurs due to autoimmune destruction of beta cells in pancreas and usually detected in individuals of age less than 18 years. Multiple markers are used to define it including autoantibodies to insulin, GAD, thyrosine phosphatases IA-2, islet cell autoantibodies and ZnT8.[20] In the present study, anti-GAD (33.1%) and anti-ATG (39.1%) were seen in nearly one third of the patients whereas thyroid peroxidase was positive in about quarter of the patients (22.6%). Our finding of anti-TPO frequency is close to Orzan et al who found 18.3% positive for anti-TPO.[19] However, findings are in contrast to a Brazilian study which demonstrated a low frequency of anti-TPO (11.8%), anti-ATG (11.8%) and anti-GAD (5.9%) among children and adolescents with T1DM.[21] We found that IA2 positivity rate was significantly higher for patients positive for anti-TPO, lower for positive anti-ATG. Positivity rate for anti-insulin IgG was significantly lower for patients with positive anti-TPO. A study conducted in China reported that prevalence of IA-2A and GADA was higher in patients having Grave's diseases or Hashimoto's thyroiditis as compared to healthy controls which indicated a potential link between islet and thyroid immunity.[22] Hwang et al. reported in his study that there was 30% prevalence of detecting at least one thyroid antibody in T1DM patients. Further it was demonstrated that GADA was significantly higher among patients with positive thyroid antibodies than patients having negative antibodies for thyroid (80.6% versus 60.6%).[23]

The present study is a single center experience from a tertiary care hospital so the findings of the study cannot to be generalized. Moreover, as nature of study is cross-sectional which limits to conclude temporality. To determine true association of thyroid antibodies and insulin antibodies, a larger study could be conducted addressing the gaps of the present study to generate a more reliable evidence regarding this phenomenon.

The positive association between Insulin and Thyroid antibodies suggests that patients with positive insulin antibodies are more likely to have thyroid antibodies. Therefore, it is imperative to test and manage these markers on a frequent and regular basis to avoid the adverse consequences over the patients suffering from Type 1 diabetes mellitus.

Conflict of interest: None declared.

References

1. Ardestani SK, Keshteli AH, Khalili N, Hashemipour M, Barekatain R. Thyroid disorders in children and adolescents with type 1 diabetes mellitus in isfahan, iran. Iran J Pediatr 2011; 21(4): 502-8.
2. Frommer L, Kahaly GJ. Type 1 Diabetes and Autoimmune Thyroid Disease-The Genetic Link. Front Endocrinol (Lausanne) 2021; 12: 618213.
3. Los E, Wilt AS. Diabetes Mellitus Type 1 In Children. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Accessed on 17th March 2023) Available from URL:https://www.ncbi.nlm.nih.gov/books/NBK441918/
4. Karuranga S, Fernandes JDR, Huang Y, Malanda B. IDF Diabetes Atlas. 8th ed. International Diabetes Federation; 2018.
5. 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.

6. Jonsdottir B, Larsson C, Carlsson A, Forsander G, Ivarsson SA, Lernmark Å, et al. Thyroid and Islet Autoantibodies Predict Autoimmune Thyroid Disease at Type 1 Diabetes Diagnosis. J Clin Endocrinol Metab 2017; 102(4): 1277-85.
7. 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: 6219730.
8. Léger J, Carel JC. Hyperthyroidism in childhood: causes, when and how to treat. J Clin Res Pediatr Endocrinol 2013; 5 Suppl 1(Suppl 1): 50-6.
9. 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.
10. 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; 23:22-6.
11. Ogarek N, Mrówka A, Jarosz-Chobot P. Thyroid diseases - ally or enemy of type 1 diabetes in children and adolescents? Pediatr Endocrinol Diabetes Metab 2021; 27(2): 117-22.
12. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. Eur J Endocrinol 2019;1 80(2): 135-44.
13. Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocr Rev 2019; 40(3): 789-824.
14. Sajid N, Riaz M, Fawwad A, Basit A. Thyroid dysfunction in subjects with type 1 diabetes at a tertiary care unit of Karachi, Pakistan. Clin Epidemiol Global Health. 2019; 7(3): 435-8.
15. Yang W, Sheng F. Factors associated with thyroid dysfunction in children with newly diagnosed type 1 diabetes mellitus. Minerva Pediatr (Torino) 2021; 73(4): 324-9.
16. Jurayyan A, Issa A, Jurayyan A, Otaibi A, Babiker I. Thyroid disorders associated with type 1 diabetes mellitus in children and adolescents from central Province Saudi Arabia. Int J Curr Res Biosci Plant Biol 2015; 2(1): 45-9.
17. Kochummen E, Marwa A, Umpaichitra V, Perez-Colon S, Chin VL. Screening for autoimmune thyroiditis and celiac disease in minority children with type 1 diabetes. J Pediatr Endocrinol Metab 2018; 31(8): 879-85.
18. Calcaterra V, Nappi RE, Regalbuto C, De Silvestri A, Incardona A, Amariti R, et al. Gender Differences at the Onset of Autoimmune Thyroid Diseases in Children and Adolescents. Front Endocrinol (Lausanne) 2020; 11: 229.
19. Spaans E, Schroor E, Groenier K, Bilo H, Kleefstra N, Brand P. Thyroid Disease and Type 1 Diabetes in Dutch Children: A Nationwide Study (Young Dudes-3). J Pediatr 2017; 187: 189-93.e1.
20. Orzan A, Novac C, Mihu M, Tirgoviste CI, Balgradean M. Type 1 Diabetes and Thyroid Autoimmunity in Children. Maedica (Bucur) 2016; 11(4): 308-12.
21. Alves C, Santos LS, Toralles MB. Association of type 1 diabetes mellitus and autoimmune disorders in Brazilian children and adolescents. Indian J Endocrinol Metab 2016; 20(3): 381-6.
22. Cai Y, Yan J, Gu Y, Chen H, Chen Y, Xu X, et al. Autoimmune thyroid disease correlates to islet autoimmunity on zinc transporter 8 autoantibody Endocr Connect 2021; 10(5): 34-42.
23. Hwang GB, Yoon JS, Park KJ, Lee HS. Prevalence of autoimmune thyroiditis in patients with type 1 diabetes: a long-term follow-up study. Ann Pediatr Endocrinol Metab 2018; 23(1): 33-7.