Original Article

Thyroid Autoimmunity in Children and Young Adults with Type 1 Diabetes and Their Siblings

Janani Ramesh[1], Sougata Mahato[2], Anju Seth[3], Ekta Debnath[4]

Introduction : Type 1 Diabetes Mellitus (T1DM) and Autoimmune Thyroid Disease (AITD) are often associated. AITD is diagnosed by the presence of antibodies to Thyroglobulin (Tg), Thyroid Peroxidase (TPO) and Thyroid-stimulating Hormone Receptor (TSHR). Considering the risk of the genetic component in diabetes and autoimmune immune diseases, this study aims study thyroid autoimmunity in children and young adults with Type 1 diabetes and their siblings.

Methods : Serum levels of free T4, TSH and anti-TPO antibody were measured in 360 children and young adults including Type 1 diabetics, their siblings and age and sex matched controls.

Results : The levels of anti-TPO antibody among the three groups were significantly different ($p<0.001$). Also anti-TPO titre and TSH levels were found to be significantly different across the 3 groups.

[*J Indian Med Assoc* 2021; **119(12):** 51-4]

***Key words* : Adolescents, Anti TPO antibody, Siblings, Type 1 Diabetes.**

Type 1 Diabetes Mellitus (T1DM) is an Endocrine disorder caused by an aberrant immune response against insulin secreting pancreatic ß-cells. The Autoimmune diseases more commonly associated with T1DM in childhood are Autoimmune Thyroid Disease, Coeliac Disease and Autoimmune Gastric Disease[1]. In Autoimmune Thyroid Disease, the major immune response is targeted against Thyroid Antigens Tg, Thyroid Peroxidase (TPO), and TSHR. The presence of antibodies to these Thyroid antigens is more common and reported to be as high as 10-20% in women[2]. AITD can be grossly divided as Graves' Disease and Hashimoto's Thyroiditis (HT). In Graves' Disease, the predominantly stimulating TSHR antibodies cause Hyperthyroidism and Hashimoto's Thyroiditis causes Hypothyroidism, depending on the Grade of Lymphocytic Infiltration[3].

But, the major population of subjects with measurable Thyroid Antibody titres is Euthyroid. The prevalence of high serum concentrations of Thyroid antibodies varies according to race and ethnic background[4]. The etiology of AITD is multifactorial due to a complex interplay of genetic changes and environmental exposures. Considering genetic components, the HLA-DR3 allele has a well-established association with AITD[2]. It has been reported that almost 50% of the genetic risk for T1DM is attributed to the Human Leukocyte Antigen (HLA) region. The HLA-DR3 genotype is highly associated with Beta-cell Autoimmunity[5].

Editor's Comment :

- We found thyroid autoimmunity to be very common in Type 1 Diabetics and their siblings.
- Subclinical hypothyroidism was the most common presentation of thyroid disease in this population. Hence annual follow-up for Type 1 diabetics should also include screening for thyroid autoimmunity.

Clustering of autoimmune disorders is observed in families of patients that have Autoimmune Diseases. According to a recent calculation, the HLA region accounts for 41% of familial clustering of type 1 diabetes[6]. This increases the risk for other Autoimmune disorders in first-degree relatives of T1DM subjects. Since many Euthyroid cases with high Anti-thyroid antibody titres ended up developing subclinical or overt hypothyroidism[4], it is important to follow up on those cases. Our study here aims to determine the prevalence of Thyroid autoimmunity in children and young adults with Type 1 Diabetes and their siblings.

Materials and Method

Subjects : The study was done in a Tertiary Care Paediatrics Hospital in collaboration with the Department of Biochemistry. The subjects were divided into three groups Group A, Group B and Group C consisting of 120 cases of Type 1 Diabetes Mellitus of age 2-18 years already diagnosed and under follow

Department of Biochemistry, Lady Hardinge Medical College (LHMC) and Associated Hospitals, New Delhi 110001

[1]MBBS, Resident and Corresponding Author

[2]MD, Senior Resident, Department of Division of Paediatric Gastroenterology and Hepatology, PGIMER, Chandigarh 160012

[3]MD, Professor, Director, Department of Paediatrics, LHMC and Kalawati Saran Childrens Hospital, New Delhi 110001

[4]MD, DNB, MNAMS, Professor

Received on : 08/11/2021

Accepted on : 23/11/2021

up at the Endocrine clinic, 120 siblings of the cases, and 120 age and sex matched controls respectively. The control subjects had no Chronic Disease or any other Autoimmune Disorder, such as Thyroiditis and T1DM. The study had the approval of the Institutional Ethical Committee.

Sampling : Venous sampling was done after an overnight fast into a plain red vial. The sample was allowed to clot and serum was separated after centrifugation. Sera were used to measure freeT4, TSH, and anti-TPO antibody. All the samples were processed in COBAS e411 using Electrochemiluminescence principle. For this study, the following cutoffs of TSH (0.5 uIU/ ml – 6 uIU/ ml) and Free T4 (0.95 ng/dl – 1.75 ng/dl) were used. An anti-TPO titre ≥35 IU/ml was taken positive for all cases included in this study.

Statistical analysis : Data was analyzed using SPSS 20 version. Descriptive statistical methods were used for continuous data and frequencies and percentages for categorical data. The normally distributed data within the three groups were analyzed using ANOVA test and skewed data used Kruskal Wallis test. Chi-square test was used to find an association between the categorical variables and expressed in odds ratio with 95% CI. p-value≤0.05 was taken as significant.

Observations

Out of 120 children in each group anti-TPO positivity was present in 30 children (25%) of group A, 10 children (8.3%) of group B and 8 children (6.7 %) of group C respectively (p<0.001).

Anti TPO titre and TSH levels were found to be significantly different across 3 groups (Table 1). Comparison of thyroid function among anti-TPO positive and anti-TPO negative in all three groups is given in Table 2. Intragroup comparisons of anti-TPO positivity are given in Table 3.

Discussion

While considering the worldwide prevalence of thyroid autoimmunity in children with T1DM, the maximum prevalence was reported by Menon et al from India (54.3%)[7]. Burek *et al* analyzed the thyroid autoimmunity in African American and Caucasian children and found the prevalence to be 50% among white children[8]. A recent meta-analytical study that reviewed the prevalence of autoimmune disorders in T1DM patients found a weighted prevalence of 18.3% for TPO positivity in T1DM patients[9]. A Turkish study by Karaguezel *et al*[10] found 38.6% TPO antibodies in diabetics as compared to 21.1% in their siblings. But in our study, we reported 25% TPO[5] positivity in T1DM children and 8.3% TPO positivity in the sibling population. The prevalence of thyroid dysfunction among the children with T1DM was 15% in our study.

Subclinical hypothyroidism (8.3%) was the most Common Thyroid Dysfunction among children with T1DM. This is in concordance with the following studies.

A Libyan study in T1DM children reported a 2.3% prevalence for subclinical hypothyroidism and 0.9% prevalence for overt Hypothyroidism, Subclinical hyperthyroidism and overt hyperthyroidism[11]. A study on T1DM children in the Iranian population[12] reported that 38.8% of T1DM children had subclinical hypothyroidism and 5.5% had subclinical hyperthyroidism. Another study in the Egyptian population also found that 11.2% of children with T1DM have subclinical hypothyroidism[13]. Thus the subclinical hypothyroidism has been the commonest presentation.

In our study anti-TPO positive subjects in group B

Table 1 — *Thyroid function and autoimmunity among the three groups*

	Group A	Group B	Group C	p - value
TSH (uIU/ml)Median (IQR)	2.71(1.81-3.68)	3.41(2.12-4.52)	2.8(1.7-4.2)	0.023*
FT4 (ng/dl)Mean ± SD	1.32 ±0.3	1.35±0.39	1.37 ± 0.29	0.392
Anti TPO titre (IU/ml) Median (IQR)	11.7(7.74-35.83)	8.17(5.39-16.83)	10.75(6.39-17.97)	0.002*

*significant at p <0.05

Table 2 — *Comparison of thyroid function among anti-TPO positive and negative in all three groups*

	Group A(n=120)		p-value	Group B(n=120)		p-value	Group C(n=120)		p-value
	Anti-TPO +ve n=30	Anti-TPO -ve n=90		Anti-TPO +ve n=10	Anti-TPO -ve n=110		Anti-TPO +ve n=8	Anti-TPO -ve n=112	
	N(%)	N(%)		N(%)	N(%)		N(%)	N(%)	
Euthyroid	17(56.7)	85(94.4)	<0.0001	4(40)	99 (90)	<0.0001	1 (12.5)	105(93.8)	<0.0001*
Thyroid dysfunction	13(43.3)	5(5.5)	<0.0001	6 (60)	11 (10)	<0.0001	7(87.5)	7(6.25)	<0.0001*
Subclinical hypothyroidism	6(20)	4(4.4)	NS	4(40)	11(10)	NS	7(87.5)	6(5.4)	NS
Overt hypothyroidism	3(10)	0(0)	NS	0(0)	0(0)	NS	0(0)	1(0.9)	NS
Subclinical hyperthyroidism	2(6.7)	1(1.1)	NS	2(20)	0(0)	NS	0(0)	0(0)	NS
Overt hyperthyroidism	2(6.7)	0(0)	NS	0(0)	0(0)	NS	0(0)	0(0)	NS

*significant at p <0.05

and group C were more commonly associated with thyroid dysfunction than the anti-TPO negative subjects in this study (Table 2). In our study, we found that among the anti-TPO positive siblings 40% had subclinical hypothyroidism and 20% had subclinical hyperthyroidism. This finding was higher than the observation of Mohn *et al*[14] who reported a 33.3% prevalence of subclinical hypothyroidism among the anti-TPO positive siblings of diabetic children. Karaguzel *et al*[10] found no thyroid dysfunction among the siblings though 13.5% were positive for the anti-TPO antibody.

Table 3 — *Comparison of anti-TPO positivity between groups*

	Group A (n-120)	Group B (n-120)	p-value	Odds ratio (C.I)	Group C (n-120)	p-value	Odds ratio (C.I)
	N(%)	N(%)			N(%)		
Anti TPO positivity	30 (25%)	10 (8.3%)	0.001* (1.70 - 7.90)	3.7	8 (6.7%)	<0.0001*	4.7 (2.04-10.68)
Anti TPOnegativity	90 (75%)	110 (91.7%)			112 (93.3%)		

*Significant at p<0.05

Table 4 — *Comparison of siblings of anti-TPO positive and anti TPO negative diabetics*

	Siblings of diabetic children with anti TPO positivity (n=27)	Sibling of diabetic children with anti TPO negativity (n=93)	p-value	Odds ratio (positivity/ negativity)	CI of odd's ratio
	N(%)	N(%)			
Anti TPO positivity	4(14.8)	6(6.5)	0.166	0.397	0.103-1.524
Anti TPO negativity	23 (85.1)	83(93.5)			
Any thyroid dysfunction	7(25.9)	10(10.7)	0.047*	2.905	0.984-8.574
Euthyroid	20 (74.1)	83(89.2)			

*Significant at p <0.05

As per our findings, 87.5 percent of the healthy controls with a positive anti-TPO titre had subclinical hypothyroidism. But in studies by Menon et al from India[7] and Mohn *et al*[14] from Italy, none of the healthy children with anti-TPO positivity had any thyroid dysfunction. In our study, the children with T1DM had more overt hypo/hyperthyroidism while the healthy children had more subclinical hypothyroidism (Fig 1).

While considering the intergroup comparisons between the groups, the risk of having anti-TPO positivity in subjects in group A was significantly higher as compared to group B and group C subjects. The group A subjects were found to be 4.7 times more likely to be positive for anti-TPO as compared to group C subjects and 3.7 times more likely to be positive than group B subjects (Table 3).

In our study, we found that within group A, anti-TPO positive children are significantly more prone to develop thyroid dysfunction as compared to those who are anti-TPO negative. Ardestani *et al*[12] reported that the chance of having thyroid dysfunction in diabetic children with autoimmunity was five times higher than the diabetics without autoimmunity.

In our study prevalence of thyroid autoimmunity among the siblings of children with T1DM (8.3%) was much lower than the diabetic children (25%) but was similar to the healthy children (6.7%). This finding

was in contrast with Mohn *et al*[14] who found higher prevalence of Autoimmune Thyroid Disease among siblings of diabetic children than healthy controls. Karaguezel *et al*[10] also showed that the siblings of the diabetics had a high prevalence of thyroid autoimmunity though lower than that observed in diabetics. They did not include a control group.

A subgroup analysis was done between siblings of anti-TPO positive diabetics and siblings of anti-TPO negative diabetics (Table 4). The prevalence of Thyroid autoimmunity was similar in both groups, though the prevalence of Thyroid dysfunction was significantly more in the former group. This was in contrast with the finding by Burek *et al* who showed that siblings of the antibody-positive diabetics had higher positivity

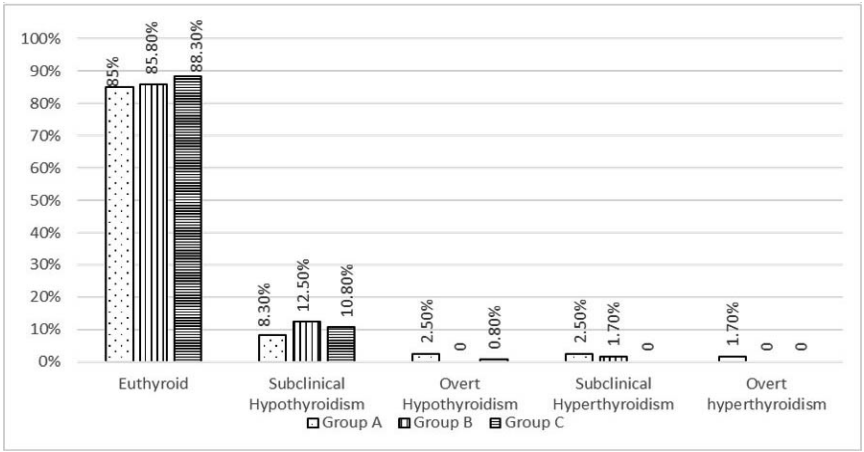

Fig 1 — Clinical Thyroid Status among Three Groups

(44%) for antithyroid antibody than those siblings antibody-negative diabetics (18%)[8]. Comparison of thyroid dysfunction between those 2 subgroups was not done in their study. The limitations of our study would be that anti-thyroid antibody was not tested and diagnosis of Autoimmune Thyroiditis was not confirmed by ultrasonography or FNAC.

Conclusion

The children with Type 1 Diabetes Mellitus have a higher prevalence of Autoimmune Thyroid Disease , assessed by anti TPO antibody titres when compared to their siblings and healthy controls. However prevalence of Thyroid Dysfunction is not different in the three groups. Siblings of diabetic children do not have a higher prevalence of either Thyroid Autoimmunity or Thyroid Dysfunction as compared to healthy controls. Hence, thyroid antibody screening should be included in the routine followup of the Type 1 Diabetics for the early diagnosis and treatment of the disease.

References

1 Kakleas K, Soldatou A, Karachaliou F, Karavanaki K — Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus (T1DM). *Autoimmun Rev* 2015; **14(9):** 781-97. DOI: 10.1016/j.autrev.2015.05.002.

2 Lee HJ, Li CW, Hammerstad SS, Stefan M, Tomer Y— Immunogenetics of autoimmune thyroid diseases: A comprehensive review. *J Autoimmun* 2015; **64:** 82-90. DOI:10.1016/j.jaut.2015.07.009.

3 Banga JP, Schott M— Autoimmune Thyroid Diseases. *Horm Metab Res Horm Stoffwechselforschung Horm Metab* 2018; **50(12):** 837-9. DOI:10.1055/a-0799-5068.

4 Orgiazzi J— Thyroid autoimmunity. *Presse Med* 2012; **41(12 PART2):** e611–25. DOI:10.1016/j.lpm.2012.10.002.

5 Taplin CE, Barker JM — Autoantibodies in type 1 diabetes. Autoimmunity 2008; **41(1):** 11-8. DOI: 10.1080/08916930701619169.

6 Hemminki K, Li X, Sundquist J, Sundquist K — Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia* 2009; **52(9):** 1820-8. DOI:10.1007/s00125-009-1427-3.

7 Menon PSN, Vaidyanathan B, Kaur M— Autoimmune Thyroid Disease in Indian Children with Type 1 Diabetes Mellitus. J Pediatr Endocrinol Metab 2001; **14(3):** DOI:10.1515/jpem.2001.14.3.279.

8 Burek CL, Rose NR, Guire KE, Hoffman WH — Thyroid Auto Antibodies in Black and in White Children and Adolescents with Type 1 Diabetes Mellitus and Their First Degree Relatives. Autoimmunity 1990; **7(2-3):** 157–67. DOI:10.3109/08916939008993388.

9 Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, Koning EJP de, Dekkers OM — Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. *Eur J Endocrinol* 2019; **180(2):** 135-44. DOI: 10.1530/EJE-18-0515.

10 Karagüzel G, Þimþek S, Deðer O, Ökten A — Screening of diabetes, thyroid, and celiac diseases-related autoantibodies in a sample of Turkish children with type 1 diabetes and their siblings. *Diabetes Res Clin Pract* 2008; **80(2):** 238-43. DOI: 10.1016/j.diabres.2007.12.007.

11 Ghawil M, Tonutti E, Abusrewil S, Visentini D, Hadeed I, Miotti V, *et al* — Autoimmune thyroid disease in Libyan children and young adults with type 1 diabetes mellitus. *Eur J Pediatr* 2011; **170(8):** 983-7. DOI: 10.1007/s00431-010-1386-1.

12 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. PMID: 23056839

13 Metwalley KA, El-Saied A-RA-H — Thyroid abnormalities in Egyptian children and adolescents with type 1 diabetes mellitus: A single center study from Upper Egypt. *Indian J Endocrinol Metab* 2014; **18(5):** 637-41. DOI: 10.4103/2230-8210.139218.

14 Mohn A, Di Michele S, Faricelli R, Martinotti S, Chiarelli F — Increased frequency of subclinical hypothyroidism and thyroid-associated antibodies in siblings of children and adolescents with type 1 diabetes mellitus. *Eur J Endocrinol* 2005; **153(5):** 717-8. DOI: 10.1530/eje.1.02008.