Study on the Prevalence of Thyroid Dysfunction in Diabetic Children

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ABSTRACT
Introduction: *Type 1 diabetes mellitus is the most common type of diabetesin children.Other autoimmune disease common in these individuals is Autoimmune Thyroiditis(15-30%).Innormal individualsthe positivity of anti-thyroid antibodiesisfound to be 2.9% - 3.4%. While in T1DM children it is between 18.5% - 24.6%.*

 Aims and Objectives:*To study the prevalence of thyroid dysfunction and its effects in childrendiagnosed with Type1Diabetes Mellitus. To correlate the effect of thyroid dysfunction based on age, gender of individual, duration of diabetes, glycemic control, lipid abnormality, BMI and growth and development in children with Type 1 Diabetes Mellitus.*

Materialsand Methods:*The present study was conducted at Chalmeda Anand Rao Institute of Medical Sciences. The study consists of 142 selected eligible Type 1 Diabetes individuals and Anti thyroidantibodies were estimated in TIDM children andcorrelatedwithage,sex of the individualandddurationofdiabetes at Chalmeda Anand Rao Institute of Medical Sciences from December 2019 to June 2021.*

Results:*Initially, 15.4% of patients were positive foranti-TPO antibodies and 14.4% patients were positive foranti-TG antibodies. Theincidence of AIT was significantly higher after a decade.*

Conclusion*: Thestudy provides definitive evidence of the associationbetween autoimmune hypothyroidism and type 1 diabetes. The incidence of hypothyroidism is higher in females, especially those with positive TPO antibodies.*

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I.   Introduction:

Type 1 diabetes mellitus is the most common type of diabetes in children. Type 1 diabetesmellitus(T1DM) is an autoimmune diseasewith absolute insulin deficiency resulting from immune mediated destruction of beta cells of pancreas[1].Other autoimmune diseases common in these individuals are thyroid disease, adrenal insufficiency and celiac disease. Among all the above mentioned diseases autoimmune thyroiditis (AIT) is mostcommon[2,3].For diagnosis ofAIT,thyroidperoxidase(anti-TPO)andthyroglobulin(anti-TG) antibodies are to be measured. The levels ofthese antibodiesdependon the sex of the individual, age of onset of hypothyroidism and duration of diabetes mellitus. In normalindividuals the positivity of anti-thyroid antibodies found to be 2.9% - 3.4%[9,10].While in T1DM children it is between 18.5% - 24.6%[11-13].There may be temporary rise in thyroid antibodies also. T1DMwith poor control may induce a low T3 state and the long term diabetic controldeterminestheT3 and TSH levels. Hypothyroidism in children may result in increased insulin synthesis.

EFFECT OF HYPOTHYROIDISM ON DIABETES:

Clinical status	Effect on blood glucose	Effect on Thyroid function
T1DM-With normal thyroid function	Normal	↓T3 ↓TSH
T1DM–in Hyperthyroidism	Poor control of glucose	↑ risk of ocular involvement
Clinical status	Effect on blood glucose	Effect on thyroid function
Hypothyroidism- in Type 1 diabetic .children	Predisposes to recurrent hypoglycemia	↑ Risk of thyroid disease

Other features of hypothyroidism in T1DM children aregrowthretardation,weightgain,menstrual irregularities, hyperlipidemia and cardiaccomplications[8].In AIT, antibodies are produced against thyroglobulin (TG), which is a colloid and thyroid peroxidase (anti-TPO), which helps in the synthesis ofthyroidhormones.In T1DM children, the prevalence of anti TPO antibody was found to be between 10.3% and 28.4% whereas anti-TG antibody was found to be between 8.8% and 14.5%. In combined presence of both these antibodies prevalence was found to be between 5.9%–7%. In children with AIT, family history of diabetes and family history of thyroid abnormalities should be taken into consideration.In adolescents, menstrual irregularities, precocious puberty, delayed puberty are encountered, intake of drugs and stressful events should be looked for Predominantly hypothyroidism (clinical or subclinical) and very few affected with hyperthyroidism are seen. As the prevalence of thyroid dysfunction in T1DM children is increasing, screening for autoimmune thyroiditis is gaining importance in recent years.

II.   Materials And Methods:

The present study was conducted at Department Of Paediatrics,Chalmeda Anand Rao Institute of Medical Sciences. The study consists of 142 selected eligible Type 1 Diabetes individuals at Chalmeda Anand Rao Institute of Medical Sciences from December 2019 to June 2021.

Type of study: Prospective observational study
Inclusion criteria:
- Age - 2 to 18 years
- All OP and IP cases presenting with Type 1 Diabetes Mellitus

Exclusion criteria:
- Children with age <2 years and >18 years
- Syndromic causes of Type 1 Diabetes Mellitus
- Drugs causing diabetes (Steroids, Phenytoin)

We got approval From Ethical Committee.

III.   Results:

142 individuals were studied.23 (16%) of the diabetic children had overt hypothyroidism.12 (8%) children with T1DM had subclinical hypothyroidism. Subclinical hyperthyroidism and overt hyperthyroidism were not detected in any case of T1DM.Among the diabetic children 30 (21%) were found positive for Anti-TPO antibodies, 21(14%) were positive for Anti TG antibodies and 19(13%) children were found positive for both Anti-TPO and Anti-TG antibodies. The overall prevalence of AIT based on the positivity of any one of these antibodies in diabetic children was 32 (22.5%).Among the children with overt hypothyroidism 17 (73%) were positive for TPO antibodies, 12 (52%) were positive for TG antibodies and 11(47%) for both Anti-TPO and Anti-TG antibodies.5 (3.5%) diabetic children had laboratory evidence of hypothyroidism but negative for thyroid antibodies.12 (8.4%) diabetic children were positive for thyroid antibodies but no laboratory evidence of hypothyroidism. None of them had the clinical features of hypothyroidism. In T1DM children with presence of any of these antibodies (anti-TPO and anti-TG), correlation was done with sex, duration of diabetes, age at onset of hypothyroidism, lipid profile including cholesterol and triglycerides, glycaemic control using HbA1C, presence of thyroid enlargement, presence of thyroid echogenicity on USG-Neck and subclinical hypothyroidism. BMI was compared in these individuals with and without AIT.2 of the 32 children (6.2%) were positive for AIT at the onset of diabetes.

Anti-TPO antibodies were found positive at 3.01 ± 3.5 years after the onset of diabetes. Anti-TG were positive 3.5 ± 2.5 years after the onset of diabetes. Both anti-TPO and anti-TG were found positive 3.6 ± 2.5 years after the onset of diabetes.
- The mean ± SD age at onset of hypothyroidism with positive TPO antibodies was 6.97 ± 3.53 years, with TG antibodies it was 6.64 ± 3.4.
- The mean ± SD BMI of the children without AIT was 15.8 ± 1.5, while the mean BMI in children with AIT was 18.5 ± 2.6.

The prevalence of goitre in the study group with positive TPO antibodies was 16 (94%), with positive TG antibodies was 13(76.5%) and it was 12 (70.6%) when positive for both antibodies.

Table 1: Logistic regression analysis to estimate the risk factors associated with autoantibody positivity in T1DM children

		P value	OR	95% C.I
1.	Sex	0.299	0.104	0.029–0.376
2.	Cholesterol	0.057	7.827	0.940–65.197
3.	Triglycerides	0.553	0.361	0.012–10.488
4.	Both	0.023	6.003	3.454–8.491
5.	HbA1C	0.482	2.225	0.239–20.670
6.	Goiter	0.003	4.044	2.001-5.992
7.	USG	0.003	5.84	4.802–5.920

P < 0.05, statistically significant- chi square test, OR- odds ratio, CI- confidence interval

Table 2: TG positivity

		P value	OR	95% C. I
1.	Sex	0.154	8.432	0.449–158.38
2.	Cholesterol	0.499	2.356	0.197–28.259
3.	Triglycerides	0.520	0.244	0.003-17.941
4.	Both	0.884	0.682	0.002–1.043
5.	HbA1C	0.354	1.234	0.008–1.432
6.	Goiter	0.002	4.470	3.04-6.558
7.	USG	0.002	5.168	4.056–6.091

P < 0.05, statistically significant- chi square test, OR- odds ratio, CI- confidence interval

In children with TPO positivity nearly 27(90%) were females and 3(10%) were males. Among TG positive children 20(95%) were females and 1(5%) was male. Both antibodies were positive in 18(94.7%) females and 1(5.3) male. Thus overall there was a female preponderance among antibody positive T1DM children. In children with positive TPO antibodies,16 (53.3%) developed thyroid enlargement (goiter) (P= 0.001, or 1.004, 95% CI 0.001 – 1.992) and 17 (56.7%) children showed diffuse hypo echogenicity on ultrasonography (P=0.002, or 2.84, 95% CI 2.01-3.774). In children with positive TG antibodies 13(53.3%) showed thyroid enlargement (goiter) (P= 0.001, or1.004, 95% CI 3.04-6.558) and 17 (56.7%) children had sonographic evidence of AIT (P=0.002, OR 5.168, 95% CI3.24-5.78).In children with both antibodies positive, goiter was seen in 12(63.2%, p=0.003) children and sonographic evidence of AIT was seen in 13 children (68.4%). In children with both antibodies positive only 1(15.3%) had subclinical hypothyroidism. Both hypercholesterolemia and hypertriglyceridemia was seen in 8(26.7%) children with positive TPO antibodies (p=0.002) while it is 7(33.3%) with positive TG antibodies (p=0.001) and 6 (31.6%) in children with both antibodies positive(p=0.001).In children with both antibodies positive poor glycemic control was seen in 9(47.4%, p=0.056).BMI of the children with AIT positive were compared with BMI in children without AIT. Statistical significance was not observed for AIT and BMI.

IV. Discussion:

The present study showed that children with T1DM had increased levels of anti-TPO and anti-TG antibodies compared with healthy individuals[20,23].It may be due to increased tendency to react against specific antigens, or a genetically impaired ability to acquire tolerance to some autoantigens, or certain common antigens present in tissues of individuals prone to autoimmune diseases or due to loss of self-recognition particularly when there is genetic or environmental trigger[24].Common genetic determinants HLA[25,26] or some genetic component outside the HLA (i.e., CTLA4 and PTPN 22), could play a role. Both T1DM and AIT are organ specific T-cell mediated diseases and have similar pathogenesis which is due to T-cell infiltration resulting in dysfunction of target organ[23].In the present study, the prevalence of positivity for anti-TPO Antibody, anti-TG antibody and the prevalence of positivity for both antibodies and AIT (at least one positive antibody) in children with T1DM were 21%, 14%, 13% and 22.5% respectively which was higher than normal individuals. In present study there was no case of clinical thyroid dysfunction. However, subclinical

hypothyroidism was present in 18% of both T1DM individuals and control group. Epidemiologic studies have shown higher incidence of AIT after elimination of iodine deficiency in endemic areas [27].

The lower prevalence of AIT in our study could be explained by the different age group of studied individuals in our study. From previous studies the prevalence of clinical and subclinical thyroid dysfunction in T1DM patients is suggested to be 13.4-20% while the prevalence of hypothyroidism and hyperthyroidism in the normal population is 5-10% and 1%, respectively. A significant percentage of them were found to have AIT very early after the onset of diabetes. Unfortunately, iodine status of the studied population was not evaluated and as a result, we could not investigate the role of iodine deficiency in the high prevalence of subclinical hypothyroidism. In our study there is higher prevalence of goiter in T1DM patients with AIT (94%) which is statistically significant. All the cases clinically suspected to have goiter were confirmed by thyroid ultrasonography.

In our study, the prevalence of AIT in female patients with T1DM was higher than that in male T1DM patients. In T1DM children with AIT, estrogen was found to increase the risk of autoimmunity by acting through the T cell pathway, while androgens usually protect against this. In our study, the prevalence of AIT is increased with age and duration of diabetes[11]. As the duration increases the prevalence of AIT increases. Thus strongly reinforces that along with initial screening, these children with AIT should have a long term follow up. In TPO positive children there was a statistical significance, while in TG and both antibody positivity there was no statistical significance. This clearly points out that children with AIT might have fluctuating glycaemic control and diabetic management can be made difficult. In T1DM children with AIT, there is significant elevation in lipid parameters including both cholesterol and triglyceride.

As the long-term morbidity is increased, these should be looked into while managing these children.Though the hypoglycaemic episodes did not have statistical significance in our study. It is a known fact these children are more prone for hypoglycaemia. Hence all patients should be warned for signs of hypoglycaemia.Another important observation of our study was that the influence of AIT on BMI, showed no statistical significance like in other studies. But, Thyroxine if given early leads to improved growth in these children. This observation has highlighted the significance of the early identification and treatment of AIT in these individuals. It was also observed that in the presence of both thyroid antibodies, the autoimmune process is more vigorous, causing AIT. Among both the antibodies, TPO antibodies were found to be more specific to detect AIT[11].

V. Conclusion:

Hypothyroidism is a predominant autoimmune disorder in T1DM children and it is mostly asymptomatic. This emphasizes the requirement of regular thyroid screening in diabetic children. Children with T1DM had higher prevalence of AIT. To conclude, the presence of thyroid antibody positivity was common among our T1DM children. Important risk factors for AIT to develop in T1DM children are increasing age, female sex and longer duration of diabetes. Hence it is to suggest that all patients with T1DM should undergo screening for AIT at the onset of diabetes and then yearly or atleast once in 2-3 years. It is beneficial to measure thyroid function indices and thyroid antibodies in individuals with T1DM regularly. If thyroid antibody is positive, then they should be followed up regularly. Current recommendation is that treatment is decided based on the level of TSH.The incidence of hypothyroidism is higher in females, especially those with positive TPO antibodies. Despite the association between positive thyroid TPO antibodies and the subsequent development of hypothyroidism, annual measurement of serum TSH levels is the preferred screening test to detect asymptomatic thyroid dysfunction. Importance of diagnosing AIT lies in the fact that these individuals are more prone to develop thyroid dysfunction and that early diagnosis helps to initiate treatment early.To summarize, screening must be done for thyroid antibodies in T1DM children to find out AIT. The patients with positive antibodies should be followed up because further deterioration of the thyroid gland may occur.

RECOMMENDATIONS:

Screening for thyroid disease in type 1 diabetic children should be initiated at diagnosis. Preferably it should be checked annually or at least every 2-3 years.The preferred method of screening is using TSH levels. Other method of screening includes thyroid peroxidase antibody.Thyroid antibody positivity alone is not an indication for treatment in these children, but they have increased risk to develop thyroid dysfunction.

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