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Original Research Article

Thyroid function and thyroid autoimmunity in type 1 diabetes mellitus: impact on glycemic control

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ABSTRACT

Background: The frequency of AITD (autoimmune thyroid disease) and prevalence of thyroid autoantibodies in T1DM (Type 1 diabetes mellitus) patients is much higher than in general paediatric population, varying widely between 3-50% and is often related to age, gender and ethnicity. Although this association has been well established in various populations, very few studies have been done in this regard in South India. The objectives of the study were to study the proportion of abnormal thyroid function and thyroid autoimmunity among T1DM subjects in comparison with general pediatric population and to compare the disease severity among T1DM subjects with and without abnormal thyroid function.
Methods: The 45 subjects diagnosed with T1DM (Group 1) and 45 age and gender matched subjects without T1DM (Group 2) were enrolled after applying the inclusion and exclusion criteria. Serum free T3, free T4 and TSH levels were tested for all the subjects in both the groups. In addition, HbA1c levels and Anti TPO antibody titers were tested for subjects with T1DM.
Results: Abnormal thyroid function was found in 15.5% of T1DM subjects, in contrast to 2.2% of subjects in the comparison group ($p=0.026$). The anti-TPO antibody titers were positive in 31.1% of T1DM subjects and among them 42.8% subjects had abnormal thyroid function. T1DM subjects with abnormal thyroid function had significantly higher number of hospitalizations ($p<0.05$) and total number of ICU admissions ($p<0.05$)
Conclusions: Abnormal thyroid function (predominantly subclinical hypothyroidism) and thyroid autoimmunity was not only more prevalent among T1DM subjects, but was also associated with poor glycemic control. Thus, highlighting the need for screening and a lower threshold for treatment.

Keywords: T1DM, Autoimmune thyroid disease, Anti TPO antibodies, Glycemic control

INTRODUCTION

Children and adolescents with T1DM are at increased risk for co-morbid autoimmune diseases compared to children in the general population. A high proportion of children and adolescents with T1DM have other organ-specific autoantibodies in addition to islet autoantibodies, and approximately 25% of the patients with T1DM are diagnosed with other autoimmune diseases. Among them, AITD is found to be most commonly associated with type 1 diabetes.[1,2] Recent studies have further identified some shared susceptibility genes responsible for the co-occurrence of these conditions.[3]

The frequency of thyroid autoimmune disease and the prevalence of thyroid autoantibodies in patients with T1DM are much higher than in general pediatric population, varying widely between 3 to 50% and is often related to age, gender and ethnic origin.[4] Clinically thyroid dysfunction can cause metabolic disturbances in T1DM, by increasing insulin resistance and impairing glucose metabolism and may ultimately undermine glycemic control in T1DM.[5,6] Therefore, regular screening could help in early identification and treatment of previously undiagnosed thyroid dysfunction in T1DM patients and may help in achieving better glycemic control in them.

Although the association between T1DM and the occurrence of thyroid autoimmunity in them has been well established in various populations, hardly few studies have been done in this regard in the Indian subcontinent, especially in the South Indian population. Hence, this study to assess the proportion of abnormal thyroid function and thyroid autoimmunity among paediatric patients with T1DM in comparison with age and gender matched controls in the general paediatric population, and to further evaluate whether the presence of thyroid dysfunction has any association with the severity of T1DM was undertaken.

Objectives

Primary objective

Primary objective was to study the proportion of abnormal thyroid function and thyroid autoimmunity among children and adolescents with T1DM in comparison with age and gender matched controls in general paediatric population.

Secondary objective

Secondary objective was to compare subject demographics and disease severity among T1DM patients with and without abnormal thyroid function.

METHODS

Type of study

Cross sectional comparative study type was used.

Source of data

Children and adolescents attending the outpatient department of a tertiary care center in Southern India.

Inclusion criteria for group 1

Pediatric subjects (i.e., less than 18 years of age) diagnosed with T1DM [according to ISPAD (International society of paediatric and adolescent diabetes) guideline] attending the outpatient department.[7]

Exclusion criteria for group 1

(1) Previously diagnosed cases of thyroid disease, (2) Any acute illness or history of hospitalization in the past 4 weeks, and (3) On treatment with drugs that could interfere with thyroid function tests.

Inclusion criteria for group 2 (comparison group)

Children and adolescents without T1DM were selected after applying exclusion criteria and matching for gender and 3-year age interval among pediatric subjects attending the outpatient department.

Exclusion criteria for group 2 (comparison group)

(1) Previously diagnosed case of thyroid disease, (2) known case of any autoimmune disease, (3) family history of any autoimmune disease, (4) any acute illness or history of hospitalization in the past 4 weeks, and (5) those on treatment with drugs that could interfere with thyroid function tests.

Sample size calculation

A minimum sample size of 45 subjects in each group, group 1 and 2, was calculated using the formula: $n=Z^2pq/d^2$

Methodology

Institutional ethical committee clearance and informed consent from the parents of each subject, and assent for children aged over 7 years was obtained from the study subjets. 45 subjects diagnosed with T1DM were included in group 1 and 45 age and gender matched subjects were included in group-2 (or the comparison group), after applying the inclusion and exclusion criteria.

A detailed history was taken from each subject in group-1, including the age at enrolment into the study, age at initial diagnosis of T1DM, duration of T1DM since initial diagnosis, parental consanguinity, family history of diabetes, family history of thyroid disorder, Required insulin dose (U/kg/day). Anthropometry measurements like height and weight of each T1DM subject was measured and BMI was calculated [BMI=Weight (kg)/Height $(m)^2$], and interpreted according to IAP growth charts.[8]

Under aseptic precautions 3 ml of venous blood sample was drawn by venipuncture from each subject in both the groups and tested for serum free T3 (Triiodothyronine), free T4 (Thyroxine), and TSH (Thyroid stimulating hormone). In addition, serum HbA1c levels and anti-TPO (Anti-thyroperoxidase) antibodies was tested for subjects in group 1. Serum free T3, free T4 and TSH levels were measured using chemiluminescence immunoassay (CLIA), and interpreted as per age specific reference ranges.[9] Normal free T3, free T4 levels with elevated TSH levels was considered as subclinical hypothyroidism and low free T3 or low free T4 levels with elevated TSH levels was considered as overt hypothyroidism. Anti-TPO antibody levels were measured in venous blood sample using enzyme linked fluroimmuno assay (ELFA), a value less than 8.0 IU/ml was considered normal according to laboratory standards and any value >8.0 IU/ml was considered as elevated anti-TPO antibody titer. Glycosylated hemoglobin levels were measured in venous sample by immunoturbidimetry method.

Statistical analysis

Data was entered into Microsoft excel data sheet and analyzed using SPSS 22 version software. Categorical

data was represented in the form of frequencies and proportions. Chi-square test or Fischer's exact test (for 2×2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. P (Probability that the result is true) of <0.05 was considered as statistically significant.

RESULTS

Thyroid function and thyroid autoimmunity among subjects with T1DM in comparison with general pediatric population (Table 1)

Among the 45 subjects in group 1, 26 (57.8%) were females and 19 (42.2%) were males. Among the 45 subjects in group 2, 27 (60%) were females and 18 (40%) were males. There was no significant statistical difference found between the two groups with respect to gender (p=0.832) and age distribution (p=0.876), indicating that the subjects in both the groups were comparable. The mean age of the T1DM subjects in group 1 and 2 was 11.42 years and 11.28 years respectively.

In group 1, a total of 7 (15.5%) subjects had abnormal thyroid function and in group 2, only 1 (2.2%) subject had abnormal thyroid function. The difference in the thyroid function status between the two groups was found to be statistically significant with a p=0.026 (p<0.05). Among the 7 subjects with abnormal thyroid function in group 1, 6 were found to have subclinical hypothyroidism and 1 was found to be overt hypothyroid. In group 2, 1 (2.2%) subject found to have subclinical hypothyroidism.

In group 1, out of the 7 subjects with abnormal thyroid function, 2 (28.6%) subjects were male and 5 (71.4%) subjects were female. Among them, 2 (28.6%) were in the age group of 5-9 years, 3 (42.9%) were in the age group of >9-13 years and 2 (28.6%) were in the age group of >13 to 17 years.

Among the 45 T1DM subjects in group 1, anti TPO antibody titers were positive in 14 (31.1%) subjects. Among these 14 subjects, 3 (21.4%) subjects were in the age group of 5-9 years, 6 (42.9%) subjects in the age group of >9-13 years and 5 (35.7%) subjects were in the age group of >13-17 years. Seven (50%) subjects were males and 7 (50%) subjects were female. Six (42.8%) T1DM subjects with positive anti-TPO antibody status, had abnormal thyroid function. While, only 1 (3.3%) subject had abnormal thyroid function among T1DM subjects who were negative for anti-TPO antibodies. This difference was found to be statistically significant with a p=0.041 (p<0.05).

Patient characteristics and disease severity among T1DM subjects with normal and abnormal thyroid function (Table 2)

T1DM subjects with abnormal thyroid function had a lower mean age at diagnosis, a longer duration of diabetes, and higher mean daily insulin requirement when compared to T1DM subjects with normal thyroid function, but these differences were not found to be statistically significant.

However, the average number of admissions to the hospital for glycemic control and the average number of ICU admissions for acute complications of T1DM were significantly higher among T1DM subjects with abnormal thyroid function when compared to T1DM subjects with normal thyroid function and the difference was found to be statistically significant with a p value of 0.032 and 0.002 respectively. The mean HBA1c levels were higher among T1DM subjects with abnormal thyroid function when compared to T1DM subjects with normal thyroid function, and this difference was statistically significant with a p=0.0214 (p<0.05)

There was no statistically significant difference found between height percentiles (p=0.603), and BMI percentiles among T1DM subjects with normal and abnormal thyroid function (p=0.119).

Table 1: Thyroid function and thyroid autoimmunity among subjects with T1DM in comparison with general pediatric population.

Patient characteristics		Group 1 (n=45)		Group 2 (n=45)		P value
		N	%	N	%	
Gender distribution	Male	26/45	57.8	27/45	60	0.832
	Female	19/45	42.2	18/45	40	
Age distribution (in years)	5-9	12/45	26.7	14/45	31.1	0.876
	>9-13	19/45	42.2	17/45	37.8	
	>13-17	14/45	31.1	14/45	31.1	
Thyroid function	Normal thyroid function	38/45	84.4	44/45	97.8	0.026
	Abnormal thyroid function	7/45	15.5	1/45	2.2	
Abnormal thyroid function	Subclinical hypothyroid	6/7	85.7	1/1	100	-
	Hypothyroid	1/7	14.7	-	-	
	Hyperthyroid	-	-	-	-	
Anti TPO antibody	Positive	14/45	31.1	-	-	
	Negative	31/45	68.9	-	-	

Table 2: Patient characteristics and disease severity among T1DM subjects with normal and abnormal thyroid function.

Patient characteristics	Group 1				P value
	Normal thyroid function		Abnormal thyroid function		
	Mean	SD	Mean	SD	
Age at diagnosis (in years)	9	4	7	5	0.385
Duration of diabetes (months)	36	36	48	43	0.446
Daily insulin requirement (U/kg/day)	1.182	10.34	1.42	0.29	0.567
Total number of hospitalizations for glycemic control	2	2	4	3	0.032
No. of ICU admissions for acute complications of T1DM	1	1	2	2	0.002
HbA1c level (%)	10.4	2.48	12.78	2.03	0.021

Table 3: Comparison of mean age at diagnosis of T1DM and duration of diabetes among T1DM subjects with normal and abnormal thyroid function.

Studies	T1DM subjects (group 1)					
	Patient characteristics	Normal thyroid function		Abnormal thyroid function		P value
		Mean	SD	Mean	SD	
Present study	Age at diagnosis (in years)	9	4	7	5	0.385
Metwalley et al,[13] 2014		14.32	5.21	7.93	3.61	<0.01
Umpierrez et al,[11] 2003		16	1	18	2	NS
Present study	Duration of diabetes (in years)	3	3	4	3.58	0.446
Metwalley et al,[13] 2014		4.1	2.2	9.5	3.6	<0.001

Table 4: Comparison of serum HbA1c levels among T1DM subjects with normal and abnormal thyroid function.

Studies	T1DM subjects (group 1)					
	Patient characteristics	Normal thyroid function		Abnormal thyroid function		P value
		Mean	SD	Mean	SD	
Present study	HbA1c levels	10.4	2.48	12.78	2.03	0.021
Metwalley et al,[13] 2014		9.3	3.5	12.4	2.3	<0.05

DISCUSSION

Our study was a cross sectional comparative study, conducted at a tertiary care center in South India. Sample size and the gender distribution of subjects in of our study was comparable with other similar studies conducted in our country and across the globe.[10-16]

Abnormal thyroid function and anti TPO antibody positivity among T1DM subjects

In the present study, the proportion of abnormal thyroid function among T1DM subjects (Group 1) was 15.5% in contrast to 2.2% in the comparison group (Group 2) and this difference was significantly higher with a p value of 0.026. Anti TPO antibody titer positivity was found in 31.1% of T1DM subjects (Group 1). There is wide variability in the prevalence of abnormal thyroid function and thyroid autoimmunity in other similar studies conducted in different countries across the globe.[10-16] This wide range of prevalence in various studies could be due to the differences among the various study groups in terms of race, ethnicity (as genetic factors are known to play a very important role in the pathogenesis of thyroid autoimmunity in T1DM), age and gender distribution of the study population and the differences in the criteria used for diagnosis in various studies. Sanyal et al a study conducted in West Bengal, India, found that 38% of their T1DM subjects had abnormal thyroid function and 24% had positive anti TPO antibodies.[10] The much higher prevalence of abnormal thyroid function in their study could be attributed to the fact that they used a lower serum TSH cut off value of >4.2 microIU/mL compared to our study where we used age specific reference ranges, where the upper limit of normal TSH level for the age group between 5 months to 20 years is >5.5 microIU/mL to diagnose subclinical hypothyroidism.

In the present study, abnormal thyroid function was more common among female subjects with T1DM, which was in agreement with other studies like Umiperrez et al, Radaideh et al and Metwalley et al as shown in Table

3.[11-13] There was no significant difference in anti TPO antibody positivity among males and females with T1DM, which was also consistent with other studies like Umpierrez et al, Radaideh et al, Al-Khalwari et al and Menon et al as shown in Table 3.[11-15] Although the presence of abnormal thyroid function and anti TPO antibody positivity was found to be more common in older age groups as in other studies like Metwalley et al, Mantovani et al and Kordonouri et al this difference was not found to be significant in our study.[13,16,17] This could probably be attributed to the difference in sample size, and perhaps a larger sample size of subjects might have made the significance of these factors more evident.

Age at diagnosis of T1DM and duration of T1DM

Our study found that the T1DM subjects with abnormal thyroid function were diagnosed at a younger age (mean age at diagnosis, 7 years) and had longer duration of diabetes (mean duration of diabetes of 4 years) when compared to T1DM subjects with normal thyroid function, but these differences were not found to be statistically significant. Other studies like Metwalley et al and Umpierrez et al also found similar differences, but only the findings of Metwalley et al were found to be statistically significant, as depicted in Table 3.[11,13]

Glycemic control

T1DM subjects with abnormal thyroid function had significantly higher number of hospitalizations for glycemic control (p=0.032) and total number of ICU admissions for acute complications of T1DM (p=0.002) when compared to T1DM subjects with normal thyroid function. The mean HbA1c levels and daily insulin requirement were also higher among T1DM subjects with abnormal thyroid function, this difference was found to be statistically significant only for mean HbA1c levels with a p=0.02. Another similar study, Metwalley et al also found significantly higher mean HbA1c levels among T1DM subjects with abnormal thyroid function (Table 4).[13]

Height and BMI

In the present study, we found no significant effect of positive anti TPO antibodies or subclinical hypothyroidism in T1DM subjects on height and BMI. This was consistent with findings in other studies like Kakleas et al Kordonouri et al, Mantovani et al.[16-18] However, Chase et al found reduced growth rates in patients with T1DM and subclinical hypothyroidism, when TSH levels were >10 microIU/ml, and in them, thyroid hormone replacement therapy lead to improved growth only in prepubertal patients.[19] Thus, signifying the importance of early detection and treatment of autoimmune thyroid disease in children and adolescents with T1DM, which could prevent growth impairment in them.

CONCLUSION

Abnormal thyroid function (subclinical and clinical hypothyroidism) is significantly more common among T1DM subjects when compared with age and gender matched subjects without T1DM (comparison group). Anti TPO antibody titers were positive in about one third of children and adolescents with T1DM in our study. Most of our T1DM subjects with abnormal thyroid function had a younger age at diagnosis of T1DM, longer duration of diabetes, and positive anti TPO antibody titers. Children and adolescents with T1DM who had abnormal thyroid function not only had higher insulin dose requirement and poor glycemic control (Higher serum HbA1c levels), but also required significantly higher number of hospitalizations for glycemic control and total number of ICU admissions for acute complications of diabetes. Thus, highlighting the need for screening and a lower threshold for treatment, as early detection has the potential to prevent significant morbidity related to unrecognized disease.

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