Original Article

Thyroid profile and autoantibodies in Type 1 diabetes subjects: A perspective from Eastern India

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ABSTRACT

Context: There has been a rise in the incidence of type 1 diabetes mellitus (T1DM) in India. The prevalence of thyroid autoantibodies and thyroid dysfunction is common in T1DM. **Aims:** The aim of this study is to determine the incidence of thyroid dysfunction and thyroid autoantibodies in T1DM subjects, without any history of thyroid disease, and the prevalence of glutamic acid decarboxylase (GAD) antibody, Islet antigen-2 antibody (IA2), thyroid peroxidase (TPO), and thyroglobulin autoantibodies (Tg-AB) in T1DM subjects. **Settings and Design:** This was a cross-sectional clinical-based study. **Subjects and Methods:** Fifty subjects (29 males, 31 females) with T1DM and without any history of thyroid dysfunction were included in the study. All subjects were tested for GAD antibody, IA2 antibody, TPO antibody, thyroglobulin antibody, free thyroxine, and thyroid-stimulating hormone. **Statistical Analysis Used:** A Chi-square/pooled Chi-square test was used to assess the trends in the prevalence of hypothyroidism. A two-tailed $P < 0.05$ was considered statistically significant. **Results:** The mean age of the subjects was 23.50 years. 9.8% of subjects were below the age of 12 years, 27.45% of subjects were of age 12–18 years, 37.25% of subjects were of age 19–30 years, and 25.49% of subjects were above 30 years. 78% were positive autoantibody for GAD, 30% for IA-2, 24% for TPO, and 16% were positive for Tg-AB. A total of 6.0% of T1DM subjects had evidence of clinical hypothyroidism, but the prevalence of subclinical hyperthyroidism (SCH) varied from 32% to 68.0% for we considered different definitions of SCH as advocated by different guidelines. All subjects with overt hypothyroidism had positive GAD and thyroid autoantibodies. One (2%) subject had clinical hyperthyroidism with strongly positive GAD, TPO, and Tg-AB. **Conclusions:** We found a high prevalence of GAD, IA2, TPO, and Tg-AB in our T1DM subjects. A substantial proportion of our subjects had undiagnosed thyroid dysfunction with a preponderance of subclinical hypothyroidism. All T1DM subjects with overt hypothyroidism or hyperthyroidism had positive GAD and thyroid autoantibodies. The high prevalence of undiagnosed thyroid dysfunction highlights the importance of regular thyroid screening in T1DM subjects.

Key words: Anti-glutamic acid decarboxylase antibody, free thyroxine, IA-2 antibody, TG Antibody, thyroid peroxidase antibody, thyroid-stimulating hormone, type 1 diabetes mellitus

Introduction

There has been a substantial increase in the incidence of type 1 diabetes mellitus (T1DM) in the last few years, growing at a rate of 3%–5% every year.[1,2] India is no exception, with a South India-based Karnataka type 1 diabetes registry reporting an incidence of 3.7/100,000 in boys and 4.0/100,000 in girls, over 13 years.[3] Recently, Kalra *et al.* reported a high prevalence (10.20/100,000 population) of T1DM in Karnal district in North India.[4] T1DM is recognized to be due to autoimmune destruction

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of beta cells in the majority of cases.[5,6] Other autoimmune diseases such as thyroid dysfunction are more common in T1DM. Immunological markers, such as the pancreatic islet cell antibodies (now known as Islet antigen-2 [IA2]), glutamic acid decarboxylase (GAD65) antibodies, and insulin autoantibodies have been documented to be present at diagnosis and may even predict future T1DM in siblings of affected subjects.[7-11] The appearance of antithyroid peroxidase (TPO), antithyroglobulin (TG) autoantibodies in T1DM precedes thyroid dysfunction. TPO antibodies are one of the major secondary antibodies associated with autoimmune thyroid disease and can be used as a diagnostic marker. The prevalence of thyroid autoantibodies and thyroid dysfunction is increased in subjects with nonthyroid autoimmune diseases such as T1DM. Screening for antithyroid antibodies in T1DM may help in early detection of autoimmune thyroid disorders. Clinically, thyroid dysfunction can cause metabolic disturbances and may undermine diabetes control. Hyperthyroidism may worsen glycemic control while hypothyroidism alters carbohydrate metabolism. Therefore, regularly screening in T1DM subjects allows early detection and treatment of thyroid dysfunction.

Objective

To study the prevalence of previously undiagnosed thyroid dysfunction in T1DM subjects and to determine the prevalence of positive autoantibodies, i.e., GAD, IA2, TPO, and Tg-AB in T1DM subjects.

Subjects and Methods

Study design and enrolment criteria

Subjects with T1DM without any previously history or symptoms of thyroid dysfunction were included in the study. Criteria for diagnosis of diabetes were as per the standard American Diabetes Association guidelines. Participants were excluded if they were pregnant or had any acute or chronic systemic illnesses as judged by the investigator or if they were receiving drugs (such as lithium or steroids) that could interfere with thyroid function tests.

Subjects

Total fifty subjects with T1DM were included in the study.

Study procedure

All subjects were tested for GAD antibody, IA2 antibody, TPO Antibody, and Tg-AB using standard kits by standard methods. The thyroid profile of subjects: free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were also tested. GAD antibody (Ab) was estimated by (radioimmunoassay) RIA (DLD Diagnostika, GMBH); IA-2 Ab by RIA (DLD Diagnostika, GMBH); TPO-Ab by CLIA (Roche, Germany-Cobas e 411); Tg-Ab by CLIA (Roche, Germany-Cobas e 411).

Based on thyroid function test results, participants were classified using following definitions: Overt hypothyroid: low serum-FT4 (i.e., <0.9 ng/dL) and TSH >10 μU/ml); subclinical hyperthyroidism (SCH): Normal serum FT4 (0.9–1.7 ng/dL); and suppressed TSH (i.e., <0.3 μU/ml). For subclinical hypothyroidism, we considered a normal serum FT4 (0.9-1.7 ng/dL) along with TSH >4.2 mIU/mL (based on Clinical Practice Guidelines for Hypothyroidism in Adults: the American Association of Clinical Endocrinologists [AACE] and American Thyroid Association [ATA] 2012)[12] or TSH >2.50 mIU/mL (based on National Academy of Clinical Biochemistry laboratory guideline).[13] Anti-TPO antibody positive: the presence of anti-TPO antibodies above 34 IU/ml. Anti-TG antibody positive: the presence of anti-TG antibodies above 115 IU/ml. GAD antibody positive: the presence of GAD antibodies above 1 IU/ml. IA-2 antibody positive: The presence of IA-2 antibodies above 1 IU/ml.

Statistical analysis

All statistical calculations were performed using the Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows (SPSS, Inc., Chicago, IL, USA). Statistical methods used were descriptive to calculate mean ± standard deviation. The prevalence of hypothyroidism and other thyroid disorders was summarized as counts and percentages. A Chi-square/pooled Chi-square test was used to assess the trends in the prevalence of hypothyroidism. A two-tailed $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of subjects are given in Table 1. Of the total 50 subjects, 29 were male, and 21 were female. Their age ranged 5–52 years (mean 23.50 years), [Table 1]. Around 9.8% of subjects were below the age of 12 years, 27.45% between age 12 and 18 years, 37.25% between age 19 and 30 years, and 25.49% above 30 years. The prevalence of hypothyroidism in the study sample is shown in Table 2. Positive GAD antibody (Ab) was detected in 39 subjects (78.0%), IA2 Ab was present in 15 (30.0%) subjects, 12 (24.0%) subjects had TPO-Ab and 8 (16.0%) had Tg-Ab, 13 (26.0%) subjects showed positivity of both GAD-Ab and IA2-Ab, and 8 (16.0%) subjects showed positivity of both TPO and Tg-Ab. The presence of all four antibodies was observed in only two subject's, i.e., 4.0% [Table 3]. The prevalence of hypothyroidism among autoantibodies is depicted in Tables 4 and 5. All subjects overt hypothyroidism had positive GAD and thyroid autoantibodies. The one subject with hyperthyroidism had positive GAD, Tg-AB, and

TPO autoantibodies. If we consider the upper normal limit of TSH as 4.2 mIU/mL (based on our kit reference as well as Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012), a total of 38% of T1DM subjects had previously undiagnosed thyroid dysfunction with 32% having SCH while 6.0% had overt hypothyroidism. As per the recent National Academy of Clinical Biochemistry laboratory guideline, considering the TSH cutoff 2.5 mIU/mL, the prevalence of overt hypothyroidism remained unchanged at 6%, but the prevalence of SCH soared significantly to 68%. Consequently, SCH was found to be significantly higher in the GAD antibody-positive subjects, $P = 0.043$. There was no significant difference in the prevalence of subclinical hypothyroidism between IA2, TG, IA2, TPO, and TG antibody positive or negative T1DM subjects. There was only one (2%) subject with overt hyperthyroidism due to Graves' disease as confirmed by radionuclide technetium scan. None of the subjects had polygrandular atrophy. Further the age-wise stratification of thyroid autoantibodies in different age groups of type 1 diabetes mellitus subjects is depicted in Table 6.

Table 1: Baseline characteristics

Parameters	Values
Number of cases	50
Age (years)	
Mean±SD	23.50±10.52
Sex (%)	
Male	29 (58.0)
Female	21 (42.0)

SD: Standard deviation

Table 2: Prevalence of hypothyroidism

Parameters	Number of cases (*n*=50)	Percentage of cases
Hypothyroidism	3	06.0
Sub clinical hypothyroidism	16*/34**	32*/68.0**

*Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9-1.7 ng/dL) TSH >4.2 mIU/mL (based on clinical practice guidelines for hypothyroidism in adults: AACE and ATA 2012). **Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9-1.7 ng/dL) along with TSH >2.50 mIU/mL (based on National Academy of Clinical Biochemistry laboratory guideline). FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, AACE: American Association of Clinical Endocrinologists, ATA: American Thyroid Association

Table 3: Frequency of positivity for the all antibodies

Positive antibody	Number of cases (*n*=50)	Percentage of cases
GAD	39	78.0
IA2	15	30.0
TPO	12	24.0
TG	8	16.0
TPO + TG	8	16.0
GAD + IA2	13	26.0
TPO + TG + GAD + IA2	2	4.0

GAD: Glutamic acid decarboxylase, IA2: Islet antigen-2, TPO: Thyroid peroxidase, TG: Thyroglobulin

Discussion

The prevalence of 26%–61% of autoantibody positivity in T1DM subjects has been reported from North India, with very few dual positive subjects.[6-8] Low antibody seropositivity is a consistent feature of T1DM in Asia, particularly in India, compared to Western T1DM population.[8,14,15] The majority of our subjects were positive for one or more autoantibodies, and this is similar to what has been shown by other landmark studies such as the SEARCH for Diabetes in the Young Study and the Finnish DIPP Study.[16,17] In our study, GAD antibody was present in 78.0% followed by 30% positivity for IA2 and 26.0% had both GAD and IA2 antibodies. The level of autoimmunity reported in the present study was among the highest reported so far compared to other Indian studies. Kochupillai and Goswami have shown 38% anti-GAD positivity while Singh *et al.* reported 61% GAD antibody and/or IA-2 antibody positive in T1DM subjects.[7,18]

Table 4: Association of glutamic acid decarboxylase and islet antigen-2 antibody between clinical and sub clinical hypothyroidism

Antibody	Percentage of cases with hypothyroidism			
	Clinical, *n* (%)	*P* (NS)	Sub clinical, *n* (%)	*P*
GAD				
Positive (*n*=39)	3 (7.7)	0.342	11*/24** (28.2*/61.5**)	0.042
Negative (*n*=11)	-		5*/10** (45.5*/90.9**)	
IA2				
Positive (*n*=15)	1 (06.7)	0.897	4*/08** (26.7*/53.3**)	0.46 (NS)
Negative (*n*=35)	2 (05.7)		12*/26** (34.4*/74.3**)	
GAD + IA2				
Positive (*n*=13)	1 (7.7)	0.765	3*/06** (23.1*/46.2**)	0.088 (NS)
Negative (*n*=37)	2 (05.4)		13*/28** (35.1*/75.7**)	

**Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9-1.7 ng/dL) along with TSH >2.50 mIU/mL (based on National Academy of Clinical Biochemistry laboratory guideline); *Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9-1.7 ng/dL) TSH >4.2 mIU/mL (based on clinical practice guidelines for hypothyroidism in adults: AACE and ATA 2012). *P*<0.05 considered as statistically significant, *P* values computed by Chi-square test, NS: Not significant, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, AACE: American Association of Clinical Endocrinologists, ATA: American Thyroid Association, GAD: Glutamic acid decarboxylase, IA2: Islet antigen-2

Table 5: Association of antibody between clinical and subclinical hypothyroidism

Antibody	Percentage of cases with hypothyroidism			
	Clinical, *n* (%)	*P* (NS)	Sub clinical, *n* (%)	*P* (NS)
TPO-AB				
Positive (*n*=12)	2 (16.7)	0.074	5*/7** (41.7*/58.3**)	0.41*/0.71**
Negative (*n*=38)	1 (02.6)		11/27 (28.9/71.05)	
Tg-AB				
Positive (*n*=8)	2 (25.0)	0.06	2*/4** (25*/50.0**)	0.64*/0.44**
Negative (*n*=42)	1 (02.4)		14*/30** (33.33*/71.4**)	
TPO + Tg-AB				
Positive (*n*=8)	2 (25.0)	0.06	2*/04** (25*/50.0**)	0.65*/0.45**
Negative (*n*=42)	1 (02.4)		14*/30** (33.33*/71.4**)	
TPO + Tg-AB + GAD + IA2				
Positive (*n*=2)	-	1.00	-	1.00
Negative (*n*=48)	3 (6.3)		16*/34** (33.3*/70.8**)	

**Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9-1.7 ng/dL) along with TSH >2.50 mIU/mL (based on National Academy of Clinical Biochemistry laboratory guideline); *Subclinical hypothyroidism, defined as a normal serum FT4 (i.e., 0.9–1.7 ng/dL) TSH >4.2 mIU/mL (based on clinical practice guidelines for hypothyroidism in adults: AACE and ATA 2012). *P*<0.05 considered as statistically significant, *P* values computed by Chi-square test, NS: Not significant, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, AACE: American Association of Clinical Endocrinologists, ATA: American Thyroid Association, GAD: Glutamic acid decarboxylase, IA2: Islet antigen-2, TPO: Thyroid peroxidase, TG: Thyroglobulin, AB: antibodies

Table 6: Age-wise stratification of thyroid autoantibodies in different age groups of type 1 diabetes mellitus subjects

Age (years), *n* (%)	Tg-AB		Total (*n*)	*P*	TPO-AB		Total (*n*)	*P*
	Positive	Negative			Positive	Negative		
<12	5	0	5	<0.0001	5	0	5	<0.0001
	100	0			100	0		
12-18	3	11	14		3	11	14	
	21.43	78.57			21.43	78.57		
19-30	0	19	19		0	19	19	
	0	100			0	100		
>30	0	12	12		4	8	12	
	0	100			33.33	66.67		
Total	8	42	50		12	38	50	

P<0.05 considered as statistically significant, *P* values computed by pooled Chi-square test. TPO: Thyroid peroxidase, AB: Antibodies, TG: Thyroglobulin

The prevalence of thyroid autoimmunity in children and adolescents with T1DM has been reported between 3.9% and 50% in various studies, and they include Hashimoto's thyroiditis and Graves' disease.[13,19] In the present study, 24.0% subjects had positive TPO antibody, and 16.0% had Tg-AB while 16.0% subjects were positive for both TPO and Tg-AB. The presence of all four (GAD, IA2, TPO, and TG) antibodies was observed in only 2 (4%) subjects. Age-wise stratification of thyroid autoantibodies in different age groups of our subjects revealed statistically significant higher thyroid autoantibodies positivity (both TPO and TG) in age group <18 years.

The management of hypothyroidism differs to a great extent in children (<12 years) and adults >12 years with different diagnostic goals. In our study, only 10% of subjects were below 12 years of age. Present, there is lack of unanimity and ever growing debate and controversy regarding the definition of normal reference range of TSH. With the availability of highly sensitive assay methods and appreciation of the fact that populations previously considered normal according to conventional TSH cutoffs, they were polluted with individuals with various degrees of thyroid dysfunction that served to increase mean TSH levels for the whole group. Noteworthy, recent laboratory guidelines from the National Academy of Clinical Biochemistry argued that more than 95% of normal individuals have TSH levels below 2.5 mIU/m.[20] Furthermore, the early detection and treatment of thyroid dysfunction in diabetes may improve outcomes. Even early treatment of SCH should be considered in T1DM, especially in children. Hence, we also considered a TSH cutoff of 2.5 mIU/mL as per the National Academy of Clinical Biochemistry laboratory guideline[20] which led to a substantial proportion (76%) of our study subjects qualifying for undiagnosed thyroid dysfunction with 68% having subclinical hypothyroidism while 6.0% had overt hypothyroidism and 2% had hyperthyroidism. However, if we consider the Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012[12] our subjects qualifying for SCH significantly drops to 32%. We did not consider separate TSH cutoffs for the adult and the children as recommended by different guidelines.[12] Particularly, a large scale Indian epidemiological study

by Marwaha *et al*. clearly suggested not to increase the upper normal limit of TSH in children compared to the adult population.[21] As per the European thyroid association guideline for the management of subclinical hypothyroidism in pregnancy and in children published in 2014, normalization is achieved in more than 70% of children with TSH >5.5–10 mu/L while it rarely deteriorates for the remaining population with elevated TSH.[22] In the same line, the AACE and ATA, 2012 clinical practice guidelines for hypothyroidism does not recommend different normative ranges of TSH for the adults and the children.[12] A large-scale epidemiological study (n = 4409) also considered an upper normal limit of 4.2 for TSH.[23]

Rattarasarn *et al*. reported subclinical hypothyroidism in 6.3% of 16 subjects who were either TPO-AB or Tg-AB positive.[24] Betterle *et al*. found 18.9% subclinical hypothyroidism in 37 T1DM subjects with TPO-AB and/or Tg-AB.[25] Fernández-Castañer *et al*. found 5 (19.2%) subjects with subclinical hypothyroidism.[26] Roldán *et al*. reported clinical hypothyroidism in 2.8% of 36 T1DM subjects with TPO-AB or Tg-AB positive.[13] Burek *et al*. reported hypothyroidism in 26% of 53 subjects with Tg-AB and/or TPO-AB; those with hypothyroidism all had both TPO and Tg-AB.[19] Fernández-Castañer *et al*. found 4 (15.4%) with clinical hypothyroidism out of their 26 TPO-AB positive T1DM subjects.[26] In our study, all T1DM subjects with overt hypothyroidism had positive GAD and thyroid autoantibodies. In our study, SCH was found in 58.3% with GAD antibody positivity and 50.0% of T1DM subjects with positive TPO-AB and Tg-AB, respectively. 50% of our T1DM subjects with both TPO and Tg-AB positive had SCH. There was no significant difference in the prevalence of SCH between GAD, IA2, TPO, and TG antibody positive or negative T1DM subjects. Overt hypothyroidism was present in 16.7 and 25.0% of our subjects with positive TPO-AB and Tg-AB antibody, respectively while 25% of the present study subjects with both Tg-AB and TPO-AB positive had overt hypothyroidism. The prevalence of SCH was also found to be significantly higher in the GAD antibody-positive subjects. However, we found no significant difference in the prevalence of SCH between IA2, TPO, and TG antibody positive or negative T1DM subjects. The one subject with hyperthyroidism had positive GAD, TG, and TPO autoantibodies.

Conclusions

A substantial proportion of our T1DM subjects had previously undiagnosed thyroid dysfunction with majority having subclinical hypothyroidism. There was high prevalence of GAD, IA2, TPO, antithyroglobulin autoantibodies, with anti-GAD being the most commonly detected one. TPO was the most common thyroid antibody detected. Both TPO and Tg antibodies were higher in the age group <18 years. All T1DM subjects with overt hypothyroidism or hyperthyroidism had positive GAD and thyroid autoantibodies. The high prevalence of undiagnosed thyroid dysfunction highlights the importance of regular thyroid screening in T1DM subjects.

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Conflicts of interest

There are no conflicts of interest.

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