

## A study on thyroid disorders in type 1 diabetes mellitus - A cross sectional observational study

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### Abstract

**Introduction:** Because of this high prevalence, lack of clinical features and the impact on morbidity, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease. **Aim:** Study to analyse the prevalence of thyroid disorders and thyroid autoimmunity among Type 1 Diabetes. **Methodology:** Cross sectional observational study, carried out at Ayaan Institute of Medical Sciences, Hyderabad. Patients were enrolled from the patient population who were admitted in the wards of general Medicine between January 2020 to December 2020. 64 patients among them satisfied criteria for inclusion into the study. Patient list did not include paediatric group since they were not attending our department. **Results:** our study confirms the association between autoimmune hypothyroidism and type 1 diabetes and suggests that all subjects with type 1 diabetes, particularly those with positive Thyroid Peroxidase antibodies, should undergo annual screening by serum Thyroid Stimulating Hormone measurement to detect asymptomatic thyroid dysfunction. **Conclusion:** There is a high prevalence of thyroid autoimmunity in individuals with type 1 diabetes. A subset of patients develops thyroid dysfunction.

**Keywords:** Thyroid, Type 1 Diabetes, Autoimmunity, Hypothyroidism, TSH

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### Introduction

Type 1 Diabetes is a common autoimmune endocrine disease in children and adolescents. It is a clinical syndrome in which the destruction of the pancreatic islet  $\beta$ -cells leads to progressive insulin deficiency and hyperglycemia, which in turn gives rise to micro vascular complications such as retinopathy, nephropathy, and neuropathy as well as macro vascular complication[1]. The presence of auto antibodies targeted against  $\beta$ -cell antigens represents the autoimmune character of Type 1 Diabetes. Due to this autoimmune basis, individuals with Type 1 Diabetes are at increased risk for the development of additional autoimmune disorders compared with the general population<sup>1</sup>. Commonly coexisting immune-mediated disorders are Autoimmune Thyroid Disease, Coeliac Disease, Addison's Disease and pernicious anaemia[2,3]. These diseases are associated with organ-specific autoantibodies: Thyroid peroxidase, thyroglobulin, Thyroid stimulating hormone receptor autoantibodies with Autoimmune Thyroid Disease endomysial autoantibodies and transglutaminase autoantibodies with Coeliac Disease, and 21-hydroxylase autoantibodies with Addison's Disease. Using these autoantibodies, organ-specific autoimmunity

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may be detected before the development of autoimmune clinical disease[3]. The most prevalent among these is thyroid autoimmunity[4]. Its prevalence varies from 8 to 50% depending on the age, sex, and ethnic origin of the subjects. In the general population, thyroid autoimmunity is more frequent in female subjects and prevalence increases with age. In diabetic patients, age and sex distributions are similar, but the prevalence is higher and increases with duration of the disease[5]. Most patients with thyroid autoimmunity are asymptomatic[6]. Even if symptomatic; symptoms may be attributed to diabetes. So, the diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult[7]. Though not clinically evident, underlying hypothyroidism has its own impact on morbidity particularly by exacerbating the coexisting dyslipidemia commonly found in type 1 diabetes and thus increases the risk of cardiovascular diseases. Because of this high prevalence, lack of clinical features and the impact on morbidity, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease.

#### Aims and Objectives

- To study the prevalence and pattern of thyroid disorders in Type 1 Diabetic patients.
- To find out thyroid autoimmune status among them.
- To correlate thyroid autoimmunity with thyroid dysfunction.
- To assess any age/gender/diabetes duration difference.

**Materials and Methods**

**Study design:** Cross sectional observational study to analyse the prevalence of thyroid disorders and thyroid autoimmunity among Type 1 Diabetes.

**Setting:** Department of General medicine, Ayaan Institute of Medical Sciences, Hyderabad.

**Approval:** The study was approved by the ethical committee of Ayaan Institute of Medical Sciences, Hyderabad.

**Study population:** Patients were enrolled from the patient population who were admitted in the wards of general Medicine between January 2020 to December 2020. 64 patients among them satisfied criteria for inclusion into the study. Patient list did not include paediatric group since they were not attending our department.

No. of patients enrolled : 71

No. of patients included : 64

No. of patients excluded : 7

**Inclusion criteria:**

Established cases of Type 1 Diabetes, diagnosed based on standard criteria [Symptoms of diabetes and a casual plasma glucose  $\geq$  200 mg/dl (11.1 mmol/l) or Fasting plasma Glucose  $\geq$  126 mg/dl (7.0 mmol/l) or 2-h plasma glucose  $\geq$  200 mg/dl (11.1 mmol/l)] and insulin dependence proved by C peptide level of < 1 ng/ml.

Exclusion criteria:

- Pregnancy

- Evidence of other autoimmune diseases like Addisons disease, vitiligo, autoimmune hepatitis, rheumatoid arthritis, Systemic Lupus Erythematosus.
- Multinodular goiter, known thyroid disease with negative thyroid autoimmunity.
- Past history of thyroid surgery or radioiodine therapy.

**Consent:**

Patients were informed about the details of the test performed and blood sample collected with consent.

**Sample collection:**

Venous blood sample collected in 8 hrs fasting state. serum separation, sample was sent for analysis.

**Method of testing:**

T3,T4, TSH-- Radio Immuno Assay.

Thyroid peroxidase -- Enzyme Linked Immuno

Antibodies-- Sorbent Assay.

**Normal ranges:**

T3 0.8– 1.4 ng/ml  
 T4 4.2– 11 µg/dl  
 TSH 0.5 – 5 mIU/ ml  
 TPOA upto 40 IU/ml

**Statistical analysis:**

Statistical analysis was done using standard formulae SPSS (Statistical Package for Social Sciences) in windows Dos version.

**Results**

**Table 1: Thyroid Status in Relation to Gender**

Thyroid Status	Total No. (IN%)	Gender	
		Male	Female
Euthyroid	56(87.5%)	29(45.3%)	27(42.2%)
Hypothyroid	8(12.5%)	2(3.1%)	6(9.4%)
Hyperthyroid	nil		

On comparing the female : male 3:1 ratio by chi square test , the p value is 0.1573 which is > 0.05 . So, the association between gender and hypothyroidism is not significant indicating that there is no

significant gender difference among hypothyroid and euthyroid type 1 diabetics as per this study.

**Table 2: Thyroid Autoimmunity Status In Relation To Gender.**

Thyroid Autoimmunity	Total (IN %)	Gender	
		Male	Female
TPOA Negative	52(81.25%)	27(42.25%)	25(39%)
TPOA Positive	12(18.75%)	4(6.25%)	8(12.5%)

On comparing the female: male ratio 2:1 by chi square test, the p value is 0.2482 which is > 0.05. So, the association between gender and thyroid autoimmunity is not significant indicating that there is no

significant gender difference among those who are positive for Thyroidperoxidase antibody and those who are negative for the same in type 1 diabetics as per this study.

**Table 3: Correlation Between Thyroid Function And Autoimmunity.**

Category	Hypothyroid	Euthyroid	Total
TPOA Negative	7(58%)	5(42%)	12
TPOA Positive	1 (2%)	51(98%)	52
Total	8	56	64

58% of Thyroid peroxidase antibody positive patients are hypothyroid whereas only 2% of Thyroid peroxidase antibody negative patients are hypothyroid. 87.5% of hypothyroid patients are Thyroid peroxidase antibody positive whereas 12.5% of them are Thyroid peroxidase antibody negative. On comparing these two values by chi square test , the p value is 0.001 which is statistically significant at 1% levels. So, the association between thyroid

autoimmunity and hypothyroidism is significant indicating that hypothyroidism is more prevalent among Thyroid peroxidase antibody positive individuals than in Thyroid peroxidase antibody negative individuals.

On assessing Thyroid Peroxidase Antibody status as a predictor for development of thyroid dysfunction, the positive predictive value is 58% and the negative predictive value is 98%

**Table 4: Thyroid Autoimmunity in Relation to Duration of Diabetes**

Autoimmune Status	Mean Duration of Diabetesin Years + SD
TPOA Positive	4.5 + 3.5
TPOA Negative	3.2 + 1.9

On comparing the the two means by student t test, the p value is 0.081 which is  $< 0.05$ . So, the association between thyroid autoimmunity and duration of diabetes is not significant indicating

that prevalence of Autoimmune Thyroid Disease is not related to duration of diabetes as per this study.

**Table 5: Thyroid autoimmunity in relation to age of the Patients**

Thyroid Autoimmunity	Mean age in years + SD
TPOA Positive	21.2 + 5.6
TPOA Negative	20 + 5

On comparing the two means by student t test, the p value is 0.478. So, the association between prevalence of thyroid autoimmunity and age of diabetics is not significant, indicating that prevalence of Autoimmune Thyroid Disease is not related to age of the patients as per this study.

#### Discussion

##### Prevalence of Thyroid autoimmunity in Type 1 Diabetes:

We confirmed the high prevalence of a second organ-specific autoimmune manifestation in individuals with type 1 diabetes. By cross – sectional analysis the prevalence of thyroid autoimmunity in our study population is 18.75%. (12 out of 64). This is in concordance with many other similar studies from various parts of the world. Most of the studies state the prevalence to be between 15 to 30%. Roldán MB et al[4] -17.6%. Initial screening of type 1 diabetic patients at the time of diagnosis, for the presence of thyroid antibodies was done by Gemma et al in march 2007[10] and O Kordonouri et al[7] in 2005 and they found out Thyroid Peroxidase Anti body positivity in 14.2% and 15.4% respectively. Study by Aaron Hanukoglu et al[8] is a multicentered cross sectional study which included both newly diagnosed as well as previously diagnosed patients. They give the prevalence as 27%. Same study says the prevalence in first degree relatives as 25%. Similar single time measurement of antibodies was done by Jennifer M. Barker et al[9] which showed the prevalence as 29%. They actually found an association between thyroid autoimmunity and positivity for Anti Glutamic Acid Decarboxylase antibodies & HLA DR3-DQ2 homozygosity. Comparable value of 26% and a similar HLA association was given by Kim EY et al[10]. In an observational cross-sectional study by Palma et al[11] the prevalence of anti- Thyroid Peroxidase Anti bodies was 10.8%. Forty-four (11.2%) new cases of Thyroid dysfunction were diagnosed during the clinical evaluation. In a study done by Yong Soo Park et al[12] twenty-nine of 115 (25.2%) type 1 diabetes patients had Autoimmune Thyroid Disease, whereas 3 of 36 (8.3%) age and sex-matched normal controls had Autoimmune Thyroid

Disease. Twenty-six of 96 (26.9%) type 1 diabetes family members had Autoimmune Thyroid Disease.

In a study by Heba-Allah Moustafa Kamal Al-D et al[13] 52 of 80 patients (65%) showed high Thyroid Stimulating Hormone levels and 25 patients (31.3%) showed positive anti-Thyro Globulin, anti-Thyroid Peroxidase levels. The high Thyroid stimulating Hormone levels were statistically significantly associated with high anti-Thyro Globulin, levels and anti- Thyroid Peroxidase levels. Thirty diagnosed type-1 Diabetes Mellitus patients are chosen for study who belong to age group of 12-30 yrs. Thirty age matched subjects without Diabetes Mellitus -1 are taken as controls. All the subjects had no history of previous thyroid diseases. The study showed that there was a significant decrease in the values of Free Triiodothyronine in type-1 Diabetes Mellitus when compared to controls. There is no statistical difference in the values of Free Thyroxine 4 and Thyroid Stimulating Hormone between type-1 Diabetes Mellitus and control groups. There was a significant increase in the values of anti-Thyroid Peroxidase and anti-Thyro Globulin antibodies in type-1 Diabetes Mellitus when compared to controls. Thus, our study on thyroid disorders in type 1 diabetes mellitus supports previous studies in terms of Autoimmune Thyroid Disease prevalence.

##### Prevalence of Thyroid dysfunction in Type 1 Diabetes:

The reported prevalence of thyroid dysfunction in diabetic populations varies widely between studies. But, thyroid dysfunction is seen particularly in those who are positive for thyroid autoimmunity and so the presence of thyroid autoimmunity is considered to predict the future development of thyroid dysfunction.

O Kordonouriet el<sup>7</sup> performed a long term, large scale study, which included 659 Type 1 Diabetes mellitus patients. The cumulative incidence of hypothyroidism at 10 years of observation time was 0.69 (0.08) in positive anti- Thyroid Peroxidase compared with 0.12 (0.05) in 539 patients with negative anti-Thyroid Peroxidase measurements ( $p < 0.001$ )

**Table 1: Parameters and their studies**

	Guillermo E. Umpierrez[15]	Our Study
N	58(F-32,M-26)	64(F-33,M-31)
Prevalence of thyroid dysfunction	33%	12.5%
TPOA positivity in patients with abnormal thyroid function	80%	87.5%
Positive predictive value of TPOA	67%	58%
Negative predictive value of TPOA	90%	98%

Our study is comparable to this study in all terms except that this study was a longitudinal study, where they did assessment for Thyroid Peroxidase Anti body every 4 years and thyroid function on yearly basis. There is no statistical difference in the values of Free Thyroxine and Thyroid Stimulating Hormone between type-1 Diabetes Mellitus and control groups. There was a significant increase in the values of anti- Thyroid Peroxidase Anti body and anti-Thyro Globulin antibodies in type-1 Diabetes Mellitus when compared to controls. In the Indian study by Menon PS et al[13], abnormal thyroid function was found in only 1 among 19 Thyroid Peroxidase Anti body patients. Similar to the report by Guillermo E. Umpierrez et al[14], all our patients with thyroid dysfunction had only hypothyroidism. Most of them were subclinical. While we didn't find any hyperthyroid patients, hyperthyroidism has been reported as a presentation of thyroid autoimmunity in Type 1

Diabetes Mellitus in several studies[16]. On the whole, in agreement with many similar reports, our study showed a higher prevalence of thyroid dysfunction mostly as subclinical hypothyroidism in type 1 diabetes than in the general population, especially in patients with positive Thyroid Peroxidase Anti bodies and is comparable to previous studies.

**Thyroid autoimmunity in relation to gender:** Generally thyroid autoimmunity is more common in females than in males, this holds good for Type 1 Diabetes Mellitus also as per many cross-sectional as well as prospective studies. But there are studies which showed equal prevalence in both the gender. In our study, though the actual number of females was high, with a F: M ratio of 2:1, it was not of statistical significance. This may be due to two reasons. 1. Actual prevalence being equal; 2. Smaller study population.

Gemma C et al[5] reported female preponderance. 18.3% females had Autoimmune Thyroid Disease whereas it was 7% in males. Olga Kordonouriet al[16] showed a similar female preponderance and they had 63% of Autoimmune Thyroid Disease patients as females.

**Thyroid autoimmunity in relation to age:** Many studies have shown that the prevalence of thyroid autoimmunity is high among older patients than younger patients. But in our study we didn't find a significant age difference between Thyroid Peroxidase Anti body positive and Thyroid Peroxidase Anti body negative individuals. This may be because of the reason that we included only patients of age >12. But there are reports, where presence of Thyroid Peroxidase Anti body is not influenced by age. Olga Kordonouri et al[16] states that the prevalence of significant thyroid antibody titers increases with increasing age of patients and reached its maximum in the 15- to 20-year age group. O Kordonouri R, Hartmann et al[7] reports the prevalence to be high in > 12 years age group.

**Thyroid autoimmunity in relation to duration of diabetes:** According to many prospective studies incidence of thyroid autoimmunity increases as years pass by since the diagnosis of diabetes. The net result would be a higher prevalence of Autoimmune Thyroid Disease among patients with longer duration of diabetes than the newly diagnosed cases. But in our study there is no significant difference in duration of diabetes between, Thyroid Peroxidase Anti body positive and Thyroid Peroxidase Anti body negative persons. This has also been confirmed in many longitudinal as well as cross-sectional studies. Maugendre D et al[17] showed that the duration of diabetes doesn't influence development of Auto-immune Thyroid Disease. The Indian study by Menon PS[13] et al also observed that the thyroid autoimmunity did not change with duration.

### Conclusion

There is a high prevalence of thyroid autoimmunity in individuals with type 1 diabetes. A subset of patients develops thyroid dysfunction. Prevalence of thyroid autoimmunity as indicated by Thyroid peroxidase antibody positivity is more than that seen among general population. Prevalence of hypothyroidism is more than that seen among general population. Most of the patients develop subclinical form of the disease thus reducing the possibility of clinical suspicion. Gender, age and duration of diabetes may or may not have a significant association with autoimmune thyroid disease.

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