

## Original Research Article

## A Study on Thyroid Profile in Type 1 Diabetes at Tertiary Care Centre

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**ABSTRACT**

The purpose of this study is to find out the prevalence and pattern of thyroid disorders in Type 1 diabetic patients. Thyroid autoimmunity is common among people with type 1 diabetes. Thyroid disorder affects a small percentage of the population. Thyroid autoimmunity is more common in the general population, as demonstrated by the presence of Thyroid peroxidase antibodies. Hypothyroidism is more common in women than in men. The majority of people have a subclinical form of the condition, which lowers the chances of clinical suspicion. Gender, age, and duration of diabetes are linked to autoimmune thyroid disease in some cases, but not in others. To summarise, our study confirms the link between autoimmune hypothyroidism and type 1 diabetes and suggests that all subjects with type 1 diabetes, particularly those with positive Thyroid Peroxidase antibodies, should be screened annually for asymptomatic thyroid dysfunction using serum Thyroid Stimulating Hormone levels.

**Keywords:** thyroid peroxidase, type 1 diabetes, TSH, autoimmunity.

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**Introduction**

Diabetes type 1 is a common autoimmune endocrine disease in children and adolescents. It is a clinical syndrome in which the destruction of pancreatic islet-cells causes progressive insulin deficiency and hyperglycemia, which in turn causes microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications [1,2].

The presence of autoantibodies directed against  $\beta$ -cell antigens is indicative of Type 1 Diabetes' autoimmune nature. Individuals with Type 1 Diabetes are at a higher risk of developing other autoimmune disorders than the general population due to this autoimmune basis. [3]. Autoimmune Thyroid Disease, Coeliac Disease, Addison's Disease, and pernicious anaemia are all immune-mediated disorders that frequently coexist. [4]

Thyroid peroxidase, thyroglobulin, and 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 are all associated with organ-specific autoantibodies. Organ-specific autoimmunity can be detected using these autoantibodies before autoimmune clinical disease develops. [5]

Thyroid autoimmunity is by far the most common of these. Its prevalence ranges from 8% to 50%, depending on the subjects' age, gender, and ethnicity. Thyroid autoimmunity is more common in females than in males in the general population, and the prevalence rises with age. The age and gender distributions in diabetic patients are comparable, but the prevalence is higher and increases with disease duration. [4]

The majority of thyroid autoimmunity patients have no symptoms [5]. Even if symptoms exist, diabetes can be blamed. As a result,

relying solely on clinical manifestations to diagnose thyroid dysfunction in diabetic patients can be difficult. Though not clinically visible, underlying hypothyroidism has an impact on morbidity, particularly by exacerbating coexisting dyslipidaemia that is common in type 1 diabetes and thus increasing the risk of cardiovascular disease.

Most researchers recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease due to its high prevalence, lack of clinical features, and impact on morbidity. Early detection has the potential to save lives by preventing significant morbidity from an undiagnosed disease.

**Aim & 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 Biochemistry, NRI Medical College/General Hospital, Guntur.

**Approval**

The study was approved by the ethical committee of NRI Medical College.

**Study population**

Patients have enrolled from the patient population admitted to the Family & General Medicine wards between January 2018 and June 2020. 50 patients match the requirements for inclusion in the study. The paediatric patient's group was not included in the patient list because they did not attend our department.

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No. of patients enrolled	:	60
No. of patients included	:	50
No. of patients excluded	:	10

**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 Addison's disease, vitiligo, autoimmune hepatitis, rheumatoid arthritis, Systemic Lupus Erythematosus.
- Multinodular goitre, 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 the blood sample collected with consent.

**Sample collection**

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

**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	ug/dl
TSH	0.5 - 5		mIU/ ml
TOP	up to 40		IU/ml

**Result interpretations**

- Any T3 /T4 value above the upper limit of normal along with a low TSH  $<$  0.5 mIU/ml is considered hyperthyroidism.
- Any T3 /T4 value below the lower limit of normal along with an elevated TSH  $>$  5mIU/ml is considered hypothyroidism.
- TSH  $>$  5mIU/ml along with normal range T3, T4 is considered as subclinical hypothyroidism.
- TSH  $<$  0.5 mIU/ml along with normal range T3, T4 is considered as subclinical hyperthyroidism.
- Thyroid autoimmunity is considered to exist if Thyroid Peroxidase Antibody level is  $>$  40 IU/ml and not to exist if it is lesser.

**Statistical analysis**

The statistical analysis was measured using standard formulae in SPSS (Statistical Package for Social Sciences), which was installed on a Windows 10 computer and MS Office 365. Baseline information such as age, gender, and duration of diabetes was collected. The thyroid status and thyroid autoimmune status of the patients were determined. When the chi-square test was performed, one of the values was less than 5. For each variable, 2 x 2 tables were constructed, and the chi-square value for each degree of freedom was calculated. Statistical significance was defined as a p-value of less than 0.05 at the 5 per cent level and a p-value of less than 0.001 at the 1 per cent level.

**Results****Table 1: Thyroid Status about Gender**

Thyroid Status	Total No. (IN%)	Gender	
		Male	Female
EUTHYROID	41(82.0%)	23(46.0%)	18(36.0%)
HYPOTHYROID	9(18.0%)	3(6.0%)	6(12%)
HYPERTHYROID	nil		

On comparing the female: male 3:1 ratio by chi-square test, the p-value is 0.1453 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 About Gender**

Thyroid Autoimmunity	Total (In %)	Gender	
		Male	Female
TPOA NEGATIVE	39(78.0%)	21(42.0%)	18(36.0%)
TPOA POSITIVE	11(22.0%)	5(10.0%)	6(12.0%)

On comparing the female: male ratio 3:2 by chi-square test, the p value is 0.2452 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 Thyroid peroxidase 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	4(36.37%)	7(63.63%)	11
TPOA POSITIVE	3(7.69%)	36(92.30%)	39
TOTAL	7	43	50

Values in tables represent row percentage. 36.37 % of Thyroid peroxidase antibody positive patients are hypothyroid whereas only 7.69 % of Thyroid peroxidase antibody negative patients are hypothyroid. 82.0% of hypothyroid patients are Thyroid peroxidase antibody positive whereas 18.0 % 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 Diabetes In years + SD
TPOA POSITIVE	5.3 + 3.2
TPOA NEGATIVE	3.7 + 2.1

On comparing 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 the 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	19.8 + 5.1
TPOA NEGATIVE	17.6+ 5.6

On comparing the two means by student t test, the p value is 0.458. 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.

#### Interpretation of Results

- Most of the Thyroid peroxidase antibody-positive individuals have abnormal thyroid function. Positive predictive value is 36.37 %.
- Abnormal thyroid function is mainly in the form of subclinical hypothyroidism.
- Hypothyroidism is more common among those who are positive for Thyroid peroxidase antibody; however hypothyroidism is seen in Thyroid peroxidase antibody-negative subjects also.
- Though the actual numbers are high, there is no statistically significant difference in age, sex, duration of diabetes between Thyroid peroxidase antibody positive and Thyroid peroxidase antibody negative individuals.

#### 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 22.0 % (11 out of 50).

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%. 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[6] and O Kordonouri et al[8] in 2005 and they found out Thyroid Peroxidase Antibody positivity in 14.2% and 15.4% respectively.

A study by Aaron Hanukoglu et al[9] is a multi centered cross-sectional study that 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[8] which showed the prevalence as 29%. In an observational cross-sectional study by Chakarova et al<sup>2</sup> the prevalence of anti- Thyroid Peroxidase Antibodies 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 [11] 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 [12] 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.

Of all patients without known thyroid disorder first screened for Autoimmune Thyroid Disease, 10.3 % (n=104) was diagnosed with hypo- or hyperthyroidism. The average prevalence of Autoimmune Thyroid Disease in the study population was 112/1000 patients. They found 128 new cases of Autoimmune Thyroid Disease.

In a study by Volzke H et al[13], Type 1 diabetic subjects had a higher risk of known thyroid disease [odds ratio (OR) 1.78, 95% confidence interval (CI) 1.11-2.85], and a higher risk of anti-Thyroid Peroxidase –Anti-Bodies compared to the reference population. Adult type 1 diabetes mellitus is associated with an increased risk of thyroid autoimmunity. A diabetes related low T3 syndrome may contribute to the differences in thyroid function between type 1 diabetic and non-diabetic subjects

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.

A study by Menon et al[14], conducted in the Department of Paediatrics, All India Institute of Medical Sciences, New Delhi in 2001, is the only Indian study available in this context. According to this study Thyroid Peroxidase, prevalence is 54.3%. This is a higher value when compared to our study as well as many other studies. But the limitation of this study is that, only 35 patients were included.

Sarah J. Glastras et al[15] give relatively lower values of 7.8% and 12.9% respectively.

While most of the studies included patients of any age, the one by Miguel Fernandez-castaner et al [16] is similar to ours. They included only adult population of age  $> 14$  years and found out the prevalence to be 27.9%

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 Kordonouri et al[8] 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  $< 0.001$ )

Guillermo E. Umpierrez et al[17] showed a prevalence of thyroid dysfunction to be 33%. All patients had hypothyroidism mostly subclinical. None had hyperthyroidism. 80% of them were positive for Thyroid Peroxidase antibodies. Among the Thyroid Peroxidase Anti body positive individuals, 83% of females and 51% of males developed hypothyroidism on follow up.

In their study, Thyroid Peroxidase Antibody positivity as a predictor for the development of thyroid dysfunction was assessed and they found out 67% positive predictive value and a 90% negative predictive value. As per their study, patients who were Thyroid Peroxidase positive were 17.91 times as likely to develop hypothyroidism as patients who were Thyroid Peroxidase negative

(95% CI 3.89–82.54). Comparison with study by Guillermo E. Umpierrez et al:

Our study is comparable to this study in all terms except that this study was a longitudinal study, where they did an assessment for Thyroid Peroxidase Anti body every 4 years and thyroid function on yearly basis.

The high Thyroid Stimulating Hormone levels were statistically significantly associated with high anti-Thyro Globulin levels and anti- Thyroid Peroxidase levels. There was a significant increase in the gland volume in diabetic patients.

Also 25% of patients showed heterogenous hypoechogenic gland texture versus 6 % in the control group which was statistically significantly different, and 50% of the patients showed increase in gland vascularity versus 12% in the control group which was statistically significantly different.

These morphological abnormalities were associated with high (Thyroid Stimulating Hormone, anti- Thyroid Peroxidase Antibody and anti-Thyro Globulin) levels but weren't significant. High Thyroid Stimulating Hormone levels were strongly positively correlated with anti- Thyroid Peroxidase Anti body and anti-Thyro Globulin.

The average prevalence of Autoimmune Thyroid Disease in the study population was 112/1000 patients. They found 128 new cases of Autoimmune Thyroid Disease, 101 cases of hypothyroidism and 27 of hyperthyroidism between 1995 and 2011 with accompanying incidences of 11.2/1000 person-years.

In a study by Völzke H<sub>2</sub> et al [13], Type 1 diabetic subjects had a higher risk of known thyroid disease [odds ratio (OR) 1.78, 95% confidence interval (CI) 1.11-2.85], and a higher risk of anti-Thyroid Peroxidase -Antibodies compared to the reference population.

Furthermore, diabetic subjects had lower serum FT3 levels than the non-diabetic references (adjusted mean 5.00 pmol/L; 95%-CI 4.88-5.12 pmol/L versus 5.27 pmol/L; 95%-CI 5.24-5.30 pmol/L). Adult type 1 diabetes mellitus is associated with an increased risk of thyroid autoimmunity. A diabetes-related low T3 syndrome may contribute to the differences in thyroid function between type 1 diabetic and non-diabetic subjects.

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

The type 1 diabetes patients with Autoimmune Thyroid Disease had longer duration of type 1 diabetes and were mainly composed of females. There was no difference in the prevalence of diabetic ketoacidosis at the onset of diabetes and no difference in the frequency of family history. Neither could we find the difference of fasting c-peptide levels between the two groups.

In the Indian study by Menon PS et al [14] 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 [17], 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. [18]

In the study by Gemma C<sup>10</sup> et al, 72% of patients with thyroid autoimmunity developed thyroid dysfunction. 68% hypothyroidism, 4% hyperthyroidism. Roldán MB et al<sup>17</sup> found 11% subclinical hypothyroidism, 3% overt hypothyroidism, 3% subclinical hyperthyroidism and 6% overt hyperthyroidism among those who were positive for Autoimmune Thyroid Disease.

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 Antibodies 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 3:2, 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 [4] reported female preponderance. 18.3% females had Autoimmune Thyroid Disease whereas it was 7% in males. Olga Kordonouri et al [19] showed a similar female preponderance and they had 63% of Autoimmune Thyroid Disease patients as females.

In our study thyroid autoimmunity is more common in females with Type 1 diabetes mellitus and thus our study supports many previous studies and contrasts few previous studies.

#### **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 Antibody 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 the body is not influenced by age.

Olga Kordonouri et al [19] states that the prevalence of significant thyroid antibody titers increases with the increasing age of patients and reached its maximum in the 15- to 20-year age group. Holl RW et al [20] found the prevalence of Autoimmune Thyroid Disease to increase dramatically with age. Jennifer M. Barker et al [5] agree the higher prevalence in older age.

In a study by Völzke H<sub>2</sub> et al [13], Type 1 diabetic subjects had a higher risk of known thyroid disease [odds ratio (OR) 1.78, 95% confidence interval (CI) 1.11-2.85], and a higher risk of anti-Thyroid Peroxidase-Antibodies compared to the reference population. Adult type 1 diabetes mellitus is associated with an increased risk of thyroid autoimmunity

In the study by Gemma C et al [6] there is a significant age difference between those who develop thyroid dysfunction and those who remain euthyroid among the Thyroid Peroxidase Anti body-positive subjects. Thyroid function abnormality being more common among those who were older at the onset of diabetes. But the age of onset does not influence the positivity of the antibodies.

In our study, we didn't find a significant age difference between Thyroid Peroxidase Antibody positive and Thyroid Peroxidase Antibody negative individuals thus supporting some previous studies and contrasting some previous studies.

The influence of age of onset of diabetes or age of the patient on development of Autoimmune Thyroid Disease may/may not be there depending on the population.

#### **Thyroid autoimmunity in relation to duration of diabetes**

According to a number of prospective studies, the incidence of thyroid autoimmunity increases with the passage of time from the diagnosis of type 1 diabetic mellitus. The overall result would be a higher prevalence of Autoimmune Thyroid Disease among patients who have had diabetes for a longer period of time as compared to newly diagnosed patients with diabetes.

Therefore, according to our findings, there is no statistically significant difference in the duration of diabetes between people who have Thyroid Peroxidase Antibody positive and those who have Thyroid Peroxidase Antibody negative. In numerous longitudinal and cross-sectional investigations, this has also been demonstrated.

According to the findings of Guillermo E. Umpierrez et al [17], the majority of participants with positive Thyroid Peroxidase

Antibodies (17 out of 18) tested positive at the start of the trial and remained positive throughout the duration of the investigation. 12 After 12 years of follow-up, only one patient who had an initial negative Thyroid Peroxidase titer had a low-Thyroid Peroxidase titer.

Thyroid Peroxidase Antibody was evaluated exclusively at the time of the start of diabetes in a prospective trial conducted by Lupoliet al. [4]. The possibility of future conversion to positive was not considered. Thyroid Peroxidase Antibody negative individuals developed hypothyroidism, although only one of these patients was later shown to be positive for the antibody.

According to our findings, there is no statistically significant difference in the duration of diabetes between people who are positive for Thyroid Peroxidase Antibody and those who are negative for Thyroid Peroxidase Anti Body, which supports some prior studies and contradicts others.

It is necessary to investigate whether the prevalence of thyroid autoimmunity is higher in people who have had diabetes for a longer period of time.

#### Conclusion

In final result, 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 with serum Thyroid Stimulating Hormone measurement to detect asymptomatic thyroid dysfunction.

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