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Prevalence study of thyroid disorders in type 1 diabetes mellitus

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Abstract
Background: Type 1 Diabetes Mellitus is a chronic endocrine disorder of children and early adults of autoimmune origin. It is often complicated by other autoimmune disorders especially autoimmune thyroid disease characterized by the presence of thyroid antibodies to peroxidase and thyroglobulin. Using these auto antibodies, organ-specific autoimmunity may be detected before the development of autoimmune clinical disease. Thus the aim of the study is to find the prevalence of thyroid disorder and thyroid autoimmunity status in type1 diabetes mellitus.
Method: Data were collected from 100 type 1 Diabetic patients. They were tested for thyroid profile (TSH, total T3 and T4) and thyroid autoimmunity (thyroid peroxidase antibodies).
Results: The prevalence of thyroid disorder and thyroid autoimmunity was found to be 14% and 18% respectively in T1DM. Out of 18 thyroid peroxidase positive patients, 14 were hypothyroid and 4 were euthyroid. Over the 14 hypothyroid, only 3 were overt hypothyroid and the remaining 11 were subclinical hypothyroid. There was female preponderance for thyroid autoimmunity in T1DM. There is also significant association T1DM and development of thyroid autoimmunity.
Conclusion: There is higher incidence of thyroid disorder in type 1 diabetes mellitus which is usually subclinical. Coexisting thyroid disorder in type 1 diabetes may have a poor outcome on glucose control. Thus there is a need for periodic screening of thyroid profile in type1 diabetes mellitus.

Keywords: diabetes mellitus, thyroid disease

Introduction
Type 1 Diabetes mellitus is a chronic autoimmune disorder of children and early adulthood due to destruction of beta pancreatic cells resulting in absolute insulin deficiency leading to both microvascular and macrovascular complications in due course of time [1].
As Type 1 diabetes mellitus is a common endocrine disorder associated with aberrant immune responses to specific β-cell autoantigens including autoantibodies to glutamic acid decarboxylase (GAD), to islet cell (ICA) and to insulin (IAA), these patients are also prone to other autoimmune disorders such as Graves‟ disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia1 [3]. Using these autoantibodies, organ-specific autoimmunity may be detected before the development of clinical disease. The most common autoimmune disease associated with T1DM is autoimmune thyroid disorder, which is characterized by the presence of thyroid antibodies especially thyroid peroxidase and thyroglobulin [4]. In type 1 DM, the prevalence of thyroid antibodies in children is 8 to 50% from various studies in different nations due to variation in age, sex, and ethnic origin of the people.

Aims and Objectives
1. To study the prevalence and pattern of thyroid disorders in Type 1 Diabetic patient.
2. To find out thyroid autoimmune status among them.
3. To correlate thyroid autoimmunity with thyroid dysfunction.
4. 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.

Study Population
100 Patients were enrolled from the patient population who attended the outpatient clinic of Diabetology, from August 2016 to July 2017.

Inclusion Criteria
Established cases of Type 1 Diabetes, diagnosed based on standard criteria.
1. Symptoms of diabetes and casual plasma glucose 200 mg/dl (11.1 mmol/l) or
2. Fasting plasma glucose 126 mg/dl (7.0 mmol/l) or
3. 2-h plasma glucose 200 mg/dl (11.1 mmol/l) and
4. Patient on insulin from the time of diagnosis of diabetes

Exclusion Criteria
1. Patients less than 14 years
2. Pregnancy
3. Evidence of other autoimmune diseases like Addisons

disease, vitiligo, autoimmune hepatitis, rheumatoid arthritis, SLE.
4. Multinodular goiter and known thyroid disease on medication
5. Past history of thyroid surgery or radioiodine therapy.

Sample Collection
Venous blood sample were collected after 8 hours fasting state. After serum separation, samples were sent for analysis.

Method of Testing
- T3, T4, TSH – Radio Immuno Assay.
- Thyroid peroxidase Antibodies - Enzyme Linked Immuno Sorbent Assay

Result Interpretations
- Any T3 /T4 value above the upper limit of normal along with a low TSH < 0.5 mIU/ml is considered as hyperthyroidism.
- Any T3 /T4 value below the lower limit of normal along with an elevated TSH > 5mIU/ml is considered as 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 TPOA level is > 40 IU/ml and not to exist if it is lesser.

Statiscal Analysis
Statistical analysis was done using standard formulae SPSS (Statistical Package for Social Sciences) in windows Dos version. Base line data like age, gender, duration of diabetes were collected. Patients were categorized based on their thyroid status and thyroid autoimmune status. The significance of difference between means in two groups was calculated using student t test and the significance of difference in proportions using chi-square test. Fisher exact test was used when any one of the values was less than 5 in chi-square test. 2 x 2 tables were constructed for each variable and chi square value for a degree of freedom calculated. Statistical significance at 5% levels was taken for p value < 0.05 and at 1% levels p < 0.001.

Observations & Results
The study was prospective, observational, non- interventional and follow up study. 100 patients were selected randomly who fulfils the criteria for the study. Following parameters were observed in our study.

Table 1

Thyroid status	Male	Female	TPO Positivity
Euthyroid	50	36	4
Hypothyroid	4	10	14
hyperthyroid	0	0	0

On comparing the female and male ratio by chi square test, the p value is 0.077 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.

Discussion
The study showed 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% (18 out of 100). 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*-17.6%; Prázný M31- 22%, Mc Canlies E - 26.6%, Maugendre D *et al* - 9-17%.
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 and O Kordonouri*et al* in 2005 and they found out TPOA positivity in 14.2% and 15.4% respectively.
Study by Aaron Hanukoglu *et al* is a multicenter 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* which showed the prevalence as 29%.
Many longitudinal studies have shown a still higher prevalence due to late appearance of thyroid peroxidase antibodies. Adriana Franzese et el diagnosed 50% of AITD patients at initial screening, remaining 50% on follow up. Longitudinal study by Guillermo E. Umpierrez *et al* has shown it to be 33% but most of tested positive in the beginning itself.
A study by Menon *et al*, conducted in Department of Pediatrics, All India Institute of Medical Sciences, and New Delhi in 2001, is the only Indian study available in this context. According to this study TPO 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 a1 and D Hansen *et al* 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* 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 type 1 diabetes supports previous studies in terms of AITD prevalence.
The reported prevalence of thyroid dysfunction in diabetic population 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 el performed a long term, large scale study, which included 659 T1D patients. The cumulative incidence of hypothyroidism at 10 years of observation time was 0.69 (0.08) in positive anti- TPO compared with 0.12 (0.05) in 539 patients with negative anti-TPO measurements (p < 0.001) Guillermo E. Umpierrez *et al* showed a prevalence of thyroid dysfunction to be 33%. All patients had hypothyroidism mostly subclinical. None had

hyperthyroidism. 80% of them were positive for TPOA antibodies. Among the TPOA positive individuals, 83% of females and 51% of males developed hypothyroidism on follow up. In their study, TPOA positivity as a predictor for 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 TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54). Miguel Fernandez-castaner investigated 111 adult T1D patients and found 15.3% thyroid dysfunction, and all of them were positive for thyroid antibodies. None of the TPOA negative individuals developed thyroid function abnormality.

Similarly in the report by Maugendre D *et al*, 24% had abnormal thyroid function among anti-TPO positive patients, while none among those who were negative for the antibody. Gemma C *et al* is in favour with this. Similar to the report by Guillermo E. Umpierrez *et al*, 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 T1D in several studies.

In the study by Gemma C *et al*, 72% of patients with thyroid autoimmunity developed thyroid dysfunction. 68% hypothyroidism, 4% hyperthyroidism. Roldán MB *et al* found 11% subclinical hypothyroidism, 3% overt hypothyroidism, 3% subclinical hyperthyroidism and 6% overt hyperthyroidism among those who were positive for AITD.

Adriana Franzese *et al* investigated DM1 patients with TPO-AB, the prevalence of hypothyroidism was 16% and that of hyperthyroidism was 4% among them. On the whole, in agreement with many similar reports, we observed a higher prevalence of thyroid dysfunction mostly as subclinical hypothyroidism in type 1 diabetes than in the general population, especially in patients with positive TPO antibodies.

Conclusion

1. There is higher prevalence of thyroid autoimmunity in type 1 diabetes mellitus
2. Most of the patients develop subclinical form of disease
3. Gender, age, and duration of diabetes have a significant association with autoimmune thyroid disease
4. Hypothyroidism is much more common than hyperthyroidism in autoimmune thyroid disease associated with type 1 diabetes

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