Study of Thyroid Functions in Patients with Type – 1 Diabetes

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Abstract

AIMS. To know prevalence of AMA, clinical and subclinical hypothyroidism in Type 1 Diabetics To correlate thyroid dysfunction in Type 1 Diabetics, with its autoimmune nature and sex in patients with Type 1 DM.

Materials and methods:
Fifty type 1 Diabetics and 50 age sex matched controls were recruited in the study. Total Serum T3, T4, TSH was assessed by RIA method and AMA was done by antibody agglutination test.

Observations:
Clinical hypothyroidism was seen in 8% of type 1 diabetics & 16% had subclinical hypothyroidism. 28% of the cases were AMA +ve. All patients with clinical and subclinical hypothyroidism were positive for AMA. There was no sex difference in prevalence of TAI. All controls were –ve for AMA. No subject in control group had clinical and subclinical hypothyroidism.

Conclusion:
Patients with type 1 DM are at increased risk of TAI and should do regular screening for it. Thyroid dysfunction in type 1 diabetics is neither related to duration of diabetics nor sex. As thyroid dysfunction can alter glycemic control, early detection and treatment of thyroid disorder in type 1 DM is important.

Key words:
Type 1 DM, Thyroid dysfunction, Thyroid autoimmunity , hypothyroidism, Anti microsomal antibody.

INTRODUCTION

In recent years, Diabetes Mellitus (DM) has assumed a pandemic proportion. It has been stated that nearly 200 million people will be affected by this disease all over the world, in next 10-15 years. Of these about 55 millions are going to be Indians. Thus India has already become Diabetic capital of the world.

About 10% of patients with Diabetes Mellitus are of Type-1 DM. It is known to have autoimmune origin, since long. Development of autoimmunity in these patients leads to destruction of β cells of pancreas resulting in diabetes which is primarily T lymphocyte mediated .[1] Though various anti B cell antibodies are present in plasma, type 1 DM is primarily T lymphocyte mediated disease[1]. It is a well known fact, that, persons suffering from one autoimmune disease are more prone to develop other autoimmune disease. Patients with Type – 1 DM are at higher risk of developing autoimmune diseases. The prevalence of Thyroid Auto Immunity (TAI) with Type – 1 DM ranges between 13% to above 50 percent [(2)]. In India not many studies have been done in this regard. Hence this study has been undertaken to know the association of TAI with Type – 1 DM.

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AIMS AND OBJECTIVIES OF THE STUDY

1. To know the prevalence of antimicrosomal antibody in patients with Type – 1 DM.
2. To know the prevalence of clinical and subclinical

hypothyroidism in these patients.
3. To correlate clinical and subclinical thyroid dysfunction in Type I DM with its autoimmune nature and with sex.
4. To correlate thyroid dysfunctions with duration of diabetes.

MATERIAL AND METHODS

Design:
It is a cross sectional case control study. It involves 50 cases (21 females and 29 males) and fifty age and sex matched controls (24 females and 26 males).

Selection of Subjects:
Cases include diagnosed patients of type 1 DM. Subjects were recruited from N.K.P. Salve Institute of Medical Sciences & Research Centre, Nagpur, Medicine and Pediatric OPD and also indoor admitted patients**.** Clearance of ethics committee, N.K.P. Salve Institute of Medical Sciences and Research Centre, was sought prior to the beginning of the project. The procedure was explained to the patients in detail and written consent was obtained.

Inclusion Criteria:
1. Diagnosed cases of Type 1 DM.
2. Subjects willing to give informed consent.

Exclusion Criteria:
1. History of pregnancy and lactation.
2. History of other autoimmune diseases.
3. Presence of concurrent psychiatric illnesses.

Control group is age and sex matched healthy individuals not taking any kind of treatment. Age was noted in years completed. The detail history of thyroid illness, number of attacks of ketoacidosis, medications, number of insulin injection per day was noted in detail. Other autoimmune disorders like SLE, Sjogren's syndrome, and Rheumatoid Arthritis were ruled out on history basis. Detail history of neurological symptoms, menstrual history and history relevant to thyroid disorders was taken. Family history of thyroid disorders was also obtained. Detail physical examination was done. Height and weight was measured. Weight was measured using krup's weighing machine with light clothing without shoes and coat. BMI was calculated from these values.

Laboratory investigations included total serum triiodothyronine (T_3), total serum tetraiodothyronine (T_4), serum thyroid stimulating hormone (TSH) and serum antimcrosomal antibody (AMA). All investigations were done by RIA method, at Pitale's Diabetes and Hormone Centre.

Total serum triodothyronine (T_3), total serum tetraiodothyronine (T_4) were done using DPC- USA RIA kits. Serum thyroid stimulating hormone (TSH) was done using DPC USA IRMA kits. Serum antimicrosomal antibody (AMA) titers were estimated with Serodia – AMC by antibody agglutination method.

Normal range for the laboratory parameters are as follows:
Total serum T3: 86 – 187 ng / dL, Total serum T4 : 4.5-12.5 µg / dL
Serum TSH : 0.3- 5.0 mlU/ mL. AMA titer of 1: 400 and more was considered to be positive.

Cases with low T3 and T4 with high TSH were considered to have clinical hypothyroidism while those with normal T3 and T4 with high TSH were considered to have subclinical hypothyroidism.

Statistical analysis :
Continuous variables in baseline characteristics are represented in mean ± S.D . Thyroid functions were compared between cases and controls by student's test, categorical variables are expressed in percentages. $P<0.05$ was taken as statistically significant. Data was analysed on statistical software intercooled stata version 8.0.

OBSERVATIONS AND RESULT
Out of the 50 cases, one male and one female were already on treatment for hypothyroidism. No patient had family history of thyroid disorder.

Results
Cases and controls are age and sex matched. Mean age of cases is 23.58 ± 6.27 years and in controls 23.42 ± 6.23 yrs. (value in mean ± S.D. table no I). Mean levels of

serum T_3 (ng/ml) was 121.53 ± 26.6 in cases and 144.29 ± 20.57 in control group (P=0.0000) (values in mean ± S.D. Table no II) which is highly significantly lower in type 1 Diabetics. Mean levels of serum T_4 in µg/dl was 8.37 ± 8.17 in cases and 7.3 ± 1.54 in controls. (P=0.3642), the difference is statistically insignificant, in diabetic and nondiabetic group. Mean serum TSH (in mlU/ml) in cases was 4.77±7.86 mIU/ml and in controls it was 1.43±0.89, significantly higher in cases than that of controls (P=0.0036 Table no II). A total of 28% of type 1 diabetics were positive for AMA with females 28.57% & males 27.58%. No subject of control group revealed AMA positivity.

Clinical hypothyroidism was seen in 8% of cases and subclinical hypothyroidism in 16% of cases. Total thyroid dysfunction (clinical + subclinical) was seen 24% of the cases. Hyperthyroidism was not seen in any case(Table no III). In control group thyroid dysfunction was not observed. AMA was positive in all cases of clinical and subclinical hypothyroidism (Fig.2.) .

Discussion

Euthyroid state is important for the various normal metabolic processes of the body. Both hypothyroidism as well as hyperthyroidism can affect diabetes control. In hypothyroidism the rate of insulin degradation is reduced which may lower insulin requirements. Young women with type 1 DM show high incidence of auto immune thyroid disorders. Thus it is important to detect and treat thyroid disorder at an early stage in patients with type 1 DM [3].

In this cross sectional study, 29 males and 21 females with type 1 DM were tested for serum antimicrosomal antibody, total Serum T_3 total Serum T_4 and Serum TSH. The results were compared with 50 controls (24 femals and 26 males). We found that AMA was positive in 28% of type 1 Diabetics (Refer Table No.3). Clinical hypothyroidism was seen in 2 males and 2 femals with a total of 4 i.e. 8% and subclinical hypothyroidism (TSH> 5 m lU/ml) was seen in 16% of the cases of which 5 were males and 3 females. Hyperthyroidism was not found in any patient. All the patients with clinical or subclinical hypothyroidism were AMA positive. No patient with AMA negativity had any kind of thyroid dysfunction.

38 cases (76%) had normal thyroid functions. Two patients were AMA positive but with normal thyroid functions. Total serum T_3 levels were significantly less in cases as compared with controls (p=0.0000) but on the other hand there was no significant difference in levels of total serum T_4 (p=0.3642) Serum TSH levels were also significantly greater in cases as compared with controls (p = 0.0036 HS) Table no 2.

Presence of antimicrosomal antibody (AMA) is not an indicator of thyroid dysfunction per se; instead its presence signifies presence of active autoimmune process in body. Those patients who show anti microsomal anti body positivity are at higher risk of developing thyroid dysfunction at a later state. Hence by doing serum AMA, the group more prone to develop TAI can be identified.

Identification of patients with concurrent Type 1 DM and clinical or subclinical hypothyroidism can help these patients to take proper treatment as hypo as well as hyperthyroidism pose problem for glycemic control in type 1 DM. Therefore identification of such condition in type I DM is important.

No statistically significant difference was seen in prevalence of autoimmune thyroid disease in boys and girls (p=0.6902). This finding contradicts many other findings in which prevalence of autoimmune thyroid disorder is more amongst girls [4, 5]. But a few studies [6, 7, 2] support our findings in which sex does not appear to be a predisposing factor for TAI (Thyroid auto immunity).

Our study reports that serum AMA can be a good marker for autoimmune thyroid disorder, as all the patients with thyroid dysfunction were positive for serum AMA (Table no.5)

Further the patients who were AMA positive but with normal thyroid functions are at higher risk of developing autoimmune thyroid dysfunction at a later stage and hence should undergo periodic screening for the same. About 5 – 15% of euthyroid women and 2% of euthyroid men have thyroid antibodies positive in

general population and are at higher risk of developing thyroid dysfunction [8].

All subjects in control group were negative for AMA. Subclinical or clinical hypothyroidism was not observed in control group.

Hansen [9] et al (2003) did a longitudinal study of prevalence of thyroid autoimmunity and after three years, follow up investigations were done. Initial study revealed 5% patients with hypothyroidism which increased to 8% after 3 years. Anti thyroperoxidase (TPO) antibodies were present in 13% of patients. They remained positive at the end of three years. 7% were positive for both thyroperoxidase and antithyyroglobulin antibodies. Those who were initially negative remained so during follow up. Onset of hypothyroidism did not correlate with duration of diabetes and no significant reduction in T_3 was seen. Hyperthyroidism was not found in their study.

Some of these findings match with our study in that, duration of diabetes was not related to onset of hypothyroidism and hyperthyroidism. Prevalence of AMA positivity was 28% in our study, serum T_3 levels were significantly reduced in cases, in which our study differs. Higher prevalence of thyroid auto antibodies could be due to two reasons:

1. There exist ethnic differences in occurrence of autoimmunity and
2. Thyroperoxidase antibody is more specific than antimicrosomal antibody.

In India only one such study has been done so far by **P.S. Menon** [2] et al examined prevalence of autoimmune thyroid disease in Indians with type 1 DM In their study thyroperoxidase antibodies were positive in 54.3% compared to control group. There was no change in prevalence of thyroid antibodies with the duration of D.M. In patients in whom TPO was negative, no case of thyroid dysfunction was seen on follow up. Prevalence of thyroid auto antibodies was similar in boys and girls. These findings correlate with our study. Similar findings were reported by 2 other studies [6, 7, 10].

Though TPO antibodies are more thyroid specific, our study evaluated association of AMA with thyroid disorder. This selection is further supported by another study[10]. Antimicrosomal antibodies correlated more with the presence of chronic autoimmune thyroiditis than thyroglobulin autoantibodies. **Roldan MB** [10] et al (1999) observed prevalence of 17.60% of autoimmune thyroid disorders in patients with type 1 DM. Euthyroidism was observed in 77% of the cases, subclinical hypothyroidism in 11%, overt hyperthyroidism 6% and subclinical hyperthyroidism in 6% of the cases.

Particularly in Indian setting where cost is the main limiting factor in healthcare, serum AMA can definitely be a better indicator than TPO as it can be done more easily and at cheaper cost.

Maugendre [7] et al reported no influence of gender in prevalence of TPO antibodies. In his study 45/258 were positive for TPO antibodies. At the end of five years, thirteen out of 45 developed subclinical and 1 patient out of 45 developed clinical hypothyroidism. No patient with TPO negativity developed thyroid dysfunction.

Predictive value of thyroid auto antibodies for the development of thyroid disorders in children and adolescents with type 1 DM was studied by **O. Kordonouri** [5] et al (2002), in a longitudinal study. A total of 10% (22/219) were positive for anti TPO antibodies. Of these 22 patients positive for anti TPO Ab, 75% had elevated TSH levels and they had decreased T_3 and T_4 levels. Progression to overt hypothyroidism with thyroid antibodies occurs in 5 – 7% per year to 20-22% [4,7] per year. It has been reported that diabetic children have reduced speed of growth velocity[2]. Rise in serum TSH above 2 mlU.ml is associated with higher rate of progression to overt hypothyroidism[5]. Prevalence of hypothyroidism was more in girls than boys. Patients with TPO positivity were 19.91 times likely to develop hypothyroidism [4].

DQBI * 0302 confers susceptibility to development of type 1 DM. Thus the same allele appears to increase risk to the development of both TAI and type 1 DM. [11]

CONCLUSION

From the present study, we conclude that

1. Patients with type 1 DM are at increased risk of thyroid autoimmunity (TAI) and should do regular screening for the same.
2. Autoimmune thyroid dysfunction is not related to duration of diabetes.
3. Since all the patients with clinical or subclinical hypothyroidism were AMA positive and no patient with AMA negativity revealed clinical or subclinical thyroid dysfunction, screening for AMA can be a better guide for the possibility of developing TAI, later on.
4. We observed no influence of gender in the prevalence of TAI.
5. As thyroid dysfunction can alter glycaemic control, early detection and treatment of thyroid disorder in type 1 DM is important.

Table No. I. Demographic Details

	Cases (n = 50)			Controls (n = 50)		
	M (29)	F (21)	Total 50	M (26)	F (24)	Total 50
Age in yrs.	24.55± 6.42	22.24± 5.94	23.58 ±6.27	24.38 ±6.12	22.37± 6.39	23.42± 6.23
Height*in cm	159.89 ±11.05	147.95 ±10.52	155.55 ±11.43	165.07 ±4.30	147.83± 9.93	156.8 ±11.46
Weight**in kg	53.55 ±7.88	43.42± 7.06	49.3 ±9.07	57.92± 7.5	47.41 ±7.51	52.88 ±9.14
B M I***Kg / m^2	20.39 ±1.67	19.76 ±2.38	20.13± 2.05	21.16± 2.3	20.49± 1.80	20.84± 2.08
Durationof DM	7.86 ±4.69	6.52 ±2.69	7.3 ±3.99—			

* P = 0.565, ** P = 0.0521, *** P = 0.0888

Table No. II. Levels of serum T_3, T_4 and TSH in type-1 Diabetics and Controls

	Serum total T_3 ± S.D. (in ng / dL)			Serum total T_4 ± S.D. (in µg / dL)			Serum TSH ± S.D. (in mlU/ mL)		
	M (29)	F (21)	Total (50)	M	F	Total (50)	M (29)	F (21)	Total (50)
Cases n = 50	121.68 ± 28.91	121.33 ± 23.72	121.53 ± 26.6	9.14 ± 11.49	7.34 ± 3.02	8.37 ± 8.17	5.14 ± 8.96	4.25 ± 6.18	4.77 ± 7.86
Control N = 50	149.74 ± 20.87	138.37 ± 18.92	144.29 ± 20.57	7.19 ± 1.59	7.43 ± 1.51	7.3 ± 1.54	1.44 ± 1.04	1.43 ± 0.72	1.43 ± 0.89
P value	0.0002 H.S.	0.0113 H.S.	0.0000 H.S.	0.3533 N.S.	0.9042 N.S.	0.3642 N.S.	0.0411 S.	0.0320 S.	0.0036 H.S.

n = number of subjects in each group, H.S. – Highly significant, N.S. – Not significant, S. - significant

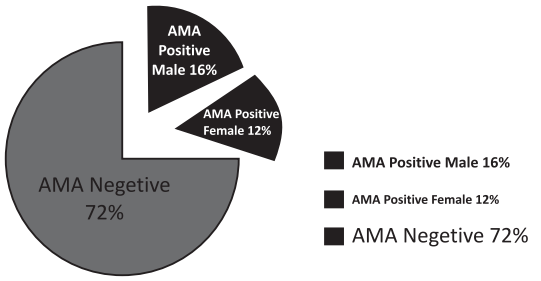
Table no. III. Incidence of Hypothyroidism in Cases and Controls

	TSH > 5 mlU / ML					
	Clinical		Total	Sub Clinical		Total
	M	F		M	F	
Cases n = 50	2 (6.89%)	2 (9.52%)	4 (8%)	5 (17.24%)	3 (14.28%)	8 (16%)
Controls n = 50	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

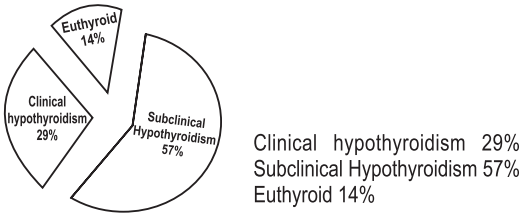
n = number of subjects in each group

Incidence of Antimicrosomal Antibody Positivity in Cases and Controls

Pie Chart showing incidence of Antimicrosomal Antibody positivity in Cases



Pie Chart showing Clinical hypothyroidism, subclinical hypothyroidism and euthyroid state in AMA positive patients



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