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RESEARCH ARTICLE

THYROID DYSFUNCTION IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN NORTHWEST RAJASTHAN, INDIA

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ABSTRACT

Objective: The prevalence of thyroid dysfunction in patients with type 1 diabetes is two to threefold higher than in the general population and occurrence of thyroid dysfunction is often diagnosed late in type 1diabetic population. Our aim is to determine the natural history of thyroid dysfunction in Indian patients with type 1 diabetes.

Methods: Sixty type 1 diabetic patients were recruited in the study from the diabetic clinic attached with S.P. Medical College, Bikaner. In addition to clinical assessment of all patients, determinations were made of thyroid function tests (thyroid stimulating hormone [TSH], thyroxine [T_4] and triiodothyronine [T_3]) and thyroid peroxidase (TPO) antibodies.

Results: Out of 60 type 1 diabetic patients, a total of 8 patients had hypothyroidism and 1 patient had hyperthyroidism. 1 patient having hypothyroidism before the onset of diabetes was excluded from the study. The mean age at diagnosis was 13±7.5 yrs for type 1diabetes and 15±9.4 yrs for hypothyroidism. Hypothyroidism was more common in female 6/59 (10.2%) than in male subjects 2/59 (3.39%) and in patients with positive TPO antibodies. There was no difference in BMI, HbA_1c, lipid profile, insulin level and c-peptide between patients with/without thyroid dysfunction.

Conclusions: The present study indicates that each child with type 1 diabetes, apart form diabetes control, should undergo regular screening of serum TSH measurements to detect asymptomatic thyroid dysfunction, particularly those with positive TPO antibodies.

INTRODUCTION

Type 1 diabetes is a heterogeneous autoimmune disease and is frequently associated with other organ-specific autoimmune diseases, including thyroid disease. Thyroid disorders are highly prevalent in the general population (Wang *et al.,* 1997). Thyroid function tests might be affected by diabetes and obesity. Cross-sectional study has reported that 7.5% of women and 2.8% of men of all ages have abnormal serum thyroid-stimulating hormone (TSH) levels (Tunbridge *et al.,* 1977). The Colorado Thyroid Disease Prevalence Study reported that among 25,862 subjects attending a state-wide health fair, 11.7% of subjects had an abnormal serum TSH concentration. Primary hypothyroidism (TSH >5.1 mU/l) was detected in 9.5% and hyperthyroidism in 2.2% of subjects, most of whom were asymptomatic (Canaris *et al.,* 2000). The prevalence of thyroid dysfunction increases with advancing age and in subjects with thyroid antibodies (Parle *et al.,* 1991). The Third National Health and Nutrition Examination Survey (NHANES III), from a sample of 17,353 people aged ≥12 years representing the geographic and ethnic distribution of the United States population, reported a prevalence of hypothyroidism in 4.6% (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.2% (0.5% clinical and 0.7% sub clinical) (Hollowell *et al.,* 2002). The prevalence of thyroid dysfunction increased from 5-8 % during the 3 years follow up period (Hansen, 2003).

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Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with type 1 diabetes (Perros *et al.,* 1995). The overall prevalence of thyroid disease was found to be 13.4% and was highest (31.4%) in type 1 diabetic females, and lowest in type 2 diabetic males (6.9%). Female patients with type 1diabetes had the highest annual risk of developing thyroid disease (12.3%) (Perros *et al.,* 1995). Hyperthyroidism occurs in 1-2% of patients with diabetes (Perros *et al.,* 1995; Mouradian and Abourizk, 1983). The prevalence of positive thyroid peroxidase (TPO) antibodies (previously referred to as thyroid antimicrosomal antibodies) has been reported in ≈80% of patients with type 1 diabetes with normal TSH levels and 10-20% of diabetic patients are having elevated TSH levels (Perros *et al.,* 1995; Mouradian and Abourizk, 1983). Most patients have sub clinical disease, and the development of diabetes usually precedes the diagnosis of hypothyroidism (Mouradian and Abourizk, 1983). However, long term prospective trials to evaluate the incidence and natural history of thyroid disorders in patients with type 1 diabetes are lacking. Therefore, we evaluated prevalence of thyroid disorders and presence of TPO antibodies in Indian population attending diabetic clinic attached to S.P. Medical College.

MATERIALS AND METHODS

Subjects: Among total patients population (6948) attending our diabetic clinic, type 1 diabetic patients were 344. The major criteria for eligibility in this study included insulin dependence

as evidence by deficient C-peptide secretion <0.6ng/ml, age <30years and the absence of hypertension, hypercholesterolemia and diabetic ketoacidosis. Out of screened 60 type 1 diabetic patient, 1 patient having hypothyroidism before the onset of diabetes was excluded from the study. In addition to monitoring their glycemic control and diabetic complications, all patients had thyroid function test (TSH, thyroxine (T_4) and triodothyronine (T_3)). The presence of TPO antibodies was also determined.

Table 1. Clinical, biochemical and immunological characteristics of patients with type 1 diabetes with or without hypothyrodism

	With Hypothyroidism	Without Hypothyroidism	t	p
No of patients	8	51	-	-
Sex (M/F)	2/6	31/20	-	-
BMI	17±5.2	17±4.4	-	-
Glycemia (mg%)	198.2±36.4	212.4±40.3	0.28	<0.9
HbA_1c (%)	7.8±1.3	8.1±0.9	0.19	<0.9
C-peptide levels (ng/ml)	0.18±0.13	0.21±0.17	0.14	<0.9
Insulin dose (U/kg)	0.68±0.20	0.61±0.24	0.29	<0.9
TSH mu/l	8±2.6	1.6±0.4	2.45	<0.02
TPO antibodies in (n%)	5(62.5)	3(5.88)	-	-
Age, diabetes onset (years)	13±7.5	14±8.4	0.8	<0.9
Age, Hypothyroidism years	15±9.4	-	-	-
Time between onset of diabetes and hypothyroidism	3±2.1	-	-	-

Data are mean ± SE

Protocol

According to the result of thyroid function tests, patients were divided into four groups: group1, normal (when total or free T_4 and TSH were in the normal range); group 2, hypothyroidism (when total T_4 was <60nmol/l and TSH >5.0mU/l); group 3 subclinical hypothyroidism (when total or free T_4 were within normal limits but TSH was >5.0 mU/l); and group 4 hyperthyroidism (when the serum TSH value was suppressed to <0.03 mU/l). To determine whether subjects with type 1 diabetes are at higher risk of developing thyroid dysfunction than the general population, the results were compared with the prevalence of thyroid dysfunction and presence of TPO antibodies that was reported in the NHANES III[5].

Measurements

Blood sugar concentration was measured using the glucose oxidase method. Plasma insulin and C-peptide were estimated by fully automated chemiilluminescence (CLIA test). Anti-insulin antibodies were estimated by radioimmuno assay. HbA_1c was measured by Ion Exchange Chromatography. Plasma Total Cholesterol, Triglycerides, VLDL, HDL, LDL were estimated by fully automated biochemistry analyzer. Urine microalbumin was tested by micral test. T_3, T_4 and TSH estimation was done by radio immuno assay and TPO (thyroid peroxidase antibody) was done by Haem agglutination assay.

Data Analysis

Continuous variables were compared by students t test and categorical variables by chi square test of independence. Data are expressed as mean ± SE. In all instances, the criterion for statistical significance was established at 0.05 before testing.

RESULTS

Fifty nine patients were enrolled in the study. The mean age at diagnosis of diabetes was 13±7.5 (<30) years. A total of 8(13.5%) patients had thyroid dysfunction with a mean age of 15±9.4 years. In the remaining subjects, the mean time between the diagnosis of diabetes and hypothyroidism was 3±2.1 years. There was no difference in BMI, lipid profile and HbA_1c at the time of diagnosis or during follow up between patients with or without hypothyroidism. The presence of TPO antibodies was associated with an increased risk of hypothyroidism. A total of 8 patients had positive TPO antibodies in which 5 patients had hypothyroidism (3 male and 2 female).

(Table 1). Hyperthyrodism was seen only in 1 patient.

DISCUSSION

The present study shows that 13.5% patients had thyroid dysfunction in type 1 diabetes. An association between diabetes and thyroid disease has long been recognized, although the reported prevalence of thyroid dysfunction in diabetic populations varies widely between studies (Gray *et al.,* 1979; Gray *et al.,* 1973 and Radetti *et al.,* 1995). Cross-sectional studies have reported a prevalence of hypothyroidism in 12-24% of female and ≈6% of male patients with type 1 diabetes, as well as in 3-6% of type 2 diabetic patients (Perros *et al.,* 1995; Gray *et al.,* 1979). The NHANES III reported a prevalence of hypothyroidism in 4.6% (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.2% (0.5% clinical and 0.7% subclinical) and positive TPO antibodies in 13% of the United States population (Hollowell, 2002). Age, sex, time of evolution of diabetes, genetic back ground and period of follow up can explain the difference across studies. This prospective study also provides good evidence of the association between autoimmune hypothyroidism and type 1 diabetes.

Population screening for thyroid dysfunction may prevent the development of overt thyroid dysfunction and may allow early treatment of hyperlipidemia (Hollowell, 2002). prevention of associated cardiovascular complications (Geul *et al.,* 1993 and Hak *et al.,* 2000) and metabolic bone disorders (Greenspan, 1999). The American College of Physicians recently published guidelines on screening for thyroid disease with a sensitive TSH test in the primary care setting (Helfand and Redfern, 1998). Dietary carbohydrates content had an influence on the magnitude of fall in serum T_3 (Mathieson *et al.,* 1986). A confounding effect of some of these factors is difficult to be excluded as there were some differences in sex distribution, age and clinical presentations. Some effects of the study method deserve further comments. TPO can be assessed by agglutination and radio immunoassay.

It is generally accepted that both are sensitive, specific and well connected (Hay and Klee, 1988). In the present study, we observed 1.6% prevalence of hyperthyroidism. The prevalence of hyperthyroidism varied from 0.5% to 3% in patients with type 1 diabetes (Perros *et al.,* 1995 and Araujo *et al.,* 2008). The reason for the different prevalence of hyperthyrodism case in our study is not known but may relate to the relatively small number of subjects and/or to the more defined population of patients with type 1 diabetes included in this study.

The presence of TPO antibodies was associated with an increased risk of hypothyroidism. Out of 8 TPO antibodies positive subjects 5 (62.5%) were found with hypothyroidism. In a survey, the use of TPO to predict hypothyroid was found to have a 67% positive predictive value (Hay and Klee, 1988). TPO positive patients were 17.91 times as likely to develop hypothyroidism as TPO negative patients (Guillermo E. Umpierrez, 2003). A total of 18 (33%) patients had positive TPO antibodies (8 men and 10 women). In one recent study, 72% TPO antibodies positive patients developed thyroid dysfunction indicating strong association of TPO antibodies with increased risk of hypothyroidism (Gemma C Gonzalez, 2007). Biochemical thyroid dysfunction and thyroid autoimmunity were evident in type 1 diabetics who were apparently euthyroid hence thyroid function tests are recommended in order to minimize the risk of undiagnosed hypothyroidism in these patients.

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