PREVALENCE OF AUTOANTIBODIES TO THYROID PEROXIDASE AND AUTOIMMUNE THYROID DISEASE IN TYPE I DIABETES MELLITUS

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Abstract- Type I diabetes mellitus (DM) is frequently associated with autoimmune thyroid disease (ATD). Association of ATD and type I DM has been described with varying frequencies but there is still debate about the situation in the Iranian population. We investigated the prevalence of anti thyroid peroxidase (anti-TPO) antibodies and ATD in children and adolescents with type I DM. A total of 145 patients with type I DM were participated in this study. They were screened for anti-TPO antibodies and TSH levels. Signs and symptoms of hypothyroidism and hyperthyroidism and the presence of goiter were sought. A group of 50 healthy unrelated girls and boys aged 11-16 years served as controls. Anti-TPO antibodies were found in 34 (23.4%) diabetic patients and 1 subject (2%) in the control group (P<0.001). Frequency of anti TPO antibodies was significantly higher in girls than boys (P<0.05). We failed to show any significant correlation between thyroid autoimmunity and duration of DM. We found that younger patients at diagnosis are more likely to be anti-TPO negative (P<0.001). Out of 145 diabetic patients, 32 (22%) had visible goiter. Subclinical hypothyroidism, hypothyroidism and thyrotoxicosis occurred in 1, 9 and 1 patients, respectively. Visible goiter was found in 2 subjects (4%) of the control group, but all of them were euthyroid. In conclusion, the evaluation of thyroid autoimmunity in type I diabetic patients may improve the diagnosis of thyroid disease in early stages. Yearly examination of anti-TPO antibodies allows identifying diabetic patients with thyroid autoimmunity.

Acta Medica Iranica, 42(4): 267-271; 2004

Key words: Autoimmune thyroid disease, Anti peroxidase antibody, diabetes mellitus type I

INTRODUCTION

Autoimmune diseases affect a substantial percentage of the population, providing a strong impetus for research into ways whereby such diseases can be detected, prevented and even cured (1,2).

It is well known that certain autoimmune diseases occur in association with each other, such as autoimmune thyroid disease (ATD), pernicious anemia, celiac disease and idiopathic adrenal insufficiency, but the most common combination is type I diabetes mellitus (DM) and ATD (2-4).

The prevalence of thyroid autoantibodies in children with type I DM varies between 3% and 50% in different countries (5-6). Thyroid autoantibodies against microsomes (AMA) tend to have more correlation with thyroid dysfunction than does autoantibody against thyroglobulin (ATA) (7). In recent years detection of antibodies against thyroid peroxidase (anti-TPO), a major antigen for microsomal autoantibody, appears to obviate the need for AMA and ATA measurement because of the improvement in specificity and sensitivity of the method (8). The prevalence of anti-TPO antibodies in

Received: 16 March 2003, Revised: 27 May 2003, Accepted: 29 Dec. 2003

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type I diabetic patients who are clinically euthyroid have been reported to vary from 10% to 21.8% (9-14), but progression to overt thyroid disorders in individuals with significant titers of anti- TPO occurs in about 50% of them within 3-4 years (10). The diagnosis of thyroid dysfunction is often made late in type I diabetic population. Up to now, there is no consensus about either the monitoring of ATD or the time point of therapeutic intervention in patients with type I DM unless clinical symptoms of hypo or hyperthyroidism appear.

The aims of the present investigation were to evaluate the prevalence of anti-TPO autoantibodies and to determine the frequency of ATD in these subjects.

MATERIALS AND METHODS

Subjects

Sera were collected from 145 children and adolescents (67 boys, 78 girls) with type I DM (mean diabetes duration 3.5 years, range 1-12 years) from October 1997 to July 2001. A group of 50 unrelated healthy girls and boys aged 11-16 years (mean age 12.8 y) served as controls. All the individuals recruited in this study were living in Tehran. Having our goals explained, the subjects were asked to participate in the study. They could interrupt their cooperation whenever they desired.

The mean age of type I diabetic patients was 13.1 (range 2-20) years and they were diagnosed as having type I DM on the basis of the World Health Organization (WHO) criteria established in 1980 (15) with the typical symptoms of hyperglycemia. About 32% of patients presented with ketoacidosis or impaired consciousness as the first manifestation of the disease and all required insulin for management of DM.

At the time of enrollment, the patients filled a questionnaire giving information about age, age at the onset of diabetes, daily dose of insulin injection, history of diabetic ketoacidosis (DKA) and occurrence of hypoglycemia. Each patient and control was asked to answer questions about personal history of thyroid disorders. We excluded subjects with positive history of previous thyroid disorders. Patients were requested to complete a questionnaire specific for thyroid symptoms by answering yes or no to a set of 25 questions regarding hypo and hyperthyroidism. Physical examination for signs of thyroid dysfunction and estimation of thyroid size by using palpation were then performed. Thyroid size was classified according to the WHO classification into grade 0, not palpable; 1, palpable but not visible and 2, visible goiter.

Methods

TSH was measured by immunoradiometric assay (IRMA) (spectria, Fenzia, Finland) and anti-TPO by enzyme linked immunosorbent assay (Radim, Rome, Italy). Commercially available kits were used to measure T4, T3 and T3 resin uptake by radioimmunoassay (RIA) on samples with abnormal TSH level (higher or lower than normal range).

The normal (reference) ranges are: anti-TPO antibodies, up to 100 IU/ml; TSH, 0.3-4.5 mU/L; T4, 4.5–12.7 µg/dl; T3, 80-220 ng/dl; T3 RU, 25-35%.

Diagnosis of ATD

In patients with significant anti-TPO titers (> 100 IU/ml), subclinical hypothyroidism was defined as TSH elevation ≥10 mU/L with normal T4 values. Hypothyroidism was diagnosed in patients with T4 values < 4.5 µg/dl and TSH values ≥ 20 mU/L and hyperthyroidism was diagnosed in patients with T4 values > 12.7 µg/dl and/or T_3 > 220 ng/dl and TSH <0.3 mU/L.

Statistical analysis

We compared variables by using the Students *t* test and chi square. A *P* value of 0.05 or less was interpreted as significant.

RESULTS

Frequency of anti-TPO antibodies among 145 children and adolescents who had type I DM was 23.4% (34:145) as compared to 2% (1:50) in the controls (P<0.001).

Frequencies and titers of anti-TPO antibodies in subjects with type I DM and normal controls are shown in table 1.

Table 1. Frequencies and titers of anti-TPO antibodies in subjects with type I DM and normal controls*.

Subjects	Anti-TPO titers (IU/ml)			
	< 100	100-200	200-500	>500
DM (n=145)	111(76.6)	16(11)	14(9.6)	4(2.8)
Normal (n=50)	49 (98)	1 (2)	0(0)	0(0)

Abbreviations: TPO, thyroid peroxidase; DM, diabetes mellitus.

*Data are given as number (percent).

Patients with elevated thyroid autoantibodies differed significantly from those without thyroid autoantibodies regarding their age, gender and age at DM onset. Frequency of anti-TPO antibodies was significantly higher in older patients (72% in the age group of 10-20 years compared to 28% in the age group less than 10 years, $P<0.001$).

Girls more frequently had significantly elevated anti-TPO antibodies than boys. As shown in table 2, anti-TPO antibodies were detected in 23 (29.4%) out of 78 females and 11 (16.4%) out of 67 males ($P<0.05$).

We found that younger patients at diagnosis of DM were more likely to be anti-TPO negative than older patients, *i.e.* the rate of patients under 5 years at diagnosis was higher in anti-TPO negative compared to that in anti-TPO positive subjects (4 versus 30) ($P<0.001$). The prevalence of anti-TPO antibodies was not influenced by the DM duration. Visible goiter were detected in 32 (22%) out of 145 diabetic subjects but subclinical hypothyroidism, hypothyroiddism and thyrotoxicosis occurred in 1, 9 and 1 patients, respectively (7.6%); these cases were characterized by higher levels of anti-TPO antibodies. Visible goiter was found in 2 (4%) out of the 50 normal controls but none of them had thyroid disease.

DISCUSSION

The prevalence of anti-TPO antibodies in type I diabetic patients who were clinically euthyroid have been reported between 10 to 21.8% (9-14). In this survey, the prevalence of anti TPO antibodies in an unselected population of children and adolescents with type I DM was 23.4%. This is a relatively high prevalence in comparison to studies in other countries (Table 3).

The wide range of prevalence in various reports may be due to differences in ethnic groups, geographic area, iodine intake, methodology and population size. Another explanation of the high prevalence of anti TPO in present study is the endemic goiter which could be found here prior to 1990 (16). The problem was resolved by universal salt iodization. The rate of ATD in countries with iodine deficiency has been reported to be low (17). It is conceivable that an increase in ATD may have occurred in our country following consumption of iodized salt used to control iodine deficiency disorders. In agreement with our study, Shahbazian *et al.* found that prevalence of postpartum thyroid dysfunction in Tehran is higher in comparison with worldwide studies (18).

However, it should be noted that in countries with normal iodine intake, the prevalence of anti-TPO positivity and ATD is variable (9-14). Titers of anti-TPO antibodies in this study showed wide distribution. Among the patients with positive anti TPO, the anti TPO titers were mostly below 500 IU/ml (88.2%, 30 out of 34), whereas only 11.8% of patients had titers greater than 500 IU/ml (Table 1); all of the patients in the latter group had ATD.

Table 2. Demographic characteristics of type I diabetic patients positive or negative for anti-TPO

Characteristics	anti-TPO Positive	anti-TPO Negative	*P* Value*
Number of patients	34	111	
Male: female	11:23	56:55	< 0.05
Age at diagnosis (years)†	10.9±4.5	6.9±4.2	< 0.001
Duration (years)†	6.8±5.2	5.6±3.4	NS

Abbreviation: TPO, thyroid peroxidase; NS, not significant.

* by X^2 test.

†mean±SD.

Table 3. Prevalence of anti-TPO in different studies

Year	Author	Country	Prevalence
1987	Rees [9]	Netherlands	10%
2002	Kordonouri [10]	Germany (Berlin)	10%
1999	Hansen [11]	Northern Europe	10%
1999	Holl[12]	South Germany	14%
2000	Maugendre[13]	France	17%
1998	Chang[14]	Taiwan	21.8%
2003	present paper	Iran	23.4%

Thyroid disorders defined as TSH elevation or suppression was found in 7.6% of patients and was significantly associated with higher titers of anti-TPO antibodies (P<0105).

In the literature, progression to overt thyroid disorders in individuals with significant titers of anti-TPO occurs in about 50% of children and adolescents with DM within 3-4 years (10). In cases of significant anti-TPO titers, thyroid function tests are recommended in order to minimize the risk of undiagnosed ATD especially hypothyroidism in these patients. Continuously elevated TSH and thyroid volume indicate a risk of developing hypothyroidism. Chase *et al.* documented reduced speed of growth in diabetic children with elevated TSH values and thyromegaly but euthyroid serum hormone levels. Treatment with L-thyroxine improved growth significantly in prepubertal children compared with age matched diabetic controls (19). In this regard, there is currently no consensus regarding the indication for therapy with L-thyroxine, particulary in patients with DM.

Girls with type I DM were more prone to develop thyroid autoimmunity than boys. This agrees with findings in the general population (20). We also found a tendency for anti-TPO antibodies to occur with increasing age in agreement with the report by Chang *et al.* (14).

Type I DM is usually caused by the loss of endogenous insulin secreting function due to selective immune mediated destruction of pancreatic B-cells (immune mediated type I_A DM). In some patients no evidence of autoimmunity is found and such patients are classified as having idiopathic (non immune mediated type I_B DM) (21). Although a minority of patients with type I DM falls in this category, it has been reported that most of them are of non-European, African or Asian descent (22). We found that younger patients at diagnosis of DM were more likely to be anti-TPO negative than older patients; this is in agreement with findings of Urakami *et al.* (23) and Hathout *et al.* (24), studies which detected that younger patients (under 5 years of age) were more likely to have type I_B DM than type I_A at diagnosis. We failed to show any significant correlation between thyroid autoimmunity and diabetes duration. This finding is similar to those of the majority of previous reports (9-13).

In conclusion, the relationship between type I DM and ATD is not fortuitous and presence of anti-TPO antibodies in 23.4% of our type I DM patients and ATD in 7.6% of them in comparison with worldwide studies suggest that the prevalence of ATD in our patients are relatively high. It is concluded that yearly examination of thyroid antibodies, particularly anti-TPO, should be a part of health assessment in patients with type I DM and in cases with antibody positivity, thyroid function tests are recommended.

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